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REVIEW

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Future directions in acute liver failure

R. Todd Stravitz[1] | Robert J. Fontana[2] | Constantine Karvellas[3] | Valerie Durkalski[4] | Brendan McGuire[5] | Jody A. Rule[6] | Shannan Tujios[6] | William M. Lee[6] | for the Acute Liver Failure Study Group

[1]Virginia Commonwealth University, Richmond, Virginia, USA
[2]University of Michigan, Ann Arbor, Michigan, USA
[3]University of Alberta, Edmonton, Alberta, Canada
[4]Medical University of South Carolina, Charleston, South Carolina, USA
[5]University of Alabama, Birmingham, Alabama, USA
[6]University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA

Correspondence
William M. Lee, Division of Digestive and Liver Diseases, UT Southwestern Medical Center at Dallas, 5959 Harry Hines Blvd, Ste 420E, Dallas TX 75390-8887, USA.
Email: william.lee@utsouthwestern.edu

Abstract

Acute liver failure (ALF) describes a clinical syndrome of rapid hepatocyte injury leading to liver failure manifested by coagulopathy and encephalopathy in the absence of pre-existing cirrhosis. The hallmark diagnostic features are a prolonged prothrombin time (ie, an international normalized ratio of prothrombin time of ≥ 1.5) and any degree of mental status alteration (HE). As a rare, orphan disease, it seemed an obvious target for a multicenter network. The Acute Liver Failure Study Group (ALFSG) began in 1997 to more thoroughly study and understand the causes, natural history, and management of ALF. Over the course of 22 years, 3364 adult patients were enrolled in the study registry (2614 ALF and 857 acute liver injury—international normalized ratio 2.0 but no encephalopathy—ALI) and >150,000 biosamples collected, including serum, plasma, urine, DNA, and liver tissue. Within the Registry study sites, 4 prospective substudies were conducted and published, 2 interventional (*N*-acetylcysteine and ornithine

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AIH, autoimmune hepatitis; AKI, acute kidney injury; ALF, acute liver failure; ALFSG, Acute Liver Failure Study Group; ALI, acute liver injury; APAP, acetaminophen; ARE, antioxidant response elements; AT, antithrombin; Caspase, cysteine-dependent aspartate-directed proteases; CPP, cerebral perfusion pressure; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; ECLS, extracorporeal liver support; ER, endoplasmic reticulum; GSH, glutathione; HRS, hepatorenal syndrome; HTS, hypertonic saline; HVP, high-volume plasma exchange; ICH, intracranial hypertension; ICP, intracranial pressure; INR, international normalized ratio of prothrombin time; iPALF, indeterminate pediatric acute liver failure; KCC, King's College criteria; KEAP, Kelch-like ECH-associated protein; LT, liver transplantation; MAP, mean arterial pressure; MARS, molecular absorbent recirculating system; MBT, ^{13}C-methacetin breath test; MOMP, mitochondrial outer membrane pore opening; MPT, mitochondrial permeability transition; NAC, *N*-acetylcysteine; NRF2, NF-E2–related factor 2; PAI-1, plasminogen activator inhibitor type 1; PALF, pediatric acute liver failure; ROS, reactive oxygen species; ROTEM, rotational thromboelastometry; RRT, renal replacement therapy; SMT, standard medical therapy; TAFI, thrombin activatable fibrinolysis inhibitor; TCR, T-cell receptor; TFS, transplant-free survival; tPA, tissue-type plasminogen activator; UPR, unfolded protein response; vWF, von Willebrand factor.

Acuteliverfailure.org is the study website.

NCT registrations: Overall registry NCT00518440; NAC studies NCT00004467, NCT00896025; OPA study NCT01548690; ^{13}C-methacetin study NCT02786836

List of study sites participating in the ALFSG, 1998-2023. University of Texas Southwestern Medical Center; Baylor University Medical Center, Dallas, TX; Medical University of South Carolina, Charleston, SC; University of Washington, Seattle, WA; Washington University, St. Louis, MO; University of California, San Francisco, and California Pacific Medical Center, San Francisco, CA; University of Nebraska, Omaha, NE; Mount Sinai. Medical Center and Columbia University Medical Center, New York, NY; Mayo Clinic, Rochester, MN; University of Pittsburgh, Pittsburgh, PA; Northwestern University, Chicago, IL; Oregon Health Sciences Center, Portland, OR; University of California, Los Angeles, CA; University of Michigan, Ann Arbor, MI; Yale University, New Haven, CT; University of Alabama, Birmingham, AL; Massachusetts General Hospital, Boston, MA; Duke University, Durham, NC; Mayo Clinic, Scottsdale, AZ; Albert Einstein Medical Center and University of Pennsylvania, Philadelphia, PA; Virginia Commonwealth University, Richmond, VA; University of California, Davis, CA; Mayo Clinic, Jacksonville, FL; University of California, San Diego, CA; The Ohio State University, Columbus, OH; University of Kansas Medical Center, Kansas City, KS; Emory University, Atlanta, GA; University of Alberta, Edmonton, Canada.

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phenylacetate), 1 prognostic [^{13}C-methacetin breath test (MBT)], and 1 mechanistic (rotational thromboelastometry). To review ALFSG's accomplishments and consider next steps, a 2-day in-person conference was held at UT Southwestern Medical Center, Dallas, TX, entitled "Acute Liver Failure: Science and Practice," in May 2022. To summarize the important findings in the field, this review highlights the current state of understanding of ALF and, more importantly, asks what further studies are needed to improve our understanding of the pathogenesis, natural history, and management of this unique and dramatic condition.

INTRODUCTION

Acute liver failure (ALF) describes a clinical syndrome of rapid hepatocyte injury leading to liver failure manifested by coagulopathy and HE in the absence of pre-existing cirrhosis. The hallmark diagnostic features, defined in the 1950s, are a prolonged prothrombin time (ie, an international normalized ratio of prothrombin time (INR) of ≥ 1.5) and any degree of mental status alteration (HE).[1] The annual incidence of ALF ranges from 2000 to 4000 cases per year in the United States.[2] As a rare, orphan disease, it seemed an obvious topic/target for a multicenter network. Thus, the Acute Liver Failure Study Group (ALFSG) was developed with this express purpose in mind to more thoroughly study and understand the causes, natural history, and management of ALF, with initial patient enrollment beginning on January 1, 1998. Over the years, the number of sites increased from the initial 12 to a peak of 23 (total 31) and enrollment continued through August 2019, funded by the National Institute of Diabetes and Digestive and Kidney Diseases from 1997 through the present. In 2010, hospitalized patients with severe acute liver injury (ALI) (defined as an INR >2.0 and bilirubin of >3.0 mg/dL but without HE) were added to the registry.[3] Over the course of 22 years, 3364 adult patients were enrolled in the study registry (2614 ALF and 857 ALI) and $>150{,}000$ biosamples collected, including serum, plasma, urine, DNA, and liver tissue. Detailed data were recorded, including clinical features, laboratory findings, clinical course, transplantation details, and outcome. In addition, 2 interventional [*N*-acetylcysteine (NAC) and ornithine phenylacetate], 1 prognostic [^{13}C-methacetin breath test (MBT)], and 1 mechanistic [rotational thromboelastometry (ROTEM)] clinical trials were conducted and published. These data and corresponding biosamples are now in the public domain. Ancillary studies using clinical data and biosamples combined with the study investigators' efforts have led to 148 published manuscripts over the past 25 years (see acuteliverfailure.org for list and manuscript links). To review accomplishments and consider next steps, a 2-day in-person conference was held at UT Southwestern Medical Center, Dallas, TX, entitled "Acute Liver Failure: Science and Practice," in May 2022. The 26 speakers covered a wide range of topics varying from molecular pathogenesis to causality assessment, clinical management, and the role of liver transplantation (LT) and other investigational approaches.

To crystallize the important findings in the field, this review summarizes the 2-day symposium highlighting the current state of understanding of ALF and, more importantly, asks what further studies are needed to improve our understanding of the pathogenesis, natural history, and management of this unique and dramatic condition.

BACKGROUND/EPIDEMIOLOGY OF ALF

ALF of necessity involves severe damage to hepatocytes. As such, the causes are numerous, ranging from prescription drugs, acetaminophen (APAP), viruses, and malignancy as well as autoimmune and rare genetic/metabolic diseases. Despite the diverse etiologies, the clinical findings are remarkably similar due to the rapidity of injury onset leading to hospitalization with the frequent development of infectious, bleeding, and other vital organ complications in a matter of days.[4] Some etiologies are relatively common (eg, APAP), while others are distinctly rare, such as herpes simplex virus infection leading to ALF (Figure 1).[5] Etiologies vary worldwide, with APAP (paracetamol) overdose being common in Europe and other developed countries, while viral hepatitis A, B, and E being common in the developing world.[6] Indeterminate ALF accounts for as few as 5% of cases in well-vetted circumstances but more than 50% where less extensive testing and phenotyping are undertaken. In certain settings, herbal and dietary supplements may represent a larger proportion of recorded cases than prescription drugs.[7]

APAP overdose appears to be the most common cause of ALF, particularly in North America and

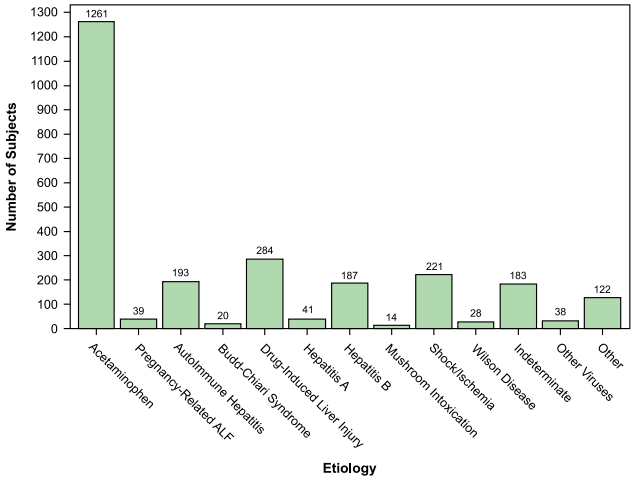

FIGURE 1 Etiologies of ALF as determined by the ALF Study Group site principal investigator and the Causality Committee; patients with ALI not included. January 1998 and August 2019. Total N = 2614 patients. Abbreviation: ALF, acute liver failure.

