Indications for Liver Transplantation in Acute Liver Failure

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Abstract

Acute liver failure (ALF) is a life-threatening condition characterised by abrupt onset of severe liver dysfunction and neurological impairment in patients without an underling chronic liver disease. Since ALF—associated mortality remains high, such patients need urgent assessment and advanced treatment to assure either spontaneous remission of liver failure or bridging them to liver transplantation (LT). To date, no universally accepted scoring systems exist to address the issue of LT in ALF and most experienced centres have developed their own criteria and indications for LT. However, due to the complexity of patient assessment and management, such decisions should be made on a case-by-case basis and by an experienced multidisciplinary team consisting of a transplant surgeon, anaesthesiologist and gastroenterologist in order to provide the best therapeutic option.

Recent studies have focused both on the general care of ALF patients and successfully bridging such patients to LT. However, despite a considerable improvement in patient care, LT remains the main therapeutic option associated with the highest survival rate in cases of severe ALF. This chapter will focus on recent evidence for assessment and early management of such patients, indication for LT, as well as recent advances in intensive care management.

62.1 Current Definition of ALF

ALF is mostly defined by a rapid deterioration of the liver function demonstrated by an international normalized ratio (INR) $\geq$ 1.5 and the development of hepatic encephalopathy within 26 weeks of jaundice in a patient with no previous history of liver disease [1]. Although, it is generally accepted that ALF presents in patients that previously had a normal liver function, patients with Wilson's disease, vertically-acquired hepatitis B virus (HBV), Budd-Chiari syndrome and autoimmune hepatitis may be included in this definition despite evidence of underlying cirrhosis due to acute presentation and similar clinical course and outcome as the general ALF population [2, 3].

The current definition of ALF has some important limitations that must be considered when the assessment of such a patient is performed. First, hepatic encephalopathy (HE) may be minimal in some patients despite a severely altered liver function. As most centres use West-Haven criteria (Table 62.1), a diagnostic of grade 1 HE may be overlooked, and the patient misdiagnosed as having no HE and hence no ALF. To avoid such situations, a thorough clinical examination should be performed in patients with acute liver dysfunction and expert help sought out. In some patients waiting for HE to occur may delay the initiation of an early treatment strategy that can decrease the chance for spontaneous recovery [5]. Secondarily, INR was not developed to assess patho-

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Table 62.1 West-Haven criteria for hepatic encephalopathy [4]

Grade	Clinical manifestation	Neurologic examination
Grade 1	Mild lack of awareness Shortened attention span	Impaired addition or subtraction Mild asterixis or tremor
Grade 2	Lethargic Disoriented Inappropriate behaviour	Obvious asterixis Slurred speech
Grade 3	Somnolent but arousable Gross disorientation Bizarre behaviour	Muscular rigidity and clonus Hyperreflexia
Grade 4	Coma	Decerebrate posturing

Table 62.2 Differential diagnostic of Acute Liver Failure

Disease	Criteria for diagnostics
Acute-on-Chronic Liver Failure	Presence of a known chronic liver disease or radiological criteria of liver cirrhosis. An exception is represented by Wilson's disease, Budd-Chiari syndrome and autoimmune hepatitis.
Pre-eclampsia and eclampsia	Presence of a second or third trimester pregnancy associated with hypertension, proteinuria and grand-mal seizures
Sepsis	Presence of an underling infection and associated organ dysfunctions
Shock	Presence of an inadequate cardiac output or oxygen delivery to the tissues
Liver metastatic disease	Presence of liver metastases on abdominal imaging

physiology of coagulation, but to guide anticoagulant therapy. As a slight increase in INR may be seen in many other clinical situations and can physiologically be observed in children [6], borderline patients should be intensively monitored and considered as "pre-ALF" until ALF can be confirmed or excluded.

Based on the timespan between de development of jaundice and HE, ALF has been classified as: hyperacute (<7 days), acute (7–21 days) and subacute (>21 days and <26 weeks). However, this classification is no longer recommended as studies have failed to demonstrate a correlation between a more rapid onset of ALF and increased mortality. Patients with acetaminophen overdose, despite having a more severe presentation of the illness, have a higher rate of spontaneous recovery and rapidly evolve towards either clinical improvement or death [7]. A delay of more than 7 days between jaundice and HE is associated with a poorer outcome, especially in cases of indeterminate aetiology. A differential diagnosis should be performed early in the course of the illness, as other diseases can present with liver dysfunction and specific treatment should be started early (Table 62.2).

62.2 Aetiology of ALF

There is a great variability regarding both epidemiology and aetiology of ALF between geographic areas. The reported incidence varies between 11.3 per million person years in Germany, 5.5 per million population in the United States and 80.2 per million person-years in the Asian-Pacific region [8, 9]. The most common cause of ALF is represented by drug induced liver injury in the western world. However, viral hepatitis still remains an issue in some countries due to the low immunisation of the population through vaccination [10].

Acetaminophen overdose remains the main cause of ALF in the western world [11]. The development of ALF after acetaminophen administration has generally been reported for doses above 150 mg/kg body weight, but case reports have noted ALF after usual prescribed doses of 3–4 g/day [12]. Patients generally present after voluntary or accidentally ingested a high dose of acetaminophen. Clinically, symptoms may be minimal during the first 24 hours and mainly consist of nausea and vomiting. During the symptomatic phase, that usually lasts from 24–48 hours, general gastro-intestinal symptoms and fatigability are present. Clinical examination reveals right upper-quadrant pain and hepatomegaly and paraclinical tests demonstrate an increase in serum transaminases. Serum bilirubin and INR may be only slightly increased. ALF is generally seen between 72–96 hours are is characterised by a severe increase in serum transaminases, metabolic acidosis, coagulopathy and increase in bilirubin levels. Neurologic dysfunction may follow shortly. In severe cases, death usually occurs between the third and seventh day after ingestion. Spontaneous remission is noted in up to 70% of patients within two weeks [13].

