Classification and Epidemiologic Aspects of Acute Liver Failure

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KEYWORDS

• Acute liver failure • Fulminant liver failure • Classification • Epidemiology • Race

KEY POINTS

- Acute liver failure is a life-threatening condition that requires early recognition and transfer to specialized centers to achieve good outcomes.
- It is not a single disease, but a whole group of varied etiologies, many of which are difficult to diagnose and lack specific treatment modalities.
- Understanding the epidemiologic aspects of the various conditions that lead to acute liver failure and their subtype classifications can help clinicians better identify and manage this condition.

INTRODUCTION

Acute liver failure (ALF) is a devastating condition with a high rate of short-term morbidity and mortality.[1] The disease has been labeled by multiple names, including fulminant hepatic failure, acute hepatic necrosis, fulminant hepatitis, and fulminant necrosis, but the preferred term is ALF.[2] It is a rare condition with a reported incidence of less than 5 cases per million population per year in the developed world and an estimated 2000 cases per year in the United States.[2,3] It should be noted, however, that accurate estimates of both the incidence and the morbidity of ALF are difficult to obtain, because many patients expire before transfer to a referral center and are thus not accounted for by estimated models.[4]

ALF, originally named fulminant hepatic failure, was defined in 1970 by Charles Trey and Charles Davidson as "a potentially reversible condition, the consequence of severe liver injury, with the onset of encephalopathy within 8 weeks of the appearance of the first symptoms and in the absence of pre-existing liver disease."[5]

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Aspects of this original definition are still in use today, although the condition has gone through multiple names and diagnostic criteria over the past 47 years. The most widely accepted definition of ALF is an abnormality in coagulation (practically an International Normalized Ratio of >1.5) with any degree of encephalopathy in a patient without cirrhosis and an illness duration of less than 26 weeks.[6] This review addresses the classification of ALF and the epidemiologic aspects of the disease, with a focus on the underlying etiology and its relationship to incidence and outcomes.

CLASSIFICATION

Since the initial definition by Trey and Davidson, there have been more than 40 different criteria that have attempted to define and subclassify ALF.[7] Of all of these definitions and classification systems, there are 4 that warrant special mention (**Table 1**). The Bernuau system, published in 1986, was the first to classify ALF into 2 subgroups: fulminant, in which less than 2 weeks pass between the onset of jaundice and symptoms of liver failure, and subfulminant, in which liver failure symptoms develop between 2 and 12 weeks after the onset of jaundice.[8]

In 1993, John O'Grady and colleagues[9] published the first classification system that accounted for the etiology, complications, and prognosis of ALF. The O'Grady system, still widely used today, subdivides ALF into hyperacute, acute, and subacute groups. Hyperacute liver failure is defined by hepatic encephalopathy (HE) developing within 1 week of the appearance of jaundice, patients in the acute group develop HE between 1 and 4 weeks, and patients with subacute liver failure develop HE between 4 and 12 weeks.

In an attempt to standardize the nomenclature and classification of ALF, the International Association for the Study of the Liver formed a subcommittee for the nomenclature of ALF and subacute liver failure. This International Association for the Study of the Liver subcommittee published their findings in 1999 and divided ALF and subacute liver failure into 2 distinct entities, rather than as subdivisions of an overarching condition.[10] ALF was defined as HE within 4 weeks of symptom onset, and subacute liver failure was defined as HE or ascites that develop between 5 weeks and 6 months of symptom onset. Because ALF was considered a separate condition from subacute liver failure by the International Association for the Study of the Liver, it was further subdivided into a hyperacute form, with the development of HE within 10 days of symptoms, and a fulminant form, with HE developing between 10 and 30 days from the first onset of symptoms.[10]

