Acute Alcoholic Hepatitis: Indication for Early Liver Transplantation

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Abbreviations

AH	Alcoholic hepatitis
DF	Maddrey's discriminant function
LT	Liver transplantation
MELD	Model for End-Stage Liver Disease

Over the last decade, gradual shifts in attitudes to transplantation of patients with alcohol-related liver disease have occurred. Timing for liver transplantation in patients with alcohol-related liver disease differs between transplant programs, although the selection process is frequently based on the 6-month sober period prior to listing. In the particular setting of patients with severe alcoholic hepatitis not responding to medical therapy, a strict application of a period of sobriety as a policy for transplant eligibility is unfair to such patients, as most of them will have died prior to the end of the 6-month sober period.

4.1 Introduction

Timing for liver transplantation (LT) in patients with alcohol-related liver disease differs between transplant programs, although the selection process is frequently based on the 6-month sober period prior to listing [1]. In the particular setting of

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patients with severe alcoholic hepatitis (AH) not responding to medical therapy, a strict application of a period of sobriety as a policy for transplant eligibility is unfair to such patients, as most of them will have died prior to the end of the 6-month sober period. Over the last decade, gradual shifts in attitudes to transplantation of patients with alcohol-related liver disease have occurred. For example, expert guidelines no longer recommended a fixed period of abstinence prior to transplantation [2, 3] and stopped listing AH as an absolute contraindication to LT, contrary to the recommendations from the preceding period [4].

4.2 Definition

Alcoholic hepatitis is defined by a rapid onset of jaundice occurring in patients with excessive alcohol consumption [3, 5, 6].

Given the overlap in clinical presentation of severe AH and acute-on-chronic liver failure with recent alcohol consumption, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Alcoholic Hepatitis Consortia proposed a new approach for the diagnosis of alcoholic hepatitis [7]: the onset of jaundice within the last 8 weeks, ongoing excessive alcohol consumption for at least 6 months with less than 60 days of abstinence prior to jaundice, aspartate aminotransferase (AST) more than 50 IU/l (international units per liter), AST/ALT (alanine aminotransferase) ratio more than 1.5, and serum bilirubin more than 3.0 mg/dl [7]. High gamma-glutamyl transferase (gGT) levels, polymorphonuclear leukocytosis, increased prothrombin time, and elevated international normalized ratio (INR) levels may be observed in patients with symptomatic or severe forms of AH. The NIAAA consortia recommended that the diagnosis of AH could be made, according to the following classification: (a) definite AH when clinical and histological documentation are available; (b) probable AH in the absence of histologic confirmation but typical liver biochemistry and exclusion of confounding variables; (c) in the presence of potential confounding variables (e.g., sepsis, shock, or possible drug-induced liver disease), the diagnosis is referred to as possible AH and a liver biopsy is recommended [7]. The histological diagnosis of AH consists in the presence of ballooned hepatocytes, Mallory bodies, and lobular neutrophils [6, 7]. In patients with severe forms, because of coagulopathy disorders, liver biopsy should be carried out via transjugular route. However, access to this technique is restricted to experienced centers.

4.3 Prognostic Factors for Severe Alcoholic Hepatitis

Maddrey's discriminant function (DF) is the most used score to assess disease severity and predict the outcome of patients with AH [8]. Severity of AH has been defined by a DF score higher than 32 and the therapeutic guidelines focus mostly on patients with DF $\geq$ 32. In untreated patients with severe forms of AH, the mortality risk at 1 month is around 20–30% [8, 9]. Other prognostic scores, such as the Model for End-Stage Liver Disease (MELD) [10], Glasgow alcoholic

hepatitis score (GAHS) [11, 12], and ABIC score (age, serum Bilirubin, INR, and serum Creatinine score) [13], are also able to predict short-term mortality. However, none of those prognostic models is significantly superior to the other [14].

In 2007, the Lille model was developed for promptly predicting short-term survival of patients with severe AH treated or not with corticosteroids. This score highlights the need to integrate the magnitude of early improvement in liver function in the prediction of short-term mortality. The model was derived from 438 prospectively enrolled patients with severe forms (DF $\geq$ 32) of biopsy-proven alcoholic hepatitis treated with corticosteroids [15]. Patients with Lille model higher than 0.45 had a drastic decrease in 6-month survival in comparison to others: 25% versus 85%. The 0.45 cut-off identified 75% of deaths [15] and the Lille model was more accurate than DF, MELD, and Glasgow ASH score in terms of prediction of 6-month mortality [15, 16]. After 7 days of medical management including or not the use of corticosteroids, the earlier identification of patients with high likelihood of short-term mortality constitutes an important advance that makes it necessary to consider all available therapeutic options.