Mushroom poisoning is frequently encountered in rural areas, especially during spring and autumn. After eating wild mushrooms the previous day, patients generally present with gastrointestinal symptoms: nausea, vomiting, diarrhoea and abdominal pain. Food poisoning is generally misdiagnosed if a careful patient history is not taken. After 24 hours, gastro-intestinal symptoms usually reside, and an apparent convalescence phase follows for 24–48 hours. ALF is noted 48–72 after mushroom ingestion and is characterised by a severe increase in serum transaminases and bilirubin levels, severe coagulopathy, HE, acute renal failure and metabolic acidosis. The main factors associated with poor survival are represented by a decrease in prothrombin index below or equal to 25% of normal values at any time between day 3 and day 10 associated with an increase in serum creatinine over 1.2 mg/dL [14].

Drug-induced liver injury (DILI) has become one of the most frequently encountered causes of ALF worldwide. Clinically, ALF has a subacute presentation with a latency between 30 and 90 days. The most commonly reported drugs are represented by antibiotics, including anti-tuberculous medication, non-steroidal anti-inflammatory agents and herbal and dietary supplements. Due to the relative long timespan between time of drug administration and symptoms, the diagnostic is challenging and requires a thorough medical history. Clinically, patients present with a mild increase in serum transaminases, low-grade HE, moderate jaundice and increased INR. Spontaneous recovery is noted in approximately 25% of patients and liver transplantation is indicated more frequently than after acetaminophen overdose [15]. A poorer outcome is seen in women, older patients, Asian ethnicity, thrombocytopenia and history of chronic liver disease.

Since the introduction of world-wide hepatitis B immunisation, the incidence of **acute viral hepatitis** has signifi-

cantly decreased. Nowadays, hepatitis A and E account for the majority of cases globally, but high incidence of hepatitis B has been noted in Eastern Europe [16]. The clinical picture of hepatitis A (HAV) infection varies from asymptomatic patients to patients with a full picture of ALF. In most cases, patients present with anorexia, nausea, vomiting, low grade fever (38–39 °C), myalgia and light respiratory symptoms. Jaundice usually is seen between one to two weeks after the infection and is accompanied by upper right-quadrant abdominal pain. Extrahepatic involvement is rarely seen, and spontaneous recovery is noted in over 50% of patients. Hepatitis B virus (HBV) infection can present as either a *de novo* infection or a flair-up in patients chronically infected. Patients with *de novo* infection are usually asymptomatic but in rare cases they can progress to ALF characterised by gastro-intestinal symptoms, fatigability, low grade fever and jaundice. HE is frequently encounter and rapidly progresses to coma. Outside LT the prognosis is poor and transplant-free survival ranges from 25–53% [17]. Hepatitis E virus (HEV) has an incubation period of three to eight weeks, followed by a short prodromal phase and jaundice is shortly seen afterwards. The incidence of HE is low and transplant-free survival is one of the highest among all aetiologies of ALF.

Wilson's disease is an uncommon cause of ALF that mainly affects women between 5 and 35 years of age. Keiser-Fleischer rings represent one of the main diagnostic criteria and can be seen in over 90% of patients with neurological involvement and in almost half of patients without neurological involvement. Most frequently encountered neurological signs are represented by ataxia, tremor and dystonia. Clinical signs also include jaundice, abdominal pain and signs of chronic liver disease. Despite its low incidence, Wilson's disease accounts for more than 10% of liver transplantations for ALF [18].

Autoimmune hepatitis presents as a chronic necro-inflammatory liver disease, affecting mainly women, that can progress to ALF. Clinical presentation is typically sub-acute with non-specific symptoms including nausea, jaundice, fatigability and abdominal pain. The diagnostic is based mainly on histopathological results accompanied by clinical and paraclinical criteria, including abnormal serum globulin levels and the presence of autoantibodies.

HELLP syndrome is a life-threatening complication of pregnancy characterised by haemolysis, an increase in serum transaminases and thrombocytopenia. HELLP syndrome is observed in 0.5–0.9 of all pregnancies, but a higher incidence has been reported in patients with pre-eclampsia (10–20%) [19]. The majority of women present between 27 and 37 weeks of pregnancy with abdominal pain, nausea and vomiting. Haemolysis is generally secondary to microangiopathic haemolytic anaemia. Factors associated with a worst outcome are younger age, headache, bilirubin >2.0 mg/dL

Table 62.3 Diagnostic criteria for HELLP syndrome

Severity	Tennessee classification	Mississippi classification
1	Platelet count <100,000/mm^3 AST > 70 U/L LDH > 600 U/L	Platelet count <50,000/mm^3 AST or ALT >70 U/L LDH > 600 U/L
2		Platelet count: 50,000–100,000/mm^3 AST or ALT >70 U/L LDH > 600 U/L
3		Platelet count: 100,000–150,000 /mm^3 AST or ALT >70 U/L LDH > 600 U/L

Legend: *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase

and low platelets (<50,000/mm^3) [20]. Two scoring systems are currently used for the diagnostic and classification of HELLP syndrome (Table 62.3).

Budd-Chiari syndrome is determined by an obstruction of the hepatic venous outflow due to either acute or chronic thrombosis of the hepatic veins. Pathophysiological consequences are represented by a decrease in hepatic blood flow and precapillary portal hypertension. In its chronic form, patients present with signs of decompensated chronic liver failure, ascites and porto-systemic collaterals. In acute presentations, due to the inability of the portal circulation to develop collaterals, patients present with ALF characterised by HE, jaundice and liver dysfunction. More than half the patients will require either transjugular intrahepatic porto-systemic shunt or LT [21].