Historically, the definition and classification of ALF in Japan was different from that of Europe and the United States.[11] In an attempt to align their definitions, the Intractable Hepato-Biliary Diseases Study Group in Japan established a task force that published its revised definition and classification in 2011.[12] The Japanese defined ALF as an International Normalized Ratio of 1.5 or greater or a prothrombin time of 40% or less of the standardized value within 8 weeks of the onset of symptoms in a patient without prior liver disease. The presence of HE was not required to meet the definition of ALF; thus, ALF was subdivided into ALF with hepatic coma (grade 2 HE or higher) and ALF without hepatic coma (no HE or grade 1 HE). Those patients who had ALF with hepatic coma were further subdivided into an acute type, with HE developing within 10 days of symptoms, and a subacute type, with HE developing between 11 and 56 days after symptom onset. Patients who meet the criteria for ALF with hepatic coma but develop symptoms between 8 weeks (56 days) and 24 weeks are categorized as having late-onset hepatic failure.

Table 1
Classification systems of acute liver failure

	Bernuau System		O'Grady System			IASL System		Japanese System		
Definition of ALF	≥50% decrease in factor II or V with HE		Severe liver injury with HE without prior liver disease			Severe liver Disfunction with HE within 4 wk without prior liver disease		INR ≥ 1.5 or PT ≤ 40% within 8 wk of symptoms without prior liver disease		
Requirement for HE	Yes		Yes			Yes		No		
Subclasses	Fulminant	Subfulminant	Hyperacute	Acute	Subacute	Hyperacute	Fulminant	With hepatic coma		Without hepatic coma
								Acute	Subacute	
Duration between symptoms and HE	<2 wk	2–12 wk	<1 wk	1–4 wk	4–12 wk	<10 d	10–30 d	<10 d	10–56 d	NA

Abbreviations: ALF, acute liver failure; HE, hepatic encephalopathy; IASL, International Association for the Study of the Liver; INR, International Normalized Ratio; NA, not applicable; PT, prothrombin time.
Data from Refs.[8–10,12]

The debate about the most appropriate definition and classification system is far from over, and all 4 of these classifications are still being used today. The O'Grady system is the most popular in the United States and Europe, whereas the Japanese system is used in Japan. Current issues of contention include a lack of consensus as to the specific cutoff in terms of coagulation parameters and the degree of alteration in consciousness required to transition from severe acute liver injury to ALF.[13] There has also been debate about whether International Normalized Ratio is the best measure of coagulation dysfunction or if it would be better to use prolongation of the prothrombin time in relation to the normal value for that particular laboratory test.[14]

Despite a lack of consensus as to the exact degree of HE required to diagnose ALF, the time frame from the onset of symptoms, usually jaundice, to encephalopathy is the basis for each of the classifications and disease phenotypes mentioned. The reason that HE plays such a central role in the classification of ALF is that the onset of HE is a marker of severe liver damage and is closely tied to increases in arterial ammonia, which itself is associated with an increased risk of intracranial hypertension and possible herniation.[15] Although the prevalence of both intracranial hypertension and cerebral edema has been decreasing, they remain deadly complications of ALF.[16,17]

Currently, there are no specific differences in the management of ALF based on the subclassification of the disease into hyperacute, acute, subacute, fulminant, or subfulminant classes. Although the most recent guidelines from the American Association for the Study of Liver Diseases state that these subclassifications are not helpful, the recently released guidelines from the European Association for the Study of the Liver state that the separation of hyperacute and ALF from subacute liver failure for prognosis and management should be considered in future guidelines.[2,14]

Hyperacute liver failure, as defined by the O'Grady system, is the development of HE within 7 days of symptom onset.[9] This is mostly commonly due to acetaminophen overdose, hepatitis A virus (HAV) infection, or hepatitis E virus (HEV) infection. Overall, the prognosis for hyperacute liver failure is good, but is highly variable based on individual etiology. Given the rapid progression of hyperacute liver failure, high grades of HE are associated with a worse prognosis.[18] The ALF presentation occurs between 1 and 4 weeks and is most commonly the result of hepatitis B virus (HBV) infection. Subacute liver failure occurs between 4 and 12 weeks and is most commonly associated with idiosyncratic nonacetaminophen drug-induced liver injury (DILI) or indeterminate causes. Unlike the hyperacute presentation, the prognosis is poor with subacute liver failure, even in the setting of minimal grades of HE.[18] It is usually the subacute liver failure cases that benefit most from emergency liver transplantation, rather than the hyperacute cases.[13]