Europe.[8] Data from the ALFSG Registry do not suggest any decline in the incidence of APAP ALF over the past 22 years, while the proportion of unintentional overdoses appears to be increasing.[9,10] Recent data[11] suggest that the 2011 mandate by the US Food & Drug Administration to cap the amount of APAP to 325 mg in combination prescription analgesic formulations was associated with a reduced number of hospitalizations for APAP hepatotoxicity and a lower likelihood of ALF cases having APAP combination products as their etiology. Given that APAP is the most commonly used medication worldwide with over a billion tablets consumed each year, a similar policy for over-the-counter APAP-containing medications might have a similar effect.[10]

Future directions

A more definitive preventive strategy for APAP toxicity could greatly diminish avoidable liver-related deaths and transplantations. Strategies include combining an antidote with the APAP parent compound (eg, s-adenosylmethionine), identification of a more benign congener of APAP, or additional regulatory actions restricting the tablet dose or amount dispensed per bottle. Better educational programs and best practice alerts in the electronic medical record are also needed for this intrinsically hepatotoxic drug to be optimally used.

Natural history and phenotypes

Since multiple etiologies of liver injury can lead to ALF, it is worthwhile to examine the several mechanisms behind the extensive hepatocyte injury required to reach the threshold of liver failure. Since the original definition of ALF by Trey and Davidson,[1] there has been a further classification of ALF into various subgroups based on the time from symptom onset to presentation with encephalopathy.[12] Hyperacute liver failure is characterized by evolution to liver failure within 3–7 days, primarily the result of APAP or ischemic liver injury.[13] Traditionally, “acute” liver failure is further defined as the evolution from initial symptoms to HE between 8 and 28 days of presentation and subacute liver failure between 5 and 12 weeks.[13] However, it makes practical sense to limit the categories to 2 groups of hyperacute and subacute since the etiologies responsible for traditional acute and subacute liver failure are similar, being largely attributable to idiosyncratic DILI, autoimmune hepatitis (AIH), and HBV.[5] The presenting features and outcome with the various phenotypes of ALF are shown in Table 1.

At presentation, hyperacute liver failure is characterized by very high serum alanine aminotransferase levels, markedly prolonged INR, and low bilirubin whereas acute/subacute liver failure is associated with lower transaminases and higher bilirubin levels. The severity of HE is most evident in hyperacute presentations, and cerebral edema is more frequently observed. Prognosis is more closely related to ALF etiology than to the tempo of evolution, although both are important determinants. In a retrospective analysis of ALFSG patients listed for LT, APAP ALF patients were more likely to die than non-APAP (24% vs. 17%).[14] As befits hyperacute patients, those with APAP-induced ALF who have been listed for LT evolved rapidly, mainly to recover without LT or to death, with a 40% transplant-free survival (TFS) rate compared with 11% for non-APAP cases (Supplemental Figure S1, http://links.lww.com/HEP/H869). The median time to death was more rapid in listed APAP-induced compared with non-APAP–induced ALF patients (2 vs. 4.5 d, respectively). Essentially, all APAP patients’ outcomes were determined within 5 days (Figure 2A). As a consequence of the variability in clinical course based on etiology, 36% (62/173) of listed APAP patients received a LT versus 66% for DILI, 86% for AIH (Figure 2B), and 71% for HBV.[14] To summarize, the now well-defined phenotypes of ALF have etiologic, clinical, and prognostic implications. APAP patients who may require LT have the most urgent need for evaluation and decision-making.

Midway through the 22-year study, the ALFSG expanded the study population by adding a separate category of patients with severe ALI but no evident HE seeking to compare the outcome of this group to those with ALF.[3] To limit the number of enrolled cases to those with the most severe injury, we defined ALI as having aminotransferases of at least 500 IU/L and an INR of 2.0 (N.B., higher than for ALF). Of interest, only 10% of patients with ALI progressed to ALF following

admission to the study. Patients with ALI were more frequently due to APAP overdose than the proportion with ALF but overall had much better outcomes than patients who developed HE.[3]

Recent trends in ALF etiologies and outcomes

Over the past 30 years, the incidence of various etiologies of ALF have waxed and waned, while the overall number of ALF cases per year in the United States has remained quite stable. Although the overall incidence of HAV and HBV infections in the United States has declined with the adoption of safe and effective vaccines, a recent uptrend appears related to local outbreaks of HAV in homeless populations and HBV related to injection drug use and high-risk sexual behavior.[15,16] Over the 2 decades of the ALFSG, overall patient outcomes have improved across etiologies.[9] Specifically, overall 21-day survival and TFS increased significantly, while numbers of patients listed and transplanted decreased. Of interest, there did not appear to be any variation in the overall disease severity at presentation but there was a decrease in the use of ICU measures including intubation, vasopressor use, renal replacement therapy, and transfusion of blood products.[9]

Future directions

Greater awareness of the importance of etiology in determining prognosis may further improve outcomes. In addition, incorporation of objective and quantitative serum prognostic biomarkers and bedside dynamic indices of global hepatic function may provide even better accuracy in identifying which individual patients require LT (see below).

Causality assessment and indeterminate ALF

Despite the use of modern radiological, serological, and molecular testing, 5%–10% of North American patients do not have an identifiable cause of ALF. The majority of these patients with "indeterminate ALF" present with a viral prodrome of fever and malaise and have a clinical picture that is similar to patients with HBV-related or AIH-related ALF.[5] Over the years, a number of ancillary studies of the ALFSG have sought to assign known causes of ALI and ALF to these indeterminate cases. However, occult HBV, herpes simplex virus, and HEV infections have not been identified. A study of 187 patients with "indeterminate ALF" applied metagenomic sequencing and failed to identify any novel viral pathogens or unsuspected cases of ALF due to known viruses.[17]

In 2016, the ALFSG assembled an Adjudication Committee of experienced hepatologists to review all cases enrolled in its registry using standardized

TABLE 1 Comparison of demographics, admission laboratory results, and outcome between different causes of acute liver failure in the acute liver failure study group registry[9]

	Acetaminophen (n = 1261)	Ischemia (n = 221)	Drug-induced Liver Injury (n = 284)	Autoimmune hepatitis (n = 193)	HBV (n = 187)	HAV (n = 41)	Pregnancy (n = 39)	All other causes (n = 405)
Age (median, y)	37	53	46	44	45	50	30	43
Women (%)	75	58	69	77	47	49	100	61
Jaundice to coma (median, days)	1	2	13	15	8	4	6	9
HE grade 3 or higher (%)	50	55%	32%	28	49	54	54	38
Alanine aminotransferase (median, IU/L)	3779	2334	635	449	1402	2229	60	582
Bilirubin (median, mg/dL)	4.3	3.8	21.6	22.8	19.9	12.0	11.2	18.6
Listed for transplant (%)	23	5	56	69	56	59	33	48
Transplanted[a] (%)	9	3	41	59	40	32	18	35
Transplant-free survival[a] (%)	69	67	31	17	24	59	67	23
Overall survival[a] (%)	77	68	70	71	59	88	82	56

Note: Data were collected between January 1, 1998, and December 2, 2022. Total number of ALF patients = 2631.
[a]Represents outcomes 21 days after admission to Acute Liver Failure Study Group Registry.

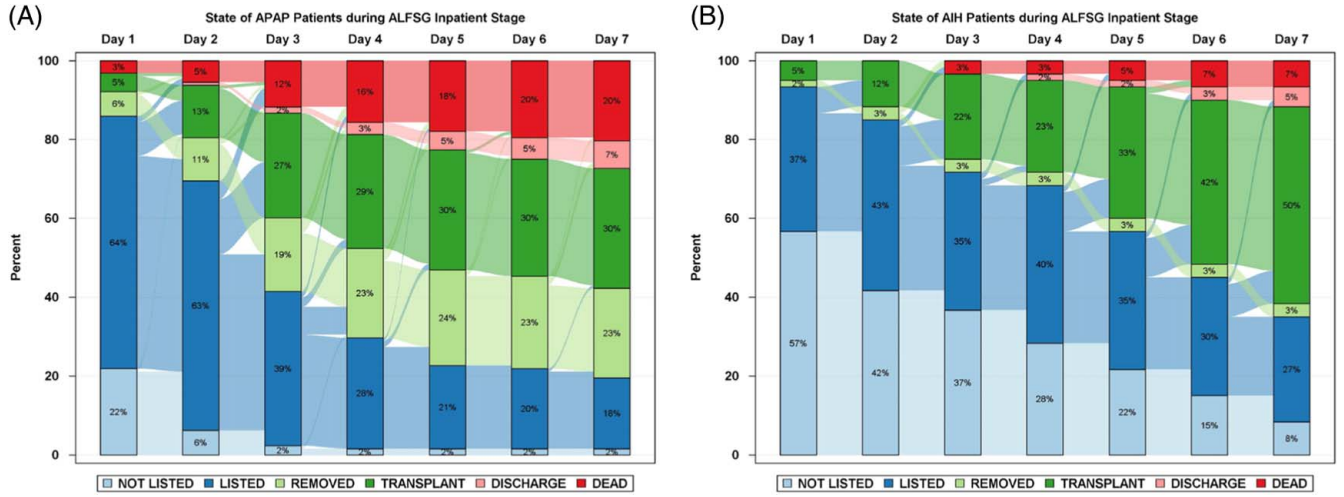

FIGURE 2 Outcomes according to study day in patients with ALF according to etiology with hyperacute ALF (APAP overdose; A) or subacute ALF (eg, AIH; B). Diagrammatic representation of events by day after registry enrollment/listing.[14] For APAP, essentially all outcomes have occurred by day 4. Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ALFSG, Acute Liver Failure Study Group; APAP, acetaminophen.

diagnostic criteria, while adding testing of some critical but previously omitted diagnostic serologies, also testing banked biosamples with new methods.[18] This approach led to a reclassification of 142 of the 303 indeterminate ALF cases (47%) to a known cause, which included 45 cases of previously unrecognized APAP overdose that were identified through detection of serum APAP-protein adducts.[19] Reclassification also included 34 cases adjudicated to probable AIH ALF using a combination of serum autoantibody profiles, quantitative IgG levels, and a review of liver histology.[20,21] Lastly, 24 cases of previously unrecognized idiosyncratic DILI were identified using an adaptation of the expert opinion causality scale published by the DILI Network (DILIN).[22] An early assessment of suspected DILI-related ALF by Reuben et al[23] from 1999 to 2008 demonstrated 133 cases attributed to over 60 individual agents, with antituberculosis drugs and sulfonamides most frequently implicated. A more recent analysis of all 277 probable DILI-related ALI and ALF cases enrolled from 1998 to 2019 demonstrated that the incidence of injury from herbal and dietary supplement products increased over time while the frequency of antimicrobials decreased with improved overall survival.[24] These data demonstrate the importance of careful prospective assessment of the etiology of ALF using standardized, predefined diagnostic criteria.