62.3 Patient Assessment

After ALF is diagnosed, generally on the ward or in the emergency department, the patient needs to undergo a thorough clinical examination and paraclinical tests need to be closely monitored in order to assess the severity of liver dysfunction and associated organ failure, to promptly commence appropriate treatment and to assess the patient as a candidate for emergency LT. In general, such patients are best managed on a high-dependency gastroenterology ward or, as in the case of severe ALF, in the intensive care unit (ICU). Treating these patients in an ICU has some advantages, although with increased patient costs. Intensive care management can provide adequate communication between key players of the multidisciplinary ALF team, offers 24/7 advanced monitoring during standard therapy, sustains organ function and provide specialised care for either organ recovery or bridge to liver transplantation.

Initial evaluation should include a neurological examination to assess the degree of HE and patient history to diagnose aetiologies that require specific treatment, such as

acetaminophen overdose. Alcoholic liver disease and malignant infiltration of the liver should be excluded as they represent general contraindications for emergency LT. Also, the presence of underling liver cirrhosis should also be actively sought out as acute-on-chronic liver failure represents the most common differential diagnostic of ALF.

Abdominal ultrasound examination is the initial imaging modality of choice in patients with ALF as is can assess liver anatomy and structure, identify liver cirrhosis and complications of liver disease, diagnose Budd-Chiari syndrome and is easily performed at the bedside. Computed tomography (CT) imaging, and especially contrast enhanced CT, can also be used if initial ultrasound examination is inconclusive, if there is a high suspicion of hepatic malignancy or to quantify the extent of hepatic vein thrombosis in Budd-Chiari syndrome. Other advanced imagining techniques, like magnetic resonance imagining, may be required to assess liver anatomy if the patient is a candidate for living-donor LT.

Patients with a low cardiac output or in shock can present as ALF due to ischemic hepatitis and neurologic impairment secondary to decreased cerebral perfusion. A transthoracic echocardiography can demonstrate an impaired left ventricle function with decreased stroke volume and left ventricular failure. Transthoracic echocardiography should be routinely performed in patients with severe ALF as part of the differential diagnosis but also to assess fluid status and cardiovascular suitability for LT. As patients with Budd-Chiari syndrome can have a subacute course of the illness, inferior vena cava thrombosis must also be evaluated as it can extend in the right atrium with significant implications for vascular anastomoses in case of LT (Fig. 62.1).

In patients with severe HE, ultrasound examination of the optic nerve sheath diameter has been advocated to predict the severity of cerebral oedema. A bilateral increase in nerve sheath diameter above 5 mm correspond with elevations in
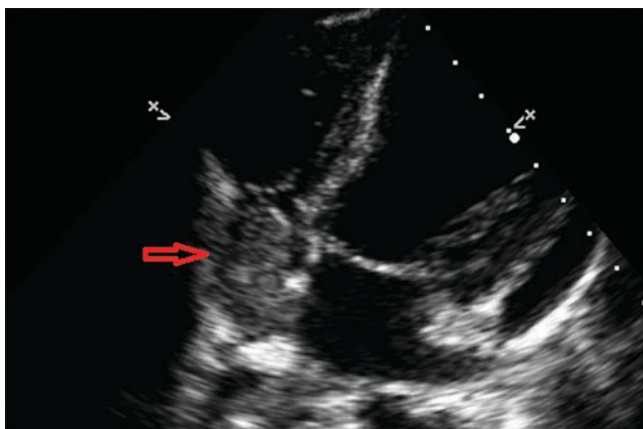

Fig. 62.1 Extensive right atrium thrombosis (red arrow) in a 18-year old patient with subacute Budd-Chiari syndrome

Table 62.4 Commonly recommended paraclinical tests for aetiologic diagnostic of ALF

Aetiology	Paraclinical tests	
Acetaminophen overdose	Acetaminophen level	
Viral hepatitis	HAV	IgM antibody to HAV
	HBV	Hepatitis B surface antigen (HBsAg); IgM antibody to hepatitis B Core (IgM anti-HBc); PCR for HBV DNA
	HEV	IgM antibody to HEV PCR for HEV RNA
Wilson's disease	Liver cupper, urinary cupper, ceruloplasmin levels Ophthalmological examination (Keiser-Fleischer rings)	
DILI	Toxicology tests	
Autoimmune hepatitis	ANA, ASMA, Immunoglobulin levels	
HELLP syndrome	Platelet count, AST, LDH Liver biopsy	
Budd-Chiari syndrome	Abdominal ultrasound / contrast-enhanced computer tomography Thrombophilia assay	
Other rare hepatotropic viruses	Antibodies to HCV; PCR for hepatitis C virus RNA, IgM antibodies to herpes simplex1, IgM antibodies to varicella-zoster virus, IgM antibodies to cytomegalovirus, IgM antibodies to Epstein-Barr virus	

Legend: *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HEV* hepatitis E virus, *IgM* Immunoglobulin M, *PCR* Polymerase Chain Reaction, *DNA* deoxyribonucleic acid, *RNA* ribonucleic acid, *ANA* antinuclear antibodies, *ASMA* anti-smooth muscle antibody, *AST* aspartate aminotransferase, *LDH* lactate dehydrogenase

intracranial pressure above 20 mmHg. However, because papillary and optic nerve oedema may take days to develop, a normal diameter of the optic nerve does not always exclude intracranial hypertension [22].

Paraclinical tests should focus to evaluate both the aetiology (Table 62.4) and the severity of liver failure as well as associated organ dysfunction (Table 62.5). Early testing should include a full blood count, coagulation parameters, routine biochemical assay, acid-base status, ammonia levels and specific tests to determine the trigger of ALF.

In patients with acetaminophen overdose, plasmatic concentrations are usually determined. However, a negative result does not exclude acetaminophen overdose since more than half of patients may have untraceable plasmatic amounts of paracetamol depending on the time and dose ingested [23]. A detailed patient history and an interview with friends or next of kin would generally identify a recent ingestion of acetaminophen. A complete toxicology screen should be

Table 62.5 Paraclinical tests at admission

Organ	Recommended tests
Liver	Serum transaminases, bilirubin (total and fractions), lactate dehydrogenase, creatine kinase, ammonia
Coagulation	Prothrombin time, INR, fibrinogen, coagulation factor V Thromboelastometry/thromboelastography
Blood count	White blood cells (including fractions), haemoglobin, haematocrit, platelet count
Renal	Urea, creatinine
Metabolic	Glycemia, lactate, triglycerides
Pancreas	Amylase, lipase
Acid-base status	pH, HCO_3^-, arterial partial pressure of CO_2 and O_2
Electrolyte	Na^+, K^+, Cl^-, anion gap

Legend: *INR* international normalized ratio

performed in patients suspected of voluntary or accidental ingestion of acetaminophen since overlap with other abuse substances like opioids, abuse drugs and alcohol is frequently encountered [24].

