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Chapter 8

Liver Transplantation in Acute Liver Failure: Indications and Outcome

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Abstract

The term acute liver failure (ALF) refers to the acute (<26 weeks) and severe worsening in liver function associated with encephalopathy in a person with no underlying chronic liver disease. ALF constitutes a critical clinical syndrome that is potentially reversible but has a very variable prognosis. No specific treatment is available, and liver transplantation (LT) is the treatment of choice in many cases. However, the challenge remains of identifying those patients with a poor likelihood of spontaneous recovery of liver function and for whom the indication and time of LT in order to guarantee survival (based on identification of prognostic factors) need to be established. In Europe, 8% of LT are due to ALF. Although the results of LT due to ALF have improved over recent years, they are still far from those seen after elective LT.

Keywords: liver transplant, acute liver failure, prognostic score, outcome

1. Introduction

Acute liver failure (ALF) is defined as the presence of acute liver injury, that is, a rise in transaminases at least three times the upper limit of normal, jaundice, and coagulopathy, together with the onset of encephalopathy in a person with no previous liver disease [1]. Exceptions to this definition include the acute onset of Wilson disease, autoimmune hepatitis, and the Budd-Chiari syndrome, as well as reactivation of the hepatitis B virus (HBV) [2].

Though no consensus exists on the severity of the coagulopathy or the encephalopathy marking the transition from acute liver injury to ALF, an INR ≥1.5 and any degree of encephalopathy are generally accepted [3]. Clinically, ALF is classified according to the interval between the onset of jaundice, considered as the initial symptom, and the encephalopathy. The ALF is considered to be hyperacute if the encephalopathy appears within

7 days of the jaundice, acute if it appears between 8 and 28 days, and subacute when it appears beyond 28 days [4]. The disease is considered chronic if it has a history of more than 26 weeks.

Table 1 summarizes the causes of ALF. Worldwide, infection is the most common cause, though in developed countries drug-induced hepatic injury is responsible for up to 50% of cases. As many as 30% of cases are of unknown etiology [5].

The main causes of death due to ALF are infection and decerebration from cerebral edema. The medical management of patients is based on support measures, early identification, and treatment of complications until spontaneous recovery of liver function or liver transplantation (LT) [6].

Establishing the indication for and time of LT in a patient with ALF should be as precise as possible in order to avoid, on one hand, unnecessary risks for a recoverable patient and on the other an increased likelihood of death associated with a delay in transplantation.

Viral
HAV, HBV, HCV, HEV
CMV, EBV, HSV, VZV, dengue
Pharmacologic/toxic
Paracetamol (acetaminophen)
Idiosyncratic drug reaction
Amanita phalloides
Vascular
Budd-Chiari
Ischemic hepatitis
Pregnancy
Preeclampsia
HELLP
Fatty liver of pregnancy
Others
Wilson disease
Autoimmune hepatitis
Lymphomas and other neoplastic diseases
Hemophagocytic lymphohistiocytosis
Cryptogenic

Table 1. Etiology of the acute liver failure.

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2. Indication for liver transplantation in acute liver failure

Liver transplantation in ALF has represented an inflection point in the survival of affected patients, who previously suffered a mortality rate of almost 85% in the pretransplant era [7].

Indicating LT too soon involves the possibility of performing the transplant in patients who may still experience spontaneous recovery with complete liver function, thereby adding the risks associated with an urgent transplant and lifelong immunosuppression, in addition to the waste of a valuable organ. However, delaying the decision to transplant in patients with ALF can increase the risk of infection, irreversible brain damage, multiorgan failure, or even death. Accordingly, selection of ALF patients who need LT should be based on the early identification of factors predicting a poor clinical outcome, as well as application of prognostic models combining different parameters. Unfortunately, the prognostic models available have certain limitations, low sensitivity and specificity, and worse predictive value than desired [8].

2.1. Predictive factors

The etiology is considered a predictive factor. Around 60% of patients with ALF due to paracetamol intoxication, hepatitis A, ischemic hepatitis, or pregnancy may survive with no need for transplantation, whereas only 30% of cases with drug-induced liver injury, autoimmune hepatitis, and various cases of unknown etiology achieve spontaneous recovery [9].

The duration of symptoms has traditionally had a prognostic value. The subacute presentation of ALF is associated with a worse prognosis than acute and hyperacute ALF, though these differences are probably conditioned by the etiology of the subacute failure [10].

Encephalopathy, although it forms part of the definition of ALF, should also be classified. Patients with grades 1–2 encephalopathy have an excellent prognosis, whereas grades 3–4 encephalopathy is associated with a low likelihood of spontaneous resolution [11] and is thus criteria for admission to the intensive care unit, with a recommendation to measure the intracranial pressure as a marker of the preservation of brain perfusion [12]. Coagulopathy, as a direct indicator of liver function, is considered to predict the severity. Generally measured using the prothrombin time (PT) or the International Normalized Ratio (INR), a PT over 90 s or an INR >4 is associated with a mortality rate above 90% [13]. Factor V levels <20% in patients younger than 30 years and levels <30% in those older than 30 years indicate a worse prognosis.

