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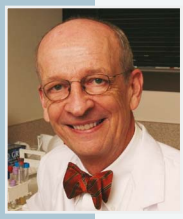

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Chapter 3

Worldwide differences in acute liver failure

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Acute liver failure (ALF) is a rare, potentially fatal complication of severe hepatic illness resulting from various causes. In a clinical setting, severe hepatic injury is usually recognized by the appearance of jaundice, encephalopathy and coagulopathy, although occasionally jaundice may even be absent in the earliest stages. ALF has been identified as a distinct clinical entity across the globe. Considerable geographical and regional differences exist in defining characteristics, etiologies and prognostic markers of ALF. A recent systematic review that evaluated 1233 published articles on ALF reported 41 different definitions with varying diagnostic characteristics to define ALF [1]. However, certain clinical characteristics in all these definitions are universal, such as absence of clinical evidence for pre-existing liver disease, presence of encephalopathy, and presence of coagulopathy. The major differences in defining ALF include the interval between onset of symptoms of acute liver injury and the occurrence of overt liver failure, defined by presence of encephalopathy and/or coagulopathy. Despite these differing definitions of ALF, the mortality reported in all reports is high and ranges from 60 to 80%. Differences in definition of ALF are

Coagulopathy and encephalopathy define the acute liver failure syndrome.

related to its heterogeneous nature, which in part relates to ethnic and etiological differences prevalent in various geographical areas. Furthermore, in English literature, the term 'fulminant hepatitis' has been used in lieu of 'ALF' but, more recently, has been discarded.

Definitions & nomenclature

In 1969, Trey and Davidson defined ALF as the occurrence of encephalopathy within 8 weeks of the onset of acute hepatitic illness in an individual without pre-existing liver disease [2]. However, in subsequent years, reports on ALF emanating globally from various tertiary care centers, used varying criteria to define ALF. While most included presence of encephalopathy as an essential criterion, presence of coagulopathy (international normalized ratio [INR] >1.5 or prothrombin time prolongation >15 s or prothrombin activity <40%) was used as an additional requirement by most centers to further define ALF. The interval between onset of acute hepatitis illness and occurrence of encephalopathy also varied from 2 to 26 weeks. Many groups do not exclude certain patients with silent pre-existing liver disease, presenting with rapid onset encephalopathy and/ or coagulopathy as ALF, such as chronic hepatitis B (CHB), autoimmune hepatitis and Wilson's disease. More controversial and generally not included in definitions of ALF are the following: superinfection of hepatitis A with chronic hepatitis C (CHC), hepatitis E (in hyperendemic areas for hepatitis E virus [HEV]) occurring in the presence of pre-existing silent liver diseases such as CHB, CHC or alcoholic liver disease [1,3]. Alcoholic liver disease has never been included since most acute alcoholic hepatitis still takes place in the setting of cirrhosis.

Duration of illness has classically included time from onset of symptoms or jaundice to onset of encephalopathy and the terms 'hyperacute' and 'subacute' are used with slightly different definitions from various sites. The importance of these distinctions rests in the difference in prognosis according to duration of illness. However, differences in duration are tied to the specific etiology as well; duration of illness is remarkably specific for each etiology. For example, most patients with acetaminophen-induced ALF demonstrate a hyperacute presentation (encephalopathy), with peak of illness being approximately 72 h after ingestion of a toxic amount of acetaminophen. The spontaneous survival frequency of 40–67% is in contrast to acute or subacute groups such as drug-induced liver injury with a survival of 7–28% [4]. There is little evidence for any chronic or slowly evolving injury due to acetaminophen. The same time frame

Acute liver failure still carries a high morbidity and mortality.