In order to improve the prediction of short-term mortality, investigators compared the combination of static (MELD, DF, ABIC) and dynamic (Lille) scores to each score alone. The three joint-effect models (DF + Lille, MELD + Lille, and ABIC + Lille) have a higher prediction to each score alone [17]. The combination MELD + Lille seems to be most accurate to predict 2-month and 6-month survival [17]. By day 7 of medical treatment, a normogram provides deciles of mortality risk; for example, 6-month mortality is less than 10% with MELD less than 15 and Lille less than 0.25, whereas 6-month mortality exceeds 70% with MELD more than 35 and Lille more than 0.7 [17]. In summary, the combination of MELD and Lille appears to be the optimal approach to identify patients with an exceedingly high risk of early mortality who should be considered for early LT.

4.4 Therapeutic Management of Severe Alcoholic Hepatitis

For patients with severe AH, European and American clinical guidelines recommend corticosteroids in the absence of contraindications to reduce 28-day mortality [3]. After the acute period, long-term management should focus on maintaining abstinence or reducing alcohol intake.

A recent meta-analysis using individual patient data of 2111 participants from 11 randomized controlled trials showed that patients treated with corticosteroids had higher 28-day survival than patients treated with either placebo/control or pentoxifylline [18]. Pentoxifylline alone or its combination with corticosteroids did not improve short-term (28-day) survival or evolution of liver injury. This meta-analysis of individual data puts an end to the controversy surrounding the efficacy of corticosteroids. However, corticosteroids cannot be viewed as an ideal treatment because they do not improve medium- (3–6-month) or long-term (>6-month) mortality [19–21].

The main purpose of the Lille model is to predict patients not responding to corticosteroids in order to switch them to alternative therapy [15]. Using the Lille model, patients may be classified as: complete responders (Lille score ≤ 0.16, ≤35th percentile); partial responders (Lille between 0.16 and 0.56, 35th—70th percentile); and null responders (Lille >0.56, ≥70th percentile) [20]. Survival impact of corticosteroids was significant in complete and partial responders, whereas it appeared negligible in null responders. Continuation of corticosteroids has been questioned in nonresponders due also to the increased risk of sepsis that, after a median day of 14 days, occurs more frequently in nonresponders than responders (42% vs 11%) and is predictive of 2-month survival [22]. European clinical guidelines stated that this suggests that corticosteroids should be interrupted in nonresponders, mostly in those classified as null responders, when considering the increased risk of development of infection [3].

During severe AH, screening of infection is crucial because 25% of patients with severe AH are already infected at admission [8]. In case of proven infection, corticosteroid therapy should be initiated only after an appropriate and effective antibiotic therapy.

To date, it is not recommended to prescribe antibiotic prophylaxis, but an ongoing randomized controlled trial is evaluating the effect of antibiotic prophylaxis. Patients with severe AH (DF≥32 and MELD>21) are allocated to receive amoxicilllin + clavulanic acid 3 g/day for 28 days + prednisolone 40 mg/day or placebo + prednisolone.

Up to now, no alternative medical treatment has been proposed. A randomized controlled trial comparing the extracorporeal liver therapy (ELAD) to standard of care did not observe significant difference in 90-day survival. As a consequence, this system is not recommended in the setting of severe AH [23]. Pentoxyfilline has no effect in the steroids or pentoxifylline for alcoholic hepatitits (STOPAH) trial, the largest multicenter, prospective, double-blind, randomized trial comparing placebo, prednisolone alone, pentoxifylline alone, and their combination in severe AH [24]. N-Acetylcysteine is an antioxidant substance that replenishes glutathione stores in hepatocytes. In a randomized controlled trial, there was no significant effect between the N-acetylcysteine and the placebo groups [25]. Moreover, N-acetylcysteine alone was inferior to corticosteroids in another randomized controlled trial [26]. Corticosteroids and N-acetylcysteine may have synergistic effects, as suggested by a randomized controlled trial that showed a better 1-monh survival of patients treated with corticosteroids and N-acetylcysteine than patients treated with corticosteroids alone [27]. However, there was no significant difference in survival between the two groups at 6 months, the primary planned end point.

