Acute Liver Failure

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Key Concepts

- Acute liver failure is defined by the deterioration of liver function tests, hepatic encephalopathy, and potentially associated dysfunction of other organs (such as acute respiratory distress syndrome, acute kidney injury, gastrointestinal bleeding, pancreatitis, sepsis) in a patient without underlying chronic liver disease.
- Untreated, the prognosis of acute liver failure is very poor, with a high mortality.
- Early recognition of acute liver failure, establishment of the etiology and relocation to a liver transplantation center, or tertiary intensive care specialized in acute liver failure are primordial measures in treating acute liver failure patients.

32.1 Introduction

Acute liver failure (ALF) is defined as the acute episode of hepatocellular severe dysfunction characterized by the deterioration of liver function tests, hepatic encephalopathy (HE), and potentially associated dysfunction of other organs [such as acute respiratory distress syndrome, acute kidney injury (AKI), gastrointestinal bleeding, pancreatitis, sepsis] in a patient without underlying chronic liver disease [1]. Untreated, the prognosis of ALF is very poor, with a high mortality. The patients with ALF should be managed in Intensive Care Unit (ICU) where therapy should be applied based on the specific etiology of ALF and should be started as early as possible. Broadly, the medical management of ALF is supportive until recovery of the native liver or until the liver transplantation is an option. Accordingly, liver transplantation is the only proven treatment option for patients who do not recover spontaneously.

32.2 Definition

ALF is the clinical entity defined by the presence of encephalopathy and coagulopathy (impaired synthetic function with INR $\geq$1.5) within <26 weeks of the onset of symptoms, in a patient without cirrhosis or underlying chronic liver disease [1, 2]. When patients develop coagulopathy without any alteration of their consciousness level is defined as ***acute liver injury*** (ALI) [1]. A severe form of ALI can precede the installation of ALF. Other used terms for ALF are "fulminant hepatic failure", "acute hepatic necrosis", "fulminate hepatic necrosis" or "fulminant hepatitis".

In 1999 the International Association for the Study of the Liver (IASL) defined the subcategories of ALF based on the duration of disease from the beginning until the occurrence of hepatic encephalopathy (HE): ***hyperacute ALF*** as less than 10 days, ***fulminant ALF*** as 10–30 days and ***subacute hepatic failure*** as 5–24 weeks [3]. The fulminant type of ALF requires the presence of HE, severe coagulopathy, markedly increases serum transaminases, and jaundice; whereas the subacute type of ALF does not necessarily have HE and is mainly characterized by severe jaundice and ascites, mild/moderate coagulopathy and serum transaminases level [1].

Acute deterioration of liver function in case of patients with chronic liver disease known also as acute-on-chronic liver failure; or after extensive liver resection or liver trauma; liver injury secondary to systemic diseases; and secondary to alcohol abuse (alcoholic hepatitis) may fulfill clinical features of ALF, but they are not considered ALF. However, exceptions are considered in case of de

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novo presentation of patients with Wilson disease, vertically acquired hepatitis B, Budd-Chiari syndrome, or autoimmune hepatitis, which may be considered ALF despite of cirrhosis, if their disease has been manifested for less than 26 weeks [1, 2].

32.3 Etiology

Through the last decades, the etiology of ALF changed, with the declining incidence of hepatitis A and B, and elevation of paracetamol (acetaminophen) overdose, especially in Western Europe and United States [1, 2]. Moreover, there are also differences in etiology between developing and developed countries such as Europe and United States characterized by high incidence of paracetamol toxicity along with drug-induced liver injury (DILI) due to prescription agents. By contrast, South Asia and Hong Kong have a higher incidence of viral hepatitis.

Etiologies of ALF are the best indicators of prognosis, and require specific management options, such as an emergency liver transplantation (LT). The clinical course of different ALF etiologies is presented in Table 32.1 [1].

Lastly, European Association for the Study of the Liver recommends the classification of ALF based on their etiologies. Therefore, the etiologies of ALF are further divided in etiologies **with** possible indication for emergency LT, and etiologies **with no** indication for emergency LT [1].

Table 32.1 The clinical course of different ALF aetiologies with permission [1]

Precipitant	Examples	Presentation
Viral	Hepatitis A, E, B (less frequent CMV, HSV, VZV, Dengue)	Acute/fulminant
Drugs/ toxins	Paracetamol (acetaminophen), phosphorous, *Amanita phalloides* Anti-tuberculous, chemotherapy, statins, NSAI, phenytoin, carbamazepine, ecstasy, flucloxacillin	Acute/fulminant and subacute/ subfulminant Acute/fulminant
Vascular	Budd Chiari Hypoxic hepatitis	Acute/fulminant and subacute/ subfulminant Acute/fulminant
Pregnancy	Pre-eclamptic liver rupture, HELLP, fatty liver of pregnancy	Acute/fulminant
Other	Wilson disease, autoimmune, lymphoma, malignancy, HLH	Acute/fulminant and subacute/ subfulminant

CMV cytomegalovirus, *HSV* Herpes simplex, *NSAI* non-steroidal anti-inflammatory, *HELLP* haemolysis, elevated liver enzymes, low platelets, *HLH* haemophagocytic lymphohistiocytosis

32.3.1 Etiologies with Possible Indication for Emergency LT

The main causes of ALF with possible indication of LT are drug related hepatotoxicity (paracetamol, idiosyncratic drug reaction), toxin-related hepatotoxicity, viral hepatitis, autoimmune hepatitis, Wilson disease, Budd-Chiari syndrome, and pregnancy related liver failure) [1].

32.3.1.1 Drug-Related Hepatotoxicity

Many drugs could be the cause of drug-induced liver injury (DILI) which is a leading cause for emergency LT [4], especially in developed countries.