Definitions vary largely in the duration from onset of symptoms to liver failure.

applies to ALF caused by ischemia, which is characterized by very rapid onset following a specific event causing poor hepatic perfusion, with a peak level of hepatic enzymes by 72 h at the latest, followed by prompt resolution when the incident cause is rectified. By contrast, drug-induced liver injury is associated almost invariably with a slower evolution, termed subacute. One interesting contrast between regions is the difference observed between hepatitis E in the Indian subcontinent versus the developed world. In contrast to the heterogeneous natural course reported from the UK, France, the USA and Japan, Indian patients have a more uniform clinical presentation and natural course, although current evidence now supports the view that the virus genotypes may determine differences in presentation. Reports from India, including more than 1000 patients with ALF, have documented that approximately 80% of patients develop encephalopathy within 2 weeks of onset of icterus and all patients present within 4 weeks of onset of jaundice [5]. Postmortem liver biopsies from these patients never show evidence of underlying chronic liver disease. The survival frequency in HEV-induced ALF has been reported to be more than 60% and this is similar to that observed for hepatitis A. Differences in genotype and in presence of previously silent underlying chronic liver disease in some patients may be an explanation for reports of ALF with differing nomenclature, definitions and natural course, resulting in subclassification of this entity.

The broadest definition is that provided in a practice guideline from the American Association for the Study of Liver Diseases (AASLD) where ALF was defined as "liver diseases characterized by the development of hepatic encephalopathy and coagulation abnormality, usually characterized by an INR of $\geq$1.5 in patients without pre-existing cirrhosis, and an illness of less than 26 weeks duration". The subcommittee of the International Association for the Study of the Liver [6], which included many regional leaders associated with ALF in 1999, tried to provide nomenclature and defining criteria for ALF and subacute hepatic failure in an effort to universalize these conditions, which is depicted in **Box 3.1**. Uniform definitions, diagnostic criteria and subclassification to categorize ALF patients would allow better comparison of various reports from different regions.

Etiologies of ALF

Differences in etiology of ALF between different parts of the world are striking. Most cases of ALF in Western countries are thought to be due to drugs and toxins with

Coagulopathy and encephalopathy are the key elements to the diagnosis of acute liver failure.

Time duration to the onset of encephalopathy after onset of symptoms is different in various definitions across the world: UK: 8 weeks; USA: includes cases up to 26 weeks; India: 4 weeks; France: 12 weeks; Japan: 8 weeks.

Box 3.1. Recommendation of the International Association for the Study of the Liver subcommittee for the definition and classification of acute hepatic failure and subacute hepatic failure.

Nomenclature

- AHF: synonyms such as fulminant hepatitis, fulminant hepatic failure and acute yellow atrophy should not be used
- SHF: synonyms such as subfulminant hepatitis, subacute hepatic failure and late onset hepatic failure should not be used

Diagnostic criteria of liver failure

- AHF: encephalopathy
- SHF: encephalopathy and/or progressive ascites

Maximum interval between onset of icterus and features of liver failure

- AHF <4 weeks
- SHF >4 weeks to 24 weeks

Subclassification

- Etiological to indicate specific cause of AHF
- Temporal to indicate the rapidity of encephalopathy
  - Hyperacute: encephalopathy within 10 days of icterus
  - Fulminant: encephalopathy between 10 and 30 days of the onset of jaundice
- Not otherwise specified (e.g., AHF or hyperacute A)

AHF: Acute hepatic failure; SHF: Subacute hepatic failure.
Data from [6].

acetaminophen being the major culprit in many countries including the USA, the UK, other European countries and Australia. The common etiologies of ALF in different parts of the world are highlighted in **Table 3.1**.

The etiology of ALF among Western countries is somewhat heterogeneous as shown in **Table 3.1**. In the UK, acetaminophen overdose was the etiology in 57% of ALF patients, whereas in the USA, France, Germany and Australia, acetaminophen was the reported etiology of ALF in 46, 7, 9 and 36% of cases, respectively. In Spain, compared with other western countries, the incidence of acetaminophen overdose is low, where it is rarely used as a method of suicide perhaps because it is not available over-the-counter [7]. Other drugs responsible include NSAIDs, antiepileptics, antimicrobial agents such as antituberculosis therapy (ATT; isoniazid, usually in combination with other medications such as rifampicin, ethambutol and pyrazinamide), antibiotics and antifungals. Phenprocoumon, an oral anticoagulant accounts for 23% of non-acetaminophen drug-induced ALF in Germany. Numerous other drugs also have been implicated as the cause of ALF, predominantly in Western countries. In one series of 133 US cases, all with ALF, the most common single drug-induced liver injury cause was ATT (19%), followed by all other antibiotics combined (23%). Complementary and alternative medications were observed in 11%, antiseizure medications in 9% and NSAIDs in 5%.

