REVIEW ARTICLE

Acute Liver Failure

A Life-Threatening Disease

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SUMMARY

Background: An estimated 200 to 500 patients develop life-threatening acute liver failure (ALF) in Germany each year. Only sparse data are currently available on the epidemiology and causes of this condition and on potential treatments for it. This article summarizes our current knowledge of the causes, clinical course, and treatment of ALF.

Method: We selectively reviewed the pertinent current literature on ALF from Germany and abroad.

Results: A shift is currently taking place in Germany with respect to the predominant causes of ALF: The leading cause was formerly acute viral hepatitis, but now more cases of ALF are induced by toxic substances, while there is also a growing incidence of cryptogenic subacute ALF. Precise epidemiological data are still lacking. Scoring systems for the assessment of ALF should take account of hepatic function, the regenerative capacity of the liver, the extent of existing extrahepatic complications, and the risk that further ones will develop. The mortality from ALF has been reduced through improved specific treatment for certain etiological types of ALF, the introduction of liver transplantation, and progress in intensive care medicine. The optimal treatment of ALF patients requires close collaboration among specialists in all of the involved clinical disciplines, as well as between peripheral hospitals and transplantation centers.

Conclusion: Precise epidemiological data on ALF are still lacking in Germany, as are prospective, randomized trials of treatments for it. It is nonetheless clear that progress has been made in its diagnosis and treatment.

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Acute liver failure (ALF) is a serious disease: Without adequate treatment the mortality is high. Various etiological factors may lead to ALF, and it may be very difficult to identify the cause in an individual case. All medical specialties may be involved. No clear, universally valid definition of ALF has yet been formulated, but its essential feature is abrupt loss of hepatic function in a patient with no history of liver disease.

Definition

Trey and Davidson (1) define fulminant hepatitis as a potentially reversible condition with occurrence of hepatic encephalopathy within 8 weeks of symptom onset; the encephalopathy may not be severe despite poor liver function. The definition most recently proposed by the Acute Liver Failure Study Group in the USA emphasizes coagulopathy (INR >1.5) (2) and distinguishes three types of liver failure according to the time of onset of coagulopathy and encephalopathy: hyperacute (<7 days), acute (7–28 days), and subacute (28 days to 6 months) (3). Longer latency is linked with higher mortality (86%) (e1). It is important for the clinician to differentiate ALF clearly from both acute-on-chronic and acute-on-cirrhosis liver failure (*Figure 1*), both of which have a much poorer prognosis (e2). As yet, there is no clearly established, universally recognized definition of ALF in the German-speaking countries or indeed in Europe as a whole. The Acute Liver Failure Study Group Germany (ALFSGG) has set itself the goal of establishing such a definition, without which there can be no uniform procedures for the management of ALF. Our intention in this review is to delineate the various forms of ALF and describe the current procedures for diagnosis and treatment. The data we present and the articles we cite were found by a selective search of the pertinent literature in PubMed/Medline.

Epidemiological data and primary causes

In the early 1980s acute hepatitis B virus (HBV) infection was viewed as the most frequent cause of ALF, but in the intervening three decades damage of the liver by toxic substances has assumed increasing importance, with acetaminophen (paracetamol) the primary culprit. In the USA (2), the UK (4), and Scandinavia (5, e3) acetaminophen poisoning is the most frequent cause (>40%); around 10% of cases in each region are due to viral hepatitis, and in up to 20% the cause is not

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ascertained. In southern Europe, Africa, and Asia, on the other hand, the viral hepatitis still predominate. In the Mediterranean region around 40% of cases of ALF are caused by hepatotropic viruses, most frequently HBV, and only 20% by toxicity; the etiology remains unclear in 30% of cases (6).

In Germany, epidemiological data of this nature are sparse and usually retrospective. Precise figures on the incidence of ALF are lacking, but the collective experience of various transplantation centers and hepatology centers leads us to assume 200 to 500 cases of ALF annually in this country. Women seem to be affected more often than men (52%–63%). A team from Bonn investigated 35 patients diagnosed with fulminant liver failure between 1998 and 2004. The authors found that the cause was acute viral hepatitis in 13 cases and toxicity in 9 cases (e4). In a study of 102 patients with ALF at Hannover Medical School, the origin was most commonly unknown (21%), followed by acute HBV infection (18%) and acute acetaminophen toxicity (16%) (7). In a retrospective study of 134 patients diagnosed with ALF (International Normalized Ratio [INR] >1.5; encephalopathy without pre-existing chronic liver disease) between 2002 and 2008, 39% of cases were found to have been caused by toxic substances primarily acetaminophen and 23% by acute infection with hepatotropic viruses (8). Interestingly, 9 patients had been taking therapeutic doses of phenprocoumon, already described by several teams of researchers, most of them from the German-speaking countries, as a cause of ALF (9).

