Acute Liver Failure

From Textbook to Emergency Room and Intensive Care Unit With Concomitant Established and Modern Novel Therapies

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Abstract: Acute liver failure is a rare hepatic emergent situation that affects primarily young people and has often a catastrophic or even fatal outcome. Definition of acute liver failure has not reached a universal consensus and the interval between the appearance of jaundice and hepatic encephalopathy for the establishment of the acute failure is a matter of debate. Among the wide variety of causes, acetaminophen intoxication in western societies and viral hepatitis in the developing countries rank at the top of the etiology list. Identification of the clinical appearance and initial management for the stabilization of the patient are of vital significance. Further advanced therapies, that require intensive care unit, should be offered. The hallmark of treatment for selected patients can be orthotopic liver transplantation. Apart from well-established treatments, novel therapies like hepatocyte or stem cell transplantation, additional new therapeutic strategies targeting acetaminophen intoxication and/or hepatic encephalopathy are mainly experimental, and some of them do not belong, yet, to clinical practice. For clinicians, it is substantial to have the alertness to timely identify the patient and transfer them to a specialized center, where more treatment opportunities are available.

Key Words: acute liver failure, emergency room, liver transplantation, intensive care unit, stem cell transplantation

(*J Clin Gastroenterol* 2019;53:89–101)

Liver failure can be classified into 3 forms: acute liver failure (ALF) occurring within 48 hours to several days and accompanied by numerous complications including infection, coagulopathy, and encephalopathy; acute-on-chronic liver failure (ACLF), with underlying chronic liver disease resulting in rapid progression of liver disease and displaying as additional jaundice and ascites; and chronic liver failure (CLF) remaining over a course of several months or years with chronic liver diseases.[1] Of these, ACLF and CLF appear frequently. The mortality rate of them ranges from 40% to 80%.[2]

ALF is generally considered to be a rare pathology.[3–5] However, it has detrimental consequences, which can often lead to multiorgan failure or even to death, if not promptly recognized and adequately treated. Orthotopic liver transplantation (OLT) remains the only effective therapy for critical patients.[6,7] In the majority of cases, ALF affects young patients, without known preexisting liver disease. Very limited exceptions include reactivation of hepatitis B virus (HBV), autoimmune hepatitis (AIH) as well as Wilson's disease (WD).[6,8,9]

Relative data indicate that up to 30% of patients with chronic hepatitis B experience HBV reactivation each year, and up to 8% of patients develop severe acute exacerbation and may progress to ACLF;[10,11] flare-ups of chronic hepatitis B can progress to ACLF with high short-term mortality.[11,12]

Etiology is quite heterogeneous and encompasses a wide variety of possible causative factors (Table 1), depending mainly on geographical distribution; ALF varies according to the etiology and center responsible for patient management.[13] The most common of them consist of toxins and drug-induced liver injury (DILI), primarily in western, industrialized societies, as well as viral hepatitis in the rest of the world.[6,14] In ALF, the liver synthetic ability is severely impaired, due to a massive cellular necrosis of hepatocytes. The clinical manifestation includes the presence of rapid progression of hepatic encephalopathy (HE), precedent by jaundice and biochemical evidence of liver injury as well as ascites and coagulation abnormalities of any degree.[1] Coagulopathy is typically characterized by a spontaneous elevation of the international normalized ratio (INR) of ≥ 1.5 (or prothrombin time > 15 s).[7,14,15] Over the last years, advances in the emergency transplantation as well as in critical care therapy have significantly contributed to an amelioration of survival.[7]

DEFINITIONS

Trey and Davidson first introduced the term "fulminant liver failure" almost 50 years ago. The original definition

Received for publication June 8, 2018; accepted November 1, 2018.
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DOI: 10.1097/MCG.0000000000001162

TABLE 1. Etiology of Acute Liver Failure

Categories	Cause	Hallmark/Comment
Autoimmune	Autoimmune hepatitis	Predominance in women
Drug induced	Acetaminophen (paracetamol)	Common, dosage dependent (Table 2)
	Various	
Metabolic	Galactosaemia	
	Hereditary fructose intolerance	
	Rey's syndrome	Young children with viral syndrome and salicylate intake
	Tyrosinaemia	
	Wilson's disease	Older children; Coombs (−) hemolytic anemia, hypouricemia, and a low alkaline phosphatase level with a high bilirubin level
Neoplastic	Metastatic mammary carcinoma	The most common representatives
	Lymphoma	
Pregnancy related	HELLP syndrome	Abdominal, pain, vomiting, headache, thrombocytopenia, elevated ALT/AST, hemolytic anemia, edema
	Acute fatty liver	Defects in fetal and maternal mitochondrial long-chain 3-hydroxyacyl coenzyme A dehydrogenase
	Toxemia	
	(Pre)eclampsia with liver infarction	Rare
	Acute hepatic rupture	
Toxic	Amanita phalloides toxin	Mushroom poisoning EU > USA
	Bacillus cereus toxin	"Fried rice syndrome"
	Carbon tetrachloride	Extremely rare
	Yellow phosphorus	Extremely rare
Vascular	Budd-Chiari syndrome	Hepatic outflow obstruction
	Ischemic hepatitis (shock liver)	History of hypotension and ischemia must be prolonged
	Right heart failure	
	Sinusoidal obstruction syndrome	After chemotherapies, before bone marrow transplantation
Viral	Hepatitis A virus	Other than hepatitis, viruses are rather rare or/and etiologically controversial. Hepatitis C is extremely rare and in the setting of other underlying hepatic diseases. Immunocompromised patients are predisposed. Hepatitis E is more common in endemic areas and mainly in pregnant women
	Hepatitis B ± Delta virus	
	Hepatitis C	
	Herpes simplex virus	
	Human herpesvirus 6	
	Varicella zoster	
	Cytomegalovirus	
	Epstein-Barr	
	Adenovirus	
	Parvovirus	
	Hemorrhagic fever viruses	
	Coxsackie B virus	
Others	Heatstroke	Rare
	Rhabdomyolysis	Due to heatstroke or drugs

HELLP indicates hemolysis elevated liver enzymes with low platelets.
This table contains information adapted from references.[9,14,17,19,43,44,60]

described a "potentially reversible condition, the consequence of severe liver injury, with an onset of encephalopathy within 8 weeks of the first symptoms' appearance in the absence of preexisting liver disease."[16] Since then, a plethora of different definitions have been suggested (Fig. 1), depending primarily on the elapse of time from the start of disease and onset of HE.[5,7,17–19] O'Grady et al,[20] for instance, proposed a further subgrouping of ALF; they introduced the term "hyperacute liver failure" for patients with a hebdomadal interval between onset of jaundice and HE. A greater interval ranging from 8 to 28 days was labeled as ALF, whereas the term "subacute liver failure" was used for an even greater interval up to 72 days. Bernuau et al[21] proposed another classification to fulminant—subfulminant, whereas the Japanese system, represented mainly by Mochida et al,[22] uses a distinction between fulminant (up to 8 weeks, subdivided to acute, subacute) and late onset with acceptable appearance of HE after jaundice up to 24 weeks. Wlodzimirow et al[23] have performed a systematic review of the literature accessible to them with regard to ALF definitions, and, surprisingly, 81 different studies used 41 different definitions, whereas 16 studies did not define ALF precisely. As an impact, comparability among studies and further analysis could be substantially impeded. It is noteworthy to mention that, contrary to expectations, a more fulminant course of ALF is associated paradoxically with a better outcome in many published studies,[5,7,17,18] and, in the majority of such cases, the etiology of the fulminant course is attributed to acetaminophen intoxication.[24]

EPIDEMIOLOGY

ALF is a rare life-threatening disorder characterized by rapid progression and death.[25] As an impact of the aforementioned discrepancy in the definition of ALF, the actual incidence of the pathology is regarded to be underdiagnosed.[18,26,27] ALF is considered to be more common in women than in men as well as in white individuals than in the rest of the races.[8,14] The median age of patients upon presentation is 38 years.[14,28] The western world has an estimated annual incidence of fewer than 10 cases per million individuals.[7] A reported rough estimation in the United States mentions about 2800 ALF cases per year.[18] The reduced causative viral incidence in the United

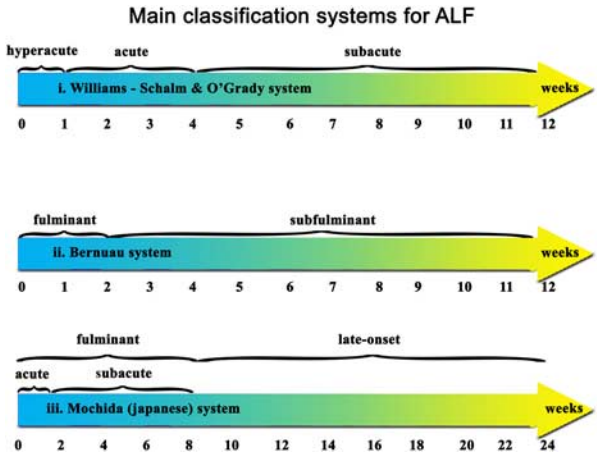

FIGURE 1. The 3 main well-established classifications for ALF. (i) Williams-Schalm and O'Grady system (ii) Bernuau system, and (iii) Mochida (Japanese) system. ALF indicates acute liver failure.