Malnutrition due to impaired caloric intake and increased catabolism is frequent in patients with AH. The recommended protein-caloric intake is often difficult to achieve orally in a significant proportion of patients with AH. A randomized controlled trial of 136 patients with severe AH treated with corticosteroids did not observe survival improvement in patients allocated to receive intensive enteral nutrition by feeding tube [28]. However, low (vs. high) daily caloric intake was associated with twofold increase in mortality, supporting that nutritional

intervention is still an important issue in the therapeutic management of patients with severe AH [28]. In the intention-to-treat analysis, there was no difference in 90-day survival.

4.5 Early Liver Transplantation: A Rescue Therapeutic Option for Severe Alcoholic Hepatitis Not Responding to Medical Therapy

4.5.1 Description of Study

In 2011, a prospective Franco-Belgian pilot study had questioned the dogma of abstinence before evaluation of candidates to LT [19]. Twenty-six patients with severe AH not responding to medical treatment were listed for LT in seven centers. The patients undergoing early LT have a higher 6-month survival rate (77%) than nontransplanted nonresponder patients, matched for age, sex, Maddrey's discriminant function, and Lille score (23%) [29]. The survival benefit was sustained during the 2 years of follow-up [29]. Three out of 26 patients resumed drinking alcohol.

These favorable results have been confirmed by two recent studies in the USA [30, 31]. The first study evaluating early LT in severe AH used a selection process very close to the one used in the princeps Franco-Belgian study. Of 111 patients presenting with severe AH, 9 (9.6%) underwent early LT. Median interval of abstinence prior listing to early LT was 30 days. Six-month survival of early transplanted patients was drastically higher than matched controls not transplanted: 89% versus 11% [30]. Two out of 9 (22%) relapse in drinking alcohol after LT. Median time to first drink was 132 days post-LT [30]. The second American single-center study [31] compared 17 patients who underwent early LT with 26 consecutive patients who underwent LT for alcoholic cirrhosis after at least 6 months of abstinence [31]. Patients with early LT for severe AH had a survival rate of 88% during a median follow-up of 1.5 years that was not significantly different to those transplanted for alcoholic cirrhosis after a sober period of at least 6 months. Deaths after LT in patients early transplanted for AH were directly related to alcohol relapse, whereas those deaths occurring in patients transplanted for alcoholic cirrhosis after a sober period were not [31]. Median time to first drink was 83 days after LT and alcohol relapse was not significantly different between AH and alcohol cirrhotic patients: 24% versus 29% [31].

American investigators from the American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH), which includes 12 US centers from eight United Network for Organ Sharing (UNOS) regions, retrospectively collected data of patients who underwent early LT for severe AH [32]. This retrospective collection included 147 highly selected early transplanted patients between 2006 and 2017 with median MELD at 39 and Lille score at 0.82. After LT, 1-year and 3-year survival rates were excellent: 94 and 84% [32]. The probability of alcohol use post-LT was 25 and 34% at 1 and 3 years after LT [32]. The rate of

alcohol relapse was higher and the time to first drink shorter in the American studies, as compared to the Franco-Belgian study. Sepsis was the main cause of deaths occurring before 1 year, whereas alcohol relapse was frequently implicated in deaths occurring later [32].

A recent mathematical model simulating survival of highly selected patients with AH showed that early LT in comparison with delayed LT (6 months of abstinence from alcohol before LT) increases by 4.5 times the average life expectancy [33].

4.5.2 Selection Process

Before the era of early LT in severe AH not responding to medical therapy, only abstinent patients were considered as candidates for LT. In a context of organ shortage, most programs require a 6-month period of abstinence, prior to the evaluation of alcoholic patients. The 6-month period of abstinence is presumed: a) to permit some patients to recover from their liver disease and obviate the need for LT and b) to identify subsets of patients likely to maintain abstinence after LT. Nevertheless, data concerning the utility of the 6-month rule as a predictor of long-term sobriety are controversial [34, 35]. Despite the frequent use of the 6-month rule, the United Network for Organ Sharing (UNOS) [36] and the French Conference Consensus on Liver Transplantation [37] did not endorse this measure as a formal recommendation.