Supraregional prospective studies are required to gain a comprehensive, up-to-date appreciation of the causes of ALF in Germany.

Acetaminophen toxicity

Most cases of ALF from acetaminophen poisoning are the result of attempted suicide, but unintentional consumption of several tablets has occasionally been

The various types of acute liver failure

documented (e5). Acetaminophen toxicity does not inevitably lead to ALF, but various risk factors increase the probability of acute liver damage even at “therapeutic doses” (e.g., 45 g daily). Comorbidity and/or the intake of other substances increase the risk of liver failure after consumption of acetaminophen (10), as does alcohol (11). Furthermore, there are indications that certain genetic polymorphisms favor toxic liver damage (12, e6).

Viral hepatitis

Viral hepatitis, above all acute HBV infection, remain the cause of a high proportion of cases of ALF. Successful vaccination programs and refined treatment approaches have drastically decreased the incidence in the industrialized nations in recent years; in less developed countries, however, acute HBV infection remains the principal cause of ALF (13, e3). It should also be borne in mind that patients with immune suppression (endogenous or exogenous) may experience reactivation of a latent HBV infection, potentially leading to

TABLE 1

Causes of acute liver failure

Toxicity		Viral hepatitis	Immunological	Metabolic	Pregnancy-related	Vascular
Acute (dose-dependent)	Idiosyncratic					
Acetaminophen	Ecstasy	Hepatitis A, B, C, (B+) D, E	Autoimmune hepatitis	Wilson disease	Fatty liver of pregnancy	Budd–Chiari syndrome
Amanita species	Phenprocoumon	HSV	GvHD	alpha-1 Antitrypsin deficiency	HELLP syndrome	Ischemia/shock Veno-occlusive disease
	Tetracycline	EBV				
	Halothane	CMV				
	Isoniazid					
	Anabolic steroids					
	Phytopharmaceuticals					

HSV, Herpes simplex virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; GvHD, graft-versus-host disease

The course of acute liver failure

FIGURE 2

ALF. Early treatment with lamivudine or one of the new potent nucleoside/nucleotide analogs may possibly diminish the virulence of the disease course and save the patient from liver transplantation (LTx) and the associated complications (14). The effect of early antiviral treatment remains to be confirmed, however, as the existing evidence comes from intervention studies, some of which had historical controls (14, e7, e8).

Other causes

The rarer causes of ALF include idiosyncratic toxic impairment. Most often tuberculostatic agents (e.g., isoniazid) are involved, but antibiotics or phytopharmaceuticals (e.g., kava, Chinese green tea, or the lichen *Usnea barbata*) may also be to blame (e9). Chemotherapeutic agents may themselves be hepatotoxic, but increasingly cases are being observed of reactivation of a latent HBV infection under treatment with immunosuppressants (above all anti-CD20 antibodies), sometimes leading to fulminant liver failure (e10). In as many as 2% of American ALF patients the cause is a fulminant first manifestation of Wilson disease (15). Five percent of cases are the result of autoimmune hepatitis (2). Further causes of ALF are listed in Table 1. A supraregional clinical database for ALF, coupled with clear treatment guidelines, would be particularly useful in these special cases.

Pathophysiology

ALF is characterized by the death of large numbers of parenchymal hepatocytes as a result of cell necrosis or apoptosis. This loss of cells ultimately leads to functional impairment of the liver. The predominant mechanism of cell death varies depending on the cause (16). Antiviral agents reduce not only the viral load but also cell death (by 80%), thus seeming to have a positive effect on disease severity and the necessity for LTx (e7). Experiments in animal models suggest that the massive loss of hepatocytes leads to a marked inflammatory reaction with infiltration of immune cells and activation of inflammatory intrahepatic cascades; this could explain the often rapid clinical deterioration with occurrence of systemic inflammatory response syndrome (SIRS) and consecutive failure of multiple organs (17) (Figure 2).