32.3.1.2 Acetaminophen (Paracetamol) Toxicity

Even if paracetamol—a widely used drug to ameliorate pain—rarely determines hepatotoxicity at therapeutic dose (<4 g/day in adults), this may occur after ingestion of large doses for suicidal purposes or nonintentional (ingestion of excessive amounts of paracetamol containing compounds such as opioid-paracetamol compounds). Hepatotoxicity can even occur at therapeutic dose, if other factors exist, like decreased glutathione reserves (in alcohol ingestion, fasting, malnutrition) or with medication known to induce cytochrome P450 system (anticonvulsants).

In the very early stages of paracetamol ingestion, the clinical syndrome is mainly characterized by severe metabolic acidosis, high lactate level, mild elevation of transaminases, minimal or any coagulopathy; being the consequence of the drug effect with liver functional mitochondrial standstill [1]. Subsequently, paracetamol hepatotoxicity is characterized by extreme high level of serum aminotransferase >10,000 IU/L, normal bilirubin level, hypoglycemia, and acute kidney injury (AKI). The progression of paracetamol induced hepatotoxicity is often rapidly to HE with coma and multiple organ failure [1].

32.3.1.3 Idiosyncratic Drug Reaction

ALF due to idiosyncratic drug reactions known as drug induced liver injury (DILI) may occur after any type of medication. It is a finding of older patients >60 years [1]. The most common implicated drugs are ***antibiotics*** (ampicillin-clavulanate, tetracyclines, macrolides, ciprofloxacin, nitrofurantoin), ***antituberculosis drugs*** (isoniazid, pyrazinamide), ***anticonvulsants*** (phenytoin, valproate), ***antidepressants*** (amitriptyline, nortriptyline), ***non-steroidal anti-inflammatory*** (NSAIDs), ***immunosuppressive agents*** (cyclophosphamide, methotrexate), and ***halothane***.

Shortly, mechanisms involved in hepatic injury are (1) the disruption of intracellular calcium homeostasis; (2) injury of the canalicular transport pumps, such as multidrug resistance–associated protein 3; (3) T cells mediated immunologic injury; (4) triggering of apoptotic pathways by tumor

necrosis factor-α; and (5) the inhibition of mitochondrial beta oxidation [5].

Herbal supplements, alternative medicine, weight loss agents and other nutritional supplements have been also associated with idiosyncratic hypersensitivity reactions, such as Ginseng, Kawakawa and St. John's Wort.

Some illicit drugs (ecstasy, cocaine and phencyclidine) have been associated with idiosyncratic hypersensitivity reactions. For instance, ecstasy induced liver injury presents as an "heat shock related liver injury" with severe hyperthermia, multiple organ dysfunction, profound coagulopathy, and severe rhabdomyolysis [1, 6].

Even rarely, consider ***DRESS syndrome*** or **D**rug **R**eaction with **E**osinophilia and **S**ystemic **S**ymptom **S**yndrome, in case of clinical picture with (1) fever; (2) severe cutaneous rash; (3) lymphadenopathy and (4) eosinophilia [1]. DRESS syndrome is a hypersensitivity drug reaction and is most frequently associated with antiepileptic or anticonvulsivants, some antibiotics/antivirals, sulphur containing compounds, and NSAIDs [1]. Broadly, DRESS syndrome is characterized by skin rash, fever, pharyngitis, lymphadenopathy, and visceral organ involvement, typically presenting within eight weeks of therapy. Liver is one of the most common organs involved in DRESS Syndrome and liver failure is the most common cause of death in these patients. Liver abnormalities manifest with hepatomegaly, increased level of serum aminotransferases, hepatitis or even liver failure. Recent studies have suggested a close relationship between Herpes Viruses and DRESS syndrome. Management of this syndrome include withdrawal of the causative drug, supportive therapy in ICU, and systemic steroids.

32.3.1.4 Toxin-Related Hepatotoxicity

Different toxins are associated with dose-related toxicity:

- *Amanita phalloides* mushroom toxin—this mushrooms poisoning is more common in Europe compared with United States, and it is manifested in the first phases by muscarinic effects (sweating, salivation, vomiting, diarrhea, and so on). Later, after 4–8 days is associated with ALF.
- Organic solvents (e.g., carbon tetrachloride)
- Yellow phosphorus
- Aflatoxins—are defined as a family of toxins produced by certain fungi—*Aspergillus flavus* and *Aspergillus parasiticus*, that are found in agricultural crops such as maize (corn), peanuts, cottonseed, and tree nuts.

32.3.1.5 Viral Hepatitis

Although viral hepatitis has become a relatively infrequent cause of ALF in Europe or United States, it remains the commonest cause of ALF in Asia and Africa, with hepatitis virus type A, B and E involvement. Importantly, if HBV is the main cause of ALF in Far East countries, hepatitis E virus (HEV) is more common in India [7], and hepatitis A virus in United States.

32.3.1.6 Hepatitis B Virus (HBV)

Hepatitis caused by virus type B can evolve to ALI or ALF. HBV infection is classified de novo (acute primary infection), reactivation of HBV infection (occurred during or after treatment-induced immunosuppression after solid organ or for hematological malignancies transplantation), or superinfection with hepatitis D virus (HDV). In the last situation, the identification of patients at risk and the administration of antiviral prophylactic treatment before the initiation of immunosuppressive therapy are mandatory with benefits [8].

32.3.1.7 Hepatitis A Virus (HAV)

Hepatitis A virus is mainly transmitted by food or drinking water polluted with infected feces being common in India [9, 10]. ALF occurs in less than 1% of cases of acute hepatitis A but could be a form of HAV evolution in older adulthood, or in patients with preexisting chronic liver disease [1]. Vaccination, as a form of prevention, is recommended for adults traveling in endemic area or for high-risk group.