Published reports from the Indian subcontinent identify hepatitis viruses as the etiological agent in more than 90% of patients with ALF. Non-A, non-E hepatitis account for 38% (although this is not further defined) and HEV is responsible for 31% of cases. There are relatively few drug-induced cases except those caused by ATTs. Other causes such as acetaminophen overdose, drug-induced liver failure, Wilson's disease and acute fatty liver

Table 3.1. Different etiologies of acute liver failure across the world.

Country (year)	Cases (n)	Drugs (%)		Viral (%)					Indeterminate category	Others (%)	Ref.
		Acetaminophen	*Other*	*HAV*	*HBV*	*HEV*	*Other viral*	*Non-A, non-E*			
USA (1998–2012)	1696	46	Antimicrobial agents (ATT, antibiotics, antifungals, antiepileptics, NSAIDs and antimetabolites) 12	2	7				13	Autoimmune (6.5) Ischemic (5), Wilson's disease (1), Budd–Chiari (1), Pregnancy (1), Other causes (5)	[23]
UK (1999–2008)	422	57	11	2	5	1			17	7	[24]
France (1986–2006)	363	7	21	5	28				18	21	[25]
Germany (2008–2009)†	109	9	32 Most importantly phenprocoumon (23% of non-acetaminophen cases), valproate, NSAIDs, sertraline and clindamycin	4	10	4	3		24	Autoimmune (3) Wilson's disease (3) Budd–Chiari (2) Malignancy (3) Pregnancy (3) *Amanita* (2) Others (4)	[26]
Australia (1988–2001)	80	36	6 Nitrofurantoin, sodium valproate, isoflurane and ketorolac	4	10			34 non A, non B		Wilson's disease (7) Budd–Chiari (3)	[27]

†Total more than 100% owing to overlap in some cases.
ATT: Antituberculosis therapy; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HEV: Hepatitis E virus.

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		Acetaminophen	*Other*	*HAV*	*HBV*	*HEV*	*Other viral*	*Non-A, non-E*		
India (1986–2009)	1223	6	ATT	1	16	31	6	38	2 (data not available)	[5]
Japan (1998–2006)	856	10	ATT, acetaminophen, anticancer agents, allopurinol and acarbose	6	42	1	2	3	Autoimmune (7) Unknown (30)	[28]

†Total more than 100% owing to overlap in some cases.
ATT: Antituberculosis therapy; HAV: Hepatitis A virus; HBV: Hepatitis B virus; HEV: Hepatitis E virus.

of pregnancy (AFLP) are infrequent. Of interest, viral hepatitis is also the most important cause of ALF in Japan with hepatitis B as the cause in 42%. Drugs were implicated as the etiology in approximately 10% cases.

Cultural practices and lifestyle habits differ greatly between geographic regions. In many Western countries, acetaminophen is freely available as an over-the-counter preparation and used for self-medication by the general public. By contrast, self-medication and easy access to drugs is not widespread in India and many developing countries. On the other hand, prevalence of hepatitis viruses dominates in south Asia.

Amanita poisoning (*Amanita phalloides*) causing ALF has been implicated as a minor fraction of US and European ALF patients and is observed when amateur mushroom hunters fail to recognize the poisonous variety [8]. However, this condition is rarely seen in eastern Asian countries including the Indian subcontinent.

Differences in etiology in a single country in patients of different races & ethnicity

In a study from the USA [9], racial and ethnic differences were observed in the presentation, etiology and outcomes of acute liver failure. Acetaminophen toxicity was particularly frequent among whites, (51.5 vs 27.7% for blacks and 20.0% for Asians). Asians had more viral hepatitis-induced ALF, particularly hepatitis B (26.0%) in this series.

Complications of ALF

Complications of ALF play a part in determination of outcome and vary by region and by etiology.

- Renal failure has been described in 40–80% of patients from Western country series depending upon the etiology and is associated with a poor prognosis.Renal failure occurs more frequentlyin patients with acetaminophen-induced ALF (70%) and in 30% of patients with other causes in Western country series, suggesting that there is a direct toxic effect of acetaminophen on the renal tubules. The other causes associated with increased incidence of renal failure include amanita poisoning and trimethoprim–sulfamethoxazole toxicity. The predominant etiology of ALF in Eastern countries is viral- and drug-induced,and accounts for a small number of renal failure cases only. In India, renal failure is reported in 10% of patients [5].

