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Acute liver failure: Current trends

Faouzi Saliba*, Didier Samuel

AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif, France; University Paris-Sud, UMR-S 785, Villejuif F-94800, France; Inserm, Unité 785, Villejuif F-94800, France

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Different terms have been used in the literature for acute liver failure (ALF), i.e., fulminant hepatitis or necrosis, fulminant and subfulminant hepatic failure, and various definitions have been proposed [1–3]. In a systematic review of 41 definitions of ALF, Wlodzimirow and co-workers identified 4 components that underlined the definition of ALF and accounted for the differences: presence and/or grading of hepatic encephalopathy (HE), the interval between onset of disease and occurrence of HE, presence of coagulopathy, and pre-existing liver disease [4].

More than 90% of the patients who developed an acute hepatitis episode would recover spontaneously. Recovery rate is even higher mainly if the triggering event is related to certain etiologies, i.e., hepatitis A virus, transient hypoxia, paracetamol intoxication, and mushroom poisoning [5,6]. The acute hepatitis episode is considered to be severe and named also "acute liver injury" (ALI) when the liver synthetic function, expressed by a coagulation marker, is reduced, namely prothrombin time ratio rate $\leqslant$50% or an international normalized ratio (INR) $\geqslant$1.5 and the disease occurs within less than a 26-week period. The acute severe episode is considered to be fulminant and named "ALF" when early neurological manifestations of the disease, mainly hepatic encephalopathy, appear. ALF is a distinct syndrome that should be differentiated from acute-on-chronic liver failure that develops in patients with decompensated cirrhosis [7].

More recently, Polson and Lee with the group of AASLD defined ALF as evidence of coagulation abnormality, usually an INR $\geqslant$1.5, and any degree of mental alteration (encephalopathy), in a patient without pre-existing cirrhosis and with an illness of $\leqslant$26-week duration. To note, patients with Wilson disease, vertically-acquired HBV, or autoimmune hepatitis may be included in spite of the possibility of cirrhosis if their disease has only been recognized for $\leqslant$26 weeks [8]. The group also highlighted that the distinctions according to the delay between onset of jaundice and HE, such as hyperacute or fulminant, acute or subfulminant and subacute, do not have prognostic significance distinct from the cause of illness. Despite various definitions in the literature, the occurrence of HE during the course of the disease appears to be the landmark of a critical progression. HE, the main complication in patients with ALF, is almost always complicated by cerebral oedema, leading to increased intracranial pressure and death by brain herniation. Therefore, early prediction of hepatic encephalopathy is essential.

The progression from a severe acute hepatitis episode or ALI to ALF remains unpredictable and this raised an essential question as to when to transfer these patients to a transplant centre and/or to a liver ICU. It is estimated that approximately 30% of these patients would develop an ALF. Patients with ALF related to viral etiology and those with undetermined cause of liver failure are more likely to develop HE and have a worse outcome. Takikawa *et al.* reported in their study that age >50, prolonged prothrombin time, elevation of total bilirubin, and non-A-E hepatitis were risk factors for encephalopathy development in patients with severe acute hepatitis [9]; these factors were close to the King's College criteria for liver transplantation for patients with non-paracetamol induced ALF. Bernuau *et al.* proposed criteria for patients with severe acute hepatitis and high risk of developing HE, according to the degree of severity of prothrombin time ratio, for immediate transfer to a liver unit with liver transplant facilities [10]. In the manuscript by Bernal and co-workers in this issue of the *Journal*, the authors did consider referral to a liver ICU in patients with ALI and ALF, progressive coagulopathy with INR >2 or PT >30 s or development of extrahepatic organ failure. Gene polymorphism might have an important role in determining patients at risk of developing ALF as it has been shown recently for acetaminophen-induced liver failure, and this would need to be confirmed with other series and determined for various etiologies [11].

In their study, Bernal and co-workers reported their huge experience on 3300 acute liver patients treated in their liver ICU since 1973, among them 2095 patients with ALF. They mainly focused on the changes that occurred during the last thirty years in the epidemiology, disease severity, therapeutics, and outcomes of patients with ALF. This is one of the biggest series ever reported in a single centre. They did observe in the recent period a significant decrease in paracetamol induced-hepatitis. This is in contrast to a constant increase observed in the United States (46%) and in France (20%) [5,6]. The difference among countries is probably related to the fact that in the early King's College experience, suicide attempt of paracetamol etiology was extremely high (60.9%) and, moreover, according to the authors, to the introduction of paracetamol sales restriction in the United Kingdom in 1988. Of note, the proportion of patients who underwent liver transplantation for paracetamol-induced ALF,

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* Corresponding author.
E-mail address: faouzi.saliba@pbr.aphp.fr (F. Saliba).