32.3.1.8 Hepatitis E Virus (HEV)

Infection caused by HEV is rare in USA or Western Europe, but it is a significant cause of liver failure in endemic areas such as Russia, Pakistan, Mexico, and India. ALF due to hepatitis E has a worse outcome in elderly, pregnant women, and patients with underlying chronic liver disease [11].

32.3.1.9 Hepatitis D Virus (HDV)

ALF occurs in 2.5–6% of HDV infections. The coinfection of HBV and HDV, or superinfection of a chronic HBV patient with HDV, can both lead to ALF, but with a higher risk in those with coinfection.

32.3.1.10 Hepatitis C Virus (HCV)

Acute hepatitis C rarely causes ALF.

32.3.1.11 Other Viral Infection

Some viruses are implied in the etiology of ALF including herpes simplex virus 1 and 2 (HSV 1, 2), varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, yellow fever virus, adenovirus, and parvovirus B19 especially in immunosuppress patients. Moreover, virus infection may be a cofactor for DILI development.

To date, ALF is a rare complication of HSV or varicella-zoster infection, which may appear especially in immunocompromised patients (such transplanted recipients or HIV infected patients), pregnant women (usually in the third trimester), those with cancer or myelodysplastic syndromes, and rarely in immunocompetent patients. In 50% of patients

with ALF caused by HSV, the skin lesion may be missing and in this case liver biopsy could be helpful for making the diagnosis. Treatment should be initiated with acyclovir (5–10 mg/kg every 8 h for at least 7 days) for suspected or documented cases [12]. As a side note, Epstein-Barr virus and CMV infection are rare causes of ALF, but blood screening for these two viruses should be done for all patients with unclear etiology of ALF.

32.3.1.12 Autoimmune Hepatitis

Patients with autoimmune hepatitis (AIH), same to Wilson disease, may have unrecognized preexisting chronic liver disease. However, if they develop hepatic failure, they should be considered as having ALF, if their disease has been manifested for less than 26 weeks. AIH should be suspected in patients with other autoimmune disorders presented with ALF. The diagnostic can be established by laboratory tests (fraction of globulin elevated, positive autoantibodies) or by liver biopsy [1].

AIH patients that develop ALF represent the most severe form of the disease; and they have the generally recommendation to receive corticosteroid therapy in early stages, if possible. Nonetheless, steroid treatment may be effective, sometimes the lack of improvement requires emergency LT.

32.3.1.13 Wilson Disease

Patients with Wilson disease represent 6–12% from ALF cases. These patients are generally young women <20 years old which present hemolytic anemia (Coombs negative), very high serum bilirubin and low alkaline phosphatase, and very increased serum and urinary cooper [13]. Accordingly, ALF in patients with Wilson disease may be precipitated by a viral infection. Common diagnostic testing for Wilson's disease includes serum ceruloplasmin, and assessment of serum and urinary cooper. Only that, the tests have high false-positive and false-negative rates, but this is unlikely to alter the management of ALF caused by Wilson's disease where LT is the ultimate choice.

32.3.1.14 Budd-Chiari Syndrome

Budd-Chiari syndrome is an uncommon condition induced by thrombotic or non-thrombotic obstruction of the hepatic venous outflow. It is characterized by hepatomegaly, ascites, and abdominal pain, and rarely presents as ALF. Early recognition and prompt treatment with anticoagulant therapy, thrombolytic therapy, and interventional radiology may result in good recovery.

32.3.1.15 Pregnancy: Acute Fatty Liver of Pregnancy and HELLP Syndrome

Acute fatty liver of pregnancy (AFLP) is a rare and severe complication of the third trimester of the pregnancy (30–38 week of gestation), caused by the free fatty acids accumulation in maternal blood and hepatocytes with the infiltration of the liver, which may cause ALF. The initial symptoms in patients with AFLP are usually nonspecific (nausea, vomiting, abdominal pain, malaise, headache), but often associate hypertension, with or without proteinuria, possibly due to preeclampsia. Signs and symptoms of ALF, including jaundice, ascites, encephalopathy, disseminated intravascular coagulopathy, and hypoglycemia can rapidly progress. Most patients develop acute kidney injury, and often progress to multiorgan failure [14]. Laboratory findings are elevated serum aspartate aminotransferase/alanine aminotransferase (AST/ALT), hypoglycemia, elevated levels of bilirubin and blood ammonia, low platelet count, and low fibrinogen. If it is not diagnosed and treated promptly, AFLP can result in high maternal and neonatal morbidity and mortality. Management of AFLP includes prompt delivery of the fetus, maternal stabilization and support, with the goals to recover damaged liver. Liver transplantation for fulminant hepatic failure caused by AFLP has been reported, but transplantation is unlikely to be needed with early diagnosis and prompt delivery of the fetus [15, 16].

HELLP syndrome defined by haemolysis, elevated liver enzyme levels, and low platelet levels, is a life-threatening condition through the third trimester of the pregnancy. Presently, the etiology of HELLP is not clear, but same to preeclampsia is due to an inadequate placental perfusion that results in placenta hypoxia and secondary in activation of coagulation cascade, thrombocytopenia, microvascular organs damage, with hepatic damage.

Same to AFLP, its presentation has nonspecific symptoms such as general altered state, nausea, vomiting, epigastric or right upper quadrant pain, and edema. The laboratory tests reveal thrombocytopenia, anemia and increase bilirubin level (secondary to hemolysis), elevated serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) and lactate dehydrogenase (LDH) levels (secondary to liver dysfunction), low fibrinogen level and increased D-dimers due to fibrinolysis/DIC. Accordingly, the most common liver histological lesions are periportal necrosis and microvascular thrombosis which can evolve into subcapsular hematomas and even to hepatic rupture. Management of HELLP syndrome consists in early recognition, stabilization of the mother, seizure prophylaxis (intravenous magnesium sulfate), treatment of hypertension, corticosteroid therapy and delivery.