EPIDEMIOLOGY

ALF is a condition that has undergone a great deal of change since it was formally defined in 1970, including changes to the definition, causes of the illness, treatment, and prognosis. Before the advent of liver transplantation, the death rate for ALF was greater than 80%.[19] Overall survival is now approximately 70%, and 2-year survival rates are up to 92.4% for those who undergo liver transplantation.[16,20] Not only has there been a dramatic improvement in the management and prognosis of ALF, but there has also been a major shift in the etiology of the disease. Worldwide, viral hepatitis remains as the most common cause of ALF, but its incidence has decreases tremendously over the past several decades in the developed world. Drug-induced liver failure, most commonly from acetaminophen, is now the most common cause of ALF in the United States and Europe.[18,21] Significant variation remains in the

etiology of ALF worldwide, but with the large amount of travel and immigration, clinicians must be on the lookout for even the rarest causes. This factor underscores the importance of a thorough workup to identify the underlying cause, because each etiology has a distinct pattern of presentation, prognosis, and, in some cases, specific treatment (**Table 2**).

Acetaminophen

Acetaminophen, also known as paracetamol or APAP in non-US territories, is the most common cause of ALF in the United States, accounting for 42% to 46% of cases.[22,23] It is even more prevalent in the UK, where rates as high 73% were reported in the early 1990s.[24] Incidence rates of acetaminophen-induced ALF in the UK have decreased dramatically since then, largely owing to legislation passed in 1998 that restricted the sale of the drug.[25] It remains, however, as the most common cause of ALF in the UK and some parts of Europe.[26] Interestingly, in a retrospective analysis from Spain from 1992 to 2000, acetaminophen only accounted for 2% of ALF cases.[3] It has been hypothesized that this rate is so much lower than those of many other European nations because acetaminophen is not available for sale over the counter in Spain.[27] In addition, the typical reason for overdose differs between the United States and the UK. Accidental ingestion-induced ALF is seen more frequently in the United States, whereas intentional overdose is more common in the UK.[22,28]

As mentioned, acetaminophen-induced ALF tends to result in a hyperacute presentation and is characterized by large elevations of aminotransferases (>10,000 IU/L) in the setting of normal or slightly elevated bilirubin levels.[14] It is one of only a few causes of ALF that has a known treatment, and if acetaminophen overdose is suspected, *N*-acetylcysteine should be administered immediately, even in the setting of negative acetaminophen blood levels.[2] Acetaminophen undergoes breakdown by the CYP2E1 pathway, yielding a toxic metabolite called *N*-acetyl-p-benzoquinoneimine that can lead to hepatic necrosis.[29] Glutathione converts acetaminophen into mercapturic acid, a nontoxic and readily excreted byproduct, rather than *N*-acetyl-p-benzoquinoneimine.[30] *N*-Acetylcysteine replenishes the glutathione stores of the liver, which helps to prevent further hepatic toxicity.[31]

Despite severe metabolic derangement and hyperacute presentation, the prognosis in acetaminophen-induced ALF is good, with spontaneous nontransplant survival of greater than 70%, and transplant survival of greater than 80% at 1 UK site.[16] The Acute Liver Failure Study Group (ALFSG) is an ongoing observational registry of

Table 2
Etiology of acute liver failure in selected countries[a]

United States	United Kingdom	Japan	Sudan	India	Spain
Acetaminophen	Acetaminophen	Unknown	Unknown	HEV	Unknown
Unknown	Unknown	HBV	HBV	Unknown	HBV
DILI[b]	DILI[b]	DILI[b]	P. falciparum Malaria/AIH	HBV	DILI[b]
HBV	Other	Other	HEV	Other	AIH
AIH	HBV	HAV	DILI[b]	HAV	Other

