

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Liver Transplantation for Alcoholic Liver Disease



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### **G&H** What is the standard treatment approach to alcoholic liver disease?

**EM** The term alcoholic liver disease (ALD) comprises a spectrum of hepatic injury including simple steatosis, steatohepatitis with or without fibrosis, severe alcoholic hepatitis (AH), and cirrhosis. Abstinence, the cornerstone of therapy for all stages of ALD, has been shown to improve the outcomes and histologic features of hepatic injury, to decrease progression to cirrhosis, and to improve survival of patients with all stages of ALD. Several pharmacologic agents have been utilized in patients with alcohol use disorder to help sustain abstinence and reduce the risk of relapse. These include disulfiram, naltrexone, acamprosate, and baclofen. Baclofen in particular has demonstrated effectiveness and safety for the maintenance of alcohol abstinence in alcohol-dependent patients even in the setting of cirrhosis.

Nutritional deficiencies, namely in protein, vitamin A, vitamin D, thiamine, folate, pyridoxine, and zinc, are commonly seen in patients with ALD. Regular assessment for these deficiencies with as-needed supplementation accompanied with a high-caloric (2000 kcal/day), high-protein (1.2-1.5 g/kg/day) diet with frequent interval feedings is strongly recommended in patients with ALD to improve nutritional status and survival.

### **G&H** How is the treatment for severe AH different?

**EM** In addition to abstinence and nutritional supplementation, specific pharmacotherapy is recommended

for patients with severe AH, which is the most severe and life-threatening type of ALD. Corticosteroids, which are the most extensively studied treatment for AH, are recommended for patients with severe AH as defined by a Maddrey discriminant function (MDF) of at least 32. In the absence of contraindications to corticosteroids, prednisolone is recommended at a dose of 40 mg/day

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and continued for 28 days if the Lille score after 1 week is less than 0.45. The Lille score is used to identify corticosteroid nonresponders and incorporates age, renal function, prothrombin time, and albumin at the initiation of corticosteroid treatment and the decrease in serum bilirubin at 7 days. A Lille score of at least 0.45 after 1 week of corticosteroid therapy indicates nonresponse, which correlates with a high risk of death with continued corticosteroid therapy. A Lille score of more than 0.56 warrants discontinuation of corticosteroids. Liver

transplantation (LT) may be considered for patients who fail corticosteroid therapy and are considered good candidates for the procedure.

### G&H Currently, how common is ALD as an indication for LT?

**EM** For nearly 2 decades, hepatitis C virus (HCV) was the most common indication for LT in the United States. However, a recent review of the United Network for Organ Sharing database showed that, as of 2016, ALD, which accounted for 24% of all LTs, replaced HCV as the leading indication for the procedure in the United States. In fact, nonalcoholic steatohepatitis (NASH), which accounted for 19% of LTs, also surpassed HCV as the second most common indication for LT. As of 2016, HCV was the third most common indication for LT, accounting for only 18% of annual LTs in the United States. This trend is expected to continue due in large part to the effective antiviral therapy for HCV that is now being utilized in the pretransplant setting.

Another interesting trend is that, compared to HCV and NASH, ALD-related LT additions were significantly younger in age and with a significantly higher severity of hepatic decompensation, as defined by a higher median Model for End-Stage Liver Disease score at the time of listing.

Recent epidemiologic studies indicate that the prevalence of alcohol use, including high-risk drinking and alcohol use disorder, has increased across all socio-demographic groups in the United States. Thus, ALD is expected to remain one of the most common indications for LT for many years to come.

### G&H How do outcomes for patients transplanted for ALD compare with those of patients transplanted for other liver diseases?

**EM** Survival of patients transplanted for ALD is comparable to survival of patients transplanted for other etiologies of chronic liver disease. However, data indicate that patients with ALD who drink after LT develop more progressive liver injury with reduced patient and graft survival. The increased mortality in patients with recurrent ALD after LT results from graft failure in the majority of cases. Posttransplant mortality also results from cardiovascular disease, de novo extrahepatic malignancies (mainly of the respiratory and digestive tracts), and suicide. Tobacco smoking is a well-established risk factor for aerodigestive tract malignancies and is likely a contributing cause for the increased mortality in LT recipients with concomitant use of alcohol and tobacco after LT.

### G&H Does early LT have a role in the treatment of severe AH?

**EM** In this setting, the term early LT is generally defined as LT for a patient with severe AH who has failed medical management that occurs before waiting the arbitrary, but

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often followed, 6-month period of abstinence. The fact is, there are currently very few effective treatment options for severe AH. Although corticosteroids are recommended as first-line therapy for severe AH, nonresponse to medical therapy, which results in 40% of patients, is associated with 6-month mortality rates of more than 70%. Corticosteroid responders who remain abstinent do well with a low risk of mortality. Not surprisingly, corticosteroid nonresponders who continue to use alcohol have a high risk of mortality. Corticosteroid nonresponders who remain abstinent have an intermediate prognosis and may be considered for LT. However, many patients with severe AH who fail corticosteroid therapy are at high risk of mortality despite abstinence. Therefore, the lack of salvage therapy for these patients is the premise for considering rescue or early LT.

