Epidemiology of Acute Liver Failure

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Acute liver failure (ALF) is an uncommon disorder that leads to jaundice, coagulopathy, and multisystem organ failure. Its definition is based on the timing from onset of jaundice to encephalopathy. In 2005, ALF accounted for 6% of liver-related deaths and 7% of orthotopic liver transplants (OLT) in the United States. Several classification systems have been developed for ALF, with the King's College criteria most widely used for prediction of OLT. Specific diagnostic tests should be implemented to identify the cause of ALF, which will help to determine its treatment and prognosis. Viral hepatitis was previously reported to be the most common cause of ALF in the United States, but acetaminophen overdose and idiosyncratic drug reactions have emerged as the most frequent causes in recent studies. Malignancy is an uncommon cause of ALF, and thus imaging studies may not be useful in this setting, but liver biopsy may be beneficial in selected cases. An overall strategy for ALF should start with identifying the cause, assessing the prognosis, and early transfer to a transplantation center for suitable candidates. OLT has emerged as a life-saving procedure leading to marked improvement in survival rates. Improved surgical techniques, immunosuppression, and comprehensive care have led to an overall survival rate of approximately 65% with OLT. *N*-acetylcysteine is effective in ALF caused by acetaminophen overdose, with results strongly related to how soon it is given rather than the route of administration. Liver support systems show potential for the treatment of ALF, but their role needs validation in large multicenter randomized trials.

Introduction

Acute liver failure (ALF) is an uncommon liver disorder characterized by an arrest of normal hepatic function leading to jaundice, coagulopathy, and multisystem organ failure. Patients with ALF may deteriorate rapidly, and although a minority of patients may recover, the majority require orthotopic liver transplantation (OLT) as a life-saving therapy. The key to optimizing treatment is early recognition and transfer of the patient to a liver unit with facilities for liver transplantation. Prior to OLT as a therapeutic option for ALF, the mortality rate was greater than 80% [1]. Survival rates have improved significantly with better understanding of the clinical syndrome, earlier recognition, intensive care monitoring, and finally, OLT [2]. In the future, the development of artificial and bioartificial liver systems may provide another treatment option for those with ALF, although these modalities remain largely theoretical. In this review, we discuss the recent epidemiology of ALF with emphasis on diagnosis, prognosis, and therapies for its various causes as well as treatments of ALF in general, with emphasis on the most recent developments.

Background

Trey and Davidson first defined ALF in 1970 as an onset of hepatic encephalopathy within 8 weeks of the first symptoms of illness in patients without preexisting liver disease. This definition was revised with the recognition that different patterns of ALF relate to etiology and prognosis and that some patients have underlying chronic liver disease. A number of classification systems have been developed for ALF. In one widely used classification system, the terms "hyperacute," "acute," and "subacute" are used to define the onset of encephalopathy after jaundice within 7 days, 8 to 28 days, and more than 28 days, respectively (Table 1). An alternative classification is fulminant and subfulminant liver failure (time from jaundice to encephalopathy less or more than 2 weeks).

Epidemiology

The incidence and prevalence of ALF have been difficult to establish because of the previous lack of a comprehensive registry or population-based surveillance programs. However, recent reports suggest an incidence of 2300 to 2800 cases of ALF annually in the United States and 400 cases annually in the United Kingdom. ALF has been estimated to represent 0.1% of all deaths in the United States and 6% of liver-related deaths [3].

Diagnosis and Prognosis

No specific diagnostic test exists for ALF, though elevated prothrombin time with encephalopathy without pre-existing liver disease has been the historical definition. Recently, cytochrome c has been suggested as a marker to detect the presence of ALF [4]. The serum cytochrome c level in ALF patients is significantly higher than in patients with acute hepatitis without ALF, chronic hepatitis, chronic hepatitis with acute exacerbation, liver cirrhosis, or hepatocellular carcinoma. Prognostic criteria have been developed for ALF due to acetaminophen and from non-acetaminophen etiologies, with the King's College criteria the most widely used for prediction of liver transplantation in ALF (Table 2).

