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NARRATIVE REVIEW

Overview of acute liver failure in India

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Abstract
Acute liver failure (ALF) is an infrequent, but serious complication subsequent to severe acute liver injury (sALI) due to various hepatotoxic agents such as hepatotropic virus(es) and drugs such as anti-tubercular medications, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and anti-cancer and anti-epileptic therapy and due to metabolic and autoimmune disease flares. ALF after sALI presents with encephalopathy associated with prolonged international normalized ratio (INR). Mortality in ALF is high and ranges between 50% and 80%. Due to severe liver damage, multiple sequels consequent to hepatic dysfunction result in complications such as hyperammonemia that culminates in encephalopathy associated with cerebral edema; innate immune paralysis resulting in increased frequency of infections and endotoxemia causing decrease in systemic vascular resistance (SVR) and tissue hypoperfusion and damage-associated molecular patterns (DAMPs) released from damaged hepatic parenchyma inducing pro-inflammatory cytokine storm, which may cause other organ dysfunctions. Certain etiologies such as hepatitis E virus and hepatitis A virus-related ALF or paracetamol-ALF (hyper-acute presentation) have better survival than remaining causes. In addition, if etiology-specific treatment (antivirals for ALF related to hepatitis B virus (HBV) or Herpes simplex virus (HSV) or N-acetylcysteine for paracetamol) is available, then the outcome with treatment is better. About half of the patients can be salvaged with medical therapy. All patients need intensive care and organ support to provide time for the liver to regenerate. Various prognostic models to predict high probability of mortality have been described, which should be used to select patient early during the disease for liver transplantation, which is associated with high long-term survival in these sick patients. The Indian National Association for Study of the Liver (INASL) recommends the ALF-Early Dynamic (ALFED) model as a preferred prognostic model in the Indian scenario, where hepatitis viruses are a dominant etiology of ALF and occur on a naïve liver with good regenerative capacity.

Keywords Acute liver failure · Hepatitis viruses · Severe acute liver injury

Introduction

Patients with acute hepatitis due to various etiologies usually have a self-limiting course and most recover within four to six weeks of the onset of acute hepatitis illness, but those having persistent or progressive jaundice with coagulopathy (international normalized ratio [INR] > 1.5), but without encephalopathy, are recognized as severe acute liver injury (sALI) and may have variable prolonged course [1, 2]. Appearance of encephalopathy in such a patient within a few hours to days or weeks is termed as ALF (Fig. 1) [2]. Thus, acute liver failure (ALF) which is associated with a mortality of up to 50% to 75% is considered an uncommon and unpredictable clinical sequel of severe acute liver injury in an individual without any past history of liver disorders [1, 2]. Patients usually present with encephalopathy following ALI (development of jaundice) and coagulopathy (defined as INR > 1.5) is frequently seen [1]. With varying icterus-encephalopathy intervals (IEI), the etiology of ALF is geographically distinct.

Definition and epidemiology

Trey and Davidson in 1969 first defined ALF as "*appearance of encephalopathy within eight weeks of the onset of acute hepatitis in an individual without pre-existing liver*

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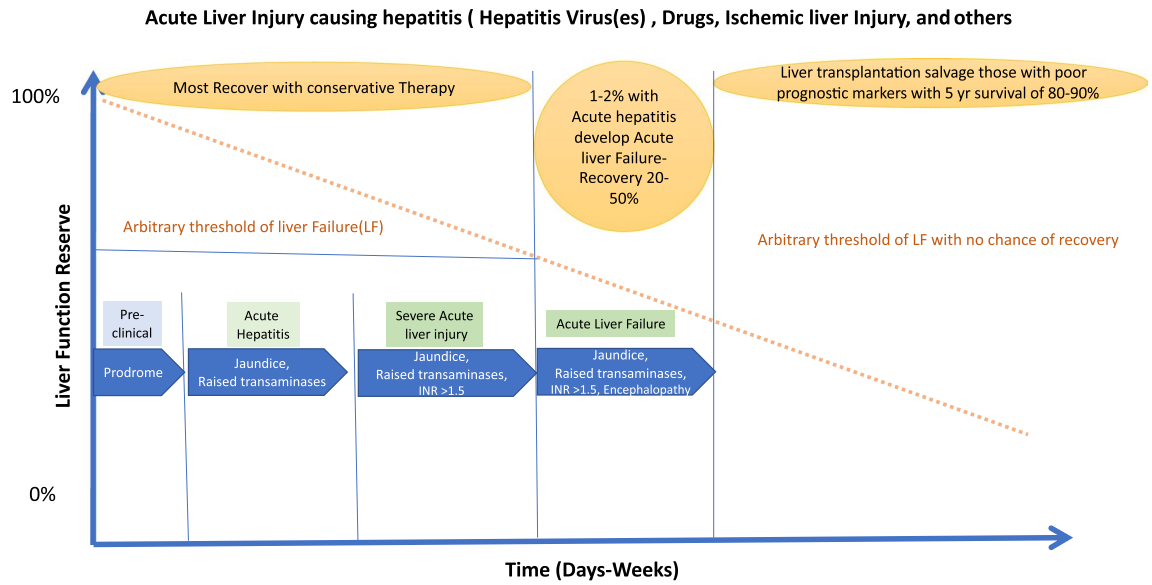

Fig. 1 The various forms of acute liver injury and severe acute live injury (sALI) and acute liver failure (ALF) with time dynamics

disease." However, over time, regional differences in etiology, natural course, complication and some demographic features in ALF were reported, resulting in variable definition of ALF [2–4]. Each definition included encephalopathy as an essential criterion, but some centers additionally included abnormal (defined as INR > 1.5) or prothrombin time (PT) prolongation by > 15 s over control or prothrombin activity < 40% [3, 4]. The essential difference in various definitions of ALF was "*the interval between the onset of acute hepatic illness and subsequent encephalopathy and varied from two to 26 weeks*" [2, 4]. In India, hepatitis virus(es) are the most frequent cause for ALF and encephalopathy occurred in all patients within four weeks of the onset of jaundice [2, 5]. The American Association for the Study of Liver Diseases (AASLD), however, defines ALF as encephalopathy ensuing within 26 weeks of the onset of acute hepatitis symptoms [3]. The recently published INASL consensus statement on ALF defines ALF as "*A clinical syndrome characterized by encephalopathy, jaundice and prolonged PT (INR > 1.5) developing in a patient without pre-existing liver disease within four weeks of the onset of symptoms. A few patients presenting with sALI mostly due to DILI may develop encephalopathy later than four weeks up to eight weeks*" [2]. Further, because the etiology of ALF is heterogenous in the west, all patients clinically do not have similar natural course and sub-classification of ALF depending upon the interval between onset of acute hepatitic illness and encephalopathy has been suggested by the British and French [2–4]. The French sub-classification categorizes ALF into (1) fulminant liver failure (when encephalopathy occurs within two weeks of the onset of jaundice) and (2) sub-fulminant (when encephalopathy occurs between two and 12 weeks of jaundice). The British sub-categorized it into three groups: (1) hyperacute liver failure (encephalopathy icterus interval seven days), (2) acute liver failure (encephalopathy icterus interval between seven days and four weeks) and (3) sub-acute liver failure (encephalopathy icterus interval within five to 24 weeks) [1, 2, 6, 7]. These regions noticed that those presenting with hyperacute or fulminant liver failure had better survival than the other ones and therefore sub-categorized them. Such events do influence on deciding high-risk patients for liver transplantation. However, in India, a large series have reported that the rapidity of onset of encephalopathy (hyperacute) and others had similar outcome probably due to homogeneous etiology. Therefore, in India, most patients are either hyperacute or acute without any difference in outcome and practically do not need any sub-categorization [2, 3, 7].

The epidemiology of ALF in India is unclear [2, 3]. There is no central registry in India for the collation of ALF frequency among patients with acute hepatitis and most data is compiled from individual centers. In addition, there is data from liver transplant (LT) centers in India regarding the number of transplants done for patients with ALF. However, there is no clarity regarding the total number of patients with ALF evaluated in LT centers as well as non-LT centers that have not published their results. During multiple epidemics of acute hepatitis documented and investigated in India, hepatitis E virus (HEV) was responsible for most epidemics and recently, small epidemics of hepatitis A virus (HAV) are reported due to increase in non-immune population (against HAV) among Indians, which may be attributed

to the improvement of hygiene, sewage disposal and use of non-contaminated water. During such epidemics, about 1% to 2% of the acute hepatitis patients develop ALF. Further, during the epidemics, pregnant females were identified to be at the highest risk of contracting the infection as well as increasing frequency of ALF markedly in up to about 20% of those with acute hepatitis [2, 3, 7].