Acute liver failure in pregnancy

- Western countries and Europe: pregnant females account for 1–3% of cases.
- India: 40–60% of females of child-bearing age who present with acute liver failure are pregnant and mostly due to hepatitis E virus, higher in India.
- Mortality is not increased due to the pregnancy, but is relatively high.
- Termination of pregnancy not indicated.
- Acute fatty liver of pregnancy: genetic predisposition, termination of pregnancy improves prognosis.

- Gastrointestinal bleeding is reported in between 7 and 20% of patients.
- Cerebral edema is the most common cause of mortality. In India, 58% of ALF patients have cerebral edema at the time of hospitalization. The mortality rate of patients with cerebral edema was 82% compared with 44% among the patients without cerebral edema [10]. Older studies from the UK reported that overt features of cerebral edema increased in frequency with increasing grades in encephalopathy. However, with the advent of intracranial pressure estimation, it would appear that most patients with ALF at the time of hospitalization have some degree of cerebral edema [11]. According to recent data, cerebral edema is less frequent now than in former years, but this may reflect earlier admission to hospital and better intensive care [12].
- Sepsis: infection is a common complication in ALF that has been documented across the globe. The incidence of infection has been reported as high as 90% in the initial series from the UK. The causative organisms were bacteria in 80% of cases and fungal infections were seen in 32% of cases. The predominant organisms are Gram-positive bacteria and the most common site of infection is the respiratory tract. In more recent reports [13], the predominant organisms reported are

Cultural practices and endemic diseases determine the causes of acute liver failure regionally:

- West (USA and Europe): drugs (acetaminophen and prescription drugs, principally antibiotics).
- East: India, Pakistan, Somalia (hepatitis A and E) Japan, Korea and China: hepatitis B and herbal remedies.
- Rarer causes: autoimmune hepatitis, Wilson's disease, Budd–Chiari syndrome, *Amanita* poisoning, metastatic infiltration of liver and pregnancy are probably worldwide in distribution.

Geographic variations in causes of acute liver failure are ethnic and cultural.

Gram negative. The incidence of infection in the authors' experience, from a single center in India is approximately 55%; the most common site of infection is the respiratory tract, and the most common organisms are Gram-negative bacilli.

Gender, pregnancy & ALF

ALF is more common in females across the world, except in Japan where it is reported to be equal in males and females. Although most etiologies favor women, except viral hepatitis, the reason for female preponderance across many etiologies is not clear. Pregnant women with ALF are widely regarded as having more severe disease with higher complication rates and mortality compared with nonpregnant females. A summary of studies reporting pregnancy and ALF is shown in **Table 3.2**.

Studies from Western countries and Japan have not highlighted this issue, as the number of pregnant patients developing ALF is relatively small. In studies from India, among all females with ALF up to 60% of females in the child-bearing age are pregnant. By contrast, the fertility rate among women of child-bearing age in the general population of India is 2.9%. Pregnancy is thought to affect the immune system resulting in greater severity of a variety of infections during pregnancy. During hepatits E virus epidemics, pregnant women [14] in their second and third trimesters get infected more frequently (12–20%) than men and nonpregnant women (2–4%) for unclear reasons. It may simply reflect a higher rate of apparent, rather than subclinical, infections. The frequency of ALF is higher (10–22%) among pregnant women with HEV infection than among men and nonpregnant women (1–2%). Hence, the mortality rate is significantly higher among pregnant women who develop hepatitis during epidemics (10–39%) than in the general population affected with hepatitis (0.06–12%). In the sporadic setting, evidence of HEV infection has been detected in 30–45% of patients with ALF. A recent study evaluated the role of viral and host factors in pregnancy outcomes in ALF [15]. The progesterone receptor gene mutations (PROGINS) were seen more in patients with ALF, and a reduced expression of progesterone receptor and progesterone-induced blocking factor, a higher IL-12/-10 ratio, and a high viral load resulted in poor pregnancy outcomes in hepatitis E. The possible reasons why pregnant females developing ALF are seen more in India may

Complications

- Renal failure is more common in Western countries (acetaminophen is associated with direct toxicity)
- Renal failure is less frequent in India (viral etiology).
- Sepsis is more frequent in Western countries, with bacterial species split between Gram-positives and Gram-negatives, whereas Gram-negative organisms are common in India.