32.3.2 Etiologies with No Indication of LT

32.3.2.1 Malignancies

Briefly, malignancies associated with hepatic failure can be divided into primary liver tumor (hepatocarcinoma and cholangiocarcinoma), and secondary liver tumor such as metastatic infiltration of the liver with adenocarcinoma (e.g.

breast, lung, colon, and gastric cancer), lymphoma, and leukemia. Laboratory blood tests usually highlight elevated alkaline phosphatase and gamma-glutamyl transferase level, or in case of lymphoma, high serum level of lactate dehydrogenase.

32.3.2.2 Vascular Causes

Acute ischemic injury of the liver. Hypoxic hepatitis (HH) is usually a consequence of another severe illness such as cardiac, circulatory or respiratory failure, being more common in ICU settings with an incidence 2.5–10%. Pathophysiological mechanism of HH is represented by the reduction of the hepatic blood flow, hypoxemia, and hepatocyte lesions ischemic or through reperfusion. Laboratory tests reveal massive and rapid raise of serum aminotransferases caused by reduced oxygen delivery to the liver. The main treatment of the HH is the correction of the underlying disease state. Using of N-acetylcysteine, other antioxidants or molecular adsorbent recirculating system (MARS) for the management of liver dysfunction is known, but published evidence does not support their effectiveness or regular use [17]. Unfortunately, the poor prognosis with hospitalization mortality rate >50% represents the most frequent cause of death due to the predisposing condition and not to the liver injury itself [18]. Liver transplantation is rarely indicated for the treatment of HH [19].

32.3.2.3 Portal Vein Thrombosis (PVT)

As already known, portal vein results by the confluence of mesenteric superior and splenic veins, and could be occluded in patients with cirrhosis, prothrombotic disorders like neoplasms (21–24%), myeloproliferative disorders and hypercoagulable disorders (10–12%), abdominal trauma, surgery, inflammatory bowel disease, or idiopathic causes (8–15%). Patients with acute PVT present pain with sudden onset in the right hypochondrium, nausea, fever, followed by acute portal hypertension, and intestinal ischemia. The diagnosis can be established by ultrasonography, endoscopic ultrasonography (EUS), MRI and magnetic resonance angiography (MRA), and CT scan. The principles of treatment are the anticoagulant treatment or thrombolysis, the treatment of underlying disease, and the treatment of complications caused by acute portal hypertension (variceal bleeding, ascites, and encephalopathy)

32.4 Epidemiology

The commonest worldwide cause of ALF remains viral hepatitis (hepatitis A, E and B). The incidence of viral etiology of ALF has declined in Europe and USA, but in case of developing countries from Asia and Africa remains the main cause of ALF. On the other side, South Asia and Hong Kong still have higher incidence of hepatitis viruses (hepatitis E in Pakistan and hepatitis B in Hong Kong).

In Europe, the commonest cause of ALF is DILI (drug induced liver injury). In developed countries from Europe and USA, drug induced liver injury (DILI) and especially paracetamol or acetaminophen induced ALF represent nowadays the most frequent etiology. In USA, nearly half of all cases of ALF over a period of 17 years (US ALFSG Adult Registry 1998–2014) were represented by paracetamol induced ALF, and in United Kingdom paracetamol remains the predominant etiology of ALF, but an exponential rise in severe poisoning was effectively controlled by the restriction imposed on drug sales in 1998 [20].

32.5 Pathophysiology

ALF is a severe organ damage having the onset with nonspecific symptoms such as malaise, nausea, vomiting, abdominal pains and dehydration, followed by the appearance of jaundice, hepatic encephalopathy, coma, coagulopathy, metabolic abnormalities, and afterwards with progression to multiorgan failure (cardiovascular, hemodynamic, respiratory, and renal systems). Therefore, the severity of clinical signs and illness depends upon the adverse metabolic consequences of liver dysfunction, the side effects of toxins released by the necrotic liver, and the degree of liver regeneration [21].

In a simplified manner, ALF is defined by a significant liver necrosis with (1) coagulopathy; and (2) HE; in a patient without underling liver disorder. It has to be noted, that liver necrosis is missing in acute fatty liver of pregnancy. It follows that a necrotic liver release neurotoxic (ammonia) and inflammatory mediators (TNF, IL-1, IL-6). As a consequence, there is a continual alteration of blood-brain barrier with its dysfunction. Glutamine accumulation due to ammonia, crosses blood-brain barrier with further alteration and increasing of oxidative stress. Inflammatory mediators cause microglial activation. Finally, dysfunction of blood-brain barrier is associating astrocyte swelling and cerebral edema.

Encephalopathy. In ALF, the encephalopathy develops in the early stages of liver failure, sometimes suddenly; it may precede the jaundice, and it manifests through drowsiness, agitation, delirium, convulsions with rapid progression to decerebrate rigidity and deep coma. As a note, HE usually develops after 7 days of jaundice [1]. Also, patients with noted jaundice who develop HE between 8 and 28 days of jaundice, develop further ALF [1]. On the other side, patients with jaundice over 3 weeks and without HE are diagnosed with chronic liver disease [1].

One well known classification of HE is based on the underlying disease [22]. ***Type A*** is associated with acute liver failure resulting from severe inflammatory and/or necrotic

Table 32.2 West Haven Criteria and Clinical Description. From [22] with **permission**

West Haven criteria including minimal HE	ISHEN	Description	Suggested operative criteria	Comment
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis Local standards and expertise required
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers	Clinical findings usually not reproducible
Grade II	Overt	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms	Clinical findings variable, but reproducible to some extent
Grade III		• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to painful stimuli	Comatose state usually reproducible

All conditions are required to be related to liver insufficiency and/or PSS (portosystemic shunting). Where **ISHEN**—International Society for Hepatic Encephalopathy and Nitrogen Metabolism

rapid onset liver disease, is associated with increased intracranial pressure (ICP) due to cerebral edema that progresses rapidly and may lead to brain herniation and death; ***type B*** is associated with portosystemic bypass without parenchymal liver disorders; ***type C*** accompanies chronic liver disease (cirrhosis) and portal hypertension with portosystemic shunts (with three subcategories: episodic, persistent and minimal); and ***type D*** associated with disorders of the urea cycle [22]. It has to be underlined, that types B and C have similar clinical manifestations [22].