A number of laboratory and clinical tests have been described as useful prognostic markers, including factor V, factor VII, α-fetoprotein (AFP), lactate, arterial pH, phosphate, ammonia, sodium, platelet count, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), International Normalized Ratio (INR), Model End Stage Liver Disease (MELD) score, and liver volume. Recently, several additional prognostic criteria have been proposed. The protein CD163 is a member of a scavenger receptor family and is expressed mainly on activated macrophages, with a soluble form of CD163 (sCD163) being released from activated macrophages. One recent study showed that the levels of sCD163 are decreased in survivors of ALF [5]. Another serum marker that may have prognostic significance is Gc-globulin, an actin scavenger that is typically reduced in patients with ALF. Patients surviving non-acetaminophen–induced ALF without liver transplantation had higher Gc-globulin levels than did non-survivors. However, no significant difference was observed in levels between the groups in patients with acetaminophen-induced ALF [6]. In another study, investigators looked at serum levels of osteopontin (OPN), a multifunctional cytokine, in patients with ALF. Patients with ALF had significantly higher OPN levels than did patients with self-limited acute hepatitis, and those with elevated serum OPN levels had a significantly worse prognosis than did patients whose serum OPN levels were not elevated [7].

Etiology

The etiology of ALF is dependent on geographic location. The breakdown of causes for ALF in the United States has changed, according to recent reports from the Acute Liver Failure Study Group. Viral hepatitis was previously reported to be the most common cause of ALF in the United States, but a recent multicenter prospective study of ALF has identified acetaminophen overdose (39% of cases) and idiosyncratic drug reactions (13%) as the most frequent causes [2]. In the UK, although acetaminophen overdose has been the most common cause for some time, its incidence has fallen with introduction of legislation to limit the amount of acetaminophen that may be purchased over the counter [8].

Table 1. Classification of ALF

	Interval from jaundice to encephalopathy
Hyperacute	<7 days
Acute	8–28 days
Subacute	29 days to 12 weeks

ALF—acute liver failure.

ALF due to idiosyncratic drug reactions

Many classic drugs are reported to exhibit potential hepatotoxicity. The well-known classically described drugs with potential hepatotoxicity include acetaminophen, anti-tuberculosis agents, anesthetic drugs of the halothane family, and nonsteroidal anti-inflammatory drugs (NSAIDS) (Table 3). However, in a patient presenting with ALF, all drugs and herbal supplements should be considered as potential causes for the disorder. These include medications recently introduced with a limited safety record; excipients present in formulations of drugs; herbal medicines, which are increasingly consumed and often not disclosed; and recreational and illegal compounds such as cocaine and synthetic amphetamine derivatives such as Ecstasy.

Recently, a number of additional idiosyncratic drug reactions leading to ALF were reported. These reports concern a broad spectrum of antibacterial and antiviral agents, antidepressants, biologic agents, and oncologic agents, many of them recently introduced. One case was an HIV–hepatitis C virus (HCV) coinfected liver transplant patient receiving interferon (IFN) alfa, ribavirin, stavudine, and didanosine who developed progressive ALF 1 day after starting standard IFN and ribavirin [9•]. The patient was retransplanted 7 days later. The explanted graft showed microvesicular steatosis and massive centrilobular necrosis. The toxicity of nucleoside reverse transcriptase inhibitors (NRTIs), particularly stavudine and didanosine, is due to inhibition of DNA polymerase-γ, which causes mitochondrial dysfunction [10], and ribavirin which potentiates didanosine toxicity [11]. Thus, HIV-HCV coinfected patients receiving NRTIs and ribavirin may develop severe liver toxicity if didanosine is used.

Rituximab, an anti-CD20 monoclonal antibody, was the reported cause of ALF in a 21-year-old woman who received rituximab for autoimmune hemolytic anemia (AIHA) [12]. The patient presented with ALF 3 days after the first dose of rituximab. Her total bilirubin and her hemoglobin were 20.5 mg/dL and 4 g/dL, respectively. She was given a second dose of rituximab at that time. She developed ALF, with tests for other causes of liver dysfunction showing no etiology. Arrangements for OLT were initiated, but the patient died within 48 hours. The autopsy showed extensive periportal hemorrhage and sub-

Table 2. King's College criteria for liver transplantation

Acetaminophen	Non-acetaminophen
pH < 7.3 (irrespective of grade of encephalopathy)	PT > 100 seconds (INR > 6.5) (irrespective of grade of encephalopathy)
Or all three of the following	Or any three of the following
1) Grade III–IV encephalopathy 2) PT > 100 seconds (INR > 6.5) 3) Serum creatinine > 3.4 mg/dL	1) Age < 10 or > 40 years 2) Etiology (non-A, non-B hepatitis, halothane, idiosyncratic drug reaction, Wilson's disease) 3) Period of jaundice to encephalopathy > 7 days 4) PT > 50 seconds (INR > 3.5) 5) Serum bilirubin > 17.5 mg/dL

INR—International Normalized Ratio; PT—prothrombin time.
(*From* O'Grady et al. [51]).

massive hepatocellular necrosis, though the mechanism was unclear.