For decades, patients with ALF have been considered to have an acquired severe coagulopathy and increased risk for haemorrhagic complications. Current research has demonstrated a balanced haemostasis in such patients, although not to the extent of that of Acute-on-chronic liver failure. In a recent large observational study, only 11% of patients experience severe bleeding complications, both spontaneous and postprocedural blood loss, despite a profound alteration in standard coagulation tests [25]. It is now generally considered that, despite being a diagnostic criterion for ALF, standard coagulation tests overestimate de severity of coagulopathy in ALF and thrombotic complications may be as frequent as bleeding [26]. Routine correction of standard coagulation tests is no longer recommended and specific factors assays can guide targeted correction of specific factor deficits. Moreover, the use of viscoelastic testing, like thromboelastometry and thromboelastography, offer a better picture of the haemostatic process and specific protocols are currently available to guide coagulation management in patients with ALF.

Liver biopsy may be needed in cases in which commonly used paraclinical tests failed to determine the aetiological cause of ALF or when imaging results are unconclusive for a chronic liver disease. The transjugular route is usually preferred as it has been associated with the lowest complication rate. Liver biopsy may also be indicated in patients suspected of Wilson's disease, DILI or autoimmune hepatitis.

In up to 5% of patients no definitive aetiology for ALF can be identified. These patients may not have been completely evaluated or initial testing was not comprehensive enough. A superficial patient history may overlook prior medical treatments, including herbal medication, and the aetiology misdiagnosed as undetermined.

As ALF progression is usually rapid and hard to predict, all patients with a significant liver injury should be examined by an experienced ALF team to assess the potential benefit of emergency LT. As increased centre experience is associated with greater transplant free survival and reduced waitlist mortality for ALF, transfer to a dedicated liver ICU should be considered early in the disease course. Proposed criteria by the European Association for the Study of the Liver [27] are presented in Table 62.6.

Patient transfer should follow the same guidelines as any other critical ill patient and, when considered appropriate, an experienced retrieval team should be used. Careful patient assessment prior to transfer should be performed and appropriate fluid resuscitation, use of vasopressors to maintain stable haemodynamics and correction of metabolic and acid-base disturbances should be addressed. The fastest transfer route, usually air transport, is recommended and monitoring of neurological status and pupillary diameter (Fig. 62.2) as well as organ function should be frequently performed. In patients with HE a case-by-case decision should be made regarding tracheal intubation and commencement of mechanical ventilation considering the severity of HE and rapid progression to coma. A central venous line placed under ultrasound guidance to minimize complications, and invasive blood pressure monitoring are recommended for targeted vasopressor support and haemodynamic monitoring.

Table 62.6 EASL criteria for patient referral to a LT centre

| Paracetamol and hyperacute aetiologies	Non-paracetamol
Arterial pH < 7.30 or HCO_3 < 18	Arterial pH < 7.30 or HCO_3 < 18
INR > 3 on day 2 or IRN > 4 thereafter	INR > 1.8
Oliguria and/or increased creatinine	Oliguria/renal failure or Na^+ < 130 mmol/L
Altered level of consciousness	Hepatic encephalopathy, hypoglycaemia or metabolic acidosis
Hypoglycaemia	Bilirubin>17.6 mg/dL
Increased lactate unresponsive to fluid resuscitation	Shrinking liver size

Legend: *INR* international normalized ratio
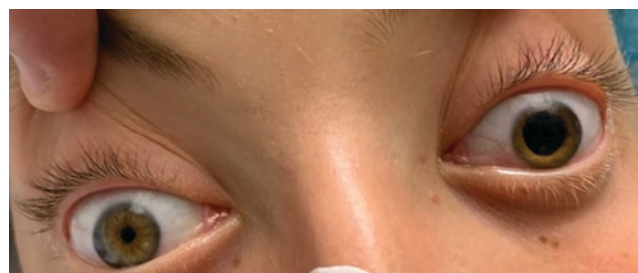
Fig. 62.2 Anisocoria developed during air transport in a patient with Acute Liver Failure

62.4 Prognostic Factors

For decades, medical research has focused on identifying factors associated with either decreased transplant free survival or unfavourable outcome after emergency LT. Most scoring systems are built around four determinants: aetiology, interval between jaundice and HE, age, and liver functional tests. Several prognostic criteria have been developed based on large cohorts of patients, but none have sufficient specificity and sensibility to be universally applied. Severity of EH is considered to be associated with a poorer outcome and patients should be routinely screened for irreversible brain damage before emergency LT is performed.

MELD is currently the most used scoring system for organ allocation in end-stage liver disease. Several studies have demonstrated its usefulness in mortality prediction for ALF. MELD scores over 30 are associated with a worse outcome [28]. However, the main disadvantage of MELD score is that it assesses only liver damage without taken into account associated organ dysfunction. Age is not only correlated with ALF mortality but also with mortality after LT. In a study performed by King's College [29] age above 45 years was associated with decreased survival after LT, especially in patients who received high dose vasopressors. However, age alone should not be considered a contraindication to LT. Other risk factors associated with a poorer outcome include time between jaundice to HE of over 7 days, presence of cerebral oedema, prothrombin time > 35 seconds and creatinine >1.5 mg/dL.