Future directions

Future ALF registries and clinical trials should use predetermined diagnostic criteria and required testing to establish the cause of ALI and ALF followed by careful case adjudication for clinical trials and before publication. Ongoing studies of indeterminate ALF cases may identify a new viral, metabolic, toxic, genetic, or an immune-mediated disease process.

Pediatric acute liver failure

Pediatric acute liver failure (PALF) is a complex, rapidly progressive clinical syndrome that is the final common pathway for many disparate conditions including metabolic, genetic, infectious, and immunological disease processes that vary in frequency by age group. Historically, children were assigned an ALF diagnosis based on the adult definition that included HE. Recognizing the challenge of accurate HE assessment in infants and children, the PALF Study Group (PALFSG, U01 DK072146) used consensus entry criteria for their longitudinal study enabling enrollment without HE.[25] These criteria were not intended to establish a definitive diagnosis but rather to identify children with ALI sufficiently severe to place them at risk for a progressive clinical deterioration that could result in LT or death. Over time, the general adaptation of these study criteria has improved our ability to compare descriptive, diagnostic, therapeutic, and mechanistic studies performed by investigators worldwide. These efforts have enabled generally agreed on approaches to the diagnosis and management of these critically ill children.[26–30]

Despite improvements in diagnosis, the cause of PALF for roughly one-third of children remains indeterminate (iPALF).[30] In these children, outcomes are generally poorer, with over 50% of iPALF progressing to death or LT.[31] iPALF occurs more frequently in children between 1 and 10 years of age (~60%), and recent studies have supported a hypothesis that a hyperinflammatory host immune response propagates

the liver injury.[32] Future efforts involving immunomodulatory agents to explore this population have the potential to shift the treatment paradigm in PALF and advance the basic understanding of immune dysregulation disorders in childhood.

Beyond iPALF, improved strategies for optimized care, specifically in the ICU setting, are needed. Etiology and age-based differences mean lessons learned from adult experiences may not be transferrable to children. An important example includes our finding that NAC, broadly beneficial in many forms of adult ALF,[33,34] did not demonstrate efficacy in non-APAP PALF.[35] Recently, there have been reports from the Centers for Disease Control and Prevention, United Kingdom, and World Health Organization demonstrating an increase in cases of idiopathic hepatitis in young children with some of them requiring emergency LT. These cases do not appear to be due to adenovirus or COVID-19 infection as initially believed, and pathogenesis studies are ongoing.[36]

Future directions

The advances in neuromonitoring/protection, hemostasis, and hemodialysis/plasma exchange that favorably impact adult ALF outcomes[37] need further study in pediatric populations. In addition, more accurate prognostic models are needed as transplant decisions remain complex in PALF. Recent reports have shown that while the cumulative incidence of listing for and receiving a LT have decreased over time, the cumulative incidence of death has not increased, suggesting those who were likely to survive with their native liver were increasingly identified.[38]

PATHOPHYSIOLOGY OF ALF

The histopathology of ALF

From the pathologist's perspective, ALF results from 2 distinct clinicopathologic mechanisms: (1) insufficient parenchyma, as when hepatocytes are lost through necrosis, to maintain adequate detoxification and synthetic requirements, and (2) hepatocyte metabolic cellular dysfunction, as seen in mitochondrial toxicity.[39] Furthermore, circulatory compromise can further exacerbate the severity of necrosis through intrahepatic vascular thrombosis, inadequate perfusion, or cellular obstruction.[40] These mechanisms lead to histological changes that fall into several distinct patterns (Figure 3, Supplemental Table S1, http://links.lww.com/HEP/H870). In hypoxic injury or APAP toxicity, the necrosis is pericentral with minimal inflammation, while necrosis from viral and AIH and most other drugs is less clearly zonal and more inflammatory. Several drugs cause mitochondrial toxicity that does not lead to necrosis but cripples the function of hepatocytes such as fialuridine[41] and sodium valproate. Sudden and severe hepatic venous outflow obstruction, as seen in Budd-Chiari syndrome or sinusoidal obstruction syndrome, is also associated with necrosis (and hemorrhage) along with portal hypertension.

Since many cases of ALF can be diagnosed through history and other noninvasive tests, liver biopsy is not performed very often in the ALF setting. However, biopsy remains an important supporting tool to diagnose malignancy, nonhepatotrophic viral infections such as cytomegalovirus, Epstein-Barr virus, and herpes simplex virus, and for patients with suspected AIH. In addition, several histological features have prognostic value regarding the need for emergent LT. For example, the degree of necrosis has been identified in several studies as related to outcome, with $>50\%$–70% necrosis identified as the tipping point for poor outcomes.[42] Ductular reaction has also been associated with poorer prognosis, since it signals the inability of the hepatocyte parenchyma to maintain numbers through cell division, prompting an ineffective stem cell response. A histological evaluation of cases of suspected idiosyncratic DILI showed that microvesicular steatosis, cholangiolar cholestasis, and hepatic fibrosis were associated with LT and death, while granulomas and eosinophils were favorable findings for survival. Few studies have examined the percent cell necrosis as an indicator of prognosis in ALF, and little has been done to use liver biopsy as a prognostic tool in this setting due to safety concerns and the potential for sampling artifact.[43]

Future directions

Careful examination of tissue samples and liver explants may further our knowledge of the injury patterns of ALF. Application of RNAseq and other molecular methods in ALF tissue may also provide insight into the biological pathways involved in liver injury and identify targets for future treatments and interventions. A central repository of liver tissue that can be analyzed and made available to the medical community would facilitate this effort. Over 300 ALF explants from the ALFSG registry are currently stored digitally and under study at NIH.

Molecular mechanisms of liver injury

ALF occurs when liver cell death from a pathogen, an aberrant immune response, or a hepatotoxic agent overcomes the liver's regenerative and adaptive capacity. In the hepatic microenvironment, stressed hepatocytes have evolved adaptive mechanisms to combat stress. Some of these include activation of NFκB signaling to block apoptosis; upregulation of antioxidant defense

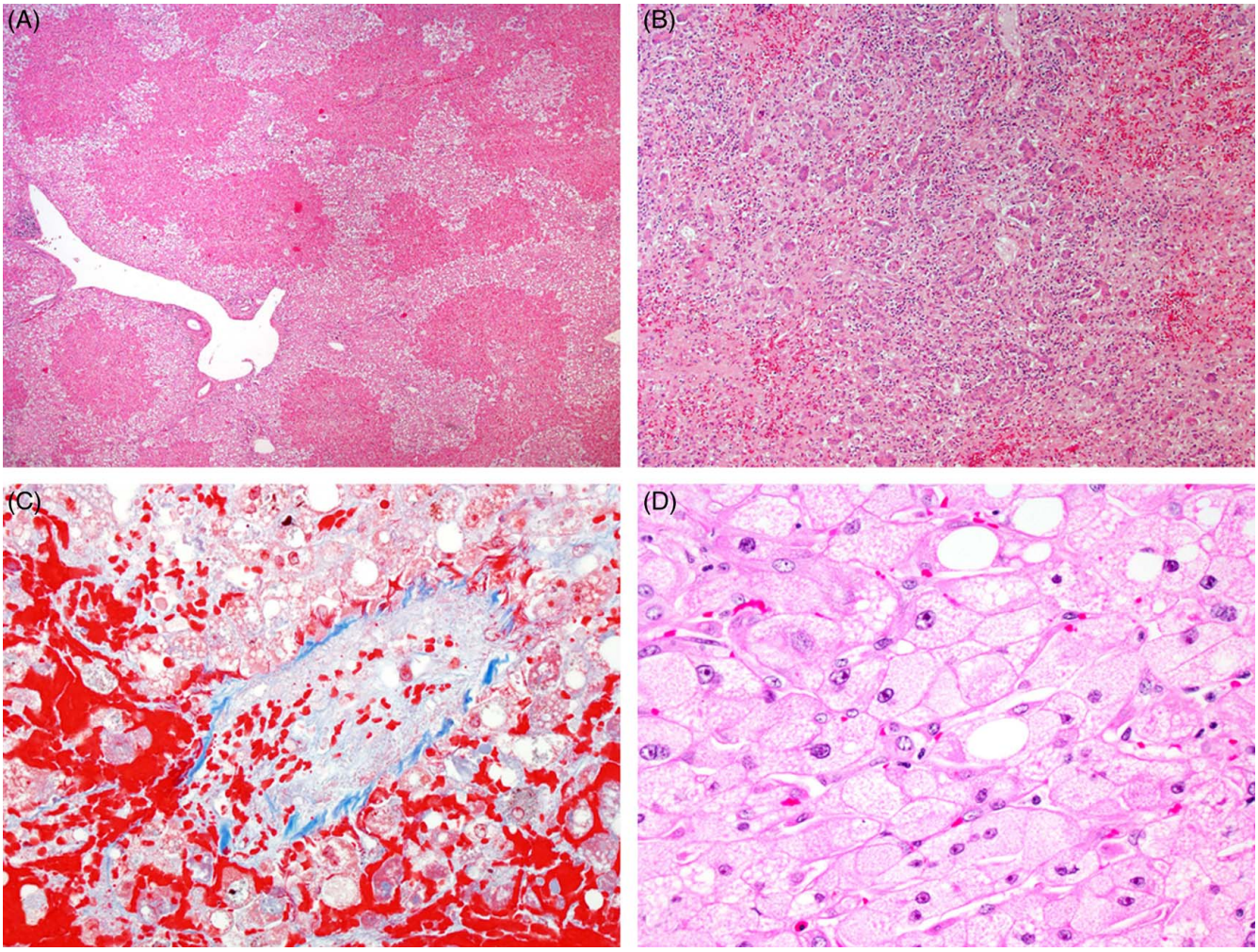

FIGURE 3 Histological injury patterns in ALF. (A) Zonal necrosis due to APAP. There is coagulative necrosis in zone 3 with preserved zone 1 hepatocytes showing steatosis. Only minimal inflammation is present (H&E, ×40) (B) Fulminant hepatic necrosis due to acute hepatitis B. There is near-complete necrosis of hepatocytes with ductular reaction and lympho-plasmacellular inflammation (H&E, ×100) C. Sinusoidal obstruction syndrome-veno-occlusive disease. A central vein, marked by the blue collagen rim, is occluded by loose connective tissue and red blood cells. The adjacent parenchyma is hemorrhagic and necrotic (Masson trichrome, ×400) (D) Diffuse microvesicular steatosis due to fialuridine toxicity. The hepatocytes are enlarged and foamy, as a result of mitochondrial toxicity (H&E, ×400). Abbreviations: ALF, acute liver failure; APAP, acetaminophen.

mechanisms such as upregulation of NRF2 to transcribe antioxidant genes and generate glutathione; activation of the unfolded protein response leading to upregulation of chaperones and decrease of client proteins; DNA repair mechanisms that are activated in response to genotoxic stressors and DNA damage; mitochondrial adaptation and activation of quality control mechanisms such as mitochondrial biogenesis, fission/fusion, and mitophagy to eliminate damaged mitochondria; and excess reactive oxygen species.[44] Due to the liver's remarkable capacity for immune tolerance, these cellular adaptive responses combined with compensatory mechanisms at the multicellular organ level (rapid increase in hepatocyte regeneration and dampening of inflammation) protect the organ from failure.