Another useful classification of HE known as The West Haven Criteria is based on the severity of manifestations. The West Haven Criteria are described in Table 32.2 [22].

32.6 Diagnosis

The typical scenario of ALF is the association of **liver damage** (a 2–3 times elevation of serum transaminases) with **altered hepatic function** (jaundice and coagulopathy) in a patient without chronic liver disease [1].

The diagnostic of acute liver failure must be considered in patients with recent onset <26 weeks of mental status changes, jaundice, but also of nonspecific symptoms such as nausea, vomiting, malaise, right upper quadrant pain [1, 2].

Based on the definition of ALF, the diagnosis work up must encompass all three criteria:

- Elevated aminotransferases level
- Hepatic encephalopathy (HE)
- Coagulopathy (prolonged INR $\geq$ 1.5 or increased PT (prothrombin time)).

Besides, the establishing of ALF diagnosis has to go through careful medical history, physical examination, laboratory evaluation, imaging studies, and liver biopsy if is necessary.

Notably, it is the early identification of the ALF etiology, because prognosis and specific treatment of ALF are dependent of its etiology, and also for the early identification of those patients who may benefit from urgent liver transplantation. When the main pathogenetic mechanism is cell necrosis or liver necrosis, patients have extremely increased serum transaminases (aminotransferases) [23]. If the liver injury is steady, patients have lower serum hepatic transaminases but severe hyperbilirubinemia [23].

Without a doubt, **medical history** can bring essential information from patient and/or from patient's family (if severe encephalopathy is present) regarding the etiology of ALF, such as medication use (including herbal and dietary supplements, illicit drugs), alcohol abuse, risks factor for

acute viral hepatitis (travel in endemic areas, transfusions, unprotected sexual contacts, occupation, body piercing), toxin exposure (mushrooms, organic solvents, phosphorus), suicidal intentions or depression, pregnancy, hepatic ischemia, malignancy, and family history of liver disease.

Physical examination of a patient with ALF must be complete and aims to identify the possible cause of ALF, and further the complications of ALF and/or the impact of ALF on other organs or systems (cerebral edema, renal failure, ARDS, and infections). It appears that the jaundice, a common sign in patients with ALF, is not always seen at presentation in paracetamol toxicity or in herpes simplex virus infection. Right upper quadrant palpation and percussion can identify hepatomegaly (in viral hepatitis, in malignant infiltration, congestive heart failure, or acute Budd-Chiari syndrome). Conversely, small liver indicates a significant loss of volume due to hepatic necrosis. The presence of ascites, especially if it develops rapidly and is accompanied by pain, suggests the possibility of hepatic vein thrombosis (Budd-Chiari syndrome).

A very important part of the physical examination is the neurologic examination in order to identify and estimate the severity of HE, and also for early identification of intracranial hypertension (ICH) or cerebral edema signs. If in patients with grade I or II HE cerebral edema is uncommon, it is present in 25–35% in those with grade III HE, and in 75% with grade IV HE [24].

Clinical signs and symptoms suggestive for intracranial hypertension caused by brain edema are reactivity of pupils, systolic hypertension, bradycardia, respiratory depression/apnea, seizure, increased muscles tension or tonus (opisthotonus or opisthotonos, decerebrate posturing). However, intracranial hypertension may increase rapidly before the onset of any clinical sign and may further result in brain death before any treatment can be initiated [24].

32.6.1 Laboratory Evaluation

Obligatory tests for ALF patients:

- Prothrombin time or INR > 1.5 is part of the ALF definition. Coagulation parameters should be monitoring 3–4 times/day but is not helpful to estimate the patient's risk for bleeding.
- Liver blood tests
  - AST and/or ALT—usual markedly elevated (very high levels >3500 IU/L in acetaminophen overdose, ischemic liver injury; high levels 1000–2000 IU/L in hepatitis B, Herpes simplex virus hepatitis, and Wilson disease). These parameters should be monitored daily.
  - Bilirubin conjugated/unconjugated level should be monitored daily—usually it is elevated. The decrease of prothrombin time/INR and bilirubin levels is seen in recovering patients, but they are raising in patients with poor prognosis.
  - Alkaline phosphatase
  - GGT
- Complete blood cell (CBC)—monitored 3–4 times/day
  - Thrombocytopenia <150,000 per mmc
  - Anemia
  - Leukocytosis or leukopenia (in Herpes simplex virus hepatitis)
- Serum chemistries—metabolic panels should be monitored more than once/day
  - Glucose—possible very low
  - Creatinine, blood urea nitrogen—possible elevated
  - Ammonia (arterial)—probably elevated
  - Serum electrolytes—sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate
  - LDH—elevated
  - Albumin
  - Amylase, lipase
- Toxicology screening—Acetaminophen level in blood, or urine toxicology
- Viral hepatitis serology—anti-HAVA IgM, anti-HBV IgM, hepatitis B surface antigen, anti-HCV virus antibodies, anti-herpes simplex/varicella zoster virus antibodies IgM, anti-HEV IgM, serologic testing for HIV
- Autoimmune markers
- Arterial blood gas analysis—metabolic acidosis, high lactate level
- For pregnant women—AST and/or ALT (<1000 UI/L), bilirubin level, low platelet count, urinalysis (proteinuria)
- For Wilson disease—AST/ALT (>2), Alkaline phosphatase/total bilirubin (<4), ceruloplasmin level (low <5 mg/dL), serum cooper (elevated >200 μg/dL), test Coombs (negative), anemia
- Infections surveillance—cultures for respiratory tract, blood, urine