Etiology

The differences in etiology of ALF among adults across the world are striking which influences their outcome (Tables 1 and 2) [1–7].

Hepatitis viruses

In India, viral etiology predominates, which is responsible for 90% of ALF cases (Table 2) [2, 5, 7, 8]. Various viral etiologies in order of frequencies, reported in published studies, include non A-non E in about 40% and HEV in approximately one-third, whereas HBV and HAV causing ALF are less frequent [2, 3, 5]. Among other causes for ALF, drugs, especially anti-tuberculosis drugs, account for 6% to 15% of the cases of ALF, whereas in the west, where safe drinking water is available, incidence of fecoorally transmitted viruses (HEV and HAV) is very low compared to developing nations, but not zero. Drugs and toxins are major attributes and acetaminophen overdose is the most commonly identified among these in the UK, the United States and Europe. ALF etiology in west is heterogenous (paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs], autoimmune hepatitis and metabolic diseases). Table 1 highlights the different etiologies of ALF across the world [2, 3, 5].

Etiology influences phenotypic presentation. Therefore, as described under definition of the ALF, the icterus-encephalopathy interval widely varies in regions with

Table 1 Etiological differences of acute liver failure regionally

Causes	India	USA	UK	France	Germany	Australia
Hepatitis virus(es)	80%–95%	25%–30%	15%–20%	53%	42%	48%
Type of virus(es) in chronological frequency	HEV, non A-E, HBV, HAV	Cryptogenic HBV, HAV	Cryptogenic HBV, HAV	HBV, Cryptogenic HAV	15%–20% Cryptogenic HBV, HAV, HEV	Cryptogenic HBV, HAV
Other viruses	1%–3%	5%	5%	1%–3%	1%	1%
Drugs	2%–11%	68%	70%–75%	30%	32%	42%
Type of drugs	ATT 70%–85%, CAM 2–5%	Paracetamol 50% NSAIDS 5%	Paracetamol 90%	Paracetamol and NSAIDS	Paracetamol and other drugs	Paracetamol and others
Miscellaneous causes	AIH flare, Wilsons, others 2%–3%	AIH, Wilsons, mushroom 2%–5%	AIH, Wilsons, AFLP 2%–5%	AIH, Wilsons 5%	AIH, Wilsons, Budd-Chiari etc 20%	Others AIH, Wilsons, Budd-Chiari 10%

Table 2 Etiology of acute liver failure in India with etiology-associated mortality

Causes of ALF	Proportion of patients
Hepatitis A virus	2%–39% (low mortality, about 45%)
Hepatitis E virus	15%–40% (low mortality, about 45%)
Hepatitis B virus	3%–14% (high mortality, about 70%)
Hepatitis C virus	Not reported
Non A-non E virus	15%–47% (high mortality, about 70%)
Drugs	5%–15% (predominantly anti-tuberculosis drugs, 60%–70%), complementary alternative medicines (CAMs)-mortality, 70%

NB:

Hepatitis virus(es): associated with about 90% of ALF

Drugs: various hepatotoxic drugs cause ALF in 5%–15%; paracetamol is an extremely infrequent cause

Rat poison containing yellow phosphorus recently described to be frequent cause of ALF in South India

Acute fatty liver of pregnancy, Wilson's disease, autoimmune hepatitis, metabolic liver diseases and hepatic venous outflow obstruction are very infrequent causes for ALF in India

etiological differences and a global consensus on its definition is therefore not available. Recently, irrespective of the region, various drug-induced acute liver injury (DILI) cases are being reported and some of these with ALF.

Drugs and complementary alternative medicines (CAM)

Recently, prospectively collected data from 2013 to 2018 was published by the Indian DILI network ($n = 1288$) [9] and the commonest causes for DILI in order were anti-tuberculosis drugs (combined ATD, 46.4%), CAM, 13.9%, anti-epileptic drugs (AED, 8.1%), non-ATD antimicrobials (6.5%), anti-metabolites (3.8%), anti-retroviral drugs (ART, 3.5%), NSAIDs, 2.6%, hormones (2.5%) and statins (1.4%). Among DILI patients, approximately 10% had or progressed to ALF and among these ($n = 124$), the most frequent etiology was anti-tubercular drugs (63%), followed by CAM (12.1%), AED (8.1%), other drugs used for central nervous system disorders (3.2%), dapsone (2.4%), ART (3.2%) and infrequently due to other drugs (for example, chemotherapeutic agents, hormone, methotrexate, NSAID and statins [5%]). The mortality rate of DILI-related ALF was 64.8%, whereas overall mortality was reportedly 12.3% [9]. ATD and CAM attributing to DILI were unique to India, being responsible as the commonest causes for DILI as well as DILI-ALF. Unlike western studies, age and gender were not identified as risk factors in the above study, rather DILI was reported predominantly among young males; however, DILI-ALF was predominantly seen among females. CAM also have been reported to be among the not-so-infrequent cause for DILI from countries including Spain (3.4%), the US (16.1%) and Iceland (16%) [10]. In these countries, CAM is often consumed as a weight-reducing agent available as dietary supplements, whereas in India, CAM is more often used for various ailments such as dermatological problems, arthritis and many chronic disorders as well as in advanced cancers (particularly in rural India and expense of modern medication or treatments) and for general well-being. However, recently from the US and Iceland, ayurvedic drug-induced DILI has been reported, showing a mixed pattern (hepatitic and cholestatic) of liver injury, which recovered within one to five months, but ALF due to ayurvedic medicines from these countries are yet to be reported [10, 11]. A recent case series and review on ayurvedic drug–induced DILI from the US mentions that consumption of ayurvedic medicine in the US has significantly increased by 57% from 2002 to 2021 [11]. The later report implicated Giloy Kwath (*Tinospora cordifolia*), a combination of Manjishthadi Kwatham and Aragwadhadi Kwatham (containing 52 and 10 individual plant extracts, respectively) and Kanchnar Guggul (containing 10 individual plant extracts) as the ayurvedic medicine causing DILI in the said case series. Ashwagandha (root of *Withania somnifera*), another ayurvedic therapy used for mood elevation and alleviation of chronic fatigue, has also been reported to cause DILI from Japan and Iceland [10].

The CAM-induced ALF is diagnosed as described by the Indian Network of Drug-Induced Liver Injury (IN-DILI) [9]. Ingestion of the CAM, which also included giloy, with the following criteria was used by IN-DILI to diagnose DILI as well as sever DILI: (a) ingestion of CAM resulting in recent onset abnormalities in liver biochemistry tests (bilirubin of at least 2 mg/dL or symptoms of liver injury with aspartate amino transferase (AST) or alanine amino transferase (ALT) > 3 times the upper limit of normal or alkaline phosphatase > 2 times the upper limit of normal) or (b) AST or ALT > 5 times the upper limit of normal without symptoms and exclusion of other competing causes for liver injury, including viral and autoimmune by appropriate serological testing and imaging studies. Severe disease was defined using international DILI expert working group criteria, i.e., bilirubin > 2 g/dL and INR > 1.5 with ascites or encephalopathy or death. Patterns of liver injury were classified as hepatocellular, cholestatic and mixed based on the R value of $> 5, \leq 2, \geq 2$, and ≤ 5, respectively, where $R = (\text{AST or ALT / ULN}) / (\text{ALP / ULN})$. Jaundice was defined as clinically apparent jaundice [9].

Other causes

Among rare causes for ALF are Wilson's disease, acute fatty liver of pregnancy, autoimmune hepatitis, amanita poisoning and Budd-Chiari syndrome [1, 2]. Rat poisons that contain yellow phosphorous (3% phosphorous,15 g) are accessible as a rodenticide in rural south India and its accidental or suicidal consumption causes ALF [2]. Among 450 patients with rat poison ingestion, 57% had ALF with a mortality in one-third [12]. This study also suggested a promising role of standard volume plasma exchange in them.