However, if these adaptive responses are overwhelmed, cells activate signals that dictate the way in which they will die (Figure 4). Regulated cell death follows the activation of specific signaling pathways and can therefore be modulated with pharmacological agents or genetic interventions.[45] Currently, over 12 cell death subroutines have been described, including apoptosis, mitochondrial permeability transition-driven necrosis, necroptosis, ferroptosis, netosis, parthanatosis, and pyroptosis, among others. With the exception of APAP-induced liver failure, which is a form of MPT-driven necrosis,[46] apoptosis is believed to be the dominant pathway leading to ALF.[47] When massive apoptosis or necrosis overtakes the liver's regenerative capacity, ALF ensues. In a patient with acute hepatitis, whether different cell death pathways are involved early versus later with ALI or ALF are largely unknown due to the lack of prospective studies with serial sampling. However, these types of studies will likely be informative since subjects who have a low likelihood of TFS after ALF (eg, those with DILI, AIH, HBV,

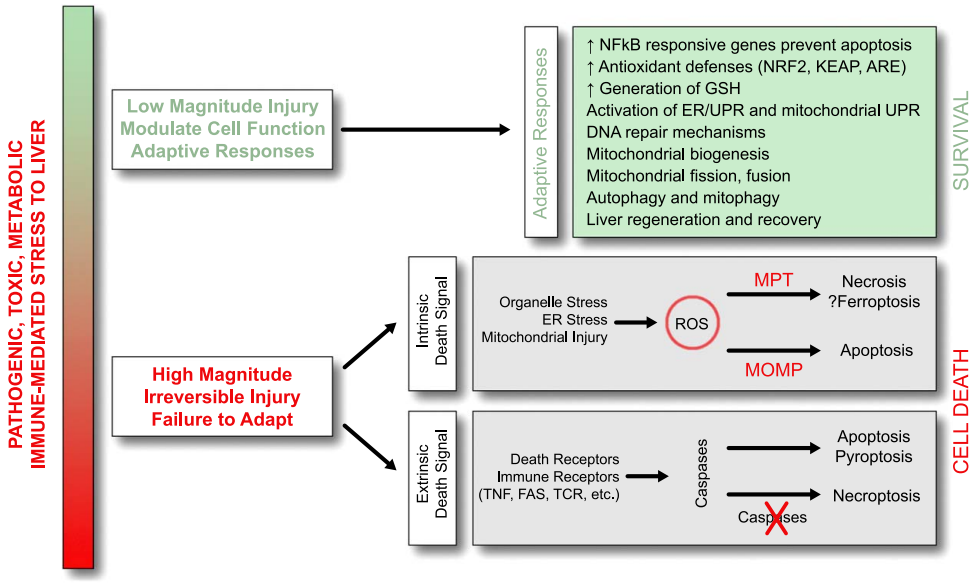

FIGURE 4 Molecular mechanisms of non-APAP liver injury. Low-magnitude toxic, metabolic, and pathogenic stress can be compensated for by molecular adaptive responses (listed in text) and the capacity of the liver to regenerate. However, when injury passes a certain threshold, the liver fails to adapt, and its compensatory mechanisms fall short, leading to cell death. The type of cell death signal and the signaling pathways that are activated dictate the cell death subroutine. While multiple cell death pathways exist, apoptosis, pyroptosis, MPT-driven necrosis, and necroptosis are the best studied. Apoptosis is the dominant cell death pathway in the liver, except in the case of APAP, which is clearly MPT-driven necrosis. While theoretically possible, to date no conclusive evidence for other cell death subroutines has been presented in hepatocytes. Abbreviations: APAP, acetaminophen; ARE, antioxidant response elements; Caspase, cysteine-dependent aspartate-directed proteases; ER, endoplasmic reticulum; GSH, glutathione; KEAP, Kelch-like ECH-associated protein; MOMP, mitochondrial outer membrane pore opening; MPT, mitochondrial permeability transition; NRF2, NF-E2–related factor 2; ROS, reactive oxygen species; TCR, T-cell receptor; UPR, unfolded protein response.

and indeterminate etiologies) are also more likely to progress from ALI to ALF.[3]

Future directions

Studies are needed to specify/assign the type of cell death pathway involved in each etiology so that specific therapies can be developed to block those pathways and slow the progression from ALI to ALF. Similarly, studies of hepatocyte defense mechanisms and liver regeneration may also identify future targets for intervention.

Role of immunologic mechanisms

In the last few years, significant progress has been made in our understanding of the immunological basis of ALF. For example, human and murine studies examining the mechanisms of recruitment (eg, CCR2/CCL2) and *in situ* functional reprogramming of monocytes and liver macrophages have increased our understanding of the roles these cells play in the pathogenesis of ALF.[48,49] Current evidence suggests that macrophages exert tissue-destructive as well as tissue-reparative functions, depending on the disease stage (M-1 necro-inflammatory vs. M-2 resolution phase).[48–53] Moreover, the expansion of monocytic myeloid-derived suppressor cells and a reduced KC bacterial clearance (through the PD-1/PD-L1 axis) have been described[54,55] that contribute to impaired antimicrobial responses and therefore increase susceptibility to infections/sepsis. Other innate immune cells can also remarkably affect the course of ALF. Platelets are among the first cells to accumulate at sites of liver injury.[40,48] Preventing platelet adhesion to the injured endothelium or disrupting platelets with neutrophil engagement affects neutrophil migration into areas of damage, thus impairing tissue healing.[48] Additional evidence supporting the contribution of neutrophils to liver repair shows that reactive oxygen species, predominantly produced by neutrophils, are important mediators that trigger the conversion of inflammatory monocytes into proreparative macrophages.[56] To date, little is known about the molecular basis of platelet function in ALF and whether manipulating platelets influences the inflammatory responses to liver injury. Recent studies discovered that pathways regulating platelet adhesion (von Willebrand factor [vWF]) or activation (CLEC-2/Podoplanin) are stimulated after APAP injury and influence neutrophil recruitment and function, while their genetic deletion or pharmacological inhibition accelerates liver repair in mice.[56,57] Collectively, these studies have identified an intricate

cooperation between innate immune cells that orchestrate resolution of inflammation and aid tissue repair in ALF.

Future directions

Additional biobanked tissue and peripheral blood samples (including lymphocyte preparations) from well-characterized patients are needed to improve our understanding of innate immune cells in the development of ALI and ALF as well as the likelihood of recovery. Studies that focus on monocytes-/macrophages targeting their activation, recruitment, polarization, metabolic rewiring, or checkpoint pathway-mediated regulation appear promising. Therapies that promote liver regeneration and/or improve immune cell function to prevent infections/sepsis are needed. In addition, studies that explore the role of activated platelets in ALF and liver tissue injury and repair as well as those identifying therapeutically relevant targets (eg, vWF, CLEC-2) are needed. Finally, assessments of the role of intestinal microbiota-derived signals during the development and progression of ALF using microbiome, metabolomic, and transcriptome-based approaches in animal models and from patients are needed to better define gut-liver cross talk in ALF.

Mechanisms of liver regeneration

The liver has a remarkable regenerative capacity after injury.[58] Many studies have shown that a compensatory regenerative response is stimulated following liver injury that plays a decisive role in the final outcome.[59,60] Most studies on liver regeneration rely on DILI models involving systemic exposure to hepatotoxicants such as carbon tetrachloride, thioacetamide, or APAP. Timely stimulation of liver regeneration in proportion to the liver injury is the most critical determinant of survival after ALF.[59,61] Following the initial phase of liver cell death and tissue injury, the regeneration and recovery phase occurs, where if a prompt compensatory liver regeneration is stimulated, liver mass and function recovers; however, if regeneration is delayed, ALF ensues.[2] The regeneration and recovery phase is therapeutically important, because medical care is most often started after the initial tissue injury phase has already occurred.