Specific prognostic factors of increased mortality have been identified in different aetiologies. Decreased survival in mushroom poisoned patients has been observed with increased prothrombin time and creatinine levels three to ten days after ingestion and a decrease in coagulation factor V under 20% has been proposed by some centres as an indication for emergency LT [30]. Patients with acute presentation of Wilson's disease and HE have almost 100% mortality. The main risk factors are represented by raised white blood cell count (WBC), bilirubin, INR, serum albumin and serum transaminases. A modified King's College score has been developed for early referral of patients with Wilson's disease to LT [31]. A cut-off value of 11 points was associated with 93% sensibility and 98% specificity (Table 62.7).

Patients with Acetaminophen overdose have a lower mortality compared with other aetiologies. However decreased survival has been observed in patients with high levels of acetaminophen. Early use of acetylcysteine has been associated with increased survival even in high dose intoxications. Viral hepatitis is generally associated with increased spontaneous remission, especially in patients with HAV and HEV.

Increased lactate has been proposed as a marker of severity in ALF. Patients presenting with high lactate levels, either due to decreased metabolism by the failing liver or tissue hypoperfusion have increased mortality rates. Lactate kinetics should be monitored closely especially in the perioperative period of LT. SOFA (Sequential Organ Failure Assessment) score and it's derivate the CLIF-SOFA score used in patients with Acute-on-chronic liver failure have been used to assess patient outcomes in patients with ALF. They may be superior to the classic MELD score as they offer a better picture of associated organ dysfunction. However, exact cut-off values to guide either proceed to liver transplantation or futility are treatment are still lacking.

The most used criteria for LT in ALF are represented by the Kings College Criteria and Clichy criteria (Table 62.8). Although validated in large cohorts of patients, their suboptimal sensibility and specificity deem careful utilisation and a case-by-case approach to either to proceed or not with LT should be considered.

The US-ALF Study Group Index has recently been described [32]. The authors identified HE grade, ALF aetiology, vasopressor support, log transformation of bilirubin and INR as significant prognostic factors associated with transplant-free survival. Based on these, they have constructed a predictive model. In the validation cohort, the US-ALF Study Group Index predicted 22-days transplant-free survival

Table 62.7 Modified King's College criteria for Wilson's disease

Score	Bilirubin (mg/dL)	INR	AST (U/L)	WBC (10⁹/L)	Albumin (g/L)
0	0–5.8	0–1.29	0–100	0–6.7	>45
1	5.9–8.7	1.3–1.6	101–150	6.8–8.3	34–44
2	8.8–11.7	1.7–1.9	151–300	8.4–10.3	25–35
3	11.8–14.7	2.0–2.4	301–400	10.4–15.3	21–24
4	>14.8	>2.5	>401	>15.4	<20

Legend: *INR* international normalized ratio, *AST* aspartate aminotransferase, *WBC* white blood cell count

Table 62.8 King's College and Clichy criteria for LT in ALF

King's College criteria	
Acetaminophen overdose	Non-acetaminophen overdose
Arterial pH < 7.30 after fluid administration *Or* all of the following: • Prothrombin time > 100 s (INR > 6.5) • Serum creatinine>3.4 mg/dL • Grade 3 or 4 HE	Prothromin time > 100 sec (INR > 6.5) *Or* any 3 of the following: • Non-A, non-B viral hepatitis, DILI or indeterminate aetiology • Time from jaundice to HE >7 days • Age < 10 or > 40 • Prothrombin time > 50 sec (INR > 3.5) • - Serum bilirubin>17.4 mg/dL
Clichy Criteria	
Presence of HE **and** Factor V levels <20% in patients <30 years of age *Or* Factor V level < 30% in patients>30 years of age	

Legend: *INR* international normalized ratio, *DILI* drug induced liver injury, *HE* hepatic encephalopathy

with a c-statistic value of 0.84. However, this predictive model has to be validated by larger multicentre studies.

Other aetiology-specific scoring systems have also been investigated in the last years. The research team from King's College developed and validated a new statistical model to predict survival in patients with paracetamol-induced ALF [33]. In their two-day model, the authors included age, cardiovascular failure, Glasgow coma scale, arterial pH, creatinine, INR and arterial lactate as well as dynamic changes from day 1 to day 2 of arterial lactate and INR. This dynamic model predicted 30-days survival in 91% of patients. The ALFA (Hepatitis A-ALF) score [34] was developed in Korea to predict LT or 30-days death in patients with acute HVA hepatitis. The ALFA score contains paraclinical values acquired on the day of ALF diagnosis: age, INR, bilirubin, ammonia, creatinine, and haemoglobin. This score accurately predicted LT or death within 30 days in 87% of patients.

A recent international consensus of 35 experts in the field of LT defined threshold criteria for futility [35]. Severe frailty, and septic patients with persistent fever despite antibiotic treatment or less than 72 hours of appropriate antimicrobial therapy were considered reasonable criteria to delay LT. Most experts agreed that any of the following $PaO_2/FiO_2 < 150$, need for vasopressor support exceeding 1 µg/kg/min and a serum lactate level > 9 mmol/l were sufficient to contraindicate LT.

62.5 Bridging Patients to Liver Transplantation

Patients with ALF are best managed in the ICU. However, the exact criteria for ICU admission vary between centres depending on personal experience, availability of ICU beds and possibility of adequate treatment in the early stages on the general ward. However, patients should be frequently monitored for severity of HE, organ dysfunction or other life-threatening conditions. Advanced haemodynamic monitoring is usually recommended since most patients are volume depleted. Adequate fluid resuscitation should be performed but overzealous volemic therapy may aggravate cerebral oedema. Arterial and central venous lines may be placed in order to have an accurate beat-by-beat reading of arterial blood pressure and central venous pressure, but measures should be taken to avoid blood stream infections. Dynamic indices of fluid responsiveness are best used to guide fluid management and they should be frequently assessed. Hypotonic solutions, like Ringer lactate, should be avoided as they carry an increase risk of cerebral oedema and progression of HE. Lactate levels are hard to interpret in ALF patients as lactate may be high due to either tissue hypoperfusion or decreased metabolism by the liver. In low grade HE, the oral route is preferred, but if HE progresses patients may require urgent intubation and, in this situation, a nasogastric tube is preferred.