Influence of etiology on mortality

In a report ($n = 1462$) of consecutive ALF over 30 years, the survival in HEV-ALF (55.1%) was significantly higher ($p < 0.001$) than ALF due to other etiologies (ATD-induced DILI, 30.0%; non-A-non-E, 38.1%; HBV, 35.9%). There were no significant differences in survival in the later groups although there was a trend towards improved survival in HEV-ALF over the past three decades (1986–1995, 50%; 1996–2005, 54.9%; 2006–2015, 61.5%) [13].

Etiology also has been found to influence the mortality frequency in ALF. In the UK, the paracetamol-induced ALF with hyperacute presentation has been reported to have about 60% to 70% survival and in India, the HEV and HAV-induced ALF have been reported to have survival in more than 50% of the patients with ALF [6, 13].

ALF mimics [2, 14]

Several tropical infections prevalent in India often present similarly as ALF. These groups of patients characteristically may be febrile and have jaundice and altered sensorium with hyper-transaminesemia (usually less than 10 times upper limit of normal (ULN), about two to three times ULN and deranged INR). These patients have a palpable liver with low-grade non-progressive encephalopathy and a definitive treatment may improve outlook in contrast to viral hepatitis-induced ALF (in whom the liver is shrunken due to massive/sub-massive necrosis). Tropical infections such as malaria, dengue, enteric fever, leptospirosis and scrub typhus should be evaluated depending on the epidemiological prevalence. Their clinical feature and diagnostic approach have been depicted in Table 3. HLH is an uncommon, but potentially fatal complication and often encountered in adults as secondary HLH. Persistent fever, splenomegaly, jaundice and the pathologic finding of hemo-phagocytosis and often in association with EBV infection need to be diagnosed early [14].

During the coronavirus disease (COVID-19) pandemic, various reports documented acute liver injury in the form of elevated transaminases and a large series from the United States reported a frequency of 6.4% of COVID patients with sALI. Most of these patients also had severe respiratory and renal involvement with poor outcome [15]. Even case reports of overt ALF have been reported due to COVID-19 infections [16, 17].

Pathogenesis [2, 18–21]

After severe acute liver injury in ALF, irrespective of etiology, four major pathogenetic events drive the clinical events and natural course of the disease [2, 7, 21]. These pathogenetic events are depicted in Fig. 2. These four pathogenetic events include (1) rapid loss of hepatocyte function resulting in the absence of ureagenesis from gut-derived ammonia causing

Table 3 Acute liver failure mimics

Disease	Clinical and laboratory distinctiveness	Diagnostic test
Severe falciparum malaria	-Fever and chills -Hepatosplenomegaly -Altered sensorium, seizure -Anemia-hemolysis -Hemoglobinuria -Renal failure -Shock can be present -Unconjugated, hyperbilirubinemia -Mild increase in AST/ALT with normal INR	-Peripheral blood smear for malaria parasite -Quantitative buffy coat test -Rapid diagnostic kit (ICT) -Combination of tests can detect with a sensitivity and specificity > 95%
Dengue fever	-High-grade persistent fever, headache, retro-orbital pain -Myalgia, arthralgia, rash -Skin and mucosal bleeds -Rise in hematocrit (dengue hemorrhagic fever-hypotension, wide pulse pressure < 20 mm Hg) OR -Complications such as encephalitis, myocarditis, hepatitis, renal failure, ARDS (dengue shock syndrome) -Mild rise in bilirubin, AST/ALT raised 5–20 times, AST > ALT -Thrombocytopenia -Evidence of muscle injury raised CPK	-NS1 antigen detection -IgM, IgG dengue serology
Leptospirosis	-Fever, headache, myalgia, abdominal pain, conjunctival suffusion, transient skin rash -Severe form, i.e. Weil's disease, with jaundice, proteinuria, hematuria, acute kidney injury, pulmonary hemorrhages, ARDS, myocarditis and hepatomegaly	-Raised CPK levels -Serological test, microscopic agglutination test, I -IgM ELISA
Scrub typhus	-Prolonged fever, headache and myalgia, breathing difficulty, delirium, cough, jaundice -Hepatomegaly -Characteristic rash: eschar early in disease -Jaundice: hepatocellular, AST/ALT raised < upper limits of normal -Normal INR	-Indirect fluorescent antibody: "gold standard" -ELISA -IgG and IgM antibodies: sensitivity and specificity > 90%

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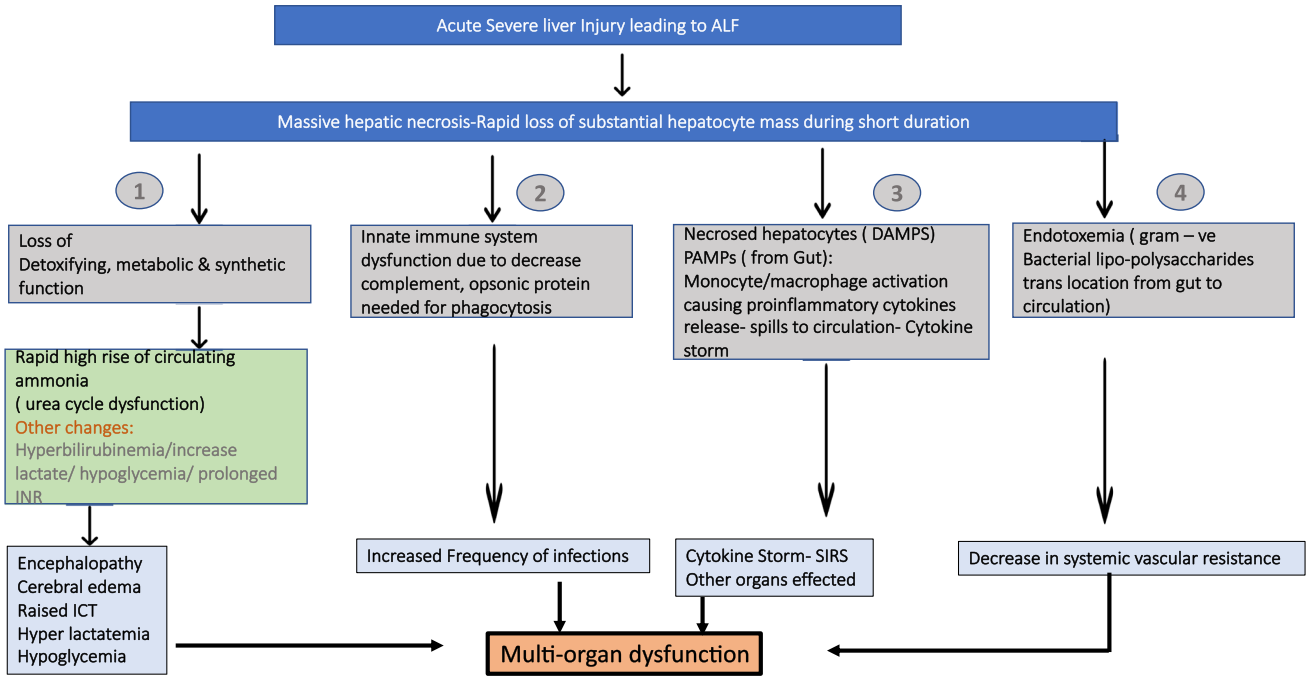