States as well as in the majority of Western Europe is attributed to better public health precautions, such as better sanitation and vaccinations. In the UK and in the USA, drug overdosing and, especially acetaminophen (paracetamol) toxicity, followed by idiosyncratic pharmaceutical reactions are known to be leading causative factors.[7,18,19] On the contrary, in the eastern developing countries, 3 viruses (hepatitis A, B, and E) are responsible for about 95% of the total ALF cases.[7] Hospital survival has been dramatically increased during the last decades in the United States and United Kingdom. This positive evolvement has been interpreted through a manifold improvement of early diagnosis, intense care unit (ICU) utilization, and the opportunity of emergent liver transplantations. The 3 leading causes of death in descending frequency include multiorgan failure, liver failure, and sepsis.[29]

ETIOLOGY

The spectrum of ALF includes a plethora of different etiological factors. A fundamental and practical classification (Table 1) of them is the distinction among autoimmune, viral, metabolic, neoplastic, toxic, pregnancy-related, pharmaceutical (drug induced), and vascular ones.[6,30] As it was previously clearly stated,[5,18,19,31] there exists a geographical distribution of certain ALF causes. In cases, wherein a certain etiology cannot be elucidated, ALF remains as indeterminate.[3,30]

AIH may also manifest as ACLF, with clinical characteristics equal to ALF.[28] It is thought that about 20% to 30% of the patients develop an acute course and to an even lesser extent ALF, which might be induced by a triggering agent including toxic injury, preceding viral infections, or therapy with immune-modifying drugs.[32] For the substantiation of diagnosis, apart from the related clinical appearance, positive serum autoantibodies, remission under glucocorticoids as well liver biopsy are required; liver biopsy in an AIH-mediated ALF setting seems to be safe and effective in diagnosing AIH, and corticosteroid therapy is not associated with sepsis or high mortality and might improve the outcome.[33] Autoantibodies that can be found in high titers in serum include, for instance, antinuclear antibody, antiactin antibody, anti–soluble liver antigen, and quantitative immunoglobulins.[17,31] Nevertheless, cases with negative autoantibodies have been reported, wherein liver histology determined the diagnosis.[34] Advanced age and high model of end-stage liver disease (MELD) score are related with lethal outcome.[32]

Drug-induced ALF is uncommon, varies geographically, and remains a common cause of withdrawal of drugs in both preclinical and clinical phases.[4,35] Its main representative constitutes acetaminophen hepatotoxicity. The latter can be either intentional (suicidal attempt) or even an inadvertent overdosing;[36] acetaminophen overdose is the leading cause of drug-induced ALF in several developed populations.[37] In the United States, acetaminophen-induced ALF represents about 46% of the overall ALF cases, being followed by idiosyncratic DILI with a percentage of 11%.[26]

Of note, acetaminophen-associated ALF has been linked to a better outcome in terms of highest rate of spontaneous recovery as well as the lowest rate of death compared with other causes.[24] On the contrary, other etiologies being implicated in ALF such as DILI or AIH have a slower course and are associated with a 27% and 15% possibility of spontaneous recovery, respectively.[24]

Moreover, antiepileptics and antimicrobial agents like tuberculosis medicine, clavulanic acid, trimethoprim—sulfamethoxazole as well as antimycotics are among the most frequent drugs that are attributed to inducing ALF.[38] A detailed list of the medications linked with the development of ALF is presented in Table 2.

Metabolic causes of ALF include, among others, the commonly implicated galactosemia, tyrosinemia, hereditary fructose intolerance, and mitochondrial disorders (Reye's syndrome) in young children and WD in older children[39–41] Specifically, Reye's syndrome is most commonly seen in children with viral infection and parallel intake of salicylate-based medication.[17] WD is a rare autosomal recessive pathology of copper metabolism and thus requires special attention. It is characterized by a systematic accumulation of copper in the liver and other organs, due to a defect of a gene responsible for copper transport and, especially a P-type ATPase (ATP7B), which is found on chromosome 13q14.3.[31] In the setting of ALF, the diagnosis can be really challenging, as elevated copper in urine can be seen in ALF regardless of etiology, and ceruloplasmin as a so-called acute phase protein can range from low to normal or even be elevated. For obtaining the diagnosis, liver biopsy is regarded as gold standard.[8] The presence of the Kayser-Fleischer (KF) iris ring in half of the patients is thought to be a relatively specific sign, albeit not pathognomonic, as other pathologies also share this ocular lesion. KF rings are observed in 95% of WD patients with neurological signs.[42] For the establishment of KF diagnosis, a slit-lamp examination is mandatory, as, in most patients, copper accumulation is not visible with the naked eye.[43] In some cases, the discrepancy of especially high bilirubin with normal alkaline phosphatase might be helpful for diagnosis,[44] although objections of the validity have also been raised.[31] Liver transplantation is indicated for WD patients who present either with ALF or with end-stage liver disease and severe hepatic insufficiency as the first sign of WD. When WD-related ALF deteriorates too quickly for conventional treatment, living donor liver transplantation is an effective therapeutic strategy.[45]

Neoplastic pathologies are well-documented causes of ALF in the literature. The most common of them encompass metastatic solid tumors, with the main representative

TABLE 2. Medications Being Linked With Acute Liver Failure[26,30,60]

Categories	Substance
Antiallergic agents	Diphenhydramine, loratadine, zafirlukast
Anesthetics	Halothane, isoflurane
Antiepileptics	Carbamazepine, lamotrigine, phenyntoin, valproate
Antibiotics	Amoxicillin-clavulanate, ciprofloxacin, clarithromycin, levaquin, nicotinic acid, nitrofurantoin, ofloxacin, trimethoprim, sulfonamides, telithromycin, tetracycline
Antidepressants	Bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, venlafaxine
Antifungals	Itraconazole, ketaconazole, terbinafine
Antineoplastic-immunosuppresive agents	Azathioprine, cytoxane, dactinomycin, etoposide, methotrexate tamoxifen
Antipsychotics (neuroleptics)	Quitiapine
Antiretrovirals	Didanosine, efavirenz
Antituberculosis	Dapsone, isoniazid, rifampicin, pyrazinamide
Biological agents	Gemtuzumab, ipilimumab
Cardiovascular	Amiodarone, diltiazem, labetalol, lisinopril, valsartan
Herbal or dietary products	Chaparral ,Germander, Jin Bu Huan, green tea extract, usnic acid, ephedra, multi-ingredient products, for example, for weight loss
Nonsteroidal anti-inflammatory drugs	Diclofenac, etodolac, indomethacin, naproxen
Hypolipidemic agents	Atorvastatin, cerivastatin, ezetimibe, fluvastatin, pravastatin, simvastatin
Tyrosine kinase receptor inhibitors	Imatinib, nilotinib, ponatinib
Various	Allopurinol, carbon tetrachloride, cocaine, disulfiram, flutamide, metfomin, Methylenedioxymetamphetamine (MDMA*: "Ecstasy"), phenprocoumon, tolcapone, troglitazone

ones being mammary adenocarcinoma as well as hematologic malignancies, with the most frequent of them being lymphomas.[14,15,17,27,31,36]

Obstetric complications like HELLP syndrome (hemolysis elevated liver enzymes with low platelets), acute fatty liver, toxemia, (pre)eclampsia with liver infarction, and acute hepatic rupture constitute known underlying causes of ALF in pregnant women.[31,44] There is accumulating pieces of evidence that (pre)eclampsia, HELLP as well as acute fatty liver in pregnancy are expressions of the same entity and hence share comparable clinical and pathogenetic elements such as platelet aggregation and vascular phenomena.[18] The management of HELLP syndrome–related ALF must be multidisciplinary, and liver transplantation, the only radical therapy for ALF, is worth attempting.[46]

More or less known intoxications that lead potentially to ALF include *Amanita phalloides* toxin,[6,14,15,17,18,23] *Bacillus cereus* toxin, Carbon tetrachloride,[17,18] and yellow phosphorus.[17] Poisoning by mushrooms such as *Amanita phalloides* is mostly seen in the west coast of the United States, central Europe as well as South Africa.[19] Of note, there exist 2 toxins, both of which are heat stable and thus are not affected by cooking. The first one is called phallotoxin and damages the cell membranes of the intestinal simple columnar epithelium, whereas the second one, α-amanitin toxin (known also as amatoxin), is attributed to be hepatotoxic and can even lead to death if doses reach 0.1 to 0.3 mg/kg.[31,47] Before signs of liver failure are seen, gastrointestinal manifestation such as vomiting and watery diarrhea (cholera like) commonly precede.[6,14,17,31] The reported mortality rate of mushroom-related ALF with conventional therapy is 1.4% to 16.9%, and Escudié's criteria established the best performance with 100% accuracy and the ability to recognize fatal cases of mushroom-induced ALF.[48] Likewise, King's College Criteria (KCC) established a good prognostic value for urgent liver transplantation indication in *Amanita phalloides*–induced ALF.[49]

Vascular etiologies involve mainly Budd-Chiari syndrome (BCS), ischemic hepatitis (shock liver), right heart failure as well as sinusoidal obstruction syndrome.[17,31] BCS is a rare pathology characterized by tender hepatomegaly and acute hepatic vein thrombosis.[19,36] It seems to be more common in young female individuals.[6] BCS-related ALF dictates prompt diagnosis and management with anticoagulation in conjunction with cancer or thrombophilic disorder evaluation; mortality might improve by transjugular intrahepatic portosystemic shunt and/or OLT use.[50]

As far as viral hepatitis is concerned, hepatitis A and B viruses rank as the most common viral causes whereas the remaining pathogens such as hepatitis E, herpes simplex, or even Epstein-Barr viruses are more likely to be found in special categories of patients such as those who are immunocompromised or during gestation. In HBV-ACLF patients, some data indicate that human mesenchymal stem cell transplantation might significantly decrease the mortality rate, without raising the incidence of severe complications.[51] Hepatitis C virus can only very rarely lead to ALF.[8,19,36,52] Other known viruses that are implicated in ALF are cytomegalovirus, varicella zoster, adenoviruses, and parvovirus B19.[36,53] By evaluating the dynamicity of MELD, MELD-sodium, ALF early dynamic model, chronic liver failure (CLF)-consortium ACLF score, and KCC for predicting outcome in viral-induced ALF, the ALF early dynamic model achieves better than MELD, MELD-Na, and CLF-C ACLF scores and KCC for predicting outcome in viral hepatitis-induced ALF.[54]