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did not change overtime and varied between 36% and 39% of the patients in the King's college experience. Current data from the European Liver Transplant Registry (ELTR) in 4903 adult patients (>16 years) transplanted for ALF, paracetamol overdose represented merely 12% of the indications [12]. Transplantation for paracetamol-induced ALF increased seven-fold from 2% (1973–1978) to 14.1% (2004–2008) [12].

A major decrease in HBV and HAV viral related etiology was observed in all reported series in Europe and in the USA. This is probably related to the vaccination campaign and the awareness of viral transmission among adults since the 1990s. In the experience of the King's college reported in this issue of the *Journal*, viral hepatitis fell significantly from 55.9% (1973–1978) to 16.6% (2004–2008) of all non-paracetamol cases. Viral etiology represented 21% of the indications of liver transplantation for ALF. Liver transplantation for ALF due to HAV and HBV decreased significantly in the last 5 years (from 1% to 0.5% and from 17.9% to 13.2%, respectively).

Treatment in the intensive care unit of patients with ALF has been limited. Before the advent of liver transplantation, the overall mortality rate in patients with acute liver failure ranged from 80% to 85%. Liver transplantation has been a major improvement and became the standard management of these patients since the late 1980s [13,14]. Bernal and co-workers reported, in the 387 patients who underwent a liver transplantation, a survival increase from 56% for the period 1984–1988 to 86% for the period 2004–2008. Survival after liver transplantation was recently evaluated in 4903 patients with ALF reported in the ELTR. One, 5- and 10-year patient and graft survival rates were 74%, 68%, 63%, and 63%, 57%, 50%, respectively. Survival became better during the period 2004–2009 compared to the previous quinquennia (p <0.001), despite that donors >60 years increased from 1.8% to 21% [12]. This has also been recently observed in the national French trial with a major improvement in the results reaching a one-year patient survival of 89% among those patients who underwent liver transplantation [15]. The reasons are probably related to several factors: (1) early transfer of patients with acute severe hepatitis to transplant centre before the occurrence of hepatic encephalopathy, (2) a dramatic decrease of patients with ALF admitted with hepatic encephalopathy grade IV in our study, (3) a significant fall in proportion of patients admitted with signs of intracranial hypertension from 76% in 1984–1988 to 19.8% in 2004–2008 in the study by Bernal *et al.* in this issue of the *Journal*, (4) early introduction of medical management mainly for paracetamol and viral etiologies, (5) improvement in the overall management of patients admitted to the liver ICU such as monitoring, prevention, and treatment of early signs of intracranial hypertension (ICH), hypothermia control, microbiological surveillance and prophylaxis, renal replacement therapy modalities, (6) technical improvement in the transplant surgery and the perioperative care. Despite a great improvement in survival rates after liver transplantation, some patients still die before, during, or after transplantation, mainly as a result of irreversible brain damage. In addition to the scarcity of organ donors, and due to the emergency conditions, poor quality grafts, which have a high risk of graft failure, are frequently used. These factors have been a limitation to the improvement in the results of liver transplantation for acute liver failure.

Medical management of patients in the ICU has mildly improved in the late 1990s and this included specific early interventions to prevent and treat ICH, hemodynamic and sepsis management, and renal replacement modalities. Despite some recent improvements, transplant-free survival rates of these patients, who were often in a good condition before the onset of ALI, remain low [10,16]. In the manuscript of Bernal *et al.*, they observed an improvement in hospital survival among patients who were not transplanted only in paracetamol etiology, non-paracetamol drug, and viral etiologies. However, in their study, the development of ICH was strongly associated with increased mortality (73.6% among 648 patients with ICH) and 55% of their most recent patients (2003–2008) who developed ICH died.

A major therapeutical improvement in the management of patients with ALF is still needed. In recent years, there has been a considerable interest in the use of newer forms of liver support that may provide a bridge until a spontaneous recovery of the liver or until an appropriate donor is available or better in order to improve transplant-free survival. A recent meta-analysis on extracorporeal liver support therapies (ELS) included eight RCTs, three addressing acute liver failure (198 participants). They showed that ELS therapy significantly improved survival in acute liver failure (risk ratio 0.70; $p = 0.05$). The number of patients needed to treat (NNT), to prevent one death from acute liver failure, was eight [17]. Therefore, there might be a potential place for the use of ELS in this setting. Over the last decade, the Molecular Adsorbent Recirculating System (MARS®) that uses albumin dialysis has been widely used. The MARS® system has demonstrated interesting results in controlled and uncontrolled trials in improving short-term survival. However, in a recent randomized controlled trial performed in 102 patients with ALF, MARS did not show superiority compared to a control group [15]. In this study, 75% of the patients were transplanted within 24 h. This highlights the difficulties to run such trials and raises a major debate on how to evaluate future ELS devices in the advent of liver transplantation.

Conflict of interest

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