Table 3.2. Studies reporting female predominance and role of pregnancy in acute liver failure.

Country	Cases (n)	Number of females overall (%)	Pregnancy	Female patients with pregnancy associated liver failure (%)	Etiology of ALF (%)	Overall mortality in pregnant females (%)	Ref.
USA	1696	1173	16	1.5			[23]
UK	422	257					[24]
Germany	109	69	3			33	[26]
Australia	80	64					[27]
India	1015	590	249	38.5	59.4 (HEV)	54	[14]
India	180	111	49/83	59	96 (HEV)	66	[28]
France	363			2			[25]
Japan	856	423					[29]

ALF: Acute liver failure; HEV: Hepatitis E virus.

be the large number of pregnant women (3%), unavailability of clean drinking water, and a high attack rate.

The mortality in pregnant females has been found to be similar to that of nonpregnant women and men, and is independent of the cause or trimester [14]. With the availability of the HEV vaccine, the scenario may change with time. Therefore, HEV has been identified as a very important cause of severe liver disease in areas of the world where >70% of the global population resides. A recent study by the WHO [16] assessed liver disease burden globally and identified that, worldwide, approximately 3.7 million people get affected by HEV with 70,000 figure mortality in 1 year.

In AFLP, which has a strong genetic component, and may have geographical variation in prevalence, termination of pregnancy is required for improving prognosis. However, there is no rationale for actively terminating pregnancy in HEV endemic regions with the hope of improving the outcome of the patient. Genotypes 1 and 2 of HEV are prevalent in hyperendemic regions where the reservoir for HEV seems to be human and cause outbreaks, sporadic acute hepatitis, ALF and acute-on-chronic liver failure [3]. Genotype 3 and 4 are more prevalent in the USA, Europe and Japan where the reservoir seems to be represented by pigs and other mammalian and avian species. In these countries, zoonotic transmission leads to autochthonous

Management: liver transplant improves survival in selected patients. Long-term transplant results are good. In absence of transplant (developing countries), prevent and treat infection and cerebral edema.

acute HEV. Genotype 3 and 4 are infrequently associated with severe liver disease and the majority of cases represent subclinical infection.

Outcome

The etiology of ALF, which differs across the world as highlighted above, is a major determinant of outcome. In the West, the etiology is heterogeneous. Acetaminophen-induced ALF has a better outcome than most other etiologies, even after development of hepatic failure. The spontaneous survival of patients who develop encephalopathy is approximately 64% and exceeds that for most other forms of ALF, such as ALF due to idiosyncratic drug toxicity (where survival without transplant is seen only in ~20% of cases). However, when acetaminophen patients do progress, they do so very rapidly. In addition, because acetaminophen-induced ALF constitutes the bulk of all ALF cases; the total number of deaths due to acetaminophen toxicity exceeds all other diagnoses. Nearly a third of patients who develop encephalopathy die. These patients are often found unsuitable for transplantation due to evidence of associated substance abuse, suicidal intent or history of prior suicidal attempts. In cases of acetaminophen-induced hepatic injury, once ALF develops, the outcome for both types of overdose – suicidal or unintentional – is similar [4].

Both from the East and West and Japan, there are reports of ALF due to ATT. In studies from India, a mortality of 70% has been reported for ATT-induced ALF [14]. Studies from India also documented that more than 90% of ALF were due to hepatitis viruses indicating a homogeneous etiology [10,14]. Therefore, when survivors and nonsurvivors were compared, the etiology was not found to be different and the multivariate analysis also could not establish etiology as an independent predictors of mortality. However, when HEV as a separate group was compared with other etiologies, such as ATT-induced ALF, the survival frequency among HEV was significantly superior to other etiologies [5]. Of course, the availability of liver transplantation greatly impacts on outcome with recent studies suggesting an overall survival in Western countries exceeding 85%.

Outcome:

- West: etiology affects the outcome.
- India and Japan: etiology appears less important; >90% have a single etiology (viral hepatitis).
- Among viral ALF, HAV and HEV have better prognoses than HBV. HCV causes ALF very rarely if at all.
- ATT-induced ALF: high mortality.