Other infrequent reported causes of ALF might be heat stroke, particularly in military personnel, athletes, or laborers requiring urgent OLT[7,14,18,44,55,56] or even rhabdomyolysis, for example, medicament associated.[14]

CLINICAL PRESENTATION AT EMERGENCY ROOM

At early presentation, nonspecific symptoms are present but could progress to complications, including cerebral edema (CE), infections, coagulopathy, cardiopulmonary as well as renal failure, and acid-base and/or metabolic disturbances.[25] Upon arrival of a patient at the emergency room, it is

substantial for the clinician to keep in mind that every alteration of mental status combined with prolongation of INR/coagulation abnormalities and jaundice should be suspected of ALF. Further complaints and signs include fever, anorexia, fatigue, abdominal pain, bleeding, and hemodynamic instability. Equally of great significance is to distinguish between decompensated liver cirrhosis and new first diagnosed manifestation of ALF. Particularly helpful is the medical history of the patient with regard to known family liver diseases, predisposing factors for viral hepatitis (eg, polytoxicomania, travel, sexual history), eating habits, and intake of medications (also nonprescribed). During the clinical examination, corresponding signs could be identified that are suggestive of chronic liver disease (eg, cachectic patient with clubbing-leuconychia, gynecomastia, spider angiomas, and advanced ascites with prominent abdominal wall veins as well as varying hepatosplenomegaly). Herpetic skin lesions, tattoos as well as possible needle tracks should also be investigated on the skin. Eye examination should rule out or confirm KF rings, which indicate corneal copper deposition in WD.[31,57] It is important to note, however, that KF rings are not specific to WD alone, because they can also be observed in patients with other chronic cholestatic disorders such as children with neonatal cholestasis or primary biliary cholangitis.[42,43] Moreover, ALF can be easily misdiagnosed, especially if the clinical course is quick enough and has hallmarks of only neuropsychiatric manifestations such as confusion and agitation with barely seen jaundice. In addition, in subacute cases, a misleading diagnosis of chronic liver disease could be made, as portal hypertension and ascites with nodular liver can be seen.[5,7] About one-third of ALF patients may be admitted to the emergency department with ascites, and 17.7% will also present a spontaneous bacterial peritonitis.[14] ALF leads to a syndrome with systemic manifestations (Fig. 2) characterized by some or even all of the following clinical hallmarks: metabolic disturbance with accompanying lactic acidosis, oliguria with acute renal injury, blood hypotension, acute lung injury/acute respiratory distress syndrome (ARDS), sepsis with possible systemic inflammatory response syndrome, hypoglycemia, and coagulopathy with clotting or bleeding tendency.[30,44,58] About 60% of the patients with ALF fulfill the criteria for systemic inflammatory response syndrome,[59] regardless of whether a bacterial etiology is found or not. Thirty percent of ALF patients develop the aforementioned ARDS or acute lung injury.[52] Critically ill patients are prone to be complicated with HE, CE, and intracranial hypertension (ICH).[3,6,31,36,60,61] These serious complications account for 65% of the patients with third-grade HE and 75% of those with fourth-grade HE.[62]

As far as acetaminophen intoxication is concerned, the recognition of ALF is usually plausible, as the history taking of the patient and clinical course are rather typical. Patients

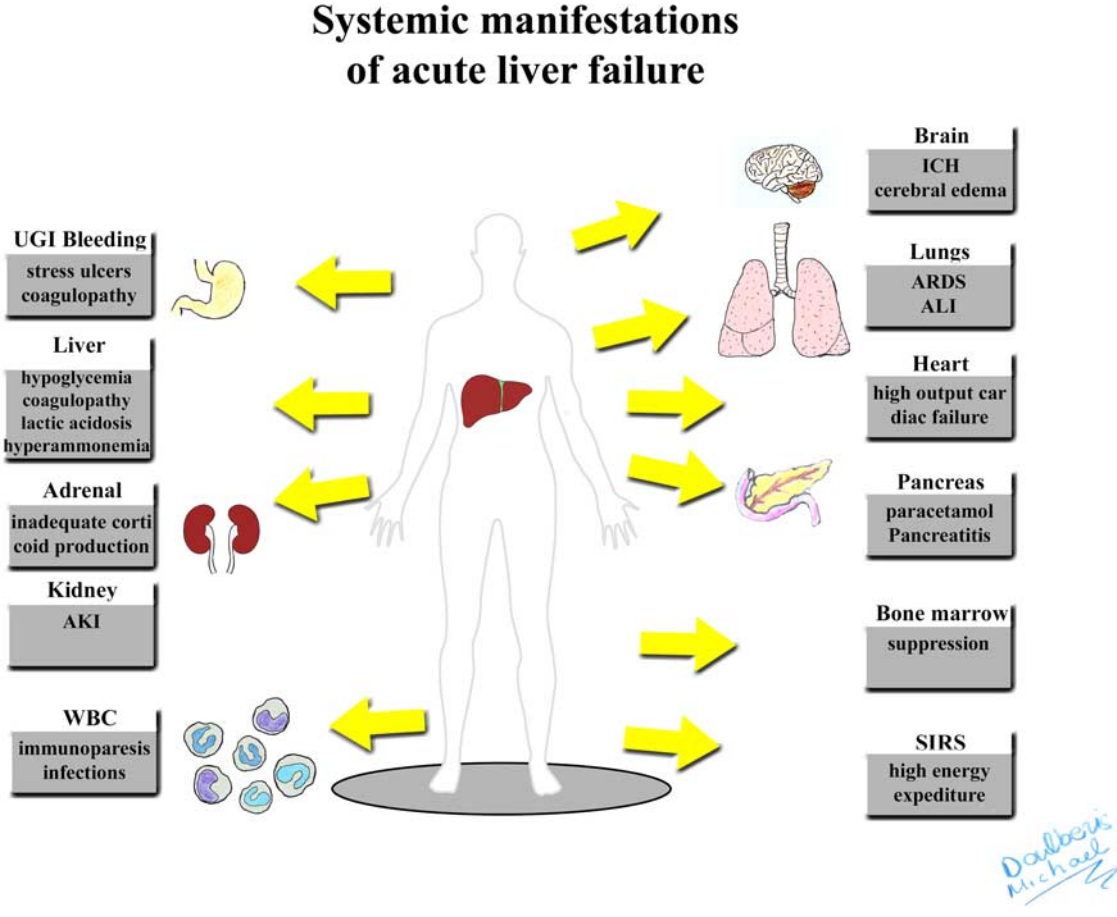

FIGURE 2. Clinical (extra) hepatic hallmarks of acute liver failure. AKI indicates acute kidney injury; ALI, acute lung injury; ARDS, adult respiratory distress syndrome; ICH, intracranial hypertension; SIRS, systemic inflammatory response syndrome; UGI, upper gastrointestinal; WBC, white blood cells. full color online

are admitted to hospital and claim the intake of the drug in suicidal attempt or accidental overconsumption. In the first case, a great increase of transaminases (up to several 100 fold) within the first 3 days is to be expected. Acute kidney injury (AKI), coagulopathy, HE, and acidosis are seen in the next stages, and patients frequently die due to sepsis and multiorgan failure. In the second case of accidental intoxication, patients present often with unconsciousness, hyperthermia, hypotension, AKI, coagulopathy, jaundice, and accompanying hypoglycemia. Patients with claimed accidental overdosing have commonly a history of alcohol addiction and take multiple pain relievers, not rarely 2 different acetaminophen preparations.[14] Moreover, acetaminophen-related ALF seems to be more frequent and severe among women.[63] Remarkably, pancreatitis could also be a complication of ALF in acetaminophen toxicity.[7,8]

In a recent relevant US study, survival was evaluated with or without OLT among ALF patients. Remarkably, acetaminophen category patients, although representing only 22% of the totally listed patients, developed a greater illness severity with higher coma grades and greater ventilator and vasopressor or renal replacement therapy support necessity, whereas a minority of them required a graft, compared with autoimmune, DILI, and HBV-related ALF patients. Thus, acetaminophen intoxication outcome evolves rapidly, resulting either in spontaneous survival without OLT or in death.[24]

Noteworthy is also the category of WD patients, on grounds that they have a very typical clinical presentation, albeit very rare; patients are admitted with HE, they are at their later puberty, and present icteric due to hemolysis and consequently exceptionally elevated indirect bilirubin as well as established liver cirrhosis.[5] Serum ceruloplasmin is typically low (mostly of cases <20 mg/dL) but can be normal in up to 15% of ALF cases. Notably, ceruloplasmin can also be low in other causes of ALF. Moreover, serum zinc is low in WD-induced ALF, thereby it appearing to be a novel parameter for diagnosis correlated with WD severity.[64] Likewise, a ratio of alkaline phosphatase to total bilirubin <4 and an AST to ALT ratio >2.2 are regarded as highly sensitive and specific predictors of fulminant WD.[65] WD along with hepatitis B and AIH consist of the 3 exclusions, wherein an underlying preexisting hepatic condition should be ruled out before ALF is diagnosed.[14]

A history of wild mushrooms' ingestion and onset in about 12 hours of watery diarrhea, mimicking cholera voluminous "rice-water stool," is suggestive of *Amanita phalloides*–related ALF.[14,30,49]