Fig. 2 Severe liver injury (sALI) leading to acute liver failure (ALF) resulting in onset of pathogenic drivers responsible for phenotypic clinical manifestations in ALF describing each form of pathogenesis correlating with clinical phenotypes: (1) detoxifying dysfunction resulting in hyper ammonemia. (2) Innate immune paralysis causing frequent sepsis. (3) Induction of pro-inflammatory cytokine storm through DAMPS and PAMPS contributing to multi-organ failure. (4) Endotoxemia causing induction of nitric-oxide production and decrease in systemic vascular resistance and relative hypovolemia

hyperammonemia, a major neurotoxin in ALF, compromised glycogen storage with reduced neo-glucogenesis manifesting as hypoglycemia and decreased synthetic function with resultant coagulation abnormalities-prolonged INR; (2) compromised innate immune system through decreased synthesis of opsonic proteins needed for phagocytosis, decrease in complement synthesis, increase in bacterial translocation from the gut to systemic circulation and resultant increase in frequency of infection perpetuating the deteriorating natural course of the disease; (3) the release of damage-associated pathogenic molecules (DAMPs) such as HMGB (high mobility group protein—a chaperon protein needed for transcription), DNA from hepatocyte and its coating protective proteins histones, which are immunogenic and result in macrophage, neutrophilic and monocyte activation with resultant increase in various pro-inflammatory cytokines and chemokines leaking to systemic circulation with resultant features of systemic inflammatory response syndrome (SIRS) and imbalance between SIRS and CARS (compensatory anti-inflammatory response), which subsequently also contribute to increased frequency of sepsis in ALF and (4) loss of resident macrophage (Kupffer's cell), which causes increased endotoxins leak into circulation (endotoxins are the lipopolysaccharide membrane constituents of gram-negative bacteria in the gut that are normally scavenged in the liver) and endotoxins induce nitric oxide synthase, which increase circulating nitrates causing vasodilatation with relative hypovolemia and decrease perfusion to vital organs and therefore, the maintenance of mean arterial pressure (MAP) in ALF is an important management strategy. The combination and interplay of these four pathogenetic drivers results in multi-organ dysfunction and mortality. Managing the resultant effects of these pathogenic drivers is the mainstay of management in ALF.

However, encephalopathy, cerebral edema and raised intra-cranial hypertension in ALF are major clinical events in ALF, which is responsible for a majority of deaths in ALF. Ammonia has been implicated as a major neurotoxin in ALF [18, 19]. Further, hyperammonemia with resultant cerebral edema may be associated with loss of cerebral autoregulation perpetuating alteration in cerebral blood flow associated with intra-cranial hypertension. Additionally, cytokine storm and often super added sepsis add to these pathogenetic processes through increased cerebral inflammatory response (microglial proliferation), which with ammonia works synergistically deteriorating the brain dysfunction [2].

Role of ammonia [18–20]

Circulating ammonia is derived predominantly from the metabolism of glutamine in the enterocytes. Intestinal epithelium, which undergoes a rapid turnover, uses glutamine

as an important energy source. Intestinal epithelium contains glutaminase as well as glutamine synthase. Glutaminase converts glutamine to glutamate and ammonia, whereas some amount of ammonia is also generated by the gut flora (urease activity) and kidney (also contains glutaminase and glutamine synthase).

The circulating ammonia is partially excreted by the kidneys, used up by the muscles (also has glutamine synthase and glutaminase) to re-synthesize glutamine, but it is converted predominantly to urea (in periportal hepatocytes) as well as glutamine (by glutamine synthase in perivenular hepatocytes) in the liver. Brain, which also contains glutamine synthase as well as glutaminase, can synthesize glutamine from ammonia and also metabolize glutamine into glutamate and ammonia.

The predominant pathophysiology of mortality in ALF is cerebral herniation caused by alteration in astrocyte function and astrocyte swelling due to cerebral edema. These lead to intra-cranial hypertension. Other important mechanisms include (a) an alteration in cerebral energy balance, (b) oxidative and nitrosative stress and (c) defective astrocytic and neuronal protein expression, which affects their structure and function.

The ammonia levels at the time of admission seem to correlate with prognosis. In one of the larger studies, evaluating the role of ammonia in ALF has shown significantly higher median level of serum ammonia among the non-survivors compared to the survivors (174.7 vs 105.0 mmol/L; p, 0.001). The authors have also shown that an arterial ammonia level of > 124 mmol/L could predict mortality with 78.6% sensitivity and 76.3% specificity and 77.5% diagnostic accuracy [19].

Hyperammonemia can potentially cause worsening hepatic encephalopathy, seizures and central hypoventilation requiring advanced life support. Moreover, pH, presence of cerebral edema and arterial ammonia at admission were found as independent predictors of mortality (odds ratios 6.6, 12.6 and 10.9, respectively) [19]. Ammonia is also documented to result in functional disturbances in neutrophils (compromised oxidative burst and phagocytosis) and prevent regeneration of hepatocytes [2]. Due to hyperammonemia in ALF, muscle glutamine synthesis increases and this glutamine is further broken down by renal glutaminase to produce glutamate and ammonia and due to increased lactate in ALF, ammonia release to systemic circulation is increased by the kidney as a process of maintaining acid-base balance, which further perpetuates hyperammonemia [2].

Loss of cerebral auto regulation [2, 20]

In both human and animal models with ALF, cerebral blood flow (CBF) has been shown to be altered leading to cerebral congestion, resulting in cerebral edema. The physiological balance of CBF, which depends upon the metabolic need of the neurons and is region-specific, seems to be disturbed in ALF. This leads to alteration in intra-cerebral pressure and cerebral water content.

Cerebral autoregulation maintains CBF within physiological range across a mean arterial pressure of 65 to 140 mmHg. Once this homeostasis is lost, slight elevation or reduction in pressure can derange CBF and lead to an increase or decrease in CBF, respectively, resulting in cerebral edema or cerebral hypoxia. In advanced (grade 3 or 4) HE, global CBF seems to be reduced even at a physiological range of blood pressure.

Complications of ALF [2, 3, 7, 18]

Patients with ALF may develop various life-threatening complications, but their magnitude varies regionally.

a) Renal failure: In the western reports, renal failure in ALF was documented in 40% to 80% of ALF. NSAIDs and acetaminophen are the dominant cause for ALF in the west and these agents are well-known nephrotoxic agents. In contrast, hepatitis virus(es) being the most common cause for ALF in India do not cause direct nephrotoxicity and therefore, renal failure has been reported in about 10% of the patients [2, 3, 5]. The other causes associated with increased incidence of renal failure include amanita poisoning and trimethoprim-sulfamethoxazole toxicity.
b) Gastrointestinal bleed: Gastrointestinal (GI) bleed has been reported less frequently from all parts of the world, despite associated coagulation abnormality in these patients. The usual reported frequency of GI bleed in most series varied between 7% and 20% [2, 3].
c) Cerebral edema: Frequency of overt cerebral edema in ALF has been reported to be present in 58% of the Indian patients at hospitalization [16]. Eighty-two per cent of these patients with cerebral edema died in comparison to 44% mortality in those without it [7, 8]. Cerebral edema, irrespective of the region, was reported to be one of the main causes for death in ALF. Both from the east and from the west, cerebral edema has been reported more frequently as the encephalopathy grade worsens [2, 3, 6, 7]. Intracranial pressure estimation assesses the intra-cranial hypertension after cerebral edema. However, intra-cranial pressure assessment using invasive methods has been replaced with non-invasive methods such as optic nerve sheath diameter (ONSD) and trans-cranial Doppler due to complications such as bleeding and infection associated with the former technique [2]. With the wide availability of such methods, the presence of

intra-cranial hypertension due to cerebral edema has been documented in all patients with ALF irrespective of the grades of encephalopathy [2, 3]. However in the west, over the years, with improvement in awareness about ALF, early referral to tertiary care center and improved intensive unit care, frequency of cerebral edema in the west is being reported to be less frequent than in former years [3].

d) Sepsis: Infections in ALF are frequent and reported from the west and India both [2, 3, 5, 6, 18]. As described under the section "Pathogenesis," immune-compromise results in both systemic and local infections such as pneumonitis as well as other site sepsis. Infection in these occurs very early in the course of the disease. The incidence of infection in the authors' experience, from a single center in India, is around 55%, the most common site of infection is the respiratory tract and the commonest organisms are gram-negative bacilli [2, 3, 5, 7, 8]. A quarter of patients in the series reported by the author had fungal infections as well [7]. From the UK, the report on ALF in early series identified that about 90% of their patients develop infection, which included bacterial sepsis in 80% and 32% had fungal infection [7]. In more recent reports, the predominant organisms reported from the west are gram-negative, but the initial reports from the UK reveal that the gram-positive organisms were isolated more frequently [21, 22].