Abbreviations: AIH, autoimmune hepatitis; DILI, drug-induced liver injury; HAV, hepatitis A virus; HBV, hepatitis B virus; HEV, hepatitis E virus.
[a] In descending order of incidence.
[b] Nonacetaminophen.
Data from Refs.[3,11,26,32,45,65]

ALF patients in the United States.[32] Comprehensive data are collected up to 3 weeks after enrollment, and prospective outcomes are also collected at 1 and 2 years. The 2-year survival rates were 89.5% for those with spontaneous recovery from acetaminophen-induced ALF who survived past the initial 3-week period.[20] Similarly, the 2-year survival rate for patients with acetaminophen-induced ALF who underwent liver transplantation was 88%.

In terms of demographics, the majority of patients with acetaminophen-induced ALF in the ALFSG cohort were white, and there were no differences in mortality among whites, blacks, and Asians.[33] Women were more likely to have acetaminophen-induced ALF than men within each of the 3 racial groups. Within the group of whites, Hispanics were less likely than non-Hispanic whites to develop acetaminophen-induced ALF.[33] Similar results were seen at 2 years among those who spontaneously recovered from acetaminophen-induced ALF. Spontaneous survivors tended to be younger, female, white, and non-Hispanic.[20] It was also found that spontaneous survivors were more likely to have active psychiatric and substance abuse issues at study enrollment, and there were more unintentional overdoses than intentional ones (52% vs 38%, respectively).[20]

Viral Hepatitis

ALF owing to viral hepatitis usually refers to infection with HAV, HBV, and HEV. Acute hepatitis C has been reported as a cause of ALF in Asian countries like Taiwan and Japan, but is exceedingly rare in Western countries.[34–36] Hepatitis D has also been reported to contribute to ALF in those with HBV by acting as a coinfection or as a superinfection.[37] Overall, viral hepatitis remains the most common cause of ALF worldwide, with much of the burden owing to HAV and HEV infection in the developing world.[18] Although the incidence in Europe and the United States is lower, it is not insignificant. Viral hepatitis accounts for 19% of liver transplants performed for ALF in Europe and for 12% of all cases of ALF in the United States.[32,38]

ALF from HAV typically leads to a hyperacute presentation and has a better prognosis than ALF from HBV.[23] Overall, less than 1% of those infected with HAV develop ALF, although it is more common among the elderly, for whom the outcomes are worse.[39,40] Currently, HAV accounts for about 4% of ALF cases in the United States, similar to the rates observed in Spain, Germany, Australia, Sweden, India, and the UK.[26] A higher incidence of 7% to 8% has been reported in Japan and Pakistan.[11,41] There was a significant decrease in liver transplants for HAV-induced ALF, as well as in overall cases of HAV in the United States between 1988 and 2005.[40] It has been proposed that the initiation of routine childhood vaccination for HAV has been the main driver of the decrease in HAV-induced ALF in the United States.[42]

Unlike ALF from HAV or HEV, ALF from HBV typically has an acute presentation.[13] ALF from HBV has a worse prognosis than both HAV and HEV, with 4% of acute HBV infections progressing to ALF.[43] Overall, the prognosis is worse for the elderly and those with multiple comorbidities. HBV infection can potentially cause ALF in 2 distinct ways: acute infection or reactivation of prior infection, either from spontaneous reactivation or immunosuppression owing to chemotherapy or other immunosuppressive medications.[28] Similar to HAV, the incidence of HBV-induced ALF has decreased dramatically in the United States from 23% between 1987 and 1991 to the current level of 8%.[32,44] This decrease has also been attributed to vaccination, because it mirrors the overall decrease in HBV infection in the United States.[42] Similar trends have been observed in countries throughout Europe.[26] HBV remains a leading cause of ALF in Japan, sub-Saharan Africa, Hong Kong, and Australia.[11,45,46] Of interest, Asian