INITIAL MANAGEMENT

Once a patient arrives at the emergency room, the suspicion of a possible ALF, alerts the clinician for a cascade of related history-based questions as well as diagnostic measures.[66] As ALF patients frequently present with circulatory instability or they are even in a state of shock state, cardiovascular support emerges as the initial step to restore and maintain intravascular volume and metabolic balance, thus avoiding further deterioration of liver function and multiple organ damage. This crucial step embodies the administration of adequate fluid resuscitation to preserve sufficient perfusion for all tissues and correction of electrolyte disturbances (especially hypokalemia and hypophosphatemia) and acid-base disorders (mixed respiratory and metabolic alkalosis most commonly, unless lactic acidosis complicates the metabolic state).[30,60] In severe cases, the implication of vasoconstrictors, and particularly norepinephrine, could be regarded as an early life-saving intervention.[66] In addition, the prevention of stress ulcers by administration of proton pump inhibitors and regular monitoring of blood glucose levels (hypoglycemia indicates poor prognosis in ALF) stand as supplementary measures in the management of ALF.[67,68] As regards the increased risk of infections, which lead even to sepsis, although the usage of broad-spectrum antibiotics is not generally recommended, the administration of empiric antibiotic therapy can be considered in a clinical setting of persistent hypotension or worsening encephalopathy for the prevention of infectious complications and further deterioration.[69–71] An echocardiography can help the distinction between circulatory insufficiency and cardiogenic shock.[72] Vitamin K serves as an additional measure that could correct or exclude any nutritional deficits. The latter could contribute to the prolonged PT/increased INR.[73] Moreover, although N-acetylcysteine constitutes the first choice of medication in cases of acetaminophen overdose, it is also regarded as an antioxidant agent and vasodilator offering benefit in non–acetaminophen-associated hepatotoxicity leading to ALF.[74,75] The recurrent monitoring of coagulation and neurological status is substantial in any patient with established liver dysfunction, as the progression to ALF significantly affects the final prognosis.

It is important to note that the mentioned rapid restoration of intravascular volume with intravenous fluids and electrolyte and acid-base disturbance corrections, as well as other cause-specific interventions can be administered in non–intensive care unit settings, thereby diminishing delay.[76]

There are some specific measures that target etiological factors and can be considered as lifesaving under certain circumstances. In cases of pregnancy complicated with AFLP or HELLP, the decision for prompt delivery is recommended.[77,78] In addition, acute presentation of HBV infection with impaired hepatic function should be treated with a nucleos(t)ide analog[79] like tenofovir or entecavir. Furthermore, it is worthy to be emphasized that nucleos(t)ide analog treatment should be considered in each patient with severe acute hepatitis B. This approach can potentially prevent the development of ALF, thereby decreasing mortality. Starting such a treatment in patients with established ALF is most likely to be too late. Relevant studies support and encourage this principle in terms of safety as well as of efficacy.[80–82]

Once BCS diagnosis is established, the timely initiation of anticoagulation in therapeutic doses and—when available—angioplasty can improve the patient's prognosis.[50] Finally, in mushroom-induced ALF, it is crucial to apply all dispensable measures, including prompt administration of silibinin (the major active constituent of silymarin), gastric lavage and activated charcoal, and enough diuresis on top of proper hydration. Nevertheless, it has to be mentioned that gastric lavage as fundamental supportive therapy for mushroom poisoning has been questioned by some authors.[83,84]

Another antibiotic usually used in practice is penicillin G and works well in various settings; it competes with amatoxin for binding sites on serum proteins and prevents hepatocyte uptake;[85] it helps to prevent the HE progression, and the recommended dosage is 40,000,000 U/d for adults and 1,000,000 U/d for children.[86] Likewise, ALF induced by

amatoxin-containing mushroom can also be treated by penicillin G, silibinin, and plasma exchange combination regimen.[87]

In specialized centers, further therapeutic modalities for critical ALF patients include the application of artificial liver support devices such as MARS (molecular adsorbent recirculating system) or fractionated plasma separation and adsorption.[57,88–90] In general, MARS and fractionated plasma separation and adsorption might have the potential to increase the probability of short-term survival of patients with ALF or ACLF and can be introduced for bridging to liver transplantation;[91] MARS therapy seems to successfully replace hepatic function in ALF, thereby allowing time for spontaneous recovery or transplantation.[92] Both approaches, however, are not appropriate for long-term therapy;[91] MARS in patients with ALF failed to show a survival improvement in the overall study cohort.[93] Moreover, therapeutic plasma exchange seems to provide a survival benefit in nontransplanted patients with ALF.[93] This approach seems to significantly improve survival above that seen with standard medical care, although the survival benefit is inferior to that seen with transplantation;[94] it is introduced early in ALF patients with an expected poor prognosis without transplantation but who have clear medical or psychiatric contraindications to surgery,[69] and its use is associated with a significant cardiovascular condition improvement in patients with worsening cardiovascular failure and vasopressor requirement while they are waitlisted for liver transplantation.[93]

It is considered substantial for the clinician to promptly calculate the mentioned score of MELD and KCC, while the timely referral to a liver transplantation center is decisive for the prognosis of ALF.[4,15] Nevertheless, during the last years, KCC have been disputed, as they have been shown to have limitations; they were developed in 1989 once OLT was not that widely established, and they are attributed to have poorer sensitivity and negative predictive value,[95,96] compared with other newer models.[97,98] Worth mentioning is a recently developed multivariable logistic regression model of the American ALF Study Group (ALFSG). The authors have included prospectively 1974 ALF patients in order to predict transplant-free survival and claimed this model to be superior to both the KCC and MELD score. Further large-scale studies are, however, warranted in order to confirm its applicability.[99]

Early referral of selected ALF patients to a specialized center with transplantation capability will permit a better depicting of patients and distinguish between the ones who may profit from an OLT (and respectively stabilize and prepare them) and the ones who have a better chance for spontaneous recovery without undergoing a transplantation. This prediction of ALF cases is not always plausible and can be challenging also for experienced clinicians, as not all acute hepatopathies lead always to ALF. It is thus advisable that all patients with poor general condition upon first presentation and those with proven etiologies that are associated with a more fulminant course such as acetaminophen intoxication should directly be referred to a center with transplantation capability and receive immediate specific as well as supportive therapy. Moreover, the relatively new practical guidelines[69] from the European Association for the Study of the Liver (EASL) include concrete suggested criteria for referral of such candidates; etiologies are classified to paracetamol (also hyperacute causality) and nonparacetamol ones. The former patients should meet the following criteria: hypoglycemia, elevated lactate unresponsive to fluid resuscitation, altered level of consciousness, oliguria and/or elevated creatinine, prolongation of INR > 3.0 on the second day or > 4.0 the next days and arterial pH <7.30 (or $HCO_3 < 18$). Regarding nonparacetamol ALF causes, required criteria include INR > 1.8 and arterial pH as well as HCO_3 limits as previously stated. In addition, bilirubin should reach a value > 300 μmol/L (17.6 mg/dL), and patients should present with oliguria/renal failure (or sodium <130 mmol/L), encephalopathy, hypoglycemia, or metabolic acidosis and appear to have a shrinking liver size (Table 3).

TABLE 3. Suggested Referral Criteria of ALF Patients by EASL[69]

Nonparacetamol Etiology	Paracetamol and Hyperacute Etiology
pH < 7.30 or $HCO_3 < 18$	pH < 7.30 or $HCO_3 < 18$
INR > 1.8	INR > 3.0 (second day) or > 4.0 thereafter
Oliguria/renal failure or sodium <130 mmol/L	Oliguria and/or elevated creatinine
Encephalopathy, hypoglycemia, or metabolic acidosis	Altered level of consciousness
Bilirubin > 300 μmol (17.6 mg/dL)	Hypoglycemia
Shrinking liver size	Elevated lactate unresponsive to fluid resuscitation

ALF indicates acute liver failure; EASL, European Association for the Study of the Liver; INR, international normalized ratio.

INTENSIVE CARE UNIT TREATMENT

ICU management focuses on the clinical presentation, identification, and management of the several complications observed in ALF patients.[100] Outcomes are better with early detection and prompt initiation of etiology-specific therapy, intensive care protocols, and OLT.

The mentioned ICH and CE consist of 2 of the challenging complications that develop in critical ALF patients and that ICU clinicians are called to confront; ICH and CE complicate about 75% to 80% of patients with ALF and grade III or IV HE, and they remain prominent causes of death.[101] ICH is frequently preceded by CE and HE and is well known to contribute to transtentorial herniation, which can lead to death.[28,57,100] Mechanisms that contribute to ICH and CE include cytotoxicity due to osmotic effects of ammonia, glutamine, other amino acids, and proinflammatory cytokines, as well as cerebral hyperemia and vasogenic edema due to the blood-brain barrier disruption with quick low molecular substance accumulation. Dysfunction of sodium-potassium adenosine triphosphatase pump with loss of autoregulation of cerebral blood flow has been implicated as a cause of hyperemia.[7,57,100–102]

There are classically described 4 grades of HE, the so-called West Haven criteria:[17,27,57,103] A variant of the aforementioned criteria is the also known Parsons-Smith scale (Table 4).[19] As regards the management of HE, sedating medications are generally contraindicated, as they can mask a potential further progression of the condition. Antipsychotic agents with a short half-life such as haloperidol can be given selectively to patients with great agitation. Ammonia-focused treatment constitutes the basis of current HE therapy in ALF setting.[7,9,100]

Once HE has advanced to grade 3, an intubation of the airway with accompanying mechanical ventilation is

TABLE 4. Grading of Hepatic Encephalopathy (Modified Parsons-Smith scale)[19]