Gender, pregnancy and pediatric acute liver failure [2, 3, 7, 23]

All over the globe in ALF, females predominate except in Japan, where the sex distribution is even between the two genders. Despite the fact that the etiology across the region is distinct, the predilection of female sex to develop ALF remains unclear. In India, as described earlier, hepatitis virus(es) are the major etiological agents particularly HEV. Various epidemiological as well as sporadic studies reveal that pregnant females are more prone than non-pregnant females and males to contact HEV infection and also develop severe liver diseases than similar male and non-pregnant female patients [7, 9]. Further, it is believed that pregnant women with ALF than non-pregnant women and males are more sicker with higher complication rates and mortality. However, the later conjecture was not evidence-based and a large study on pregnant ALF due to viral hepatitis from India disproved this conjecture indicating that in India pregnant females with ALF (except in acute fatty liver of pregnancy or severe pre-eclamptic toxemia-induced ALF) do not benefit from the termination of pregnancy [23].

There are few pregnant ladies developing ALF in the west and therefore do not constitute a major problem in management. In India, about 60% of the females with ALF in the child-bearing age are pregnant, whereas the fertility rate among similar population in general is 2.9% [2, 3, 7]. It is believed that pregnancy is an immuno-compromised state with predilection to contact various infections and manifest usually in more severe form [24].

Pregnancy as a predisposition to ALF in India could be due to (1) large pregnant population (3%), (2) unavailability of potable drinking water and (3) predilection of pregnant females to contract HEV infection. Hepatitis E virus is regarded as an important cause for severe liver disease across the globe, where > 70% of the global population resides. The Global Disease Burden study by the World Health Organization identified approximately 3.7 million people who are infected by HEV annually and 70,000 of them die due to HEV-induced severe liver disease of whom a large proportion are pregnant [25].

Acute fatty liver of pregnancy (AFLP) on the other hand is more frequent in the west than in India [2, 3, 7]. Ending pregnancy is needed for improving prognosis in AFLP. But, termination of pregnancy may not be appropriate in those with HEV-ALF, because (1) HEV ALF, in comparison to other causes for ALF, has the lowest mortality [3] and (2) the mortality rates of ALF-HEV with pregnancy, ALF-HEV in females without pregnancy and males with ALF-HEV are similar and not higher, indicating that during pregnancy, once ALF develops, does not influence the natural course [25–29]. Genotypes 1 and 2 of hepatitis E virus are prevalent in hyper-endemic regions, where the reservoir for HEV seems to be human and causes outbreaks, sporadic acute hepatitis, acute liver failure and acute-on chronic liver failure [26]. Genotypes 3 and 4 are more prevalent in the US, Europe and Japan, where the reservoir seems to be represented by pigs and the zoonotic transmission is considered to be the cause for infection of human beings, leading to autochthonous acute HEV. Genotypes 3 and 4 have not been reported to be associated with severe liver disease and most cases appear to represent sub-clinical infection [26]. The details of ALF and pregnancy have been described in a distinct article in the present issue.

Data on pediatric ALF (PALF) in India is scarce and predominantly reported from the tertiary care centers [29]. Briefly, as reported by various centers that have been provided in details in the INASL consensus document on ALF [29], the predominant etiologies of PALF as reported are hepatitis virus(es); hepatitis A virus and mixed hepatitis E and A viral infection (46% to 94%) and indeterminant causes (6% to 22%). However, herpes simplex and cytomegalo virus–induced ALF as well as metabolic liver diseases have been infrequently described. In younger children with high bilirubin, lower synthetic dysfunction, low sugar and

non-glucose-reducing substances in urine indicate metabolic liver disease as a cause in children. In such children, history of consanguinity in parents and repeated previous history of abortion in mothers usually exist. Such children usually manifest liver dysfunction within a few months of birth and tend to have longer interval from jaundice to encephalopathy and much higher bilirubin, but lower transaminases, gamma-glutamyl transferases (GGT) and INR than the viral causes for ALF. Infrequently hemophagocytic lymphohistiocytosis (HLH) subsequent to viral infection also has been described. Other possible causes such as Wilson's disease, ATD, anti-epileptics and autoimmune diseases also have been implicated in causing PALF.

INASL consensus states that "the recognition of encephalopathy may be difficult in children and ALF should be considered in a young child with coagulopathy, which is not correctable with vitamin K. An INR> 2.5 even without high bilirubin or transaminase should also be considered to be ALF" [29].

Outcome

The etiology of ALF, which is regionally varied, influences outcome, particularly in the west where the etiology is heterogenous. Paracetamol is a major cause for ALF in the west. Paracetamol-induced ALF presents rapidly (hyperacute) with a spontaneous survival rate of 64%, which is significantly higher than similar outcome due to other causes including ALF due to idiosyncratic drug toxicity (spontaneous survival in 20% of cases) [3, 6, 7]. However, paracetamol-induced ALF may progress very rapidly in some. The paracetamol being the frequent ecology in the west constitutes the bulk of all ALF patients in these regions and therefore, total deaths due to paracetamol toxicity exceed all other diagnoses. Nearly one-third of these patients who develop encephalopathy die. Paracetamol overdose, whether suicidal or unintentional, presenting with ALF has similar outcomes [2, 3].

In India, acetaminophen overdose-induced ALF is infrequent. The drug-induced ALF is due to anti-tuberculosis therapy (ATT). The mortality in ATT-ALF has been reported to be 70% [9, 27]. In India, about 90% to 95% of ALF are due to hepatitis viruses (homogeneous etiology) [2, 3, 7]. ATT-induced ALF constitutes about 6% to 15% of all ALFs [5]. Therefore, the etiology could not be identified as an independent predictor of mortality [3, 7, 8]. However, when HEV was compared separately with each individual etiology such as HBV ALF, ATT-induced ALF and non-A-non E-ALF, Wilson's disease-associated ALF and autoimmune ALF, the survival frequency among HEV was reported to be better than other etiologies [2, 3, 28]. These survival frequencies reported are transplant-free survivals. Liver transplantation is an established therapy in end-stage liver disease and with transplantation, overall survival exceeds 75% [2, 3, 29].

Causes for death in ALF

Major complications in ALF usually associated with death include cerebral edema, infections, seizures, bleeding due to coagulopathy and renal failure [2, 3]. These events infrequently get further aggravated by electrolyte and acid base imbalance and hypoglycemia [2, 3, 21].

Cerebral edema and herniation are the commonest causes for mortality in ALF [2, 7, 8]. Data suggests that cerebral edema is relatively uncommon in recent years compared to older studies, but this may reflect earlier admission to hospital and better ICU care [2, 29].

The management strategies are directed towards preventing and treating these complications as these develop. The management of ALF has been discussed in detail in a separate article of this issue and therefore, details of management are not provided in this article.

Management [29, 30]

ALF is a result of severe acute liver injury (sALI) and occurs on a naïve liver in most patients. Having immense regenerative capacity such as liver injuries is potentially reversible without sequels. However, the regenerative process takes some arbitrarily variable duration, during which as explained in the "Pathogenesis" section (severe hepatocyte loss with loss of their function, cytokine storm, innate immune system paralysis and endotoxemia-induced decrease in SVR), the pathogenetic drivers may result in life-threatening complication. Therefore, the basic concept in managing ALF lies in preventing death and provides various organ supports as and when necessary to provide time for the liver to regenerate resulting in spontaneous recovery. These complications may be seen during presentation or may ensue subsequently. These may occur in isolation or in combination. Management of every complication is crucial to improving the overall outcome. Although encephalopathy and cerebral edema are among the commonest presenting features, complications such as sepsis, AKI, and GI bleed may worsen cerebral edema and lead to death. However, all patients with ALF may not recover with medical management and some may not have adequate hepatic regeneration with a progressive deterioration. Identification of those unlikely to improve with medical management early during the

natural course of the disease, provides opportunity to subject them to liver transplant with which about 75% to 80% of such sick patients survive in the long term [29]. Therefore, prognostic models to identify patients with high probability of mortality have been developed and used in day to day practice [29]. In this issue of the *Journal*, management of ALF has been dealt in a separate article. The basic management concepts are provided in Table 4.

All ALF patients should be managed in intensive care units (ICU). The basic concept of management is providing various organ supports as and when needed. Delay in starting therapy leads to poor outcome. Various complications and management strategies targeted to treat these patients are important components of medical management. The medical management described below is an excerpt from the INASLs consensus recommendations [29]. The evaluation for complications and essential management strategy in brief are provided in Table 5.