Enteral nutrition should be promptly initiated, if no contraindications (severe shock, gastro-intestinal dysfunction or ileus), as muscle wasting, and gastro-intestinal bacterial translocation are common findings in malnourished states associated with a worse outcome. Hypoglycaemia is a common in patients with severe ALF due to impaired gluconeogenesis, hyperinsulinemia and depleted glycogen stores. Glycaemia should frequently be monitored, and a continuous glucose infusion should be started if hypoglycaemia occurs. As hyperglycaemia increases intracranial pressure, a tight glucose control should be applied with a target blood glucose levels between 150–180 mg/dL [27].

Specific aetiological treatment should be promptly initiated to increase the likelihood of spontaneous remission (Table 62.9). N-acetylcysteine (NAC) was demonstrated to improve outcome in non-acetaminophen ALF. In a recently published trial [36], the use of an empirical therapy of 150 mg/kg in 100 ml 5% dextrose over 1 h, then 70 mg/kg over 20 h, followed by continuous infusion over 24 h of 150 mg/kg caused a reduction in mortality and need for transplantation. Also, early administration of NAC decreased the severity of HE, hospital stay, need for ICU admission and incidence of organ failure.

Hepatic encephalopathy represents one of the most severe organ dysfunctions associated with increased mortality in ALF patients. Although pathophysiological mechanisms are

Table 62.9 Aetiologic treatment of ALF

Aetiology	Specific therapy
Acetaminophen overdose	Gastric lavage and activated charcoal; NAC: loading dose of 150 mg/kg in 5% dextrose over 15 m; maintenance dose is 50 mg/kg given over 4 h followed by 6 mg/kg administered for up to 72 hours.
HVB	Antiviral therapy with entecavir or tenofovir
Autoimmune hepatits	Prednisone 40–60 mg/day
Wilson's disease	Continuous renal replacement therapy; Plasma-exchange
Budd-Chiari syndrome	Transjugular intrahepatic portosystemic shunt or surgical Porto-systemic shunt; Systemic anticoagulation
Mushroom poisoning	Gastric lavage and activated charcoal; High-dose Penicillin G 300,000–1,000,000 U/kg/day; Silymarin 30–40 mg/kg/day Albumin dialysis
HELLP syndrome	Delivery of the foetus
Herpes simplex virus	Acyclovir 5–10 mg/kg q 8 hours

Legend: *NAC* N-acetylcysteine, *HVB* hepatitis B virus, *HELLP* Hemolysis, Elevated Liver enzymes and Low Platelets

poorly understood, accumulation of liver toxins and systemic inflammation are key factors in the development of cerebral oedema and intracranial hypertension (ICH). Intracranial pressure (ICP) monitoring has been advocated to guide specific therapy, but its use is not universally accepted due to high complications rates including intracranial bleeding and infection. In an international survey [37] only 55% of centres used invasive ICP monitoring. The main indications were papillary abnormalities, renal failure, elevated ammonia levels and cardiovascular instability. New non-invasive techniques applying transcranial Doppler are becoming more popular, but their use is dependent on expertise. When measured, an ICP above 20 mmHg mandates urgent treatment. The aim is to decrease ICP and maintain a cerebral perfusion pressure above 50 mmHg in order to minimize cerebral ischemia. General measures taken to lower ICP include maintaining a neutral head position and raising the head at an angle of 20° to facilitate venous drainage. Prophylactic treatment of seizures is not recommended, but they should be promptly managed if diagnosed. Osmotic diuretics have long been used to lower cerebral oedema. Mannitol, in doses of 0.5–1 g/kg intravenously lowers ICP from >60 mmHg to 20 mmHg. However, its effects are short-lived and serious complications can occur. Plasma osmolarity should be closely monitored and mannitol administration stopped if it exceeds 320 mOsm/L. Common side-effects of mannitol therapy include hypernatremia, hyperosmolarity and fluid overload in patients with renal failure. Decreasing arterial pressure of carbon dioxide ($PaCO_2$) to levels between 25–30 mmHg is associated with a decrease in cerebral blood flow and ICP due to cerebral vasoconstriction. This can be obtained in mechanically ventilated and sedated patients by increasing the minute-volume. However, a low $PaCO_2$ for more than 72 hours has been associated with a worse neurological outcome [38]. Hypertonic saline, with a target of plasma sodium levels between 145–155 mEq/L, has been used to prevent and treat ICH. Sodium levels should be frequently monitored, and therapy guided as such that not to increase sodium by more than 16 mEq/L in 24 hours in order to avoid pontine demyelination. Hypothermia has historically been used to decrease cerebral metabolic rate. In patients with ALF at high risk of ICH, lowering the body core temperature to 33–34 °C did not confer a survival benefit or a lower incidence of ICH [39]. Routine hypothermia is not recommended, but temperature management should be applied to maintain normothermia and specially to avoid fever. Sedation has also been applied to decrease the cerebral metabolic rate or to facilitate mechanical ventilation in intubated patients. Propofol is frequently used due to its rapid onset, short context-sensitive half-life and effects in decreasing the risk of seizure activity. However, careful dose titration and short duration of therapy should be applied to avoid propofol infusion syndrome. Sedation breaks should be offered to allow for neurological examination in order to assess the severity of HE.

Cardiovascular changes associated with ALF are similar with those of sepsis. Patients have a hyperdynamic haemodynamic pattern characterised by an increased cardiac output and low systemic vascular resistance. Secondary to these changes, the mean arterial pressure is usually decreased, and this predisposes patients to tissue hypoperfusion. Cardiac arrhythmias are frequent and range from supraventricular tachycardia, premature supraventricular or ventricular beats to atrial fibrillation. These are mostly due to accumulation of bilirubin and bile salts, viral myocarditis or acid-base and electrolyte abnormalities. ST segment changes on the EKG may be encountered but are rarely of pathological significance. Patients should routinely be investigated for underlying cardiac disease, especially those who require cardiovascular support. Normovolemia should be maintained in the ICU and dynamic tests to assess fluid responsiveness (stroke volume variation, pulse pressure variation) should guide fluid management. Noradrenaline is the recommended vasopressor of choice and a mean blood pressure > 75 mmHg should be maintained to assure cerebral and renal perfusion.