Liver regeneration following toxicant-induced ALI is dose dependent. Thus, a moderate overdose and moderate injury results in proportional liver regeneration, leading to complete recovery.[3] However, after severe overdoses, regeneration is inhibited, resulting in expansion of injury, liver failure, and death (Figure 5). Using the APAP overdose model, recent studies have identified several pathways involved in liver regeneration after ALI, including Wnt/β-catenin signaling, EGFR signaling, bile

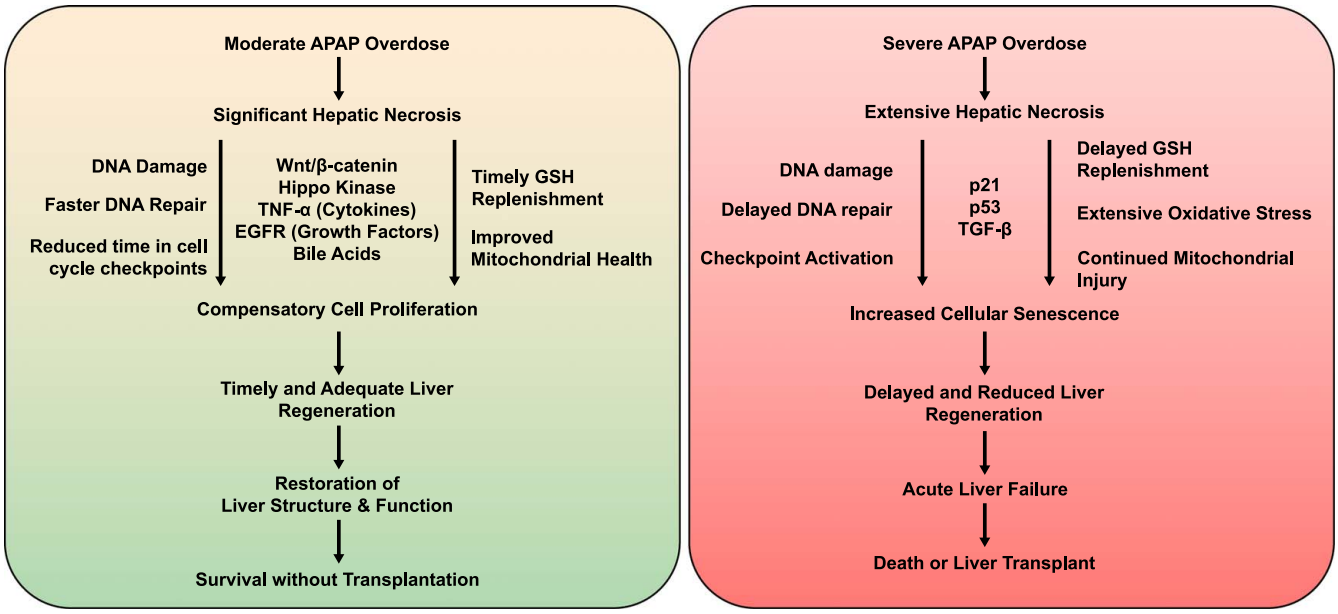

FIGURE 5 Mechanisms of liver regeneration and recovery after APAP overdose. Studies show that survival after APAP overdose depends on the extent of stimulation of the compensatory liver regeneration. Following moderate overdose, timely initiation of compensatory cell proliferation is driven by activation of pro-mitogenic signaling involving cytokines, growth factors, bile acids, and pathways such as Wnt/beta-catenin. This is further supported by timely GSH replenishment that mitigates the oxidative stress, improves mitochondrial health, and accelerates DNA repair, which is a key regulator of cell cycle progression. During severe overdose, these mechanisms are actively inhibited due to extensive oxidative stress and tremendous DNA damage, which inhibit cell cycle progression and induce cellular senescence. A 2-fold approach involving mitigation of oxidative and DNA damage along with supplementation of pro-mitogenic signals could be the key to successful regenerative therapies against APAP overdose. Abbreviations: APAP, acetaminophen; GSH, glutathione.

acids, TGFβ signaling, Hippo Kinase signaling, and DNA damage and repair system. In addition, infiltrating immune cells including macrophages and neutrophils are required for liver regeneration during ALF.[62]

Future directions

Characterization of the mechanisms that ultimately promote or inhibit human liver regeneration in ALF is needed to identify which pathway is most important so that therapies that enhance regeneration can be developed.

Pathogenesis of fulminant viral hepatitis

Viral hepatitis-related ALF is typically caused by HAV and HBV and, to a lesser extent, by herpes viruses.[63] The vast majority of individuals infected by these viruses do not develop ALF and may even have inapparent, subclinical infections. It is unlikely that these viruses are abnormally virulent; no evidence of specific subvariants of HAV, for example, have been found to cause ALF.[64] Rather, it seems more likely that ALF due to common viruses may be caused, in some instances, by single-gene inborn errors of host immunity.[65] For example, the discovery of autosomal recessive IL-18BP deficiency as a genetic etiology of viral ALF provided proof of principle that viral ALF can be caused by single-gene inborn errors selectively disrupting liver-specific immunity to viruses. It also pointed to IL-18 as an anchor molecule in the pathogenesis of viral ALF.[66] Uncontrolled inflammation leading to massive hepatocyte death seems to be the mechanism underlying the pathogenesis of viral ALF. The ALFSG is currently exploring the role of APAP ingestion inducing greater severity of illness, converting a severe injury to liver failure.

Future directions

More thorough genome-wide screening approaches and in-depth experimental studies will be necessary to elucidate the genetic basis of viral ALF. Further study of the specific roles of hematopoietic cells (cytotoxic lymphocytes and macrophages) and nonhematopoietic cells (hepatocytes) is required to advance our understanding of the immune and genetic pathogenesis of viral ALF.

Diagnostic biomarkers: acetaminophen-protein adducts

APAP-associated hepatotoxicity represents the most common form of ALF worldwide. Previous research in animal models and in clinical studies has identified APAP-protein adducts as a biomarker of APAP liver injury.[67,68] The metabolic pathway of APAP was delineated in the 1970s, leading to use of NAC as an antidote. APAP-protein adducts are formed during the oxidative metabolism of APAP by the cytochromes P450 of the liver.[69] Adducts formed in the liver on glutathione depletion are released into the peripheral circulation when hepatocytes rupture and release their contents.[70] A very sensitive and specific assay that uses HPLC with electrochemical detection[19] allows the determination of precise adduct concentrations in human serum in a number of clinical contexts.[70–72] Serum APAP-protein adducts are highly correlated with serum alanine aminotransferase elevations in patients with APAP-related ALI. Serum adduct values above 1.1 nmol/mL have a sensitivity and specificity of 97% and 95%, respectively, in patients with APAP liver injury and an alanine aminotransferase value >1000 IU/L.[19] A point-of-care immunoassay formatted as a lateral flow assay[72] is in development and will allow for rapid and accurate detection of APAP-protein aducts in patients with liver injury in the future. Since the time between APAP overdose and initiation of NAC therapy has been shown to correlate with outcome, the early recognition of APAP overdose may lead to better outcomes and fewer patients requiring LT. Finally, the ALFSG has recently reported that APAP hepatotoxicity may be a cofactor in up to 24% of patients with acute viral hepatitis presenting with ALI/ALF (Lee WM, et al., 2023, unpublished manuscript). The rapid point-of-care detection of APAP-protein adducts will lead to earlier administration of NAC and further improvement in outcomes.

Future directions

Completion of licensing trials for a point-of-care APAP-protein adduct assay will greatly facilitate emergency room management of APAP overdose patients. In addition, greater availability of this highly sensitive and specific assay may lead to improved outcomes in patients with acute viral hepatitis who frequently use APAP-based antipyretics and may benefit from NAC therapy as well as those indeterminate patients who actually have unrecognized APAP-related ALF.

ALF MANAGEMENT

Due to its rarity, heterogeneity, and the high mortality of ALF, there are few prospective randomized studies exploring the optimal management of ALF. Consequently, the management of ALF remains largely center specific with reliance on expert opinion-based recommendations. Nonetheless, with the guidance of

experienced liver units and multicenter consortia, consensus recommendations are emerging. For example, an 11-nation survey of liver transplant centers in the EUROALF Consortium highlights many similar, rather than disparate, practices among the highest-volume ALF centers in Europe.[73] The following discussion points to some of these similarities as well as areas that require further study. Advances in the management of patients with ALF have greatly improved TFS of patients with ALF from ~10% in the 1980s to >60% in contemporary series.[9,74] Multiple reasons account for this improvement, particularly in the prophylaxis against and management of cerebral edema and general improvements in intensive care. The observation is particularly striking in APAP-induced ALF, where LT is now used in fewer than 10% of patients.[75]

ALF prognosis

Determining an individual patient's prognosis is a central consideration in ALF management since emergent LT in many instances appears to be the only life-saving option. The clinician's challenge is to properly identify the high-risk patients while simultaneously avoiding LT in patients who would otherwise survive with supportive medical treatment. To help in this effort, several prognostic models have been created to predict short-term outcomes (either mortality or transplant-free survival). These models must not only be accurate, but they also need to be applied early in the disease process since the decision to transplant is often made within 48–72 hours of presentation. Ideally, these prognostic models are also dynamic and provide objective, quantitative data regarding liver regeneration or recovery versus disease progression over time.

The King's College Criteria (KCC) was the first published and the most widely referenced ALF prognostic model. Developed in 1989 by O'Grady et al,[76] the model is stratified by etiology (APAP vs. non-APAP ALF) and predicts mortality. While this has been modified slightly, both early models were highly specific but lacked sensitivity, particularly in more modern cohorts. The initial revision made to the APAP KCC was to include lactate (with either early value >3.5 mmol/L or postresuscitation value >3.0 mmol/L) to improve sensitivity.[77] A third, dynamic model has also been created for APAP ALF that involves 2 models applied on days 1 and 2 of admission.[78] This dynamic model is reported to have good discrimination and calibration, but sensitivity and specificity were not provided. Other prognostic models in ALF have significant constraints that limit their application, including the Clichy Score,[79] which was derived from a limited population of patients with acute viral hepatitis and suffers from poor specificity. Similarly, the model for end-stage liver disease (MELD) score suffers from variable discriminatory cutoffs and predictive values.[80,81]

More recently, the ALFSG published a 5-variable Prognostic Index that predicts 21-day TFS rather than death.[82] This model dichotomizes the etiology as either favorable (APAP, ischemia, pregnancy-induced, and HAV) or unfavorable (indeterminate, DILI, AIH, HBV, and Wilson disease) and also uses easily accessible bedside clinical data from the day of admission (total bilirubin, INR, HE grade, and vasopressor use). The model significantly outperformed the KCC and MELD score with high specificity. Using a TFS threshold of 80%, the model is conservative and rarely predicts TFS in patients who would otherwise die without LT. However, it may overestimate the potential need for LT, particularly in those patients with a favorable etiology (such as APAP) who have deep coma.

Metabolic probe tests that rely on liver-based metabolism or blood flow such as the indocyanine green clearance test or lidocaine MEGX test have been used in cirrhosis and in experimental ALF but lack discriminatory value in milder stages of liver injury.[83] Recently, the ALFSG reported the utility of the MBT, a noninvasive point-of-care test that was serially administered to 76 patients with ALI and ALF of varying etiologies.[84] Recovery of orally administered ^{13}C-methacetin as $^{13}CO_2$ on day 1 was significantly higher in those patients who survived compared with those who died or underwent LT (10.2 vs. 1.9% dose recovery-/hour, respectively; $p < 0.001$). The day 1 test result combined with ALF etiology yielded an Area Under the Receiver Operating Characteristic curve = 0.92, higher than that provided by KCC or MELD scores. Furthermore, serial measurement of the MBT in a subgroup of patients showed failure to improve over time in those dying or undergoing LT.