32.6.2 Imaging Study

- Abdominal CT scan—for liver dimensions, density, spleen dimensions, evidence of hepatocellular carcinoma or intrahepatic metastases, hepatic vein occlusion
- Abdominal ultrasound—same information as CT scan but it is more available, no risk, noninvasive, and cheaper; with Doppler—establish the presence of flow in the hepatic veins, hepatic artery, and the portal vein.
- Cerebral CT scan/MRI—cerebral edema, hemorrhage

Liver biopsy is indicated when medical past history, laboratory evaluation or imaging studies failed to identify the

etiology of ALF, or patient needs liver transplantation. If coagulopathy is present, percutaneous biopsy is contraindicated, although transjugular liver biopsy is a choice. Nonetheless, the results of liver biopsy can bring useful information in malignant infiltration, autoimmune hepatitis, lymphoma, herpes simplex hepatitis (viral inclusions), and Wilson disease [1].

32.7 Treatment

32.7.1 General Principles and Organ Specific Management

ALF is a highly unpredictable disease, which can evolve to a life-threatening situation within few hours. The main part of ALF patients should be managed in ICU, and moreover, or in centers specialized on liver transplantation. If a patient with ALF is admitted in a hospital without liver transplantation, this patient must to be transferred in a liver transplantation center as soon as possible [1], before the progression of coagulopathy or HE, and the onset of increased intracranial pressure. Briefly, it is recommended to take in consideration the transfer of the patient to a liver transplantation center or tertiary intensive care unit in case of evolution into grade II HE, INR > 1.5 and the onset of hypoglycemia.

Cardiovascular management. Hemodynamic disturbances in ALF patients are caused by low systemic vascular resistance and intravascular volume depletion by extravasation of fluid in extravascular space. So that, there is positive response to appropriate volume loading. Hypotensive ALF patients should be initially resuscitated with crystalloids, or sometimes normal saline fluids [1]. A keynote factor it is to avoid hyperchloraemia because of its severe side effects [1]. Later, volume loading may be done by the association of crystalloid fluids with Ringers lactate or balanced solution. Dextrose solution should be added in patients with hypoglycemia. Albumin is not indicated, because its role in ALF has not been investigated [1]. When fluids are administrated it is important to avoid excessive volume loading because it may worsen cerebral edema [24] and prognosis.

When fluid resuscitation is not efficient, vasopressor support is required in order to maintain the mean arterial pressure of 60–75 mmHg and the cerebral perfusion pressure of 50–60 mmHg. The first drug of choice is norepinephrine with a dose starting of 0.05 μg/kg/min IV. Vasopressin in low dose of 1–2 U/h, is the second choice, for patients who do not respond adequately to norepinephrine, but it has been suggested to be detrimental with cerebral complications [25].

Respiratory management. In case of encephalopathy progression, hypoxia or respiratory failure, the patients with ALF may require invasive or noninvasive ventilatory support. Ventilation settings and parameters should be protective such as low tidal volume 6–8 mL/kg (ideal body weight) and PEEP to maintain an open lung with low tidal volume [26]. The main outcome is to avoid hypo- or hypercapnia. Obviously, adequate airway care, physiotherapy and periodic infections surveillance assure good prognosis.

Metabolic and nutritional management. Nutritional support is essential for the treatment of ALF patients, because they have increased resting energy expenditure. Oral or enteral nutrition is preferred whenever is possible, in order to counteract the loss of muscle mass, gastrointestinal hemorrhage and gut microbiome translocation, together with the monitoring of serum ammonia. If enteral nutrition is not possible or enough, parenteral nutrition is an option. Proton pump inhibitors should be used only for the period of parenteral nutrition, taking into account the possible risk of ventilator associated pneumonia and *Clostridium difficile* infection.

Hypoglycemia is a particular risk for ALF patients, especially when ALF is caused by paracetamol (acetaminophen) overdose, and it is associated with increased mortality. Nevertheless, the symptoms of hypoglycemia may be confused or overlapped with those of HE. Consequently, frequent monitoring of blood glucose level (at 2 h) is mandatory. Correction of hypoglycemia with concentrated glucose/dextrose bolus therapy or boluses may sometimes be necessary but can cause hyperglycemia that exacerbates an elevated intracranial pressure.

Renal management. Acute kidney injury (AKI) is a complication of ALF in 30–50% of cases, and it is associated with increased hospitalization and mortality. Risk factors for developing AKI in ALF patients are paracetamol induced ALF, prolonged hypotension, preexisting kidney disease, increased age, systemic inflammatory response syndrome (SIRS) and infection [27]. Measures to avoid the appearance of AKI are prompt treatment of hypotension, infections, and avoiding nephrotoxic drugs (including radiological contrast agents). If acute renal failure develops, renal replacement therapy must be set up early preferably by using venovenous hemofiltration technique. In ALF patients with AKI, the main indications for renal replacement therapy are hyperammonemia, acidosis, hyponatremia and others metabolic disturbances, fluid balance and temperature control [28].

Infection surveillance and management. Patients with ALF are at high risk for developing infections (viral, bacterial or fungal), sepsis and septic shock. The main sites of infections are respiratory tract (pneumonia), urinary tract and blood stream. The most frequently involved microorganisms are Gram-negative enteric bacilli, Gram-positive cocci, fungal organisms and sometimes reactivation of a preexisting infection with CMV. Clinical diagnosis is difficult because the signs and symptoms of infections may be absent, and the only indirect sign is worsening of HE or renal dysfunction. Routine and frequent microbiological surveillance

(sputum, urine, blood) is the safest way to detect and treat on time ALF associated with infections. Prophylactic antibiotics can reduce the incidence of infections, but studies have shown no benefit on survival [29]. Antibiotics should be given only in case of infection signs, positive culture results, clinical deterioration of HE, or for patients waiting emergency liver transplantation [1].