Grade	Vigilance	Neurology	Glasgow Coma Scale
0 or subclinical	Normal	Only seen in neuropsychometric testing	15
1	Minor lack of awareness, shortened attention span	Apraxia, tremor, incoordination	15
2	Lethargy, disorientation, personality change	Ataxia, dysarthria, flapping tremor	11-15
3	Confusion, somnolence to semistupor, response to stimuli	Ataxia, flapping tremor	8-11
4	Coma	With or without decerebration	< 8

appropriate;[14,61,100] ICU admission with airway controlling and CE decreasing by hypertonic saline, mannitol, hypothermia, and sedation are commended as a bridge to liver transplantation.[100,104] Of note, the establishment of a primary prophylaxis should be considered in ICU patients with gastrointestinal bleeding, so that an overt HE can be avoided.[105]

Interestingly, there is a lot of debate in the literature with regard to intracranial pressure (ICP) monitoring, without, however, consensus. Its significance is theoretically at least plausible, as the seamless monitoring could identify early an ICH and allow a rapid and targeted therapy. There are 2 basic categories of ICP monitoring, an invasive and a noninvasive one. Although invasive methods are regarded as more accurate and thus the so-called gold standard, their usage is rather limited due to the possible complications and the lack of significant evidence supporting a clear clinical benefit for the patient. Infections along with intracranial hemorrhage (bleeding accounts for up to 10% of ALF patients) constitute the most reportable complications after catheter insertion on grounds of the preexisting coagulopathy.[18,106,107] Several ALFSG, including the American one, recommend the placement of ICP monitoring in patients with high-grade HE.[106] With regard to the noninvasive modalities to monitor ICP belong among others the transcranial Doppler, jugular bulb oximetry, serial CT of the head, and pupillometry. The limitation of such noninvasive diagnostic methods is the necessity for a baseline imaging.[100] Nevertheless, a recent retrospective study that evaluated the accuracy of 3 noninvasive ultrasound-based monitoring modalities, deduced that none of these were able to detect reliably a concurrent ICP elevation, documented with invasive monitoring.[107]

In this respect, cerebral perfusion pressure (CPP), defined as the gradient between mean arterial pressure and ICP plays a substantial role for the management of CE.[100,108] Particularly, ALF patients with CE have been found to have a relatively better outcome when a low ICP with simultaneous adequate CPP is maintained.[100,108] On the contrary, prolonged low values of CPP (< 50 mm Hg) along with elevated ICP (> 40 mm Hg) have been associated with detrimental consequences in both neurological as well as posttransplant terms.[109]

Patients with ALF often develop concomitant AKI, via a number of pathogenic mechanisms such as renal hypoperfusion, direct drug-induced nephrotoxicity causing acute tubular necrosis, or sepsis/systemic inflammatory response, which contributes to increased morbidity and severe prognosis.[68] Moreover, ACLF patients display an AKI high incidence correlated with 30-day and 90-day mortalities.[110] The majority of critically ill ALF patients are admitted to the ICU with certain volume depletion, often due to gastrointestinal bleeding, which contributes to prerenal kidney injury. Fluid resuscitation should not be aggressive, as well as the usage of vasopressors over fluids to maintain stable blood pressure. Dopamine is superior to norepinephrine, due to the advantage of the first on oxygen delivery in the peripheral tissues.[14,28,100] The early introduction to renal replacement has been a modality that is being adapted by several transplantation centers.[7,14,28,57,100]

Coagulopathy is also seen in ALF patients being hospitalized in ICU. This is a consequence of massive hepatocellular necrosis, which affects the production of both anticoagulation and procoagulation factors with further increase of INR. Simultaneous thrombocytopenia can also be found in patients with known multiorgan failure.[9,28,57,100] Contrary to CLF, such patients develop a reduction of factors II, V, VII, and X, whereas factor VIII is increased, as a result of acute inflammation. It is believed that there is overall a predisposition for hypercoagulation, which can lead to deep vein thrombosis.[100] It is important to note that, despite a bleeding diathesis, clinically important bleeding is infrequent in ALF patients; bleeding complications in ALF patients are indicators of rather severe systemic inflammation than of coagulopathy and hence portend a poor prognosis.[111] Again, current well-described detailed protocols[112] are also utilized for the management of coagulopathy before and following insertion of an ICP monitor.

Infections constitute a known complication of ALF. Bacterial infections induce systemic inflammation that may result in organ failure and ACLF through complex mechanisms leading to a high risk of short-term mortality;[113] infection is one of the most fatal complications in ALF, particularly when accompanied by multiorgan failure, with a reported incidence of up to 90%;[28,54] liver failure complicating sepsis/septic shock has an important impact on mortality in ICU patients;[114] and streptococcal toxic shock syndrome is complicated with acute liver and renal failure, ARDS, and disseminated intravascular coagulation.[115]

Functional monocyte damage and consequent immune paresis contribute to increased susceptibility for infections in ALF.[9,116] The most common infections include pneumonia, urinary tract infection, and catheter-associated bloodstream infection.[57] The causative microbes are mainly bacteria with slight predominance of Gram-negative bacilli over Gram-positive cocci, whereas fungal infections occur rarely.[28] Although no survival benefit has been demonstrated by the use of antimicrobial prophylaxis, the current guidelines suggest antibiotic coverage particularly in patients with high-grade of HE (3/4) and definitely in those who are intubated or require renal replacement therapy.[100] A combination of a beta lactam antibiotic (eg, piperacillin/tazobactam or a carbapenem according to the local nosocomial-resistant microbes) with vancomycin is recommended.[28] Nevertheless, the spread of multidrug-resistant bacterial infections nowadays has reduced the efficacy of usually used antibiotics.[117] Surveillance for infection with daily chest x-ray and regular cultures of blood, tracheal aspirate, and

urine should be undertaken, whereas central lines should be monitored periodically for signs of infection in order to be removed or replaced, and their tips should be cultured as well. Isolation of a potentially harmful microbe in cultures should be followed by prompt modification of antibiotic scheme. In case of deterioration of clinical presentation without any laboratory finding or positive culture, an enhancement of antibiotic treatment with the addition of aminoglycoside or polymyxin E (also known as colistin) is suggested. If the patient's condition is refractory to the latter change, the addition of antifungal coverage (eg, micafungin) is reasonable.[100]

Hypoglycemia may also appear in the setting of ICU in ALF patients. The diminished capability of liver for gluconeogenesis along with emesis and poor oral intake lead to exhaustion of glycogen stores. Immediate therapy as soon as hypoglycemia is recognized is recommended, as the neurological consequence might be detrimental. Blood glucose levels should be monitored closely (at least 4 hourly) in patients with severe liver failure. Severe liver injury–induced hypoglycemia is one of the causes of hypoinsulinemic hypoglycemia; hypoglycemia is improved by glucose infusion, although the liver injury is not improved.[118] A reasonable blood glucose target is 6.0 to 10 mmol/L (108 to 180 mg/dL), using hypertonic dextrose solutions if necessary. Repeated low concentrations of dextrose-based intravenous solution of 5% to 10% should be avoided, because they may cause a nondesired hyponatremia with the known negative impact on brain edema.[7,57,61]

LIVER TRANSPLANTATION

Upon the arrival of liver transplant for ALF, the survival rate has improved considerably. Liver transplant for ALF accounts for 8% to 10% of all transplant cases.[7,60,119] The 1-year survival rates are 79% in Europe and 78% to 84% in the United States and fall to 71% 4 years later.[119] Remarkably, the survival of patients being transplanted due to CLF appears to be higher than that of patients being transplanted due to ALF. Postulated reasons for this include the emergent setting of operation, the higher incidence of immunologically mediated graft dysfunction as well as the coexisting organ failure(s).[120] Criteria, which should be met in order for a patient to qualify for OLT, are the well-described and above-mentioned KCC (Table 5).[3,17,19,28,44] As regards acetaminophen hepatotoxicity, KCC criteria have a strong positive predictive value for ICU-related death without transplantation.[3,44] Interestingly, living donor liver transplantation can be introduced in ALF patients with grade IV encephalopathy, with a success rate comparable to that of non-ALF patients undergoing liver transplantation.[121]

Advances in medicine of critical care have significantly enhanced the spontaneous survival in ALF patients from 15% to 40%.[31] Among patients being listed for transplantation, 37% will recover spontaneously without the need for OLT, and it is estimated that as many as 20% of ALF patients may be transplanted without actual necessity.[31]

NOVEL THERAPIES

Beyond the above-mentioned and well-established therapies for ALF, there do exist some additional, less evidence-based ones. Because of their experimental character, they do not have a place, at least yet, in clinical application.