Serum biomarkers of prognosis

There has been a growing interest in identifying prognostic serum biomarkers that alone or added to available prognostic models (KCC, MELD, and ALFSG Prognostic Index) might improve discrimination for ALF LT candidates. Physiologically, the serum biomarker may be increased in subjects with more severe ALF or decreased in those with impaired or exhausted regeneration.[85] However, most of the biomarkers are not reliable or specific enough for individual patient decision-making. Several factors must be considered if these newer scoring systems are to be useful additions to clinical practice. Ideally, biomarkers included in future prognostic indices must be widely available, have rapid turnaround time, and be highly reproducible. Serum AFP, lactate, and platelet counts meet these criteria while serum Gc globulin and osteopontin do not.

The ALFSG has evaluated 18 potential prognostic biomarkers: serum AFP;[86] apoptosis-associated proteins;[87] serum actin-free Gc-globulin;[88] serum

glycodeoxycholic acid;[89] sRAGE/RAGE ligands;[90] plasma osteopontin;[91] circulating MBL, M-, L-, H-ficolin and CL-1;[92] plasma galectin-9;[93] serum FABP1;[94,95] serum hepcidin;[96] serum Lct2;[97] miRNAs;[98] factor V;[99] thrombocytopenia;[100] and sCD163.[101] Most of these biomarkers reflect the severity of hepatocyte necrosis, while a few of them, AFP and early time-point miRNAs, reflect hepatic regeneration.

ALFSG biosamples have been used to test 4 genetic susceptibility biomarkers: keratins 8 and 18 (K8/K18) gene variants that may predispose to adverse ALF outcomes;[102] polymorphisms of genes encoding putative APAP-metabolizing enzymes (UGT1A1, UGT1A6, UGT1A9, UGT2B15, SULT1A1, CYP2E1, and CYP3A5) as well as CD44 and BHMT1;[103] distribution of SNPs of genes that may be associated with human behavior (SNP rs2282018 in the arginine vasopressin gene and SNP rs11174811 in the AVP receptor 1A gene);[104] and SNP rs2277680 of the CXCL16 gene frequency in the HBV-ALF population.[105] However, the strength of these associations is limited, and larger cohorts of patients with ALF are needed to validate these findings.

Future directions

Predicting the clinical outcome of a patient with ALF will likely require a combination of biomarkers of pathogenic processes such as cell death, hepatic regeneration, and degree of inflammation at several time points that may be combined with other clinically based prognostic models such as the KCC, MELD, or ALFSG PI. Studies that use proteomic, transcriptomic, and genomic techniques from large groups of patients with ALF who have been prospectively monitored will likely prove valuable but will require ready accessibility.

Specific therapies for ALF

Overall management of adult ALF is primarily care of the ICU patient discussed in detail below. Few specific therapies are directed at a single underlying etiology: use of nucleoside analogs for hepatitis B ALF[106] and the use of NAC for non-APAP ALF cases.[33,34] A randomized controlled trial of NAC in non-APAP showed significant improvement in TFS in the treated group, but this has, to date, not garnered FDA approval for the non-APAP indication.

Cerebral edema and neuroprotective strategies

The pathogenesis of cerebral edema in ALF is multifactorial and complex.[107] Cerebral edema develops in proportion to arterial ammonia concentration,[108] supporting the long-held notion that the generation of osmotically active glutamine from ammonia and glutamate within astrocytes causes cell swelling and an increase in brain volume. More recent data incriminate other mechanisms, including neuroinflammation, altered gene expression of cell volume-regulating genes, altered neurotransmission, and increased cerebral perfusion, a process exacerbated by peripheral and *in situ* synthesis of proinflammatory cytokines and loss of cerebrovascular autoregulation. A small pilot trial of ornithine phenylacetate as an ammonia-lowering agent conducted by ALFSG suggested that it was safe and appeared to lower ammonia somewhat; larger trials will be necessary.[109]

Intracranial pressure monitoring

Data from both the UK and North America have demonstrated decreasing rates of intracranial hypertension (ICH) from cerebral edema in ALF and an associated decline in the use of invasive intracranial pressure (ICP) monitoring over the past 20 years.[9,110] There are no trials (randomized or otherwise) that demonstrate a benefit from ICP monitoring in patients with ALF. Two ALFSG studies have retrospectively compared adult patients managed with and without invasive ICP monitors,[110,111] and although outcomes were similar, those with ICP monitors received more critical care interventions for ICH. Patients with ICP monitors tend to be younger and listed for LT, in whom the identification of prolonged increased ICP and/or low cerebral perfusion pressure should caution clinicians proceeding to transplant to avoid poor neurologic outcome. Although placement of ICP monitors always raises concern of intracranial bleeding complications, intracranial bleeding is uncommon in patients with ALF (5%–7%). The administration of prohemostatic agents before ICP monitor placement is routine practice and reasonable considering that bleeding complications carry significant mortality (50%).[112] However, the optimal prophylactic prohemostatic agents and their efficacy in decreasing bleeding complications of ICP monitor placement require further study.

Noninvasive bedside techniques for dynamic estimation of ICP include transcranial Doppler and optic nerve sheath diameter ultrasound. In the latter case, an optic nerve sheath diameter >0.48 mm correlated with ICP $>$ 20 mm Hg, the usual threshold to warrant invasive monitoring.[113] However, studies have demonstrated poor correlation of optic nerve sheath diameter with ICP monitors and also low interindividual reproducibility.[114] Transcranial Doppler ultrasound has been used to quantify cerebral blood flow and determine patterns of cerebral hypoperfusion.[115] Transcranial Doppler ultrasound does not detect early

stages of cerebral edema and can be negatively affected by systemic hemodynamics and volume status.

Management of ICP

Patients with ALF should be closely monitored in a quiet ICU environment with frequent assessment of vital signs and neurologic status (Table 2). The head of the bed should be kept >30 degrees from horizontal and vigorous suctioning and movement of intubated patients minimized to avoid surges in ICP. Head CT scanning is insensitive to the development of cerebral edema in ALF[123] and may present logistical challenges with patient positioning and transportation but is frequently used to exclude intracranial bleeding when there is unexplained clinical deterioration or before and after ICP monitor placement.

Prophylactic measures to prevent the development of cerebral edema may be partially responsible for a ~50% decrease in its incidence, as well as some of the improvement in overall survival of patients with ALF. Raising serum sodium to hypernatremic levels (145–155 mEq/L) with hypertonic saline (HTS) was an effective prophylaxis against ICH compared with managing patients at normal serum sodium.[116] The earliest reasonable administration of continuous renal replacement therapy (CRRT) has also increasingly been advocated in patients at high risk of developing cerebral edema (ammonia >150 μM, hyperacute presentation, high-grade HE, need for vasopressors, and infection), as it lowers serum ammonia.[117]

First-line therapy for established cerebral edema should include the administration of bolus osmotic agents such as mannitol (if patient is making urine) or HTS, which draw water from astrocytes and decrease brain volume.[120] A recent randomized trial of mannitol versus HTS showed equivalent reduction in ICP, with a lower incidence of rebound ICH and renal dysfunction in those treated with HTS.[124] However, as cerebral edema progresses, rebound ICH usually occurs after both therapies. Hypotension due to systemic vasodilation raises concern of brain anoxia, in which management of the cerebral perfusion pressure (MAP minus ICP) becomes critical with vasopressors (norepinephrine ± vasopressin) as well as agents that lower ICP.

Central cooling of patients with ALF and high-grade HE has been studied as both prophylaxis against and therapy for ICH based on extensive data in laboratory animals.[125] In a randomized study of prophylactic hypo- versus normothermia, hypothermia did not confer benefit in preventing ICH or improving outcomes.[118] Cooling patients with established ICH to 32–33 degrees has been shown to bridge 14 patients to LT,[121] but it was of no value in a multicenter retrospective cohort.[126] Similar to other areas of neurocritical care, targeted temperature management, which ensures the patient has a temperature of <37.8 °C to avoid cerebral venodilation, is a practical minimum goal in patients with ALF, which can frequently be attained using cooling blankets.[127] Similarly, patients with spontaneous mild hypothermia (36 °

TABLE 2 Management of intracranial pressure in patients with ALF

Therapeutic maneuver	Goal	Comments	Reference
Prophylaxis against cerebral edema			
Elevate head to 30 degrees; neck in neutral position	Improve cerebral venous return		
Induced hypernatremia	Serum sodium 145–155 mmol/L	HTS or CRRT	[116]
Early CRRT	Ammonia lowering; correct hypo-osmolality	No anticoagulation, citrate and heparin acceptable	[117]
Prophylactic Hypothermia[a]	35°C–36°C	Allow spontaneous hypothermia	[118][a]
Respiratory alkalosis	PCO_2 35–40 mm Hg (avoid excess hypocarbia or hypercarbia)	Allow spontaneous hyperventilation if pCO_2 < 35 mm Hg	[119]
Treatment of established cerebral edema			
Mannitol boluses	ICP < 25 mm Hg	0.5–1.0 g/kg body weight if patient making urine	[120]
Hypertonic saline boluses	ICP < 25 mm Hg	Many regimens	[119]
Vasopressors	MAP > 65 mm Hg CPP > 60 mm Hg	Norepinephrine ± vasopressin	[119]
Therapeutic hypothermia	32°C–34°C	Cooling blankets, extracorporeal circuits or external cooling device (eg, Arctic Sun)	[121]
Deeper sedation	Coma	Barbiturates, propofol	[122]

Note: Treatment of established cerebral edema should include all of the prophylactic measures noted.
[a]Randomized, controlled trial of prophylactic management under hypothermic versus normothermic conditions was negative.
>Abbreviations: CPP, cerebral perfusion pressure; CRRT, continuous renal replacement therapy; HTS, hypertonic saline; ICP, intracranial pressure; MAP, mean arterial pressure.

C), frequently observed in patients with ALF on CRRT, should *not* be actively warmed.

Future directions

Future studies should target lowering of ammonia directly, as well as comparing newer agents for sedation and analgesia in patients with ALF. Prospective studies using a protocolized administration of HTS in both prophylactic and therapeutic roles should be undertaken. Development of accurate, reliable, and sensitive means to noninvasively monitor ICP remains an important unmet need.