Imatinib is a selective tyrosine kinase inhibitor used in chronic myeloid leukemia. ALF following imatinib therapy has been described previously. Investigators from a recent study described a 46-year old woman with cytomegalovirus (CMV) who was started on imatinib [13]. The patient's liver function tests were monitored monthly for the first 12 months of imatinib treatment and were normal. After 18 months, imatinib was stopped temporarily due to significant cytopenias, and it was restarted 2 weeks later. After restarting the drug, the patient presented with nausea and vomiting. Blood tests were performed for the first time in 5 months and showed elevated aminotransferases. Imatinib was discontinued, but the patient progressed to ALF. OLT was performed, but she died 3 days later from sepsis. The explanted liver showed evidence of recent severe necrosis and severe cholestasis. Although imatinib-induced ALF had been reported previously, this is the first report of ALF due to chronic imatinib therapy, and it may have implications for long-term monitoring of liver tests with chronic imatinib therapy if other cases are reported.

Multiple recent reports have emerged of ALF due to presumed idiosyncratic reactions to medicines across a wide spectrum of classes. Three case reports of severe hepatotoxicity due to the macrolide antibiotic telithromycin were recently reported [14]. Within a few days of receiving telithromycin, one patient presented with severe acute hepatitis and two with ALF. The first patient spontaneously recovered after discontinuation of telithromycin. One of the latter two patients required OLT, and the other died. Histologic examination in these two patients showed massive hepatic necrosis. Other causes of ALF were excluded in all three patients. The antidepressant duoloxetine, a recently introduced dual uptake inhibitor, was recently reported to cause ALF [15]. A 56-year-old woman presented with jaundice 6 weeks after her duoloxetine dosage was increased from 30 to 60 mg daily. Despite aggressive medical management, the patient's condition deteriorated, and the decision was made to withdraw care. Postmortem liver biopsy showed centrilobular hepatocellular dropout with hemorrhage and ballooning degeneration and focal portal fibrosis and edema.

Orlistat, a lipase inhibitor increasingly used in the treatment of obesity, has been reported to cause ALF [16]. In this case, the patient presented with ALF 12 weeks after starting orlistat for weight reduction. Liver biopsy showed areas of bridging and panacinar necrosis. The patient underwent OLT, and the explanted liver showed submassive hepatocyte necrosis. ALF is the most common cause of drug withdrawal in the United States. Post-marketing surveillance for drug hepatotoxicity is essential, and a low threshold to suspect drug-induced liver injury in a timely manner is imperative. The importance of reporting these cases cannot be overemphasized.

Infectious causes

Although acetaminophen overdose is the most common cause of ALF in the United States and the UK, viral hepatitis, including hepatitis A and B, remains the most common cause in other parts of the world, including France and Japan, whereas hepatitis E is the most common cause in India. Viral hepatitis leads to ALF in only a small number of cases (<1%). With the possible exception of HCV infection, each of the five primary hepatotropic viruses (A through E) has been implicated in ALF. The risk is lowest with hepatitis A (0.35% of cases), but it increases with age at time of exposure. Acute hepatitis B infection (HBV) may lead to ALF in 1% of patients, and greater than half the cases of ALF in patients positive for HBV are due to delta virus rather than to hepatitis B alone. Reactivation of HBV is now a well-recognized complication in infected patients who undergo cytotoxic chemotherapy for cancer, with the clinical condition ranging from an asymptomatic rise in aminotransferases to ALF [17••].

Patients from HBV-endemic areas should be screened for hepatitis B surface antigen (HBsAg) because prophylactic cytotoxic chemotherapy with nucleoside analogs like lamivudine has been shown to decrease the incidence and overall morbidity of HBV reactivation significantly.