Hepatic encephalopathy

One of the principal symptoms of liver failure is hepatic encephalopathy (HE). The continuum of HE is divided into four stages, all of which can be reversible (18). The clinical symptoms of HE are listed in Table 2. Progression from stage II to stage III is considered to show irreversible liver damage; spontaneous recovery is rare, and in most cases the patient is transferred to a transplantation centre, listed at Eurotransplant, and undergoes LTx as soon as possible. The pathogenesis of HE is complex and not yet fully elucidated. Genetic variations of the glutamine gene may have an important role in the development of HE in ALF (19). Moreover, a central part in the genesis of HE is played by

TABLE 2

Classification of hepatic encephalopathy (West Haven criteria)

Stage	Clinical findings	Asterixis	Electro-encephalogram
I	Euphoria, depression, slight disorientation, slurred speech, sleep disturbances	+/-	Triphasic waves
II	Lethargy, moderate disorientation	+	Triphasic waves
III	Marked disorientation, can be roused when somnolent	+	Triphasic waves
IV	Coma, initially still reacts to pain stimuli	-	Delta activity

TABLE 3

Scoring systems for severity of acute liver failure/necessity of transplantation

Scoring system/criteria		Evaluation/prognostic factors
Kings' College criteria	Acetaminophen toxicity	Arterial pH <7.25 (independent of stage of hepatic encephalopathy) OR two out of three of the following criteria and clinical deterioration: – INR <6.5 – creatinine >300 µmol/L – hepatic encephalopathy grade 3–4
	Other causes	INR >6.5 (independent of stage of hepatic encephalopathy) OR three out of five of the following criteria (independent of stage of hepatic encephalopathy): – age <10 or >40 years – etiology: unclear, medication-toxic – time from icterus to encephalopathy >7 days – INR >3.5 – Bilirubin >300 µmol/L
Clichy criteria (e19)		Hepatic encephalopathy grade 3 or 4 and – factor V <20% age <30 years) or – factor V <30% (age >30 years)
MELD (23)		$10 \times (0.957 \times \ln_{\text{serum creatinine}} + 0.378 \times \ln_{\text{bilirubin}} + 1.12 \times \ln_{\text{INR}} + 0.643)$
CK-18/modified MELD		$10 \times (0.957 \times \ln_{\text{serum creatinine}} + 0.378 \times \ln_{\text{serum CK-18/M65}} + 1.12 \times \ln_{\text{INR}} + 0.643)$
BiLE score		Bilirubin (µmol/L)/100 + lactate (mmol/L) + 4 (for cryptogenic ALF, Budd–Chiari syndrome, or phenprocoumon toxicity) – 2 (for acetaminophen toxicity) ± 0 (for other etiologies of ALV)

BiLE score, bilirubin-lactate-etiology score; CK, cytotokeratin; INR, International Normalized Ratio; MELD, model of end-stage liver disease

ammonia (NH₃), which, as a neurotoxin, seems to be involved in the formation of cerebral edema (e11). The serum concentration of NH₃ does not correlate with the degree of encephalopathy, however, and the HE is not always directly dependent on the severity of liver failure. Nevertheless, worsening HE in an optimally treated patient with ALF is viewed as an unfavorable prognostic factor and is thus taken in account when calculating risk scores (3, e12).

Supervenient acute renal failure

In up to 80% of cases, ALF causes acute renal failure. Direct toxicity of acetaminophen, aflatoxin, or non-steroidal anti-inflammatory drugs may be responsible (e13), but most frequently the primary causative factor is tubular necrosis owing to hypotension or ischemia/reperfusion. For this reason, early targeted crystalloid volume replacement is essential to avoid arterial hypotension and ensure adequate renal perfusion. Norepinephrine or the vasopressin analog terlipressin can be employed for this purpose (20, e14). If dialysis is indicated, continuous treatment is preferred because most patients show signs of circulatory instability. Studies have shown that high-volume filtration improves the hemodynamics in patients with massive systemic inflammation (21). It is vital to initiate renal replacement therapy as early as possible in patients with volume-refractory acute renal failure in the context of hepatorenal syndrome.

Overall, however, the prospect of successful treatment is very limited, particularly in advanced ALF. The mortality rate in advanced stages of the disease is 38% without transplantation (7).