The histologic findings have also been proposed as predictors of the outcome and the likelihood of spontaneous recovery. Though some series have related the risk of death with the presence of >50% hepatocyte necrosis, the little representativity of the samples together with the risk involved in performing a liver biopsy in patients with coagulopathy generally advise against routine histologic study in patients with ALF, and nor should the decision to transplant be based on biopsy findings. A liver biopsy could be indicated in cases of diagnostic doubt, especially to rule out neoplastic causes, which contraindicate LT [14]. Other factors, such as age, body mass index, serum bilirubin, creatinine, hypoglycemia, lactate levels, and pH changes, can also be considered determinant.

All these factors help to identify patients with ALF who have a worse prognosis. Recently, the EASL established recommendations for the early transfer to transplant centers of patients with ALF if they fulfill the following criteria [15]:

- ALF due to paracetamol or hyperacute causes:
  - Arterial pH <7.3 or HCO_3 <18
  - INR >3.0 day 2 or >4 thereafter
  - Oliguria and/or elevated creatinine
  - Altered level of consciousness
  - Hypoglycemia
  - Elevated lactate unresponsive to fluid resuscitation
- Non-paracetamol:
  - Arterial pH <7.3 or HCO3 <18
  - INR >1.8
  - Oliguria/renal failure or Na <130 mmol/L
  - Encephalopathy, hypoglycemia, or metabolic acidosis
  - Bilirubin >300 μmol/L (17.6 mg/dL)
  - Shrinking liver size

2.2. Prognostic models

The currently available prognostic models should be applied continuously during the follow-up and clinical management of patients with ALF, even though they are not universally accepted or their recommendations established.

In 1989, the King's College Hospital criteria (KCC) were established (**Table 2**) [16]. These are based on cohort studies and are widely used at the present time. They are based mainly on the etiology, differentiating between ALF secondary to paracetamol and ALF of other causes. They are highly specific, that is, patients who fulfill these criteria have a high likelihood of death if they do not undergo LT. However, their sensitivity is low, as seen from the death of patients who do not meet the criteria, especially in patients with causes other than paracetamol [17]. A meta-analysis found a specificity of 82% for etiologies other than paracetamol and 92–95% for causes related with paracetamol. The sensitivity was about 68%. Both sensitivity and specificity increase if the criteria are applied dynamically [18]. In an attempt to improve the predictive value of the KCC, the measurement of lactate as an indicator of tissue dysfunction and failure of hepatic clearance has been added to the criteria in the UK. This is particularly useful in cases of paracetamol toxicity. An admission arterial lactate >3.5 or >3 mmol/L after fluid resuscitation is a marker of poor prognosis [19, 20].

AFL due to paracetamol

- Arterial pH <7.3 after resuscitation and 24 h since ingestion
- Three following criteria:
  - Hepatic encephalopathy grades 3–4
  - Serum creatinine >300 mol/L (3.4 mg(dl)
  - INR >6.5

ALF not due to paracetamol

- INR >6.5
- Three out of five following criteria:
  - Etiology: indeterminate etiology hepatitis, drug-induced hepatitis
  - Age <10 years or >40 years
  - Interval jaundice encephalopathy >7 days
  - Bilirubin >300 mol/L (17 mg/dl)
  - INR >3.5

Table 2. King's College criteria.

The Clichy criteria, established in 1986, also derive from cohort studies in patients with fulminant hepatitis B (**Table 3**) [21]. Validation studies found less accuracy than for the KCC, with a positive predictive value of 89%, but a negative predictive value of 36%. They are, therefore, very deficient for identifying potential survivors without a LT [22].

The MELD score (**Table 4**), adopted by the United Network for Organ Sharing (UNOS) and The Organ Procurement and Transplantation Network (OPTN), has been validated as a predictor of short-term mortality in patients with hepatic cirrhosis. Retrospective studies have shown that the MELD score has a similar predictive value to the KCC for AFL-associated mortality [23]. In the USA, the prospective data from the Acute Liver Failure Study Group (ALFSG) showed that a MELD >30 in patients with ALF due to paracetamol has a negative predictive value of 82%, such that patients with a MELD <30 have a high likelihood of survival without a LT and with a slightly lower score in cases not related with paracetamol [24].