Table 3. Drugs causing ALF

Common causes	Rarer causes
Paracetamol, halothane, isoniazid/rifampicin, NSAIDs, sulphonamides, flutamide, sodium valproate, carbamazepine, Ecstasy	Phenytoin, isoflurane, enflurane, tetracycline, allopurinol, ketoconazole, methyldopa, amiodarone, tricyclic antidepressants, propylthiouracil, gold

ALF—acute liver failure.
(*From* O'Grady [52]).

Regimens from most published studies continue lamivudine 1 to 2 months after the completion of chemotherapy, although treatment is usually more prolonged in patients who have undergone hematopoietic stem cell transplantation (HSCT) or anti-B– or T-cell therapy. However, for patients with evidence of previous HBV infection (HBsAg-negative and anti-HBc positive patients), no current data justify the use of prophylactic lamivudine. Thus, screening for past infection is not needed, though reductions in HBsAg titer and transient reappearance of HBsAg have been reported. An exception to this practice is for those receiving HSCT or anti-B– or T-cell therapies because reactivation of HBV and ALF has been reported in this group, and prophylactic lamivudine should be considered strongly.

Hepatitis E is common in parts of Asia and Africa, and the risk of developing ALF increases to over 20% in pregnant women in these areas, with the highest risk during the third trimester. Uncommon causes of viral ALF include herpes simplex 1 and 2, herpesvirus-6 (HHV6), varicella zoster, Epstein-Barr virus, and CMV. Six patients with ALF due to herpes simplex virus were recently described in case reports [18,19]. Two of these six patients were immunocompetent and four were immunocompromised, with one of the immunocompetent patients being pregnant. Another case report described ALF due to varicella zoster in a girl with acute lymphoblastic leukemia in remission [20]. In addition, two cases of ALF related to HHV6 occurring in immunocompetent patients were described [21]. Both patients had a favorable outcome, one after treatment with valganciclovir and one after OLT in addition to ganciclovir. Viral origin was evidenced in each case by the detection of high amounts of HHV6 DNA in liver tissue by polymerase chain reaction (PCR) assay. Thus, recognition of specific infectious causes for which therapy may be available is important in treatment and avoidance of OLT. Another recently reported case of ALF was in a 13-year-old female patient with acute parvovirus B19 infection who presented with ALF and severe hemophagocytosis and who subsequently developed sepsis and died [22]. The autopsy showed focal lobular inflammation suggestive of acute hepatitis, presence of macrophages showing erythrophagocytosis, and extensive centrizonal necrosis. A paper from India published last year reviewed 25 cases of severe falciparum malaria presenting as ALF [23]. When compared with 25 patients with virally induced ALF, these patients had significantly lower hemoglobin, total leukocyte count, platelet count, and aminotransferase levels. Prothrombin time was elevated in all patients with viral ALF and in only one patient with malarial ALF. Of patients with viral ALF, 76% died; of patients with malarial ALF, 24% died. Several antiviral agents have proved beneficial in virally caused ALF. Lamivudine has been reported to be effective in ALF due to HBV [24••]. Similarly, valganciclovir and acyclovir seem to have a role in ALF due to CMV and herpes simplex virus 1 and 2, respectively.

Malignancies

Malignancy is an uncommon cause of ALF, with most reported cases being metastatic tumors or primary hepatic lymphomas. The mechanism of ALF in neoplastic infiltration is multifactorial, with possibilities including hepatic ischemia or infarction due to massive invasion of the liver by tumor cells, parenchymal infarction due to portal vein occlusion by tumor thrombi, and nonocclusive infarction of the liver due to shock from such other causes as sepsis or heart failure. Harrison and Crosby [25] postulated that livers extensively replaced by malignant cells may be more susceptible to milder degrees of hypotension or hypoxemia. In cases of lymphomatous infiltration, cytokine-mediated microscopic hepatic ischemia has been implicated [26].

The diagnosis of ALF due to malignancy is typically made at autopsy. Previously, only seven adult cases of ALF due to leukemia have been reported in the literature. However, this year, the first case of T-cell promyelocytic leukemia presenting as ALF was reported [27]. The diagnosis was made by transjugular liver biopsy showing extensive infiltration of the liver parenchyma with lymphocytes consistent with T-cell promyelocytic leukemia. In addition, a case of ALF due to liver metastases from prostate adenocarcinoma was described [28]. Additional cases of melanoma, small cell lung cancer, and lymphomatous infiltration of the liver have been reported, for which imaging studies did not reveal any evidence of neoplastic infiltration of the liver [29,30•]. One unique case of ALF in primary hepatic lymphoma was diagnosed only after pathologic examination of the explanted liver. This patient underwent successful OLT and was treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and rituximab chemotherapy after transplantation [31]. If remission can be maintained in such patients, OLT should not necessarily be excluded as a potential therapy.