Diagnostic procedures

An essential aid to diagnosis is laparoscopic liver biopsy, which provides a larger volume of tissue for examination than transjugular biopsy. Biopsy procedures cannot always be performed, however, because of the high risk entailed in patients with liver damage. A detailed history must be taken (direct or indirect anamnesis, with particular attention to alcohol consumption and medication) to ascertain the time course of the symptoms, exclude the much more frequent acute-on-chronic liver failure with pre-existing liver cirrhosis, and then establish the etiology of ALF. Are there any indications of previous liver disease (steatosis, fibrosis)? What was the patient's alcohol intake, and what medications, fungi, and/or phytopharmaceuticals were consumed? Are there any signs of sepsis or ischemia (previous cardiogenic shock)? Has the patient made trips abroad, had unprotected sexual intercourse, or undergone immunosuppressant treatment? What other diseases has the patient had?

If ALF is suspected, comprehensive laboratory examinations and diagnostic imaging must be carried out immediately. On one hand, laboratory parameters that help to establish the severity of liver damage (ALT,

TABLE 4

Specific treatment of acute liver failure

Cause	Treatment	Dosage
Acetaminophen	N-Acetylcysteine	600 mg/kg/day total dose
Amanita species	Silibinin	20–50 mg/kg/day
Acute hepatitis B	Lamivudine Entecavir Tenofovir	100–300 mg/day* ¹ 0.5–1 mg/day* ¹ 245 mg/day* ¹
HELLP/AFLP	Delivery/cesarean section	
Autoimmune hepatitis	Prednisolone	1–2 mg/kg/day
Budd–Chiari syndrome	TIPSS/surgical shunt	
Herpes simplex hepatitis	Aciclovir	3 x 10 mg/kg/day* ¹

*¹ Data inconclusive: adaptation to renal function may be necessary

AST, GLDH) and cholestasis (gamma-GT, AP, bilirubin) and the extent of the liver's synthesizing capacity (INR/Quick test, albumin), and excretion function (NH₃) must be determined. On the other hand, accompanying complications in other organs have to be identified (blood gas analysis, lactate, differential blood count, creatinine, urea). These parameters provide essential pointers to the likely outcome and several of them are included in prognostic scoring systems. It is also crucial to identify the cause of ALF by means of appropriate laboratory tests, for example:

- Determination of drug level (acetaminophen)
- Toxicological screening (amphetamines, barbiturates, benzodiazepines, cannabinoids, Ecstasy, cocaine, methamphetamines, opiates, tricyclic antidepressants)
- Viral diagnosis (HAV, HBV, HCV, HEV, HIV, HSV, CMV, EBV, VZV)
- Tests for possible genetic causes (ceruloplasmin, ferritin, transferrin saturation, alpha-1 antitrypsin)
- Autoimmune causes (ANA, SMA, AMA, ANCA)
- In women of child-bearing age, a pregnancy test.

As for diagnostic imaging, duplex sonography of the portal vein and hepatic veins is obligatory to detect any pre-existing liver disease (portal hypertension, cirrhosis) or a vascular etiology (e.g., Budd–Chiari syndrome).

Scores for assessment of prognosis

The introduction of LTx improved the prognosis of ALF considerably, to survival rates of ca. 85% at 1 year and 80% at 3 years (4, e15–e17). Although LTx ultimately constitutes the only curative treatment for ALF, it is clinically challenging in that contraindications have to be swiftly excluded and a suitable donor organ has to be available at the right time. Accurate assessment of the severity of ALF and the potential variability of the prognosis in a given patient are thus essential for scheduling LTx. Prognostic markers that permit effective differentiation among the various possible courses

of ALF are required. At the same time, patients whose liver is capable of recovery with supportive treatment must be differentiated from those who urgently need LTx, because the complications, e.g., life-long immunosuppression or postoperative ischemic-type biliary lesions (ITBL), cause high morbidity (3.9% for ITBL) (e18) and increased mortality (22).

Several different scoring systems are currently in use for the clinical assessment of the prognosis of ALF (Table 3). All of these scores are based to some extent on four crucial factors: on one hand the liver's capacity for synthesis and the degree of hepatocyte damage, as reflected in the laboratory by the INR and serum bilirubin respectively, and on the other hand the development and grade of encephalopathy (or the associated cerebral edema) and the occurrence of multiple organ failure and the resultant metabolic crisis.

Recent studies have identified serum lactate and phosphate (e20), high body mass index, advanced age (e21, e22), and surrogate markers of cell death (16) as additional predictive or diagnostic factors. A central goal of future initiatives should be evaluation of new molecular markers and the various scoring systems in prospective studies with large numbers of patients (e23).