Respiratory failure

Respiratory failure and hypoxemia become more important complications as patients with ALF progress to high-grade HE.[128] The etiology of hypoxemia is multifactorial in the setting of systemic vasodilation; assessment of volume status becomes increasingly difficult. Bedside echocardiography (transthoracic or transesophageal) has supplanted more invasive venous pressure measurements in many centers to guide fluid replacement.[119]

The occurrence of acute lung injury is associated with worse outcomes in patients with ALF.[128] Guidelines for ventilator management in patients with ALF are gleaned from the general critical care literature. Most recommend a low PEEP strategy (5–10 mm Hg) and low tidal volumes, recognizing that extrapolation of data from other patient populations (eg, those with septic shock) to those with ALF may not be valid.[119]

Infection and hypotension

Immune dysregulation is not only involved in the pathogenesis of the ALF syndrome but also plays a major role in the incidence of infection, a major determinant of outcome.[129,130] Mechanisms of immune dysfunction include defects in adaptive and innate immunity in patients with protective barriers compromised by introducing intravascular devices, urinary catheters, and endotracheal tubes. Nosocomial infections with gram-positive and gram-negative organisms as well as fungal infections occur late after presentation of ALF and, consequently, are more frequent in subacute liver failure. Unfortunately, studies have not shown that broad-spectrum prophylactic antimicrobials improve outcome.[131,132] Surveillance cultures of blood, urine, and sputum are recommended, particularly in patients with subacute liver failure and those being considered for LT. Broad-spectrum antibiotics should be administered to patients with ALF with unexplained hypotension, an increase in SIRS, or unexplained deterioration to high-grade HE.[133] Once a pathogen has been identified, de-escalation of antibiotic coverage is appropriate. Fungal infections may arise later in the course of a patient with ALF and portend a poorer prognosis.[134]

Patients presenting with ALF are frequently hypotensive, the result of intravascular volume depletion and systemic vasodilation. The algorithm for managing hypotension in patients with ALF is similar to other critical illnesses and includes assessment of serial lactate levels to ensure adequate perfusion of peripheral vascular beds. Volume should be administered first, and normal saline is appropriate. In persistently hypotensive patients after volume repletion, vasopressor drips should be added (norepinephrine is preferred),[119] a search for infection initiated, and empiric antibiotics considered. Failure to reach a MAP $>$ 65 mm Hg on a norepinephrine drip is a poor prognostic sign and may result from severe ALF SIRS, which is difficult to distinguish from sepsis;[135] vasopressin should be added to the norepinephrine drip.[119] Relative adrenal insufficiency has been identified by cosyntropin stimulation tests in patients with ALF, and hydrocortisone (200 mg bolus IV or 50 mg IV q6h) should be considered empirically in vasopressor-resistant hypotension.[136] Plasma exchange removes vasodilatory cytokines and should be considered within this algorithm, as it reliably improves hypotension.[137]

Future directions

A critical care ALF registry may prove useful regarding preferred ventilator and vasopressor strategies. Future prospective studies are needed to demonstrate which subpopulations of ALF (eg, those with subacute liver failure and/or awaiting LT) may benefit from prophylactic antimicrobial therapy. The role of plasma exchange within the treatment algorithm for hypotension requires further study.

Hemostasis in ALF

By definition, ALF is associated with deranged hemostasis. Each of the 3 phases of coagulation is affected (Table 3). In general, hemostatic proteins synthesized by the liver are decreased, while those from endothelial cells are increased as a result of the SIRS.[142] In patients with ALF, primary hemostasis is characterized by mild-to-moderate thrombocytopenia, which is proportional to the severity of systemic inflammation[100] and would be expected to impair blood clot formation. However, one mechanism of the decline in platelet count is their activation and clearance, yielding procoagulant microparticles, which may compensate for their numerical

TABLE 3 Summary of abnormalities in hemostasis in humans with ALF

Laboratory	Primary site of synthesis	Abnormality in ALF	Potential effect on hemostasis	References
Primary hemostasis				
Platelet count	Bone marrow	Decreased	Impaired	[100]
von Willebrand factor	Endothelium	Increased	Enhanced	[138]
ADAMTS-13	Liver	Decreased	Enhanced[a]	[138]
Platelet microparticles	Circulation	Increased	Enhanced	[139]
Secondary hemostasis				
Procoagulant factors: II,V,VII,IX,X,XI,XII	Liver	Decreased	Impaired	[140]
Anticoagulant factors: protein C, S, AT	Liver	Decreased	Enhanced	[140]
Factor VIII	Endothelium	Increased	Enhanced	[140]
Fibrinogen	Liver	Decreased	Impaired	[140]
Fibrinolysis				
Antiplasmin	Liver	Decreased	Impaired	[141]
TAFI	Liver	Decreased	Impaired	[141]
Plasminogen	Liver	Decreased	Enhanced	[141]
PAI-1	Endothelium	Increased	Enhanced	[141]
tPA	Endothelium	Increased	Enhanced	[141]

[a]Very low ADAMTS has been documented in patients with ALF. However, vWF multimer size was also shown to be low, leaving the functional significance of low ADAMTS-13 as yet uncertain.

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ALF, acute liver failure; AT, antithrombin; PAI-1, plasminogen activator inhibitor type 1; TAFI, thrombin activatable fibrinolysis inhibitor; tPA, tissue-type plasminogen activator; vWF, von Willebrand factor.

depletion.[139] In addition, endothelial cells increase vWF in the circulation, increasing platelet aggregation and adherence,[138,141] another potential mechanism of compensation for thrombocytopenia. In secondary hemostasis, liver-derived, pro- and anticoagulant proteins are both decreased, yielding relative rebalance.[140] However, hypercoagulability may be favored by very high levels of endothelially derived factor VIII. Fibrinogen levels are often low in ALF due to decreased hepatic synthesis, which would be expected to exert an anticoagulant effect.[140]

Although the primary and secondary phases of hemostasis in ALF are thus largely "re-balanced," the state of the fibrinolytic system appears to be decidedly tipped in the procoagulant direction.[138,141] Among nearly 700 patients with ALI and ALF, *in vitro* blood clot lysis time was above 180 minutes, the upper limit of measurability in this assay, in 64%.[138] As with primary and secondary hemostasis, liver-derived proteins involved in fibrinolysis are generally decreased and endothelium-derived proteins are increased. To define the sum balance of all of these abnormalities, the ALFSG prospectively assessed global hemostasis in whole blood using ROTEM in 200 patients with ALI and ALF.[143] The majority, 73% and 62%, had abnormalities in clot formation from extrinsic and intrinsic clotting cascades, respectively. However, clot stability was almost never impaired, which appears to be consistent with *in vitro* clot lysis time. An increased number of abnormal ROTEM parameters were associated with bleeding complications as well as with ALF severity and a poorer prognosis.

Although bleeding complications were reported in nearly 30% of patients with ALF in early series, recent studies suggest a rate of only ~10%.[112] The vast majority of these bleeding complications arise from presumed stress-induced mucosal disease of the stomach, a consequence of the SIRS in patients with critical illness of diverse causes. Other less common sites include central catheter- or ICP monitor-insertion sites. The severity of ICP monitor bleeding was, not surprisingly, associated with high mortality considering the pressure effects of bleeding within the confinements of the cranium. The use of packed red blood cell transfusions for patients with ALF has been declining over the past 20 years,[9] with a contemporary target hemoglobin of 7–8 g/dl extrapolating from non-ALF literature.[119] In ~1800 patients of the ALFSG Registry, bleeding was directly associated with mortality in only 2%.[112] Regarding conventional coagulation tests, the INR did not discriminate between patients with ALF who did or did not develop bleeding complications,[112] while lower platelet count was associated with both bleeding complications[112] and poor outcome.[100] Patients with ALF frequently require invasive procedures for optimal management, including dialysis and central venous catheters, and ICP monitors. Most experts recommend a trial of parenteral vitamin K at the time of initial

hospitalization in patients with ALF, since roughly one-third may be vitamin K deficient, particularly those who are jaundiced.[144]

Future directions

Prospective, randomized studies are needed to determine whether prophylactic blood component repletion in patients with ALF undergoing invasive procedures decreases bleeding complications. Goals of repletion require definition, particularly for the administration of plasma, which confounds the critical utility of the INR as a prognostic marker and may exacerbate volume overload and cerebral edema. Evidence-based criteria are needed to guide targets for blood parameters before invasive procedures considering recent data that "more is not better." Biomarkers reflecting bleeding risk are needed since it is clear that the INR does not reflect bleeding risk in ALF. Future studies should incorporate the real-time use of ROTEM to help guide clinicians in procoagulant factor transfusion before an intervention. Finally, studies on the safety and efficacy of prophylaxis against deep venous thrombosis in patients with ALF (eg, heparin vs. pneumatic leg compression devices) are needed.

Renal replacement therapy

Acute kidney injury (AKI) is frequently encountered in patients with ALF and is proportionate to the SIRS.[145] AKI on presentation is usually due to volume depletion/pre-renal azotemia. Acute tubular necrosis may occur later in specific circumstances where the etiology of liver injury is also a nephrotoxin (APAP, trimethoprim-sulfamethoxazole, and *Amanita* poisoning). Rarely, hepatorenal syndrome may occur late in the clinical course of ALF and is thought to have a similar pathogenesis as hepatorenal syndrome in cirrhosis but has not been explicitly studied. In addition to urinary catheter placement for output assessment, urinalysis and urine sodium is important to differentiate these causes of AKI.

CRRT has become almost routine in the critical care management of patients with ALF. Early introduction of CRRT should be considered in patients with high and/or increasing serum ammonia (e.g., at a sustained level of >150 μmol/L), even in the absence of AKI criteria.[119] New data imply that CRRT reduces serum ammonia and improves neurological and overall patient outcomes proportional to the early timing and cumulative dose of CRRT.[117,146–148] Provided that continuous (and not intermittent) renal replacement modalities are employed, there is no therapeutic difference in ammonia clearance between hemodialysis, hemofiltration, or hemodiafiltration. Continuous veno-venous hemofiltration has the advantage of being the simplest circuit with potentially lower rates of circuit clotting. Despite concerns about the need for anticoagulation with CRRT circuits, there is no evidence that citrate or heparin increases the risk of bleeding complications in patients with ALF.[112,149] Hence, if circuit clotting at <24 hours occurs without anticoagulation, citrate regional anticoagulation or heparin may be considered.