32.7.2 Treatment for Specific Etiology of ALF

It has to be noted that advanced liver injury or damage with ALF may not benefit from specific therapies [23].

Acetaminophen overdose. Paracetamol or acetaminophen overdose has characteristically at presentation AST > 10,000 IU/L and at least twice the value of ALT, and normal bilirubin [1]. N-acetylcysteine (NAC) is the specific antidote for acetaminophen or paracetamol overdose. However, NAC should be prescribed for ALF of unknown etiology, because it has benefits regarding cerebral edema, hemodynamic, oxygen delivery, consumption, and prognosis. If NAC is given during first 8 h after acetaminophen overdose, it decreases dramatically the hepatotoxicity and death. The dose of NAC for ALF patients is 150 mg/kg/1 h, followed by 12.5 mg/kg/h for 4 h and 6.25 mg/kg/h for the next 67 h. However, it is advisable to exclude NAC in case of "advanced coma" [23].

Viral hepatitis. In case of ALF secondary to hepatitis virus B infection, antiviral therapy with nucleoside/nucleotide analogues such as LAM, adefovir (ADV), entecavir may be useful. They also need to be administered in patient with indication for liver transplantation in order to prevent post-transplantation recurrence.

Patients with herpes simplex virus infections and hepatitis should receive Acyclovir (5–10 mg/kg every 8 h) for at least 7 days.

Mushroom poisoning. ALF secondary to *Amanita phalloides* poisoning benefits from early administration of activated charcoal that binds the amatoxin. It is highly recommended.

Autoimmune hepatitis. Also, autoimmune hepatitis may benefit from corticosteroids. They reduce the need for liver transplantation.

Budd-Chiari syndrome. Patients can benefit from anticoagulant therapy, thrombolytic therapy, interventional radiology (TIPS—transjugular intrahepatic portosystemic shunt placement), and surgical decompression, all in order to restore hepatic venous drainage.

Wilson disease. These patients benefit from plasma exchange for copper removal until liver transplantation is an available option.

Acute fatty liver of pregnancy. The main treatment is emergency delivery, after mother stabilization.

32.7.3 Specific Treatment of ALF

Management of ALF patients is primarily tackling the main manifestations that defines ALF such as coagulopathy, HE, and cerebral edema.

Treatment of coagulopathy. Severe coagulopathy in ALF is caused by the inadequate liver production of coagulation factors—II, V, VII, IX and X, often doubled by the fall of platelet number less than 100,000 per mmc. Prophylactic administration of fresh frozen plasma is not recommended, because published data has not shown to decrease mortality, and further can interfere with the tests for liver assessment function and may lead to fluid overloading. Exception is made in case of a planned invasive procedure or in the presence of profound coagulopathy (INR > 7). Platelet administration is recommended when platelet count is below 10,000 per mmc, or before an invasive procedure when platelet count is <50,000 per mmc.

Hepatic encephalopathy. The treatment of HE is focused on the decreasing ammonia production by gut microbiota and the avoiding of aggravating factors of HE such as infections, gastrointestinal bleeding, constipation, and sedatives. One option treatment is Lactulose (nonabsorbable disaccharide) but it has controversial efficacy in ALF, and it is associated with bowel distention, dehydration secondary to diarrhea, and hypernatremia. Usually it is oral administered, and a better option is lactulose enema. Other alternatives are Metronidazole—but may be neurotoxic in ALF, Neomycin—should be avoided because is nephrotoxic, Rifaximin—used often for HE in patients with chronic liver disease.

Cerebral edema. It is a finding of 25–35% patients with grade III HE, and of 75% of patients with grade IV HE. Cerebral edema followed by elevated ICP, brain ischemia and finally by brainstem herniation is the most common cause of death in patients with ALF. Liver transplantation is the only choice treatment for cerebral edema, and the rest of measures reduces cerebral edema and elevated ICP being only supportive until transplantation. An ICP > 30 mmHg and an arterial ammonia >200 μg/dL are predictive for brain herniation and death.

Intracranial pressure monitoring. It is an indication for patient with grade III/IV HE—in order to diagnose elevated ICP and guiding the treatment. Even if the monitoring of ICP can be done using epidural, subdural, parenchymal or intraventricular catheters, in the case of patients with ALF are preferred the use of epidural/subdural catheters because they are less invasive, with lower risk for hemorrhagic complications and infections. Prior to catheter placement, a CT scan of brain should be done, and coagulopathy must be corrected. ICP should be maintained <20 mmHg.

Transcranial Doppler ultrasound is a noninvasive investigation that can be used to estimate the ICP, as an alternative to invasive monitoring.

32.7.3.1 Measures to Prevent ICP Elevation

- Treatment of elevated ICP aims to maintain the ICP less than 20–25 mmHg, and the cerebral perfusion pressure above 50–60 mmHg.
- Minimizing patient agitation or stimulation—placing patient in quiet rooms, reduction of sensorial stimulation, nasogastric tube placement only in intubated and sedated patient with gentle and rare endotracheal suctions.
- Patient head elevation at 30° improves jugular venous outflow.
- Avoid volume overloading.
- Administration of hypertonic saline to induce hypernatremia with maintaining of serum sodium level between 145 and 155 mEq/L will decrease water influx into brain and reduce cerebral edema.
- Hyperosmotic agents can reduce brain edema, but only temporary. A bolus of Mannitol 0.5–1 g/kgc administrated IV, repeated once or twice can correct episodes of ICP elevation and improves survival [24], with the condition to maintain serum osmolality less than 320 mOsm/L.
- Hyperventilation is a method to reduce elevated ICP, but with limited efficacy over time (after 48 h). Every mmHg reduction of $PaCO_2$, reduces the cerebral blood flow by 2–3% and restore autoregulation. Moderate hyperventilation, with a $PaCO_2$ between 25 and 30 mmHg is indicated in patients with severe elevated ICP and at risk of brain herniation.
- Induced coma with barbiturates (pentobarbital, thiopental) or propofol, in order to reduce cerebral metabolic rate and cerebral blood flow in refractory patients.
- Glucocorticoids are not indicated and should not be used, because studies have not shown to be beneficial in ALF patients.