Treatment

Liver transplantation

Potential candidates for LTx must be selected and allocated to a transplantation center without delay, even before diagnostic procedures have been concluded. Contraindications such as florid alcohol or drug abuse, systemic organ ischemia, or an unfavorable social prognosis with regard to compliance following transplantation must be excluded, and the patient's general health must be critically evaluated. A patient considered suitable for LTx must then be listed for transplantation without delay. In the period 1995 to 2005, patients with ALF made up 3.9% of all those listed for LTx in the area covered by the United Network for Organ Sharing in the USA (2).

In a prospective study of 308 patients with ALF, 84% of those who received early LTx (median 3.5 days after listing) were still alive 3 weeks after their original admission to the hospital. The rate for patients without LTx was only 35% (24). The level of evidence, however, was low.

Conservative treatment

High-dose N-acetylcysteine (NAC) is an established specific treatment for acetaminophen-induced ALF (Table 4). A recent prospective multicenter study carried out by the ALFSG in the USA shows that administration of NAC in three successive dosages for a total of 72 h (150 mg/kg/h for 1 h, then 12.5 mg/kg/h for 4 h, and finally 6.25 mg/kg/h for 67 h) can also be beneficial in non-acetaminophen-induced ALF. Administration of NAC resulted in a significantly higher survival rate among patients with hepatic encephalopathy grade 1 to 2 who did not receive a transplant

(40% with NAC versus 27% without NAC; $p = 0.043$). Therefore, NAC appears to represent a reasonable treatment option in the early stages of ALF, particularly in view of its low rate of adverse effects (e24). Apart from NAC, the keystones of conservative treatment of ALF are intensive therapy of SIRS to stabilize the hemodynamics, safeguarding of the airways and early mechanical ventilation (in patients with impaired consciousness), measures to prevent cerebral edema (raising of upper body, compensation of hyponatremia, osmotic therapy with mannitol), and monitoring and early management of infections. Specific treatments for ALF are presented in *Table 4*.

Liver replacement systems

The rationale for extracorporeal liver support measures is that they should form part of the survival strategy to keep a patient alive until such a time as a suitable liver becomes available for transplantation. However, the data obtained to date are insufficient to support an evidence-based recommendation regarding the use of liver replacement procedures in patients with ALF. One meta-analysis suggests that such measures may have a clinical benefit in acute-on-chronic or acute-on-cirrhosis liver failure (25) but is severely limited by the pronounced heterogeneity of the liver replacement systems included, the patient collectives investigated, and the accompanying conservative standard treatments.

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GLOSSARY

Abbreviations

ALD:	alcoholic liver disease
ALF:	acute liver failure
ALFSG(G):	Acute Liver Failure Study Group (Germany)
AMA:	antimitochondrial antibodies
ANA:	antinuclear antibodies
ANCA:	antineutrophil cytoplasmic antibodies
AOC:	acute-on-chronic
AP:	alkaline phosphatases
CMV:	cytomegalovirus
CVP:	central venous pressure
EBV:	Epstein–Barr virus
GGT:	gamma-glutamyltransferase
GvHD:	graft-versus-host disease
HAV:	hepatitis A virus
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HE:	hepatic encephalopathy
HEV:	hepatitis E virus
HIV:	human immunodeficiency virus
HRS:	hepatorenal syndrome
HSV:	herpes simplex virus
INR:	international normalized ratio
ITBL:	ischemic-type biliary lesions
LTx:	liver transplantation
MAP:	mean arterial pressure
MELD:	model of end-stage liver disease
NAFLD:	non-alcoholic fatty liver disease
NH ₃ :	ammonia
SIRS:	systemic inflammatory response syndrome
SMA:	smooth muscle antibodies
VZV:	varicella zoster virus

KEY MESSAGES

- The current data on the epidemiology, causes, and treatment options for acute liver failure (ALF) are sparse.
- Toxic damage of the liver is gradually displacing acute viral hepatitis as the predominant cause of ALF.
- Liver function, hepatic regeneration capacity, and extent and risk of extrahepatic complications should be taken into account in scoring systems to evaluate the severity or prognosis of ALF.
- The mortality of ALF has been lowered by specific treatments for individual causes, by the introduction of liver transplantation, and by improvements in intensive care medicine.
- Close cooperation among all clinical disciplines and between peripheral hospitals and transplantation centers is vital for optimal management of ALF.

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