Management of encephalopathy and cerebral edema [3, 7, 19, 29, 30]

Neurologic support

Patients should be kept in 20° to 30° head-up tilt to facilitate venous drainage. Stimulus to aggravate ICP should be avoided. Control of agitation is important because it may lead to the elevation of the ICP. Before placement of invasive devices such as endotracheal tube and mechanical ventilation, adequate analgesia and judicious use of sedation are required in patients with grade III/IV encephalopathy. No single standard agent for sedation is recommended in patients with ALF due to insufficient evidence.

A major component of neurologic care is based on infection prevention, maintaining cerebral blood flow and reduction of circulating ammonia levels. Simultaneously, it is also of critical importance to stratify patients based on the risk of mortality without transplant. This treatment should be

Table 4 Concept of management in acute liver failure

1. ALF is a potentially reversible disease due to two important drivers of recovery
   a) Liver has a tremendous capacity to regenerate
   b) Hepatic necrosis provides stimulus for the regeneration of hepatocytes
2. Before recovery and effective regeneration:
   a) Death occurs due to complications of liver failure
3. Management goal (medical):
   a) Therefore, the primary goal is to keep the patient alive and stable and buy time for liver regeneration
   b) Intensive supportive care has a central role in providing various organ supports and maintain the vital organs
4. Certain specific issues are important to assist liver regeneration:
   a) Definition-diagnosis to be clearly ascertained. ALF mimics must be suspected if patient is febrile and specific etiological tests should be performed. ALF per se due to various etiologies have specific treatments
   b) Evaluation of the killer complications is the part of management strategy to device prevention and specific management
   c) Removal of pathogenic drivers such as inflammatory cytokine, drivers of such cytokine such as DAMPS, neurotoxins such as ammonia from the system which results in the complication, which kills, by plasmapheresis and CRRT

Table 5 Aggressive supportive therapy—Intensive care unit care

Team needed: gastroenterologist/intensivist/transplant surgeon
1. Fluid and electrolyte: normal saline or plasma-lyte-148 is preferred (serum sodium to be kept at 140–150 meq/L; hypertonic saline if needed)—Hartman solution or ringer lactate to be avoided. Avoid rapid correction of serum sodium; > 8 mEq/L in 24 h to be avoided—fluid monitoring by renal function and IVC diameter
2. Hepatic encephalopathy and seizure: mechanical ventilation to be done in advanced encephalopathy
3. Features of cerebral edema (raised ICT): mannitol 0.5 g/kg (20%)–175 mL 10 min (to be avoided if serum osmolality > 320 and evidence of acute kidney injury (AKI) is present and invasive monitoring as well as external stimulus to be avoided)
4. Coagulopathy: FFP/cryoprecipitate/platelets not recommended (only to be given in presence of bleeding/invasive procedure)
5. Hypoglycemia—25%–50% dextrose bolus to be given with monitoring of blood glucose
6. Acute kidney injury as well as high arterial ammonia of > 122 µmoles/L and/or lactate > 3 milimoles/L: CRRT is recommended with avoidance of nephrotoxic drugs with monitoring to prevent hypovolemia
7. IV antibiotics/antifungals to be instituted (in referred patients and those with advanced HE) – antibiotic preference to be done as per microbial sensitivity pattern in the treating institute and surveillance for infection to continue
8. Hemodynamic monitoring—MAP to be maintained at 65–70 mmHg and if necessary, inotropes can be used and choice of inotrope recommended is noradrenaline
9. N-acetylcysteine: 150 mg/kg 250 mL 5% dextrose—1 h: 50 mg/kg—4 h: 100 mg/kg—16 h: 100 mg/kg over 16 h, may be repeated until encephalopathy and INR normalize *(meta-analysis 7 studies: better overall survival, transplant-free survival, posttransplant survival)**
10. Daily prognosis evaluation: counseling for transplant

*INASL consensus: J Clin Exp Hepatol 2022 | Vol. 12 | No. 2 | 726–728

considered and implemented before the onset of other multi-organ failures or brain stem herniation, which practically renders liver transplant futile.

The role of ICP monitoring and targeted therapy, even though practiced at some centers, in improving survival is unclear and may be associated with complications such as bleeding. Invasive ICP monitoring is being gradually replaced by non-invasive methods for ICP monitoring such as ultrasound-guided estimation of optic nerve sheath diameter (ONSD) and middle cerebral artery Doppler. However, these methods are limited by inter-observer and intra-observer variations and need to be validated in further studies.

Osmotherapy [18, 21, 29, 30]

Intravenous mannitol Mannitol brings the cerebral water content down and affects the blood's rheological properties. Clinically overt cerebral edema develops as the ICP rises to over 20 to 25 mmHg for more than five minutes. The usual dose is 0.5 to 1 g/kg, 20% solution, over five minutes of intra-venous bolus and repeat as long as the serum osmolality is < 320 mOsm/L. The response after a bolus may be expected 15 to 60 minutes post-injection. Adverse effects include a paradoxical increase in ICP (in about 20% of patients) and high doses can result in acute kidney injury (AKI) and damage to the blood-brain barrier. Mannitol is effective in mild to moderate intra-cranial hypertension and is less effective when the ICP is over 60 mmHg. The use of mannitol should be avoided in oliguric/anuric patients (with renal failure), rather ultrafiltration with continuous renal replacement therapy (CRRT) to maintain intra-vascular volume, while preventing increased central venous pressure, is recommended.

Hypertonic saline (3%) It is recommended to maintain serum sodium concentration between 145 and 150 mmol/L with an infusion of hypertonic saline, which has been reported to decrease intra-cranial hypertension and is used in the standard care in patients with ALF.

Rescue therapy

Going by the data suggesting that barbiturates could be of value in controlling intra-cranial hypertension of the head injury, intravenous thiopentone has been considered in ALF complicated by unresponsive intra-cranial hypertension. The recommended dose of thiopentone is a loading dose of 3 to 5 mg/kg (maximum 500 mg) over 15 minute, followed by a continuous infusion at 0.5 to 2.0 mg/h. Continuous ICP and arterial blood pressure monitoring should be done during infusion as it can cause hypotension. Other rescue therapies such as hypothermia and intra-venous phenytoin have not shown to improve survival.

Ammonia-lowering strategies [29, 30]

Lowering arterial ammonia by therapeutic measures has been documented to improve survival in experimental models of ALF. Lactulose and antibiotics as ammonia-lowering measures are not recommended. Concepts on protein restriction as the source of increase ammonia generation in the gut are being revised. Newer agents such as phenyl acetate and probiotics, having capacity to consume ammonia, are being considered. Other ammonia-lowering agents such as L-ornithine L-aspartate (LOLA) and L ornithine phenyl acetate (LOPA) have been shown to alleviate hyperammonemia in experimental animal models with improvement of cerebral edema and improved outcomes although their efficacy in human ALFs is yet not substantiated by evidence.

Sodium benzoate combines with glycine to form hippurate, which is water-soluble and gets excreted in urine easily and may decrease arterial ammonia levels. However, therapeutic trials in humans show conflicting results. It has never been used in patients with acute liver failure.

Rifaximin may have a role in lowering ammonia in patients with ALF and needs to be explored.

In a trial by the USALF study group, significantly better 21-day transplant-free survival was shown in patients treated with N-acetyl cysteine (NAC) compared to placebo; however, the overall survival between the treated and control group was similar.

Recently, it has also been shown that the high flow continuous renal replacement therapy (CRRT) can reduce ammonia levels and is associated with improved survival.

Therapies towards management of complications [29, 30]

Prevention and treatment of infection

Conventional ICU care about asepsis in critically sick patient is usually followed to treat patients with ALF, which includes aseptic nursing techniques. Most of the bacterial infections occur in the first three days of admission. Hence, prophylactic broad-spectrum parenteral antibiotics should be started as soon as possible after admission. Prophylactic antibiotics have been shown to reduce the risk of infections. Addition of oral non-absorbable antibiotics does not confer any advantage over parenteral antibiotics. Surveillance cultures should be continued even after starting antibiotics.