As regards N-acetylcysteine recommended in acetaminophen-induced ALF, the narrow therapeutic window limits its administration. Therefore, novel therapeutic strategies that can offer broadly protective effects against ALF are warranted. In this respect, apart from mitochondrial oxidative stress, several other cellular processes, including phase I/phase II metabolism, endoplasmic reticulum stress, sterile inflammation, microcirculatory dysfunction, autophagy, and liver regeneration, are involved in ALF pathogenesis, thereby offering novel targets for developing effective therapeutic strategies against acetaminophen-related ALF.[37] For instance, autophagy is activated in response to acetaminophen overdose in certain liver zone areas, and autophagy pharmacological activation protects against acetaminophen-related ALF.[122] Moreover, p53 demonstrates a protective role in regulating acetaminophen metabolism and disposition, thereby offering a novel therapeutic target for acetaminophen-induced ALF.[123] The gut microbial metabolite, 1-phenyl-1,2-propanedione, is also involved in aceteminophen-induced rhythmic hepatotoxicity, by depleting hepatic-significant antioxidant glutathione, thereby signifying that gut microbiota might be an additional target for decreasing acetaminophen-related ALF.[124]

Human hepatocyte transplantation has been introduced as an alternative to liver replacement for ALF. Specifically, one of the main indications for human hepatocyte transplantation therapy is ALF[125,126]; human hepatocyte transplantation has been actively perused as an alternative to liver replacement for ALF.[127] In this regard, 37 patients with ALF have been treated with human hepatocytes for drug-induced, viral, and obscure ALF. Ten of these patients received intraportal hepatocyte infusions, with 2 making a full recovery without the requirement of OLT, and 3 were

TABLE 5. King's College Hospital Prognostic Criteria (Left) and UNOS Criteria (Right)[44,58]

Kings College Criteria		
Nonparacetamol Hepatotoxicity	**Paracetamol Hepatotoxicity**	**UNOS Criteria for Status 1 Listing**
Prothrombin time > 100 s	Arterial pH <7.30 (7.25 if given N-acetyl cysteine)	Onset of encephalopathy of any degree 8 wk after the acute liver failure onset
Prothrombin time > 100 s Any 3 of the following: unfavorable etiology (seronegative or drug-associated fulminant hepatic failure), Jaundice > 7 d before encephalopathy, age <10 or > 40 y prothrombin time > 50 s serum bilirubin > 300 mmol/L	Or all of the following: prothrombin time > 100 s, creatinine > 300 mcmol/L, grade III encephalopathy	Absence of preexisting liver disease Life expectancy of <7 d and in the intensive care unit requiring either mechanical ventilation, renal dialysis, or with severe coagulopathy (INR > 2.0)

INR indicates international normalized ratio.

successfully bridged to transplantation.[128–131] Recent data indicate that domino hepatocyte transplantation, by using livers that would not meet transplantation criteria, is one of the available alternatives to treat ALF patients; it might be an excellent strategy to increase cell supplies for hepatocyte transplantation.[132]

Compared with solid organ transplantations, cell transplantation advantages include the potential to treat more patients with a substantially less invasive procedure, and leaving the native organ in situ with regeneration potential. Clinical hepatocyte transplantation safety and short-term efficacy have been proven. However, present challenges include a reduced cell source, decreased cell viability following cryopreservation, and poor engraftment of cells into the recipient liver with consequently a limited lifespan.[127,133,134] Therefore, alternative stem cell sources including pluripotent stem cells, fibroblasts, hepatic progenitor cells, amniotic epithelial cells, and mesenchymal stem/stromal cells can be introduced to generate induced hepatocyte-like cells, with each technique exhibiting advantages and disadvantages. Mesenchymal stem/stromal cells transplantation had beneficial effects, especially in ACLF patients.[1] However, long-term functionality of transplanted hepatocyte-like cells and the potential carcinogenic risks of administering stem cells have yet to be proven.[127]

Research has focused also on HE potential novel therapies, as a substantial body of evidence has signified that inflammation acts in concert with ammonia in HE pathogenesis, and inflammatory mediators have a significant role in modulating the cerebral effect of ammonia. Relative novel and potential therapeutic strategies include hypothermia, minocycline, nonsteroidal anti-inflammatory drugs, tumor necrosis factor-alpha antagonists, and p38 inhibitors, which seem to ameliorate systemic inflammation—neuroinflammation, improve or reverse neuropsychiatric manifestations, and prevent the onset and progression of HE in patients and/or animal models of ACLF. These data point to the possible therapeutic utility of decreasing inflammation in HE therapy, and translation of these experimental data to the clinic may provide novel and promising therapeutic approaches for patients with HE secondary to ALF or chronic liver failure.[135,136] In this regard, recent evidence suggests the role of fecal microbiota transplantation in the treatment of HE with promising results, although additional research is needed.[137] Moreover, as hepatic autophagy is an essential mechanism for ammonia detoxification because of its support of urea synthesis, its augmentation has the potential for the treatment of both primary and secondary causes of hyperammonemia.[138]

CONCLUSIONS

ALF still remains a rather rare but often fatal entity, which requires high clinical suspicion and alertness. The sooner a patient is identified with ALF, the sooner the transfer to specialized centers with the capability of a high-level multidisciplinary intensive care, and the more the possibilities exist for a favorable outcome. Usage of the aforementioned calculation tools along with EASL suggested referral criteria[69] could contribute to such a decision-making.

CE with ICH and infections rank among the most common causes of death in critical ALF patients. OLT is offered as an option for selective patients and has overall and remarkably improved ALF survival in the last decades. The leading cause of ALF in the western societies is drug-associated ALF and, particularly acetaminophen overdose, whereas, in the less developed societies, viral hepatitis remains a significant causative burden. Beyond the well-established treatments, future large-scale studies are warranted for a further validation of modern experimental therapies such as hepatocyte or stem cell transplantation and novel therapeutic strategies targeting acetaminophen intoxication and/or HE before the current problems are overcome and a consensus is achieved for a clinical appliance.

REFERENCES

1. Cao Y, Zhang B, Lin R, et al. Mesenchymal stem cell transplantation for liver cell failure: a new direction and option. *Gastroenterol Res Pract*. 2018;2018:9231710.
2. Blachier M, Leleu H, Peck-Radosavljevic M, et al. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol*. 2013;58:593–608.
3. Bernal W, Lee WM, Wendon J, et al. Acute liver failure: a curable disease by 2024? *J Hepatol*. 2015;62 (S1):S112–S120.
4. Devarbhavi H, Patil M, Reddy VV, et al. Drug-induced acute liver failure in children and adults: results of a single center study of 128 patients. *Liver Int*. 2017;12:3218–3221.
5. Simpson KJ. How i diagnose and treat acute (fulminant) liver failure. *Eur Med J*. 2015:87–89.
6. Gotthardt D, Riediger C, Weiss KH, et al. Fulminant hepatic failure: etiology and indications for liver transplantation. *Nephrol Dial Transplant*. 2007;22(suppl 8):8–11.
7. Bernal W, Wendon J. Acute liver failure. *N Engl J Med*. 2013;369:2525–2534.
8. Singh T, Gupta N, Alkhouri N, et al. A guide to managing acute liver failure. *Cleve Clin J Med*. 2016;83:453–462.
9. Cardoso FS, Marcelino P, Bagulho L, et al. Acute liver failure: An up-to-date approach. *J Crit Care*. 2017;39:25–30.
10. Kim H, Kwon JH, Kim YH, et al. Favorable effect of corticosteroids in treating acute-on-chronic liver failure underlying chronic hepatitis B. *Hepatobiliary Pancreat Dis Int*. 2018;17:210–213.
11. Gustot T, Moreau R. Acute-on-chronic liver failure vs. traditional acute decompensation of cirrhosis. *J Hepatol*. 2018;69:1384–1393.
12. Zhao R, Wu W, Zhou Z, et al. Prognostic utility of novel biomarkers in acute-on-chronic liver failure (ACLF) associated with hepatitis B: a multicenter prospective study. *Hepatol Res*. 2018. Doi: 10.1111/hepr.13251. [Epub ahead of print].
13. Rodrigues-Filho EM, Fernandes R, Garcez A. SOFA in the first 24 hours as an outcome predictor of acute liver failure. *Rev Bras Ter Intensiva*. 2018;30:64–70.
14. Punzalan CS, Barry CT. Acute liver failure. *J Intensive Care Med*. 2016;31:642–653.
15. Hadem J, Tacke F, Bruns T, et al. Etiologies and outcomes of acute liver failure in Germany. *Clin Gastroenterol Hepatol*. 2012;10:664.e2–669.e2.
16. Trey C, Davidson CS. The management of fulminant hepatic failure. *Prog Liver Dis*. 1970;3:282–298.
17. Patton H, Misel M, Gish RG. Acute liver failure in adults: an evidence-based management protocol for clinicians. *Gastroenterol Hepatol (N Y)*. 2012;8:161–172.
18. Craig DGN, Lee A, Hayes PC, et al. Review article: the current management of acute liver failure. *Aliment Pharmacol Ther*. 2010;31:345–358.
19. O'Grady JG. Acute liver failure. *Postgrad Med J*. 2005;81:148–154.
20. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet*. 1993;342:273–275.
21. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. *Semin Liver Dis*. 1986;6:97–106.
22. Mochida S, Nakayama N, Matsui A, et al. Re-evaluation of the Guideline published by the acute liver failure study group