Americans are more likely have ALF from viral hepatitis, in particular HBV, than are white or black Americans.[33]

ALF as a result of HEV infection, like that associated with HAV, presents as hyperacute liver failure with a good overall prognosis and low mortality.[14] Although most cases in the United States and Europe are the result of travel to endemic countries like Russia, Pakistan, China, Mexico, and India, spontaneous cases of HEV have been reported.[47,48] ALF from HEV is very rare in the United States. A recent analysis from the ALFSG demonstrated that only 0.4% of patients with ALF had an acute HEV infection.[49] Evidence of a prior HEV infection was seen in 43.4% of patients with ALF from other causes, however, which is a much higher percentage of prior HEV infection than the 21% that is seen in the general US population. A possible explanation suggested by the authors is that patients may have acquired the HEV immunoglobulin G antibody via passive transfer from blood or plasma products, which they received before being enrolled in the study.[49] Elderly patients and those with chronic liver disease tend to have worse outcomes.[50] HEV has been known to have a predilection for pregnant women, especially in the third trimester, and the classic teaching has been that pregnancy is associated with worse outcomes. Recent studies have questioned this association and demonstrated that the prognosis for pregnant women with HEV-induced ALF is the same as that of nonpregnant women or men with HEV-induced ALF.[51]

Nonacetaminophen Drug-Induced Liver Injury

ALF owing to nonacetaminophen drug intake is difficult to diagnose and treat. The condition tends to appear as a subacute presentation, which can make identifying the causative agent difficult. Overall, ALF from nonacetaminophen DILI, also called idiosyncratic DILI, accounts for 11% of ALF cases in the United States and is the second leading cause of ALF behind acetaminophen.[32] Although the incidence is a little lower in Europe, with less than 10% of DILI patients progressing to ALF, the morbidity and mortality associated with this condition are tremendous: up to 80% of these patient die or require emergency liver transplant.[52]

From a demographics standpoint, ALF from DILI is one of the few types of ALF that has a higher incidence among the elderly, those older than 60 years, than among young patients.[26] A study from the ALFSG in the United States found ALF from DILI occurs more often in women, a result that was also observed in Spain.[52,53] Racial differences in prevalence and etiology have also been noted. Asians were much more likely to develop ALF from an herbal supplement than were blacks or whites (16.0% vs 3.4% vs 3.8%, respectively), and both blacks and Asians were more likely than whites to develop ALF from DILI (24.4% vs 24.0% vs 14.9%, respectively).[33] Similarly, when the white patients were subdivided by ethnicity into Hispanic or non-Hispanic white, the Hispanic group was more likely to have DILI-induced ALF than the non-Hispanic whites (29% vs 13.4%). It should be noted that the Hispanic group was also more likely to be on tuberculosis medications at the time of ALF presentation, which may account for the increased rates of ALF from DILI.

Overall, the most common classes of medications that result in ALF from DILI in the United States are antibiotics, antituberculosis medications, and antiepileptic agents.[53] The causative agents vary greatly from region to region, with drugs like flutamide, cyproterone acetate, and nimesulide more common in Latin America and phenprocoumon as a major cause of DILI-induced ALF in Germany.[54,55] A partial list of commonly encountered prescription and illicit drugs that can induce ALF is listed in **Box 1**.

Box 1
Common medications and drugs known to cause acute liver failure

Allopurinol
Amiodarone
Carbamazepine
Ciprofloxacin
Cocaine
Efavirenz
Herbalife
Hydroxycut
Isoniazid
Kava Kava
Ketoconazole
Labetalol
Ma Juang
MDMA
Phenytoin
Pyrazinamide
Statins
Valproic acid

Abbreviation: MDMA, 3,4-methylenedioxy-*N*-methylamphetamine.