Any unexplained drop in blood pressure, reduced urinary output, worsening encephalopathy and development of severe acidosis or features of disseminated intravascular coagulation (DIC) should be considered signs of sepsis. In the setting of unresponsive fever, leukocytosis and deterioration of neurologic status after initial improvement and

presence of renal failure, fungal sepsis should be strongly considered and anti-fungals should be started.

Hemodynamic support

ALF patients have altered cardiovascular physiology in the form of high cardiac output, low systemic vascular resistance and relative arterial hypotension. Therefore, an adequate cardiovascular filling pressure by maintaining the mean arterial pressure (MAP) between 60 and 65 mmHg is helpful in preservation of various organ perfusion. Vasopressors are indicated when MAP falls below 60 mmHg despite adequate intra-vascular volume replacement. Norepinephrine is the vasopressor of first choice.

Coagulopathy

The coagulopathy of ALF may be clinically silent or may manifest as bleeding. Infusion of fresh frozen plasma (FFP) is indicated only for active bleeding or before invasive procedures. The risk of GI bleed from stress ulcers can be reduced by the prophylactic use of sucralfate.

Mechanical ventilation

The lungs are relatively spared in ALF and standard modes of mechanical ventilation may be considered. Most patients will endure ventilation with minimal or no sedation. Assisted ventilation is recommended by the INASL consensus in advanced encephalopathy and in patients with overt features of cerebral edema [2].

Renal support

Continuous forms of renal support therapy may reduce cerebral perfusion pressure by decreasing cerebral edema through rapid osmolar shifts and ammonia reduction and are preferred to conventional hemodialysis or intermittent hemofiltration.

Nutritional and metabolic support

ALF is a hypercatabolic state, where energy requirements can be increased by 60% and are further accentuated by complications such as sepsis. Although both enteral and parenteral routes can be used, the former is preferred. Protein restriction is not recommended in ALF patients. Branched chain amino acids (BCAA) offer no additional advantage, except in patients requiring frequent dialysis in whom large BCAA losses may occur. Dyselectrolytemia is common (most commonly hypokalemia, hypomagnesemia, hypophosphatemia and hypocalcemia) and must be corrected.

Almost 50% of ALF patients develop hypoglycemia, which can be sudden and may confound the interpretation of altered mentation. Glucose requirements vary highly and require frequent monitoring at two to three-hour intervals. Whenever the blood glucose level falls below 60 mg/dL, an intravenous bolus of 50 to 100 mL of 50% dextrose should be administered. The amount of water administered as a solvent for dextrose should be minimized by providing solutions concentrated to 25% to 50%.

Plasma exchange and bioartificial liver support systems [29–33]

Plasma exchange (PLEX) has recently been shown to improve transplant-free survival in patients with ALF. Randomized controlled trials as well as systematic reviews and meta-analysis of all studies in ALF using both high-volume and standard-volume plasma exchange have shown to provide survival benefits in patients with ALF. At present, many centers both in Asia and Europe have recommended plasma exchange as the first line of specific management in ALF. Plasma exchange has been documented to remove the offending cytokines, reduce arterial ammonia levels and improve the liver function profile and the systemic hemodynamic parameters, thereby improving transplant-free survival. Irrespective of the etiology of ALF, PLEX has been documented to benefit in altering the pathogenetic drivers of ALF and provide benefit. However, other bio-artificial liver support systems such as molecular adsorbent re-circulating systems (MARS), single pass albumin dialysis (SPAD) and fractionated plasma separation and adsorption (FPSA), even though documented to improve various biochemical and hemodynamic parameters in ALF, have failed to provide transplant-free survival benefits. Bio-artificial liver assist devices (LAD), including viable liver cells in culture within bioreactors, have not been shown to significantly improve survival among ALF patients and their role is presently for research purpose only.

Etiology-directed therapy [29, 30]

In certain specific etiologies of ALF, the treatment of underlying etiology or offending agent has been found to improve survival. The role of anti-virals in specific scenario such as HBV-ALF and HSV-ALF (tenofovir, entecavir for HBV and specific drugs such as acyclovir and valacyclovir for HSV) has been recommended. In HBV ALF, between tenofovir and entecavir, the former is preferred in patients with renal failure due to its safety profile. The doses of anti-virals should be modified depending upon the renal function and creatinine clearance. In patients with ATD or any other DILI-ALF, the offending drug should be immediately discontinued. In HEV-ALF, presently there is no data on the use

of ribavirin, even though in chronic HEV among post-solid organ transplant immune suppressed patients and in selected patients with HEV associated ACLF, it can be effective.

Activated charcoal is used for gastric decontamination and high doses of NAC are recommended in paracetamol toxicity and should be started within 48 hours of ingestion in recommended doses [21]. In autoimmune hepatitis-associated ALF, early glucocorticoid treatment even though controversial has been recommended in various guidelines and position papers. When steroids are started, the caution and monitoring of infection and prophylaxis to prevent infections are usually practiced.

In pregnancy and acute liver failure, ALF worsens both maternal and fetal outcome. Increased risk of bleeding is not an indication of termination of pregnancy. The management of pregnant patients with ALF is like other ALF patients. Complications need to be managed on a case-to-case basis. However, owing to high maternal and fetal mortality of 10% and 50%, respectively, in acute fatty liver of pregnancy (AFLP) presenting with ALF, immediate termination of pregnancy needs to be considered. AFLP is mostly reversible after fetal delivery. As delivery of the fetus is the only effective treatment for pregnancy-induced ALF, it should be decided in a multi-disciplinary team approach involving an obstetrician, hepatologist, intensivist and surgeon.

Liver transplant and prognostic models [2, 3, 5, 19, 29, 33–38]

Prognostic models [2, 3, 5, 30, 34, 35, 39–42]

Liver transplant (LT) has been well established as a curative option in ALF when done in appropriate time. Prognostic models are therefore necessary to identify patients who will need transplantation or should continue medical therapy. Many prognostic models from all around the globe have been described. Each of these models in summary have highlighted the following important facts. Age and etiology in most reports are important variables influencing survival. Those with HAV, HEV, acetaminophen toxicity and AFLP-induced ALF survive more frequently. Patients with DILI, autoimmune hepatitis, HBV and cryptogenic ALF have lower spontaneous survival (< 30%). Wilson's disease with ALF has poor survival. Among the dynamic variables, the degree of encephalopathy was documented to influence survival—patients with encephalopathy grade of III or more in comparison to less advanced encephalopathy (I and II) died more frequently.

There are many prognostic models to predict outcome in ALF such as King's College Criteria (KCC) [38], Clichy Criteria [39], MELD score [40], MELD Na score [41], clinical prognostic indicator (CPI) score [42] and ALFED score [35]. There are many variables common to these scores such as high bilirubin levels, coagulopathy (prolonged INR), higher grades of encephalopathy, presence of raised ICP, advanced age and jaundice to encephalopathy interval more than a week, which are associated with ominous outcome. Newer prognostic markers such as serum lactate, phosphates and Gamma globulin are being evaluated and need validation. Most of the scoring systems have high positive predictive value (PPV) for mortality; however, none of these is an ideal score that can segregate survivors from non-survivors with 100% sensitivity, specificity, PPV and negative predictive value (NPV). Failure to identify patients who will benefit most from emergency LT is the major limitation of these scores [34]. In addition, dynamic assessment with these scores including clinical judgment should be the standard of care rather than one-time assessment at baseline.

Among the prognostic models, King's College Hospital Criteria for liver transplantation as a prognostic model are popular in all transplant centers globally and have been widely used [38] (Table 6). Although these criteria are specific and predict mortality, these are not very sensitive in predicting cases that will need transplantation. Unfortunately, so far, none of the currently available models has consistently demonstrated very high accuracy in predicting outcome [34].