- Confusion or coma (hepatic encephalopathy 3–4)
- Factor V <20% of normal if age <30 years or factor V <30% if age >30 years

Table 3. Clichy criteria.

$$9.57 \times \log^{e(\text{creatinine})} + 3.78 \times \log^{e(\text{bilirubin})} + 11.2 \times \log^{e(\text{INR})} + 6.43$$

Table 4. MELD (MELD calculator).

In an attempt to improve the prognostic accuracy in ALF patients, other indicators of liver dysfunction have been suggested, such as measures of hepatic metabolism with markers labeled with indocyanine green [25], as well as predictive models of mortality used in other clinical situations. The APACHE II system, designed to predict mortality in intensive care patients, has also been applied in ALF patients, but no cut point has been set demonstrating that it is superior to the KCC and nor can it be applied early on [26].

A prognostic index designed by the ALFSG included variables at the time of presentation of the condition, such as bilirubin, encephalopathy grade, INR, phosphorus, and serum levels of M30 (a direct marker of hepatocyte apoptosis). Although the prognostic value of this index was greater than the KCC and MELD score, measurement of M30 is not generally available [27].

Comparison between these different models, which share some parameters, has found no superiority of one over the others, and no universal recommendations have been established. It is, however, accepted that ALF should be strictly assessed at the reception center and, if the patient meets the criteria for a poor prognosis, they should be referred as soon as possible to a transplant center where the available predictive models can be applied dynamically, mainly the KCC and Clichy criteria, to determine the indication for LT. American and European series show that 50% of patients admitted with ALF receive a LT [28]. Once the indication for a transplant has been made, the patient is included on the active list, in most countries with a higher priority than patients with other indications, thus ensuring an early transplant, usually within days of being placed on the list.

If a donor organ becomes available, the situation of the patient should be reassessed by the transplant team, in order to identify a likely clear improvement after transplant or else an absolute contraindication for transplant, mainly the presence of irreversible brain damage.

3. Outcome of liver transplant in acute liver failure

In Europe LT due to acute or subacute liver failure accounts for some 8% of LT. Patient survival after LT for this reason is 79, 71, 69 and 61%, at 1, 3, 5 and 10 years, respectively [29]. This survival rate is slightly lower during the initial years (first and third) than LT for other reasons but then becomes similar. Most deaths occur between the first and third years posttransplant due, mainly, to neurologic complications and sepsis [30]. Some centers have reported survival rates of up to 86% [31]. Overall survival is probably greatly influenced by patient age, with data from the European Transplant Registry showing 1- and 5-year survival of 51 and 42% in patients older than 60 years [29].

3.1. Factors influencing the results

Multiple factors have been associated with the outcome of patients who receive a LT due to ALF. Three studies [4, 32, 33] have identified a recipient age above 45–50 years as a poor prognostic factor, attributing this to the reduction in physiologic reserve with effect from these ages [4]. A body mass index (BMI) >29 was identified in one study [32]. On the other hand, no specific factor associated with the severity of the ALF, such as coagulopathy, has been found to be associated with a poor prognosis, although the degree of kidney failure, mechanical ventilation, and the use of inotropic drugs were found to be predictive factors in these studies.

Such donor characteristics as age >60 years, ABO incompatibility [34, 35], and the use of a split or small liver have also been related with worse results [18, 36].

Survival has improved greatly over the last decade. This is the result of better management of ALF patients, leading to a lower incidence of pretransplant complications (e.g., renal failure, respiratory problems, sepsis), a lower grade of encephalopathy, and the use of more isogroup grafts. Identification of prognostic factors as well as the creation of transplant indication criteria like the Clichy [37] or King's College [16] criteria has also contributed to this improvement. The earlier indication for transplant, which in turn contributes to the use of more compatible organs and the patient receiving the transplant in better conditions, has been the foundation for the improvement in results over recent years.

The rapid localization of organs for transplant in ALF patients is an important factor that has also contributed greatly to the better results. In countries like Spain, with a high donation rate, it proves relatively easy to find a compatible organ fairly quickly, with 50% of these patients receiving a transplant within 24 h of becoming active on the waiting list, while the mean time to transplant is 40 h. In Spain this has resulted in only around 7% of ALF patients dying while still on the waiting list compared with 30% in the USA [38].

Thus, the optimal selection of candidates for transplant plus the identification of poor prognostic factors and the exclusion of those patients who will not benefit from LT due to their situation have contributed to the improved results. The development of extracorporeal bioartificial systems, improved organ procurement, and the use of organs from living donors can all contribute to future improvements.

4. Conclusion

Acute liver failure is a potentially severe clinical condition that is associated with a high rate of mortality. Selection of those patients who will benefit from a liver transplant should be based on the early identification of prognostic factors. Survival of patients who receive a transplant due to ALF has improved over recent years, though it is still somewhat lower than that of patients who receive a LT for other reasons.

Conflict of interest

The authors have no conflict of interest to declare.

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