Respiratory dysfunction may be encountered especially in patients with severe HE. Non-invasive ventilation is not recommended and endotracheal intubation to protect the airway from aspiration pneumonia is preferred. Mechanical ventilation should follow lung protective strategies, even in non-ARDS patients. Inspiratory pressures and respiratory rate should be titred to obtain a tidal volume of 6 ml/kg/ideal body weight and to maintain a normal arterial CO_2 and O_2 partial pressures. Hypercarbia should always be avoided as it increases cerebral blood flow and hypocarbia should only be applied for brief periods in severe ICH. Low levels of PEEP should be applied in non-ARDS patients as not to impair venous drainage through the superior vena cava. Care should be taken to prevent ventilator associated pneumonia and appropriate use of physiotherapy and patient positioning should be used.

Infections are common in ALF and patients are frequently at risk of developing sepsis and septic shock. Severe infections may contraindicate LT and so patients should undergo routinely bacteriological screening. As severe systemic inflammation is frequently encountered in these patients, the diagnosis of sepsis becomes difficult. Standard markers, such as a raised white blood cell count, are a common finding in non-infected ALF patients. C-reactive protein is synthetised by hepatocytes and may de decreased in infected patients with severe liver failure. A high grade of suspicion should be maintained, and cultures should be performed in patients with severely progressive HE [40]. Prophylactic antibiotics should not be routinely administered as they increase the risk of multi-drug resistant bacteria. Empirical antibiotherapy may be administered in patients with progres-

sive grade III or IV HE, hypotension requiring vasopressor support and at least 2 SIRS criteria. Broad spectrum antibiotics are generally used to cover both Gram-positive and Gram-negative bacteria.

Acute kidney injury (AKI) is one of the most frequent extra-hepatic organ dysfunctions in patients with ALF and is associated with a worse outcome. In most cases renal hypoperfusion, direct drug-induced nephrotoxicity and systemic inflammation are responsible for the rapid decline in kidney function. Maintaining renal function is crucial in patients with ALF. This should be done my maintaining an adequate kidney perfusion pressure, early treatment of infections and avoidance of nephrotoxic medication. In AKI patients, urgent treatment and early initiation of renal replacement therapy should be considered as fluid overload, acid-base and electrolyte abnormalities may aggravate HE and ALF. Continuous renal replacement therapy is preferred to intermittent dialysis as it avoids the rapid metabolic and haemodynamic changes associated with intermittent dialysis. Outside AKI, the use of high-volume hemofiltration has been associated with an increased removal of ammonia and improvement in neurologic dysfunction and may be applied in patients with increased ICP where standard measures have failed [41].

Coagulation management in patients with liver disease has been extensively studied in the last years. Although standard coagulation tests are still used for the diagnosis of ALF, they do not accurately reflect haemostasis. Thromboelastometric studies have demonstrated that in general the haemostatic balance is maintained in ALF patients: the decreased synthesis of pro-coagulant factors is compensated by an increased in coagulation factor VIII and a decrease in anti-coagulant factors [26]. Fresh frozen plasma administration for correction of standard coagulation tests in the absence of clinical signs of bleeding is not recommended. However, specific factors deficits should be corrected if invasive procedures or surgery is planned and guided by thromboelastic tests. Factor concentrates, as fibrinogen and pro-thrombin complex are generally recommended as they avoid the complications of fresh frozen plasma administration like fluid overload and transfusion related acute lung injury. Platelet transfusion in recommended to maintain levels between 50,000–70,000/μL before invasive procedures. Although not universally accepted, in bleeding patients, platelet count should be maintained above 50.000/μL. Fibrinogen concentrate can be administered to maintain fibrinogen levels between 150–200 mg/dL [42].

62.6   Extracorporeal Liver Support Systems

Ideally, extracorporeal liver support systems (ECLS) should assist 3 major hepatic functions: detoxification, biosynthesis and regulation. To date, no system successfully

Table 62.10 Main indications for Extracorporeal liver support systems

Acute liver failure
Acute-on-chronic liver failure and one of the following:
Hepatic encephalopathy
Severe jaundice
Acute kidney injury
Severe pruritus
Acute intoxications (e.g. Mushroom poisoning, acetaminophen overdose)
Posthepatectomy liver failure
Primary graft non-function after liver transplantation

managed to accomplish this. Two types of ECLS have been introduced into clinical practice: artificial-ECLS and bioartificial-ECLS. Artificial-ECLS are based on the principles of adsorption and filtration and are aimed at removing circulating toxins by using membranes with different pore sizes and adsorbent columns. Bioartificial-ECLS are hybrid systems that incorporate hepatocytes, either human or porcine, in a bioactive platform. Their primary aim is to improve detoxification and support liver synthesis. ECLS have been used in different clinical situations with conflicting results (Table 62.10).

The most common used artificial-ECLS in clinical practice are MARS (Molecular Adsorbent Recirculation System) and Prometheus (Fractionated plasma separation and adsorption).