Imaging studies for such patients may not demonstrate evidence of metastatic or primary disease, and thus, liver biopsy may be beneficial in selected cases of ALF when a diagnosis is not readily apparent.

Vascular causes

Vascular causes of ALF are not common, though ischemic hepatitis without ALF is very common. Vascular causes of ALF include hypoxic hepatitis (commonly referred to as ischemic hepatitis), portal vein thrombosis, and hepatic arterial thrombosis in addition to both left heart and right heart congestive heart failure. The role of heart failure was illustrated by a reported case of ALF due to unrecognized peripartum cardiomyopathy [32]. Patients with hepatic vein outflow obstruction, and in particular, those with Budd-Chiari syndrome (BCS), may present with ALF. BCS is caused by obstruction of the hepatic venous outflow tract resulting from obstruction of the hepatic veins, the inferior vena cava, or both and is associated with hypercoagulable states. These patients may decline rapidly and require urgent transplantation if successful decompression of the obstruction is not achieved. One report described a 32-year-old patient with factor V Leiden mutation who presented with BCS and ALF. Her total bilirubin was 2.8 mg/dL and creatinine was 2.1 mg/dL. She was successfully treated with a transjugular intrahepatic portosystemic shunt (TIPSS) [33]. TIPSS in acute BCS should be considered as a direct therapy to relieve the hepatic vein obstruction and possibly avoid OLT in those with and without ALF [34].

Metabolic causes

Inherited and acquired metabolic disorders are uncommon though important causes of ALF and include acute fatty liver of pregnancy, fructose intolerance, galactosemia, lecithin-cholesterol acyltransferase deficiency, Reye's syndrome, tyrosinemia, and Wilson's disease. A recent report described the second case of deficiency of transaldolase, an enzyme that links the pentose phosphate pathway to glycolysis. The clinical course of this patient was characterized by intractable liver failure and progressive myocardial hypertrophy, and the patient died at the age of 18 days from respiratory failure [35]. Finally, a case of Schmidt syndrome or type 2 autoimmune syndrome was reported in a patient presenting with ALF due to hypotension caused by severe autoimmune adrenalitis [36].

ALF due to autoimmune hepatitis

A recent study suggested that ALF is not an uncommon presentation of autoimmune hepatitis (AIH) [37•]. Patients with acute presentation of AIH with ALF differ significantly from those with typical presentation of chronic hepatitis with regard to encephalopathy, albumin levels, and bilirubin levels. Liver biopsies in those with acute presentation showed significantly less fibrosis and greater interface hepatitis, lobular disarray, lobular hepatitis, hepatocyte necrosis, zone 3 necrosis, and submassive necrosis. Those with ALF due to AIH had higher rates of death and more often required OLT, though four of 10 patients responded to standard therapy for AIH.

Miscellaneous

Other causes of ALF include toxins (eg, *Amanita phalloides* and *Bacillus cereus* toxins), HELLP syndrome of pregnancy (hemolysis, elevated liver enzymes, and low platelet count), and heat stroke.

Treatment

An overall strategy should be developed for each patient with ALF. This program should start with identification of the cause, assessment of prognosis, and possible candidacy for liver transplantation. Early transfer to a transplantation center cannot be overemphasized if there is concern for ALF. A search for the cause of ALF should be undertaken to identify treatable causes, including acetaminophen overdose, viral etiologies (HBV, CMV, herpes simplex), and autoimmune or vascular causes (BCS).

Treatment of acetaminophen overdose

Oral *N*-acetylcysteine was introduced in the United States in the 1970s. An initial dose of 140 mg/kg is followed by 17 doses of 70 mg/kg every 4 hours for a total of 72 hours. In 2004, the US Food and Drug Administration (FDA) approved an intravenous formulation of *N*-acetylcysteine (Acetadote; Cumberland Pharmaceuticals, Nashville, TN). The FDA-approved dosing for Acetadote is for continuous infusion over 20 hours. The infusion is continued past the 20-hour recommended duration when the hepatic enzymes have not been judged to be declining sufficiently. However, in practice, most patients continue intravenous *N*-acetylcysteine until the hepatic encephalopathy has resolved and the INR is less than 1.5. *N*-acetylcysteine is most effective when given within 8 hours of acetaminophen overdose. Death is uncommon if it is given within 16 hours [38], and *N*-acetylcysteine may still be beneficial even when the interval has been more than 24 hours after acetaminophen exposure [39].