of Japan in 1996 to determine the indications of liver transplantation in patients with fulminant hepatitis. *Hepatol Res*. 2008;38:970–979.
23. Wlodzimirow KA, Eslami S, Abu-Hanna A, et al. Systematic review: acute liver failure—one disease, more than 40 definitions. *Aliment Pharmacol Ther*. 2012;35:1245–1256.
24. Reddy KR, Ellerbe C, Schilsky M, et al. Determinants of outcome among patients with acute liver failure listed for liver transplantation in the United States. Ourselin S, Joskowicz L, Sabuncu MR, Unal G, Wells W, editors. *Liver Transplant*. 2016;22:505–515.
25. Maher SZ, Schreibman IR. The clinical spectrum and manifestations of acute liver failure. *Clin Liver Di*. 2018;22:361–374.
26. Tujios SR, Lee WM. Acute liver failure induced by idiosyncratic reaction to drugs: Challenges in diagnosis and therapy. *Liver Int*. 2018;38:6–14.
27. Lee W. Acute Liver Failure. *Semin Respir Crit Care Med*. 2012; 33:36–45.
28. Trotter JF. Practical management of acute liver failure in the intensive care unit. *Curr Opin Crit Care*. 2009;15:163–167.
29. Fontana RJ, Ellerbe C, Durkalski VE, et al. Two-year outcomes in initial survivors with acute liver failure: results from a prospective, multicentre study. *Liver Int*. 2015;35:370–380.
30. Wang D-W, Yin Y-M, Yao Y-M. Advances in the management of acute liver failure. *World J Gastroenterol*. 2013;19:7069–7077.
31. Larson AM. Acute liver failure. *Disease-a-Month*. 2008;54: 457–485.
32. Buechter M, Manka P, Heinemann FM, et al. Potential triggering factors of acute liver failure as a first manifestation of autoimmune hepatitis-a single center experience of 52 adult patients. *World J Gastroenterol*. 2018;24:1410–1418.
33. Anastasiou OE, Dogan-Cavus B, Kucukoglu O, et al. Corticosteroid therapy improves the outcome of autoimmune hepatitis-induced acute liver failure. *Digestion*. 2018;98:104–111.
34. Polson J, Lee WM. American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. *Hepatology*. 2005;41:1179–1197.
35. Kuna L, Bozic I, Kizivat T, et al. Models of drug induced liver injury (DILI)—current issues and future perspectives. *Curr Drug Metab*. 2018;19:830–838.
36. Singanayagam A, Bernal W. Update on acute liver failure. *Curr Opin Crit Care*. 2015;21:134–141.
37. Yan M, Huo Y, Yin S, et al. Mechanisms of acetaminophen-induced liver injury and its implications for therapeutic interventions. *Redox Biol*. 2018;17:274–283.
38. Reuben A, Koch DG, Lee WM. Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a US multicenter, prospective study. *Hepatology*. 2010;52:2065–2076.
39. Alam S, Lal BB. Metabolic liver diseases presenting as acute liver failure in children. *Indian Pediatr*. 2016;53:695–701.
40. Li H, Byers HM, Diaz-Kuan A, et al. Acute liver failure in neonates with undiagnosed hereditary fructose intolerance due to exposure from widely available infant formulas. *Mol Genet Metab*. 2018;123:428–432.
41. Dias Costa F, Moinho R, Ferreira S, et al. Acute liver failure related to inherited metabolic diseases in young children. *An Pediatr (Barc)*. 2018;88:69–74.
42. Grupchev DI, Radeva MN, Georgieva M, et al. In vivo confocal microstructural analysis of corneas presenting Kayser-Fleischer rings in patients with Wilson's disease. *Arq Bras Oftalmol*. 2018;81:137–143.
43. Pandey N, John S. Kayser-Fleischer Ring. *StatPearls*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29083643.
44. Whitehouse T, Wendon J. Acute liver failure. *Best Pract Res Clin Gastroenterol*. 2013;27:757–769.
45. Huang Y, Takatsuki M, Soyama A, et al. Living donor liver transplantation for wilson's disease associated with fulminant hepatic failure: a case report. *Am J Case Rep*. 2018;19:304–308.
46. Yoshihara M, Mayama M, Ukai M, et al. Fulminant liver failure resulting from massive hepatic infarction associated with hemolysis, elevated liver enzymes, and low platelets syndrome. *J Obstet Gynaecol Res*. 2016;42:1375–1378.
47. Escudié L, Francoz C, Vinel J-P, et al. Amanita phalloides poisoning: reassessment of prognostic factors and indications for emergency liver transplantation. *J Hepatol*. 2007;46:466–473.
48. Kim Y-J, Lee HJ, Ryoo SM, et al. Prognostic value of decision criteria for emergency liver transplantation in patients with wild mushroom induced acute liver injury. *Hepatobiliary Pancreat Dis Int*. 2018;17:210–213.
49. Kieslichova E, Frankova S, Protus M, et al. Acute liver failure due to amanita phalloides poisoning: therapeutic approach and outcome. *Transplant Proc*. 2018;50:192–197.
50. Parekh J, Matei VM, Canas-Coto A, et al. Acute Liver Failure Study Group. Budd-chiari syndrome causing acute liver failure: a multicenter case series. *Liver Transpl*. 2017;23:135–142.
51. Chen B, Wang Y-H, Qian J-Q, et al. Human mesenchymal stem cells for hepatitis B virus-related acute-on-chronic liver failure: a systematic review with meta-analysis. *Eur J Gastroenterol Hepatol*. 2018;30:1224–1229.
52. Jayakumar S, Chowdhury R, Ye C, et al. Fulminant Viral Hepatitis. *Crit Care Clin*. 2013;29:677–697.
53. Suzuki T, Kawada J, Okuno Y, et al. Comprehensive detection of viruses in pediatric patients with acute liver failure using next-generation sequencing. *J Clin Virol*. 2017;96:67–72.
54. Shalimar, Sonika U, Kedia S, et al. Comparison of dynamic changes among various prognostic scores in viral hepatitis-related acute liver failure. *Ann Hepatol*. 2018;17:403–412.
55. Boni B, Amann CA. Exertional heat illness resulting in acute liver failure and liver transplantation. *J Spec Oper Med*. 2017;17:15–17.
56. Castro RRT de, Costa Filho R, Nóbrega ACL da. Fulminant liver failure in a street runner: effects of heat stroke. *Rev Assoc Med Bras*. 2018;64:208–211.
57. Farley KJ, Warrillow SJ. Acute liver failure. *Anaesth Intensive Care Med*. 2015;16:174–179.
58. Lee WM, Squires RH, Nyberg SL, et al. Acute liver failure: summary of a workshop. *Hepatology*. 2008;47:1401–1415.
59. Rolando N, Wade J, Davalos M, et al. The systemic inflammatory response syndrome in acute liver failure. *Hepatology*. 2000;32(pt 1):734–739.
60. McPhail MJW, Kriese S, Heneghan MA. Current management of acute liver failure. *Curr Opin Gastroenterol*. 2015;31:209–214.
61. Macdonald S, Mehta G, Jalan R. Acute liver failure. *Med (United Kingdom)*. 2015;43:683–685.
62. Habib S, Shaikh OS. Drug-induced acute liver failure. *Clin Liver Dis*. 2017;21:151–162.
63. Rubin JB, Hameed B, Gottfried M, et al. Acute Liver Failure Study Group. Acetaminophen-induced acute liver failure is more common and more severe in women. *Clin Gastroenterol Hepatol*. 2018;1:936–946.
64. Sintusek P, Kyrana E, Dhawan A. Value of serum zinc in diagnosing and assessing severity of liver disease in children with wilson disease. *J Pediatr Gastroenterol Nutr*. 2018;67: 377–382.
65. Korman JD, Volenberg I, Balko J, et al. Screening for Wilson disease in acute liver failure: a comparison of currently available diagnostic tests. *Hepatology*. 2008;48:1167–1174.
66. Bower WA, Johns M, Margolis HS, et al. Population-based surveillance for acute liver failure. *Am J Gastroenterol*. 2007;102:2459–2463.
67. Krag M, Perner A, Wetterslev J, et al. Stress ulcer prophylaxis in the intensive care unit: an international survey of 97 units in 11 countries. *Acta Anaesthesiol Scand*. 2015;59:576–585.
68. Moore JK, Love E, Craig DG, et al. Acute kidney injury in acute liver failure: a review. *Expert Rev Gastroenterol Hepatol*. 2013;7:701–712.
69. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, Clinical practice guidelines panel, Wendon, J, Panel members, Cordoba J, Dhawan A, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. *J Hepatol*. 2017;66: 1047–1081.
70. Flamm SL, Yang Y-X, Singh S, et al. AGA Institute Clinical Guidelines Committee. American Gastroenterological