In the first pilot study evaluating early LT in severe AH not responding to medical therapy, the selection process of patients to be placed on the waiting list was very strict [29]: first decompensation of liver disease; biopsy-proven AH; failure to respond to medical therapy; free of severe co-morbidities or personality disorders; patients and family members had to adhere to lifelong total alcohol abstinence; presence of supportive family members having a close, continuous relationship with the patient; absolute consensus within the medical, nursing, and surgical teams [29]. The stringency of the selection process was shown by the fact that, in two participant centers, only 3% of patients admitted for severe AH had a favorable addictive profile allowing them to be selected for early LT [29].

The selection process of American investigators was slightly different: some patients with severe psychiatric disorders or with drug addiction were selected; previous liver decompensation before the index hospitalization was allowed; histological confirmation of AH was not requested; the process to reach the consensus between team members of the transplant unit was not specified [20, 21].

In recipients relapsing alcohol drinking after LT, heavy drinking is the most risky pattern. The factors associated with heavy drinking after LT were younger age and shorter period of abstinence prior LT [38]. It is associated with the development of significant fibrosis in 30–40% and recurrence of cirrhosis on the liver graft in around 6% of cases. The rapid progression of fibrosis in recipients with heavy drinking explains that one-third of the recurrence of cirrhosis occurs in less than 5 years and that cirrhotic recipients at cirrhotic stage disclose a high rate of liver complications.

Some experts feared that this new selection process without a prior period of abstinence could reduce organ donation. However, this fear is not supported by the survey of a representative sample of US donors showing that 82% of them were neutral about the early LT program for severe AH in the absence of response to corticosteroid therapy [22].

In all transplant centers, substance abuse specialist and psychiatrists are mandatory in the pretransplant evaluation and in the posttransplant follow-up, but it is not enough. When considering the need to select candidates with a lower risk for relapse, it has become mandatory to develop new scores with higher predictive value of prediction of abstinence following LT [39]. Such an approach requires statistical methods adapted to this objective that will integrate all the already available predictive factors of abstinence [40, 41].

4.6 A Change of Paradigm

It is likely that progressive but drastic change in patient perception, clinician practice, expert guidelines, and selection process of patients with alcohol-associated liver disease will occur due to early LT [42]. Indeed, a French survey observed that the rate of LT centers performing early LT before and after 2011 increased from 35% to 70% and that the vast majority of French liver transplant centers did endorse early LT as a therapeutic option in highly selected patients with severe AH not responding to medical therapy [43]. The vast majority of French liver transplant centers reported that except for one selection criterion, the selection process was similar to that of the princeps study: strong social support, no prior presentation of severe AH, and absence of a severe coexisting psychiatric disorder. Similarly, from May to October 2017, an American survey [44] observed that half of the American transplant centers reported performing at least one early LT and most of them realized less than five procedures per year. The fear of increased risk of alcohol relapse was the main reason raised by the centers not performing early LT. Unlike the French centers, less than two-thirds of American centers required that the patient should be unaware of having an underlying chronic liver disease. The shift in American and French practices of selection was followed over the time by a gradual reduction in the length of alcohol abstinence before listing [43]. Indeed, 76% of French centers applied the 6-month abstinence rule when listing patients before 2011, whereas only 29% retained this rule as a selection principle after 2011 [43].

In summary, since the princeps Franco-Belgian study, all recent studies have confirmed early LT as a rescue option in patients with severe AH not responding to medical therapy. Early LT improves survival with an acceptable rate of alcohol relapse, adequate adherence to immunosuppressive regimen, and without any concern in terms of graft function. These results explain why the European Association for the Study of the Liver (EASL) clinical guidelines have recommended early LT for highly selected patients with severe AH not responding to medical therapy. Larger prospective multicenter studies with new insights into the selection and the

identification of candidates to such an approach are needed to better define the target population to this rescue therapeutic option.

Key Points

- Corticosteroids improve one-month survival of severe forms of alcoholic hepatitis.
- Non-response to medical therapy is associated with high-risk mortality.
- Early liver transplantation may be proposed to highly selected patients not responding to medical therapy.
- Early liver transplantation is associated with high benefit in nonresponder to medical therapy.
- Alcohol relapse seems to be similar between early liver transplantation and liver transplantation after a 6-month sober period prior to liver transplantation.
- Progress is warranted to better define the target population.

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