OLT

ALF accounted for 7.8% of OLT activity in 2005. Approximately half of the patients with ALF undergo transplantation; the rest either have contraindications to transplant or deteriorate while listed on the transplant registry. With the improvement in surgical techniques, immunosuppression, and comprehensive care, OLT offers an overall survival rate of approximately 65% [40]. In the past 2 years, three published retrospective trials have shown similar overall survival [41–43]. The first trial included 40 patients and had a 1-year patient survival rate of 61.3%; OLT list time of less than 48 hours also improved outcomes [41]. The second trial

included 15 children who underwent OLT. Children aged under 1 year and those aged 1 to 16 years had 1-year survival rates of 67% and 83%, respectively (*P* not significant) [42]. The last trial included 31 patients who underwent OLT, with 61.8% survival at 3 months and 52.9% at 3 years [43]. Contraindications to OLT include multisystem organ failure, irreversible brain damage, uncontrolled sepsis, extrahepatic malignancy, and cerebral edema with sustained increase in the intracranial pressure above 50 mm Hg.

Liver support systems

Primarily due to organ donor shortage, extracorporeal liver support systems have been developed to support patients with ALF until either an organ becomes available for transplantation or until they recover. These systems are divided into biologic, non-biologic (artificial), and bio-artificial (hybrid techniques) devices. Biologic devices are meant to replace all hepatic functions by using animal or human livers or a hepatocyte bioreactor. Non-biologic devices aim to detoxify the patient through dialysis-derived techniques. Bioartificial devices combine both techniques. Most of the available data are for non-biologic support systems, namely the Molecular Adsorbent Recirculating System (MARS; Teraklin AG, Hamburg, Germany). This device was developed in 1993 and applied for the first time in humans in 1996. It is based on the principles of dialysis, filtration, and adsorption.

A systematic review published last year concluded that liver support systems do not significantly affect mortality when compared with conventional medical therapy in children [44]. Another study involved 13 patients treated with MARS, with overall mortality of 85% in a setting without timely liver transplantation [45]. However, several other promising case reports and non-randomized trials have been published. A patient presenting with ALF due to *A. phalloides* intoxication was successfully bridged to transplantation using MARS [46]. In a series of seven patients treated with MARS, four were successfully bridged to transplantation, two recovered, and one died [47]. Also, 10 patients with HBV-related ALF treated with MARS have been reported. Three patients were alive at 3 months of follow-up, and one patient was successfully bridged to liver transplantation [48]. In this same study, significant improvements were observed in hepatic encephalopathy grading, mean arterial pressure, plasma rennin activity, bilirubin, ammonia, and creatinine levels before and after MARS. A larger study published earlier this year included 338 patients with acute or chronic liver failure who received treatment with the Artificial Liver Support System (ALSS), the main parts of which include a plasma separator (Plasmacure PS-06, Kuraray Co., Japan), an activated carbon absorber (YT-hemoabsorba, Yatai Inc., China), and a bilirubin adsorption column (Medisorba BL-300, Kuraray Co., Japan). These patients were compared with 312 patients treated with conventional medications [49]. The 30-day survival rates were better in the ALSS group, and this treatment appeared to be efficacious and safe. MARS therapy also seemed effective for postoperative ALF in a surgical hepatobiliary unit [50].

Liver support systems appear to be exciting tools for the treatment of ALF irrespective of its cause. Enough data are available to prove the safety of some of the systems. The definitive role of liver support systems in treatment of ALF needs further validation in large multicenter randomized trials.

Conclusions

Acute liver failure is a rare manifestation of liver disease and constitutes a medical emergency. The most common causes of ALF in the United States are drugs (notably acetaminophen) and hepatotropic viruses. However, many other conditions can lead to ALF, and clinicians should be aware of these possibilities in their efforts to identify causes of ALF that have specific therapies. Immediate evaluation should be undertaken, and the patient should be referred to a center where liver transplantation is available.

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