Association Institute Guidelines for the diagnosis and management of acute liver failure. *Gastroenterology*. 2017;152: 644–647.
71. Bernal W, Auzinger G, Dhawan A, et al. Acute liver failure. *Lancet*. 2010;376:190–201.
72. Khan R, Koppe S. Modern management of acute liver failure. *Gastroenterol Clin North Am*. 2018;47:313–326.
73. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the study of liver diseases position paper on acute liver failure 2011. *Hepatology*. 2012;55:965–967.
74. Sales I, Dzierba AL, Smithburger PL, et al. Use of acetylcysteine for non-acetaminophen-induced acute liver failure. *Ann Hepatol*. 2013;12:6–10.
75. Rabinowich L, Wendon J, Bernal W, et al. Clinical management of acute liver failure: Results of an international multicenter survey. *World J Gastroenterol*. 2016;22:7595–7603.
76. Carrion AF, Martin P. Non-intensive care unit management of acute liver failure. *Clin Liver Dis*. 2018;22:389–401.
77. Liu J, Ghaziani TT, Wolf JL. Acute fatty liver disease of pregnancy: updates in pathogenesis, diagnosis, and management. *Am J Gastroenterol*. 2017;112:838–846.
78. Ronen J, Shaheen S, Steinberg D, et al. Acute fatty liver of pregnancy: a thorough examination of a harmful obstetrical syndrome and its counterparts. *Cureus*. 2018;10:e2164.
79. Belongia EA, Costa J, Gareen IF, et al. NIH consensus development statement on management of hepatitis B. *NIH Consens State Sci Statements*. 2008;25:1–29.
80. Jochum C, Gieseler RK, Gawlista I, et al. Hepatitis B-associated acute liver failure: immediate treatment with entecavir inhibits hepatitis B virus replication and potentially its sequelae. *Digestion*. 2009;80:235–240.
81. Tillmann HL, Zachou K, Dalekos GN. Management of severe acute to fulminant hepatitis B: to treat or not to treat or when to treat? *Liver Int*. 2012;32:544–553.
82. Jochum C, Maischack F, Anastasiou OE, et al. Treatment of fulminant acute Hepatitis B with nucles(t)id analogues is safe and does not lead to secondary chronification of Hepatitis B. *Z Gastroenterol*. 2016;54:1306–1311.
83. Smith MR, Davis RL. Mycetismus: A review. *Gastroenterol Rep*. 2016;4:107–112.
84. Santi L, Maggioli C, Mastroroberto M, et al. Acute liver failure caused by amanita phalloides poisoning. *Int J Hepatol*. 2012;2012:487480.
85. French LK, Hendrickson RG, Horowitz BZ. Amanita phalloides poisoning. *Clin Toxicol (Phila)*. 2011;49:128–129.
86. Enjalbert F, Rapior S, Nouguier-Soulé J, et al. Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol*. 2002;40:715–757.
87. Li Y, Mu M, Yuan L, et al. Challenges in the early diagnosis of patients with acute liver failure induced by amatoxin poisoning: two case reports. *Medicine (Baltimore)*. 2018;97:e11288.
88. Ye Y, Liu Z. Management of Amanita phalloides poisoning: a literature review and update. *J Crit Care*. 2018;46:17–22.
89. Rifai K. Fractionated plasma separation and adsorption: current practice and future options. *Liver Int*. 2011;31(suppl 3): 13–15.
90. Őcze B, Fazakas J, Zádori G, et al. MARS therapy, the bridging to liver retransplantation - Three cases from the Hungarian liver transplant program. *Interv Med Appl Sci*. 2013;5:70–75.
91. Lodes U, Jacob D, Meyer F. Acute liver failure, acute-on-chronic liver failure, hepatorenal syndrome, hepatopulmonary syndrome and portopulmonary hypertension, artificial liver support on the ICU. *Zentralbl Chir*. 2017;142:275–286.
92. Hanish SI, Stein DM, Scalea JR, et al. Molecular adsorbent recirculating system effectively replaces hepatic function in severe acute liver failure. *Ann Surg*. 2017;266:677–684.
93. Bernal W, Williams R. Beyond KCH selection and options in acute liver failure. *Hepatol Int*. 2018;12:204–213.
94. Larsen FS, Schmidt LE, Bernsmeier C, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. *J Hepatol*. 2016;64:69–78.
95. McPhail MJW, Wendon JA, Bernal W. Meta-analysis of performance of Kings's College Hospital Criteria in prediction of outcome in non-paracetamol-induced acute liver failure. *J Hepatol*. 2010;53:492–499.
96. Shakil AO, Kramer D, Mazariegos GV, et al. Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. *Liver Transpl*. 2000;6:163–169.
97. Rutherford A, King LY, Hynan LS, et al. Development of an accurate index for predicting outcomes of patients with acute liver failure. *Gastroenterology*. 2012;143:1237–1243.
98. Speiser JL, Lee WM, Karvellas CJ. Predicting outcome on admission and post-admission for acetaminophen-induced acute liver failure using classification and regression tree models. Menezes GB, editor. *PLoS One*. 2015;10:e0122929.
99. Koch DG, Tillman H, Durkalski V, et al. Development of a model to predict transplant-free survival of patients with acute liver failure. *Clin Gastroenterol Hepatol*. 2016;14:1199.e2–1206.e2.
100. Rajaram P, Subramanian R. Management of acute liver failure in the intensive care unit setting. *Clin Liver Dis*. 2018;22:403–408.
101. Paschoal FM Jr, Nogueira RC, Oliveira ML, et al. Cerebral hemodynamic and metabolic changes in fulminant hepatic failure. *Arq Neuropsiquiatr*. 2017;75:470–476.
102. de-Lima-Oliveira M, Salinet ASM, Nogueira RC, et al. Intracranial hypertension and cerebral autoregulation: a systematic review and meta-analysis. *World Neurosurg*. 2018;113:110–124.
103. Ford RM, Sakaria SS, Subramanian RM. Critical care management of patients before liver transplantation. *Transplant Rev*. 2010;24:190–206.
104. Kodali S, McGuire BM. Diagnosis and management of hepatic encephalopathy in fulminant hepatic failure. *Clin Liver Dis*. 2015;19:565–576.
105. Amodio P. Hepatic encephalopathy: diagnosis and management. *Liver Int*. 2018;38:966–975.
106. Kok B, Karvellas C. Management of cerebral edema in acute liver failure. *Semin Respir Crit Care Med*. 2017;38:821–829.
107. Rajajee V, Williamson CA, Fontana RJ, et al. Noninvasive intracranial pressure assessment in acute liver failure. *Neurocrit Care*. 2018;29:280.
108. Paschoal FM, Nogueira RC, Ronconi K, et al. Multimodal brain monitoring in fulminant hepatic failure. *World J Hepatol*. 2016;8:915–923.
109. Shimono N, Ishibashi H, Ikematsu H, et al. Fulminant hepatic failure during perinatal period in a pregnant woman with Wilson's disease. *Gastroenterol Jpn*. 1991;26:69–73.
110. Chen N, Chen X, Ding X, et al. Analysis of the high incidence of acute kidney injury associated with acute-on-chronic liver failure. *Hepatol Int*. 2018;12:262–268.
111. Stravitz RT, Ellerbe C, Durkalski V, et al. Bleeding complications in acute liver failure. *Hepatology*. 2018;67:1931–1942.
112. Rajajee V, Fontana RJ, Courey AJ, et al. Protocol based invasive intracranial pressure monitoring in acute liver failure: feasibility, safety and impact on management. *Crit Care*. 2017;21:178.
113. Cai J, Zhang M, Han T, et al. Characteristics of infection and its impact on short-term outcome in patients with acute-on-chronic liver failure. *Medicine (Baltimore)*. 2017;96:e8057.
114. Woźnica EA, Inglot M, Woźnica RK, et al. Liver dysfunction in sepsis. *Adv Clin Exp Med*. 2018;27:547–551.
115. Zavala S, Arias M, Legua P. Fulminant streptococcal toxic shock syndrome. *J R Coll Physicians Edinb*. 2018;48:33–35.
116. Fujiwara K, Yasui S, Yonemitsu Y, et al. Analysis of infectious complications and timing for emergency liver transplantation in autoimmune acute liver failure. *J Hepatobiliary Pancreat Sci*. 2016;23:212–219.
117. Piano S, Brocca A, Mareso S, et al. Infections complicating cirrhosis. *Liver Int [Internet]*. 2018;38(suppl 1):126–133.
118. Anno T, Kaneto H, Shigemoto R, et al. Hypoinsulinemic hypoglycemia triggered by liver injury in elderly subjects with low body weight: case reports. *Endocrinol diabetes Metab case reports*. 2018;pii:17–0155.

119. Olivo R, Guarrera JV, Pyrsopoulos NT. Liver transplantation for acute liver failure. *Clin Liver Dis*. 2018;22:409–417.
120. Fontana RJ. Acute liver failure including acetaminophen overdose. *Med Clin North Am*. 2008;92:761–794.
121. Yang H-R, Thorat A, Jeng L-B, et al. Living donor liver transplantation in acute liver failure patients with grade iv encephalopathy: is deep hepatic coma still an absolute contraindication? a successful single-center experience. *Ann Transplant*. 2018;23:176–181.
122. Chao X, Wang H, Jaeschke H, et al. Role and mechanisms of autophagy in acetaminophen-induced liver injury. *Liver Int*. 2018;38:1363–1374.
123. Sun J, Wen Y, Zhou Y, et al. p53 attenuates acetaminophen-induced hepatotoxicity by regulating drug-metabolizing enzymes and transporter expression. *Cell Death Dis*. 2018;9:536.
124. Gong S, Lan T, Zeng L, et al. Gut microbiota mediates diurnal variation of acetaminophen induced acute liver injury in mice. *J Hepatol*. 2018;69:51–59.
125. Fitzpatrick E, Mitry RR, Dhawan A. Human hepatocyte transplantation: state of the art. *J Intern Med*. 2009;266:339–357.
126. Dhawan A, Puppi J, Hughes RD, et al. Human hepatocyte transplantation: current experience and future challenges. *Nat Rev Gastroenterol Hepatol*. 2010;7:288–298.
127. Lee CA, Sinha S, Fitzpatrick E, et al. Hepatocyte transplantation and advancements in alternative cell sources for liver-based regenerative medicine. *J Mol Med (Berl)*. 2018;96:469–481.
128. Habibullah CM, Syed IH, Qamar A, et al. Human fetal hepatocyte transplantation in patients with fulminant hepatic failure. *Transplantation*. 1994;58:951–952.
129. Soriano HE, Wood RP, Kang D-C, et al. Hepatocellular transplantation (HCT) via portal vein catheter in a patient with fulminant liver failure. † 746. *Pediatr Res*. 1996;39:127–127.
130. Fisher RA, Strom SC. Human hepatocyte transplantation: worldwide results. *Transplantation*. 2006;82:441–449.
131. Squires RH, Shneider BL, Bucuvalas J, et al. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr*. 2006;148:652–658.
132. da Fonseca Cardoso LM, Moreira LFP, Pinto MA, et al. Domino hepatocyte transplantation: a therapeutic alternative for the treatment of acute liver failure. *Can J Gastroenterol Hepatol*. 2018;2018:2593745.
133. Iansante V, Mitry RR, Filippi C, et al. Human hepatocyte transplantation for liver disease: current status and future perspectives. *Pediatr Res*. 2018;83 (1–2):232–240.
134. Anderson TN, Zarrinpar A. Hepatocyte transplantation: past efforts, current technology, and future expansion of therapeutic potential. *J Surg Res*. 2018;226:48–55.
135. Luo M, Liu H, Hu S-J, et al. Potential targeted therapies for the inflammatory pathogenesis of hepatic encephalopathy. *Clin Res Hepatol Gastroenterol*. 2015;39:665–673.
136. Lee G-H. Hepatic encephalopathy in acute-on-chronic liver failure. *Hepatol Int*. 2015;9:520–526.
137. Nardelli S, Ridola L, Gioia S, et al. Management of hepatic encephalopathy not responsive to first-line treatments. *Curr Treat Options Gastroenterol*. 2018;16:253–259.
138. Soria LR, Allegri G, Melck D, et al. Enhancement of hepatic autophagy increases ureagenesis and protects against hyperammonemia. *Proc Natl Acad Sci USA*. 2018;115:391–396.