The use of herbs and supplements is increasing quickly, and currently more than 50% of the US population is taking some kind of herb or supplement.[56] Subsequently, ALF from herbs and supplements has been increasing over the past 10 years and now accounts for 20% of ALF owing to DILI, up from 12%.[57] Recent data from Hillman and colleagues[58] show that ALF owing to supplements and herbs has worse outcomes, lower transplant-free survival, and higher rates of transplant than ALF owing to prescription medications. This finding underscores the importance of a thorough history, with specific questions regarding supplement and herbal use from both the patient, if possible, and the family. In 2012, the National Institute of Diabetes and Digestive and Kidney Diseases and the National Library of Medicine created a website called LiverTox (www.livertox.nih.gov), which provides a free and comprehensive assessment of medications and herbal products and their potential to induce DILI.[59] It is an invaluable clinical tool that should be consulted when the diagnosis of DILI, and especially DILI-induced ALF, is suspected.

Other Etiologies

The incidence of ALF owing to other etiologies ranges from 11% to 23%, depending on the definition of "other," which varies from study to study.[28] Some of the more common conditions that fall into this category include autoimmune hepatitis (AIH), Budd-Chiari syndrome, Wilson disease, ischemic hepatitis, malignant liver infiltration, pregnancy complications, mushroom poisoning, and other viruses including herpes simplex virus, cytomegalovirus, Epstein-Barr virus, and varicella.

AIH is one of the more common causes of ALF among this group of diseases. It accounts for 5% of cases in the United States and usually has a poor spontaneous recovery rate.[32] Although AIH is technically a chronic liver disease and would normally be excluded as a possible cause of ALF, acute cases of previously unrecognized and undiagnosed AIH are considered an exception to this rule.[2,14] It is often difficult to differentiate DILI-induced ALF from AIH-induced ALF owing to their similar appearance on laboratory tests and subacute presentations.[60] A liver biopsy may be helpful to diagnosis AIH, especially when autoantibodies are negative.[2] From a demographic standpoint, patients with ALF from AIH tend to be female, Caucasian, young, and overweight or obese.[61]

Ischemic hepatitis, also called hypoxic hepatitis or shock liver, is another relatively common condition that is frequently grouped in this category. Ischemic hepatitis is considered to be a secondary form of ALF; thus, transplant is not warranted and treatment centers on correcting the underlying cause.[14] It is more common in elderly patients, especially those with comorbidities like cardiovascular disease, severe heart failure, or severe sepsis.[62] Illicit drug use with cocaine or 3,4-methylendedioxymethamphetamine have also been reported to induce ALF owing to ischemic hepatitis.[18] The ALFSG has documented that ischemic hepatitis accounts of 4% of ALF cases in the United States, although other sources have reported rates of 6%.[32,63] It should be noted that a documented episode of hypoxia is not required to make the diagnosis. Like other causes of hyperacute liver failure, ALF from ischemic hepatitis has a good prognosis with a spontaneous recovery rate of 58% to 64%.[23]

Wilson disease is a rare cause of ALF, accounting for 2% to 3% of cases of ALF in the United States.[2] Like AIH, Wilson disease is considered to be an exception to the rule that ALF cases must not have an underlying chronic liver disease. These patients tend to be young, usually less than 20 years old, with a high bilirubin to alkaline phosphatase ratio on laboratory workup.[14] ALF from Wilson disease is universally fatal without a liver transplant, so prompt recognition is of the utmost importance.[64]

SUMMARY

ALF is a life-threatening condition that requires early recognition and transfer to specialized centers to achieve good outcomes. It is not a single disease, but rather a whole group of varied etiologies, many of which are difficult to diagnose and lack specific treatment modalities. Understanding the epidemiologic aspects of the various conditions that lead to ALF, along with their subtype classifications, can help clinicians to better identify and manage this devastating condition. Further evaluation and study from groups like the ALFSG are of tremendous importance to continue to advance our understanding of ALF, with the goal of improving not only short-term survival, but also the long-term morbidity associated with this condition.

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