Prognostic models

The ability to predict which patients with ALF will recover with medical management alone and who will succumb without liver transplantation is of paramount important. Static variables that correlate with survival

are age and etiology. Patients with HAV, HEV and acetaminophen toxicity, and AFLP have better survival rates than those with drug-induced, autoimmune, hepatitis B and cryptogenic ALF, where spontaneous survival rates are <30%. Patients with Wilson's disease or malignancy-induced ALF rarely survive [17]. While the former are prime transplant candidates, the latter are consigned to hospice or home. Among the dynamic variables, the degree of encephalopathy is a strong predictor of outcome. Patients with advanced coma grade (3 and 4) have poorer survival compared with those with grade 1 and 2 coma.

Multiple prognostic models have been proposed for ALF. The Kings College Hospital (KCH) criteria for liver transplantation, proposed by O'Grady *et al.* [18], have continued to be popular, although these criteria are specific but not very sensitive in detecting cases that will proceed to die, and therefore need transplantation.

Unfortunately, no model has consistently demonstrated a reliable accuracy in predicting outcome. A complexity of this process is that transplantation alters what the real outcome would be for transplanted cases are usually recorded as 'nonsurvivors'. In a large Indian study [10], the following variables present at admission have been identified as independent risk factors for patient outcomes: age ≥40 years; bilirubin ≥15mg/dl; prothrombin time prolongation ≥25 s; and clinical features of cerebral edema. With an increasing number of risk factors, mortality increases and with three or more factors it is 93%. In another study from India, clinical prognostic indicators age ≥50 years, jaundice encephalopathy interval >7 days, grade 3 or 4 encephalopathy, presence of cerebral edema, prothrombin time ≥35 s, and creatinine ≥1.5 mg/dl. Presence of any three out of six clinical prognostic indicators was superior to Model for End Stage Liver Disease or KCH in identifying survivors and nonsurvivors [19].

ALF is a dynamic process in which variables determining prognosis at admission change over time, and thus, the clinical course varies accordingly. A new prognostic model from India, ALF early dynamic model [20] is based on four variables: arterial ammonia, serum bilirubin, international normalized ratio and hepatic encephalopathy grade >2. This model takes into account the values of these variables over 3 days. The performance of the ALF early dynamic model has been reported to be superior to the KCH criteria and the Model for End Stage Liver Disease score.

Management

The general principles of care are the same across the world. All patients are managed in intensive care units. Organ support systems are used as

required. Liver transplantation has improved the survival in these patients. In the USA, 25–29% of patients with ALF are subjected to liver transplantation [21]. In the largest published cohort of patients who underwent liver transplant for ALF across Europe [22], the patient survival at 1, 5 and 10 years was 74, 68 and 63%, respectively. The graft survival was 63, 57 and 50% over the same duration of follow-up. The survival rate has progressively improved over time. Similar results are reported from the USA and Japan. Liver transplantation is not widely available in developing countries; hence, the management is mainly supportive with organ support, prevention and treatment of infections, and control of cerebral edema.

In low-endemic regions, sporadic cases of locally acquired HEV infection, mainly caused by genotypes 3 or 4 are reported. In a series of 14 patients from France who underwent solid organ transplantation and were on immunosuppression, all patients presented with unexplained elevation of liver enzymes and were detected to have acute HEV infection [23]. All patients were infected with genotype 3 HEV. Eight out of 14 patients developed chronic hepatitis, and chronic hepatitis may progress to cirrhosis in immunosuppressed patients.

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Summary

- Considerable geographical and regional differences exist in defining characteristics, etiologies and prognostic markers of acute liver failure.
- In Western countries, drug-induced acute liver failure including acetaminophen accounts for most cases; in the East, viral hepatitis comprises the majority of cases.
- Outcomes for certain other viral infections (hepatitis A virus/hepatitis E virus), and acetaminophen are better than for other etiologies.
- Pregnant females are more prone to develop acute liver failure, but mortality is not increased by pregnancy.
- Different prognostic models are described across the world, dynamic models have been described recently.
- Management is conservative and includes organ support and liver transplantation in selected patients.

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