Table 6 King's College (UK) and Clichy (France) prognostic criteria in acute liver failure predicting high mortality

Non-paracetamol-induced ALF	Paracetamol-induced ALF
• Prothrombin time > 100 s or Any three of the following: • Age < 10 or > 40 years • Etiology: non-A, non-B hepatitis, drug-induced hepatitis (halothane) • Icterus-encephalopathy interval > 7 days • Prothrombin time > 50 s (INR > 3.5) • Serum bilirubin > 17.5 mg/dL	Plasma pH < 7.30 or Prothrombin time > 100 s (INR > 6.5) and serum creatinine > 3.4 m dL in patients with grade 3 to 4 encephalopathy

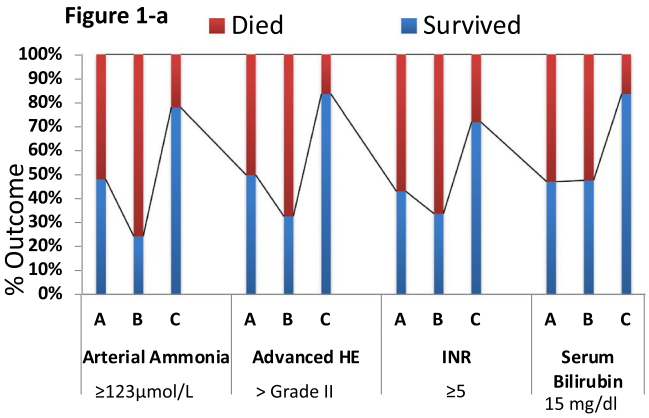
NB: Clichy Criteria (France) for poor prognosis in patients with acute liver failure

- Factor V levels < 20% of normal in patients < 30 years of age
- Factor V levels < 30% of normal in patients > 30 years of age

Multiple prognostic models have been reported from India [2, 8, 16, 30, 34, 35, 42]. The following variables present at admission were identified as independent predictors of poor outcome: (if) age ≥ 40 years; (ii) bilirubin ≥ 15 mg/dL; (iii) prothrombin time (PT) prolongation by ≥ 25 s; (iv) clinically overt cerebral edema [8]. Mortality increases with increasing number of above-risk factors; with three or more factors, it was 93%. In another Indian study, clinical prognostic indicators (CPI) included age ≥ 50 years, icterus encephalopathy interval > 7 days, grade 3 or 4 encephalopathy, presence of cerebral edema, PT ≥ 35 s, and creatinine ≥ 1.5 mg/dL. Presence of any three of six CPIs was superior to model for end-stage liver disease (MELD) or King's College Hospital (KCH) criteria in identifying survivors and non-survivors [42].

ALF is a dynamic disease, in which variables determining prognosis at admission change over time and thus, the clinical course also varies. A dynamic prognostic model, named as ALF early dynamic (ALFED) model, was reported, which included four variables: arterial ammonia, serum bilirubin, INR, and hepatic encephalopathy, which were identified as the independent predictors of outcome at admission [2, 35]. This model evaluated the dynamicity of these four variables over three days and documented that the prediction of outcome using these variables on Day 3 was markedly superior to the prediction based on admission parameters. Recently, INASL recommended the ALFED prognostic model to be more appropriate for the Indian sub-continent because it was derived from the cohort of Indian patients who had predominantly viral etiology unlike in the west, where viral etiology as a cause for ALF is infrequent [2].

ALFED is one of the first dynamic models that assessed ALF patients dynamically over a period of three days rather than considering variables at baseline. The ALFED model study identified ALFED model had an AUROC of 0.91 in the derivation cohort and of 0.92 in the validation cohort and showed similar increase in mortality with increasing risk scores from 0 to 6 (Fig. 3). The ALFED model performed better than KCH criteria and the MELD score, even when their three-day serial values were considered. In the validation cohort, an ALFED score of ≥ 4 had an excellent PPV and NPV of 85% and 87%, respectively. Further, in each patient, the model could predict survival on Day 3 (score 1 through 6; Table 7) of hospitalization. Those with scores of 1 to 3 had a survival frequency of about 80% or more and those with ≥ 4 had a mortality risk of > 80% [2, 7, 35]. These parameters at baseline were also independent predictors of mortality, but the dynamic assessment made these parameters as also model for survival. In India, ALF etiology is hepatitis virus and usually, individuals without any underlying chronic liver pathology develop ALF. In ALF, along with hepatic necrosis, the hepatocyte regeneration simultaneously sets in. Therefore, with liver regeneration these predictive parameters change and hence, dynamic assessments are important to identify the outcome more accurately.



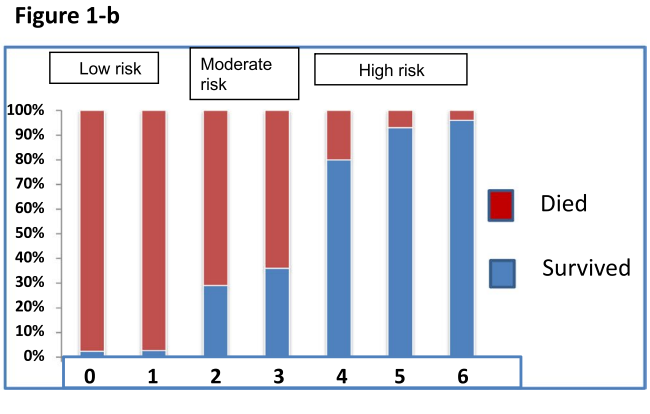


Fig. 3 ALF-Early Dynamic Model (ALFED model) derivation and stratification as per ALFED score (0 to 6). **a** Arterial ammonia, grade of encephalopathy, INR and serum bilirubin were independent predictors of outcome on multi-variate analysis [7]. ROC curve determined discriminant/cut-off values for each of these variables to predict mortality were mentioned above under each variable. (A) Mortality and survival (outcome) in those with baseline high > cut-off level. (B) Outcome in those with persistent high cut-off level or increasing from lower levels to > cut-off level on Day 3. (C) Outcome in those with lower level than cut-off levels and persistent from Day 1 to 3 or declining levels from higher level to low < cut-off levels. For each variable, the mortality increased with persistently high level from baseline or increased to cutoff levels from lower levels on Day 3, while mortality decreased for each variable if the variable levels decreased from higher levels to or remained low below cut-off levels on Day 3. This dynamicity of independent predictors of outcome was used for prognostic modelling. **b** On Day 3, each of these variable was scored for individual patients with ALF and sum of the scores determined as per Table 3. Also indicates outcome in patients with score 0 to 6 indicating increasing mortality as the score progresses. These scores do change from baseline to Day 3 (either increased or decreased above cut-off levels on Day 3) indicating that this model can be a predictor of survival as well as mortality

Table 7 Acute liver failure-Early Dynamic (ALF-ED) prognostic model

Variables over three days Assessed on the third day of hospitalization	Score assigned
Hepatic encephalopathy (persistent or progressed to grade > 2)	2
INR (persistent or increased to ≥ 5)	1
Arterial ammonia (persistent or increased to ≥ 123 µmol/L)	2
Serum bilirubin (persistent or increased to ≥ 15 mg/dL)	1

Each of the variables above on Day 3 of hospitalization carries a score determined on the strength of the beta integer of the odds ratio identified in multi-variate analysis to predict mortality. Each of the above variables was an independent predictor of mortality. Total score is 6. On Day 3, a score of 4 is associated with 90% mortality, whereas score 1 is associated with about 5% mortality. With increasing score, mortality increases and with decreasing score over three days, mortality decreases. Score > 4 list for transplant; score < 4 treat medically

Liver transplantation [2, 36, 37]

Overall, the five-year survival after deceased donor orthotopic liver transplantation (DDLT) as well as live donor liver transplantation (LDLT) ranges from 50% to 75%. In experienced centers, outcome with split liver grafts is comparable with that after use of full-size organs. In patients who have sepsis and multi-organ failure before OLT, survival is significantly low. The use of auxiliary partial OLT may be considered a form of temporary liver support in most recipients and has a comparable survival rate. In up to 65% of patients surviving one year, withdrawing immunosuppression can result in graft atrophy. LDLT has been more frequently used in children. However, in Asian countries, LDLT is the most frequent form of LT among adults with an excellent five-year survival. Selection and categorization of patients who need transplantation, who will survive with medical treatment and in whom transplant will be futile remain the cornerstone in improving outcome in the management of ALF.

Declarations

Conflict of interest SKA declares that he has no conflict of interest.

Disclaimer The authors are solely responsible for the data and the contents of the paper. In no way, the Honorary Editor-in-Chief, Editorial Board Members, the Indian Society of Gastroenterology or the printer/publishers are responsible for the results/findings and content of this article.

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