32.7.4 Experimental Therapies

- Induction of moderate hypothermia with core temperature 34–35 °C by cooling blankets, has been shown to reduce ICP and improves cerebral perfusion pressure but with the risk of cardiac depression or arrhythmias, shivering, infection, and bleeding.
- Indometacin (indomethacin) in bolus of 0.5 mg/kg can be considered in patients with elevated ICP refractory to standard treatment [30].

32.7.5 Artificial Liver Support Devices

The aim of **extracorporeal systems** use is to be a "bridging therapy" until liver transplantation.

- Extracorporeal albumin dialysis. Extracorporeal systems that uses albumin as a scavenging molecule are MARS (Molecular Adsorbent Recirculation System) and SPAD (Single-Pass Albumin Dialysis) [31]. Prometheus (Fractionated Plasma Separation and Adsorption) is another form of albumin dialysis [31]. Bleeding is a significant problem for MARS [31]. Even if, MARS is the most studied albumin dialysis technology in ALF, further randomized studies are needed [31]. Overall, extracorporeal liver support systems seem to increase survival in ALF [32] but further studies are a requisite.
- **BAL (Bioartificial liver) system** is a bioreactor with liver cells which temporarily replaces the hepatic functions. BAL systems are a temporary option in therapy of ALF or the treatment of acute-on-chronic liver failure [33, 34]. They also can assure for short term the endogenous regeneration of the native liver [33].
- **Plasma exchange** has been shown to improve survival in patients with ALF, and to modulate immune dysfunction, if used on timely (first 3 days after ICU admission) [1].

32.7.6 Liver Transplantation

Orthotopic liver transplantation is the only therapeutic choice in end-stage liver disorders such as cirrhosis, chronic hepatitis, ALF, chronic hepatic failure or metabolic diseases [35]. Contraindications for liver transplantation are malignancy, irreversible brain damage, uncontrolled infection, and severe pancreatitis [1].

32.8 Prognosis

One important step in the management of ALF patients is the early selection of patients who recover spontaneously, or of those who benefit from liver transplantation, and of those who do not benefit from liver transplantation [1]. For this reason, several criteria for emergency liver transplantation have been developed. Newly, it seems that the combination of hypoglycemia, coagulopathy, and lactic acidosis predicts better death or liver transplant in comparison with the King's College criteria [36].

King's College Criteria for transplant is the most widely model used for ALF selection that benefit from liver transplantation Table 32.3 [1, 2].

Model for End-stage liver disease (MELD) score is a scoring system also used to predict survival among ALF patients based on the laboratory values of serum bilirubin, creatinine and the INR. MELD score >32 are predictive for high mortality.

Table 32.3 King's College Criteria adapted from [2] with permission

Acetaminophen overdose	Nonacetaminophen overdose
Arterial pH < 7.30 *or* **all of the following**:	Prothrombin time > 100 s (INR > 6.5) *or* **any three of the following**:
• Prothrombin time > 100 s (INR > 6.5)	• Non-A, non-B hepatitis; idiosyncratic drug reaction; halothane etiology
• Creatinine level >3.4 mg/dL (>300 µmol/L)	• Time from jaundice to encephalopathy >7 days
• Grade 3/4 encephalopathy	• Age <10 years or >40 years
	• Prothrombin time >50 s (INR > 3.5)
	• Serum bilirubin level >17.4 mg/dL (300 µmol/L)

32.9 Conclusions

ALF is a life-threatening illness, with multiorgan damaging associated with numerous complications, and very poor prognosis, being caused by various etiologies. Despite the numerous advances on pathophysiology, intensive care treatment, and transplantation techniques from the last decades, is still characterized by increased mortality.

Early recognition of ALF, establishment of the etiology and relocation to a liver transplantation center, or tertiary intensive care specialized in ALF are primordial measures in treating ALF patients.

Equally important is the identification of patients with great probability of spontaneous recovery but also of patients who may benefit from emergency liver transplantation.

Liver transplantation is the only one proven liver replacement therapy that reduces mortality. One year survival rates following emergency liver transplantation are >80% [1].

Self Study

Questions

1. **Which statement is true?**
   (a) Cirrhosis with Budd-Chiari syndrome is considered ALF when diagnosed within 26 weeks
   (b) Paracetamol hepatotoxicity is characterized by extreme high level of serum aminotransferase (AST/ALT) > 10,000 IU/L.
   (c) Ecstasy induced liver injury presents with no hyperthermia
   (d) Drug-induced liver injury (DILI) is a leading cause for emergency liver transplantation
2. **Which statement/statements is/are true?**
   (a) Drug induced liver injury may occur after any type of medication
   (b) HELLP syndrome defined by haemolysis, elevated liver enzyme levels
   (c) N-acetylcysteine (NAC) is the specific antidote for acetaminophen or paracetamol overdose
   (d) Extracorporeal systems that uses albumin as a scavenging molecule are MARS (Molecular Adsorbent Recirculation System) and SPAD (Single-Pass Albumin Dialysis)

Answers

1. **Which statement is true?**
   (a) Correct.
   (b) Correct.
   (c) Ecstasy induced liver injury presents as an "heat shock related liver injury" with severe hyperthermia, multiple organ dysfunction, profound coagulopathy, and severe rhabdomyolysis.
   (d) Correct.
2. **Which statement/statements is/are true?**
   (a) Correct
   (b) Correct
   (c) Correct
   (d) Correct

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