Future directions

A prospective, randomized study of initiating CRRT on admission versus awaiting fulfillment of AKI criteria is warranted among patients with ALF at high risk for developing cerebral edema or with high ammonia levels. Studies to define the optimal administration of CRRT should also be undertaken, in particular, the safety and efficacy of citrate versus heparin-based anticoagulation to maximize circuit patency, quantitative ammonia-lowering capacity according to mode of CRRT, and dose of renal replacement therapy (standard vs. high-volume CRRT).

Extracorporeal liver support (ECLS)

The aim of ECLS (artificial and bioartificial) in ALF is to supplement liver function as a 'bridge' to definitive LT or native liver recovery. To achieve that end, artificial devices use selective membranes of various pore sizes and adsorbent affinities to remove specific serum toxins from circulating blood, whereas bioartificial (*i.e.,* cell based) liver systems incorporate cell lines or hepatocytes into a bioactive platform to support endogenous hepatic detoxification, metabolic and synthetic functions, and additional endogenous functions of *in vivo* hepatocytes.[150,151]

Artificial liver support in ALF

In essence, CRRT is the simplest form of artificial ECLS/blood purification; however, it does not remove protein-bound toxins. Therapeutic plasma exchange has been demonstrated to improve transplant-free survival in ALF likely due to removal of damage-associated molecular patterns, leading to improved hemodynamic stability.[137] In a randomized study of 182 patients with liver failure who received standard medical therapy (SMT; n = 90) or SMT plus high-volume plasma exchange (HVP) for 3 days (n = 92), survival to hospital discharge was 58.7% for patients treated with SMT + HVP versus 47.8% for the patients who received SMT alone (Hazard Ratio for HVP versus SMT with stratification for LT 0.56; [95% CI, 0.36–0.86; $p = 0.0083$]).[137] In a subgroup nested cohort study of 30 of these patients with ALF, patients undergoing HVP

had significantly reduced circulating levels of damage-associated molecular patterns, TNF-α, IL-6, and IL-8.

The molecular adsorbent recirculating system (MARS) removes water-soluble and albumin-bound toxins with a molecular weight cut-off of 65 kDa and may be beneficial for patients with ALF. In a propensity-matched controlled study of 104 patients with ALF treated with MARS and 416 untreated ALF controls, MARS was associated with improved 21-day TFS when combined with biochemical variables and hemodynamics, on multivariate analysis, particularly in APAP-ALF.[152] However, a randomized, prospective study in France failed to show survival benefit of MARS, potentially due to the confounding impact of early LT (74% of all patients were transplanted).[153] Other recognized concerns with MARS include the potential for worsening thrombocytopenia, circuit thrombosis, the high cost of disposable circuits, and the need for training of bedside nurses. Furthermore, clinical criteria for MARS initiation and the optimal duration and flow rates during a MARS session remain unclear.

Bioartificial liver support in ALF

Recently completed studies of commercially available bioartificial liver support therapies such as ELAD (Vital Therapies; C3A human-derived hepatoblastoma cell platform) and Hepatassist (Alliqua Biomedical; porcine hepatocyte-based bioreactor) both failed to show survival benefit in ALF. Potential future bioartificial devices using human liver organoids are under development.[154] Such devices will require production of an abundant, high-quality supply of human hepatocytes. This is likely to be achieved by expansion and differentiation of stem cells either *in vitro*[155,156] or *in vivo*.[157] Advantages of induced pluripotent stem cells include the ability to create a cryopreserved and renewable source of hepatocytes that do not have issues with zoonoses and have variable but known donor HLA and genetic characteristics that should lead to improved immunological compatibility with individual patients.[158] Investigators in the UK are also exploring the potential for cell-based therapies such as allogeneic human macrophages to enhance liver regeneration and recovery in patients with APAP overdose.[159,160] Alternately, stem cell expansion may be accomplished through production of chimeric humanized animals (eg, pigs).[161,162]

Future directions

Practical considerations regarding further studies of ECLS include whether a biological component is sufficiently more effective considering its increased cost and complexity. Other challenges include maintaining reliable central venous access, circuit thrombosis, the need for anticoagulation in patients with declining platelet count, and operator experience. Furthermore, patient selection, optimal duration, and study endpoints need to be clarified.

The evolving role of LT in ALF

For patients with ALF who fail maximal medical therapy, LT is frequently indicated; however, the severity of multiorgan failure and presence of concomitant psychosocial factors may complicate listing decisions for LT.[4,163,164] In APAP-ALF, 70% of patients will spontaneously recover without LT, while other etiologies of ALF carry a $\leq$40% TFS.[5] Data from the European Liver Transplant Registry reported a 1-year overall survival of 74% in patients with ALF studied between 1988 and 2009.[165] More recently, prospective data from the ALFSG were combined with data on the same patients in the Scientific Registry of Transplant Recipients to assess outcomes among consecutive patients with ALF listed for LT (January 1998 to October 2018).[166] Of 624 patients with ALF listed for LT, 398 (64%) underwent LT, 100 (16%) died without LT, and 126 (20%) recovered spontaneously. One-year and 3-year post-LT survival rates were 91%, and 90%, respectively. Comparing patients who died on the waitlist versus those who received LT, the former had more severe multiorgan failure (increased vasopressor use, mechanical ventilation, and renal replacement therapy). Increasing age (adjusted OR: 1.02), APAP etiology (aOR: 2.72), requirement for vasopressors (aOR: 4.19), grade 3/4 HE (aOR: 2.47), and MELD (aOR: 1.05 per unit) were independently associated with death on the waitlist. Similar to previous studies, APAP overdose presents a clinical dilemma, since while it has the highest potential for spontaneous recovery, waitlisted patients with APAP also have the highest rate of pretransplant death.[14]

Future directions

Future investigations are needed to explore whether other factors such as donor characteristics (eg, deceased cardiac donors) and *ex vivo* normothermic perfusion can potentially expand the donor pool accessible to patients with ALF awaiting LT. Furthermore, potentially expanding recipient transplant criteria with more granular "futility criteria" particularly when comparing patients with APAP and non-APAP ALF patients are needed as organ allocation policies evolve.

Future clinical trials in patients with ALF: lessons from the ALFSG experience

Multidisciplinary, multicenter research consortia must continue to conduct well-designed randomized,

TABLE 4 Conducting future clinical trials in ALF: challenges and possible solutions

Design aspects	Challenges	Possible solutions
Recruitment	Difficult to enroll target sample size due to rarity and acuity of the syndrome Acuity and severity of illness introduces emotional stressors into obtaining consent Study sites lack training on best practices for the process of consent	Outreach to neighboring centers for referrals Provide study site personnel training in obtaining consent to improve the patient/family's understanding of the study, and thus improve enrollment Identify mechanisms of informed consent such as exception from informed consent in time-sensitive settings
Blinding	Depends on the intervention—more difficult with device or surgical interventions	Consider sham or, at a minimum, blinded outcome assessments
Outcomes	Need objective measures that are relevant to patient improvement Common to measure TFS but the targeted effect size can be difficult to define Transplant times vary by etiology and center	Consider what is most important to patient and clinical communities (mortality, quality of life) Consider the mechanism of action of the experimental intervention to define the outcome of interest (mortality, TFS, change in clinical labs) If transplant is not part of the outcome, then account for transplant as an intercurrent event. Etiology is a known prognostic factor and should be adjusted for in the analysis
Follow-up	ALFSG commonly looked at 21-day TFS but also captured long-term outcomes at 3, 12, and 24 mo Missing data occurs with longer follow-up; participants lost to follow-up	During the study planning stages, consider approaches for participant contact beyond in person visits (eg, phone, text, email) Frequent contact at some level can help with retention
Intercurrent events	Events, most importantly, transplant, that alter the measurement of defined outcomes (most importantly, transplant)	Consider a composite outcome that includes death and transplant (ie, TFS) Consider competing risk and survival analyses for certain outcomes to account for transplant if not part of your outcome

Abbreviations: ALFSG, Acute Liver Failure Study Group; TFS, transplant-free survival.

controlled clinical trials to improve outcomes in the ALF patient population. ALF is very rare, and patients are critically ill and evolving rapidly, 2 factors that hinder ready enrollment of large numbers. Some of the challenges encountered by the ALFSG during 21 years of enrollment into the Registry across 4 prospective clinical trials are outlined in Table 4. The acuity and severity of patient presentation in concert with altered mentation requires a next-of-kin if they are available. Obtaining informed consent from health proxies for a clinical trial of a critically ill patient remains difficult even when the appropriate individual can be identified. Mechanisms for obtaining emergency informed consent may need to be invoked. Blinding study personnel to treatment arm is particularly difficult in studies involving devices and might be addressed by a sham arm or blinded outcome assessment. Immediate data capture is 100% effective since patients enrolled are generally in an ICU setting; however, retention in follow-up is challenging, particularly for patients with APAP-ALF. Redundant methods of maintaining contact with enrollees would be helpful. Even serious adverse events require special definition in patients in whom adverse events, LT, and mortality are expected. Finally, data analysis must account for the confounder of LT that provides a rescue from possible death, a highly different outcome, and requires a clear definition *a priori.* A composite outcome such as TFS is often the flawed solution; competing risk and survival analyses to account for the role of LT should be considered.

SUMMARY

Much has been learned over the past 2 decades about characteristics and disease evolution in ALF, given the variety of etiologies implicated. Management and outcomes including need for LT depend largely on etiology and severity of illness at presentation. Improvements in ICU care have included, if anything, less intensive support. Progress in clinical outcomes has been associated with reduced rates of ICH/cerebral edema, particularly in patients with APAP-ALF. Early renal replacement therapy and, potentially, therapeutic plasma exchange have recently been established as central to ALF management. Post-LT outcomes for ALF have improved significantly and are comparable to other causes of liver disease. Better understanding of pathogenetic mechanisms will enhance early treatment strategies for specific etiologies. Clinical management questions remaining include (1) optimizing use of blood products and CRRT, (2) best sedation strategies, and c) most effective use of antimicrobials. Future therapeutic studies of potential bioartificial devices will require production and transport of an abundant, high-quality

supply of human hepatocytes for bioreactor use. Finally, future transplant studies can assist in potentially expanding donor and recipient pools with more specific "futility criteria."

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