In MARS dialysis, blood is circulated against an albumin-contained solution. The filter contains a high-flux membrane with small porosities (<50 kDa). Toxins are cleared by diffusion and are bound by the albumin dialysate. Initial studies have demonstrated a significant removal capacity for bilirubin, bile acids, creatinine and urea [43] and an improvement in HE. A large multicentre study failed to demonstrate an improvement in survival in patients with ALF. However, patients on MARS had a higher change of receiving a liver transplant [44]. A meta-analysis that included 4 randomised trials comparing MARS with standard medical therapy has demonstrated a slight increase in survival in patients with ALF [45]. In the Prometheus system, plasma is fractionated through an albumin-permeable filter with a cut-off of 250 kDa. Albumin and plasma proteins cross the membrane and pass through two columns, an anion-exchanger and a neutral resin adsorber. The plasma is then returned to the blood circuit where it undergoes conventional high-flux haemodialysis. In clinical studies, the use of Prometheus was associated with an improvement in liver functional tests. However, a large multicentre study failed to demonstrate a survival benefit in patients with Acute-on-chronic liver failure [46]. Based on these evidence, current guidelines do not recommend the routine use of ESLD in patients with ALF [27].

The use of plasma-exchange (PE) in patients with ALF offers some theoretical benefits: higher removal of molecules compared to ESLD and substitutes plasma products includ-

ing coagulation factors, improvement in haemodynamic parameters and related organ dysfunctions [47] and enhanced recovery in specific patient populations [48]. In a recent large open randomised controlled trial, the use of high-volume PE has been associated with increased transplant free survival. This was attributed to attenuation of innate immune activation and improvement of multi-organ dysfunction [49]. Current guidelines suggest that PE may be of greater benefit in patients if it is applied early in the disease course and in those patients who will benefit from emergency LT [27].

62.7 Timing of Liver Transplantation

The optimal timing for LT has long been debated without reaching an international consensus. In lack of evidence to guide the optimal timing for LT, the decision should be made by an experienced team on a case-by-case basis taken into account the severity of liver dysfunction and associated organ failures, progression of HE, severity scores, futility and co-existing disease as well as organ availability. As mentioned, such patients are best managed in a dedicated LT centre and early referral is useful in decision-making.

Patients fulfilling current transplant criteria should be listed for emergency LT and re-evaluated if a suitable organ graft becomes available. Based on existing criteria, an algorithmic approach to properly address the timing of LT in patients with ALF should soon follow. Patients who fulfil transplant criteria and have multiple factors associated with a poor prognosis, as well as patients in whom HE is rapidly progressing should undergo emergency LT. As previously mentioned, a clinical evaluation of co-morbidities, severity of ALF and extrahepatic organ failure and their prognosis should proceed the decision to continue with LT. The patient's family as well as a psychiatrist should also be involved in patients who ingested hepatotoxins in a suicidal attempt. A "wait and see" approach is more suitable in patients who exhibit signs of improvement under standard medical care and in patients with acetaminophen overdose without HE. A good liver graft is recommended in such patients, as well as living-donor LT and, outside severe ALF, incompatible ABO LT is seldom required. Patients with irreversible brain damage, sepsis, associated pancreatitis and rapidly increasing vasopressor support are rarely suitable candidates for LT.

Three type of LT have been described in patients with ALF: deceased—donor LT (DDLT), living—donor LT (LDLT) and auxiliary LT. Auxiliary LT has been used since more than 30 years ago based on the potential regeneration of the native liver if sufficient time is provided by by-passing it with a partial liver graft in an orthotopic position. The auxiliary liver should maintain partial hepatic function to assure survival until regeneration of the native liver is complete. When the native liver is regenerated, immunosuppression is progressively reduced, and this leads to graft atrophy. The

surgical intervention is technically challenging and should be performed in well-experienced centres. Outcome data are limited to a low number of cases. A recent study reporting data from 13 preadolescents undergoing auxiliary-LT showed a 100% survival and with 10 patients being off immunosuppression therapy [50]. Older studies showed survival rates between 63% and 85% with different immunosuppression-free rates [51]. Patients considered suitable for auxiliary—LT are generally children and young adults because of their excellent regenerative potential. Also, auxiliary—LT should be the considered in aetiologies for associated with rapid liver regeneration such as acetaminophen overdose, HVA, HVE and mushroom poisoning.

A whole liver graft is preferred in ALF patients, especially in those with severe HE and associated organ dysfunction. However, due to urgency of LT and declining number of organ donors, as well as decreasing graft quality, many centres are performing more LDLT in detriment of DDLT. The use of marginal liver grafts from older donors and those with advanced hepatic steatosis has been associated with a negative impact on post-LT survival and perioperative complications [29]. The use of ABO-incompatible liver grafts has also been advocated. Such patients require extensive pre-transplant preparation and advanced protocols are in place [52]. However, data from the ELTR registry show a worse graft and recipient survival in patients with ABO-incompatible grafts [53], and hence, this option should be reserved for extreme cases that require emergency LT and no other liver grafts are available. As mentioned, LDLT is becoming extensively used outside Asia, in Europe and the Unitated States. However, this technique carries significant ethical issues, and a psychologist should always be involved since next of kin may experience emotional pressure to donate. Patient outcomes are good, are survival is similar to that reported for elective LDLT [54].

Changes in practice and early referral of such patients to dedicated liver ICU has significantly improved outcomes over the last years. A Scottish audit showed a constant improvement in spontaneous survival over time in ALF due to acetaminophen and non-paracetamol aetiologies [55]. This improvement was also observed even in the sickest patients meeting King's College criteria and in those undergoing LT. The main causes for mortality following LT for ALF are infection and sepsis, progressive organ failure and liver graft dysfunction or failure.

62.8 Conclusion

In conclusion, ALF is a rare but life-threatening organ dysfunction associated with increased mortality and morbidity if appropriate measures are not urgently applied. Such patients are best managed in dedicated liver intensive care units by experienced multidisciplinary teams and expert consult

should be sought out early in the course of the disease. Early assessment is required in order to diagnose aetiology as well as associated organ dysfunction and initiate appropriate treatment. Management of ALF patients has significantly improved in the last years and spontaneous recovery without the need for LT is frequently encountered. However, criteria for indicating LT and the optimal time to perform it remain under debate and to date no scoring system can predict with sufficient accuracy and precision patient outcome. Patients should be listed for emergency LT early in the course of ALF and when a suitable liver graft is available the decision to proceed or not to LT should be made individually based on severity and progression of the disease.

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