In the landmark French-Belgian study by Mathurin and colleagues that was published in 2011, 26 patients with severe AH who did not respond to a course of corticosteroids underwent early LT. The cumulative 6-month and 2-year survival rates were significantly higher among patients who received early LT than those who were not transplanted. Since publication of this article, the proportion of transplant centers offering early LT for patients with severe AH has notably increased. Attitudes regarding early LT for severe AH appear to be shifting in the United States as well. Several recent small single-center studies have looked at this issue, with encouraging results. In a recent 12-center retrospective analysis of 147 patients who underwent early LT for severe AH, the American Consortium of Early Liver Transplant for Alcoholic Hepatitis reported 1- and 3-year survival rates of 94% and 84%, respectively, which are very similar to survival outcomes in patients undergoing LT for other indications.

**G&H** How were the candidates selected for early LT in these studies? Were there significant selection differences between the European and US studies?

**EM** Although the US studies that reported on the role of early LT for severe ALD are largely retrospective, the landmark French-Belgium study was a prospective study that incorporated strict selection criteria. According to their study protocol, patients with severe AH (as defined

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by a MDF of >32) who did not respond to medical therapy (Lille score  $\geq 0.45$  after 7 days of corticosteroids) were selected according to the following mandatory criteria: severe AH as the first liver-decompensating event, presence of close family support, absence of severe coexisting or psychiatric disorders, and patient agreement to adhere to lifelong total alcohol abstinence. In addition, the selection process required the consensus of 4 decision-making circles—circle 1: nurse, resident, and fellow; circle 2: addiction specialist; circle 3: senior transplant hepatologist; and circle 4: transplant surgeon and anesthesiologist.

A recent tool to further assist in the psychosocial evaluation of a LT candidate, especially one with ALD, is the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT). The SIPAT utilizes a standardized evaluation process to identify candidates at risk for negative psychosocial outcomes after transplant by analyzing a total of 18 risk factors divided into 4 domains: patient readiness, social support, psychological stability, and substance abuse. While the SIPAT was not specifically used in the psychosocial evaluation of candidates in the French-Belgian study, it is often used as part of the evaluation process in many US transplant centers. Although the SIPAT is an excellent supplementary tool for evaluating candidacy for LT, the decision to list ultimately relies on the multidisciplinary selection committee.

**G&H** How was the 6-month rule established, and is it officially mandated?

**EM** The 6-month rule is an arbitrarily assigned length of sobriety that many LT centers impose on patients with ALD prior to LT. However, there are no national or international mandates on sobriety lengths with regard to candidacy for LT. In 1997, recommendations generated from a National Institute of Health workshop on LT advised a minimum abstinence period of 6 months before LT in patients with ALD. This became known as the 6-month rule. Although initially implemented to provide time to evaluate the improvement of hepatic function, which was commonly observed after 3 to 6 months of sobriety, the 6-month rule was later arbitrarily used by many LT centers as a predictor of post-LT alcohol recurrence. However, the 6-month rule is a weak predictor of alcohol relapse after LT and has not been shown to affect survival after LT. In fact, data suggest that abstinence is most durable only after 5 years of sobriety. Often, strict adherence to the 6-month rule may result in unnecessary delays in listing patients, especially for those with severe AH, whose 6-month mortality exceeds 70%.

Recent consensus panels in the United States and Europe recommend that 6 months of alcohol abstinence before LT should no longer be used as an absolute rule or a defining factor in determining a patient's candidacy for LT. However, the 6-month rule has become so ingrained in the practice of nontransplant and transplant professionals that, in addition to the negative stigma of alcoholics and the risk for alcohol relapse after LT, it has defined many referral practices. Studies have shown that a large majority of candidates with end-stage ALD who are otherwise eligible for referral for LT are not being referred. This pattern of inefficient referrals leads to many untimely and avoidable deaths.

**G&H** Why is LT controversial in patients with ALD?

**EM** LT for ALD remains somewhat controversial for 2 main reasons. First, the public continues to hold a negative perception of LT for alcoholics. Multiple surveys have revealed that the public and even health care providers view organ allocation to patients with ALD, which is perceived as a self-inflicted disease, less favorably than those with inherited or acquired liver disease. Second, great concern remains regarding the risk of alcohol relapse after LT to the point that the transplanted liver may be viewed as a “wasted organ” in the event of alcohol relapse after LT. This concern is magnified in the case of severe AH when periods of sobriety prior to LT are often unrealistic compared to the high mortality rates without LT.

However, attitudes appear to be shifting, even though LT for AH is a relatively new practice in the

United States. It was not all too long ago that AH was generally considered an absolute contraindication for LT.

### G&H Does the possibility of transplanting patients with ALD affect the recruitment of donor livers?

**EM** This is another controversial issue. As mentioned previously, ALD is often perceived as a self-inflicted disease that is less favorable than an inherited or acquired liver disease. However, for more than 3 decades, LT has been performed for patients with HCV, which is a self-inflicted disease in many patients. In a recent online survey to measure attitudes on LT, although over 80% of respondents were at least neutral toward early LT for patients with AH, nearly 25% indicated that LT for patients with AH would make them hesitant to donate their organs.

### G&H How often does alcohol relapse occur after LT for ALD, and what are the main risk factors?

**EM** Alcohol relapse after LT is not uncommon and is reported to occur in 10% to 60% of recipients of LT for ALD. Although graft function and patient survival are not affected by occasional drinking, relapse into harmful drinking—which occurs in approximately 15% to 20% of patients and is defined as more than 2 drinks/day for women and more than 3 drinks/day for men—does decrease long-term graft function and patient survival. The presence of psychiatric comorbidities, younger age at the time of LT, and a shorter period of sobriety prior to LT are factors associated with harmful drinking after LT.

Similar to HCV recurrence after LT, harmful drinking after LT accelerates the natural history of ALD with more rapid progression of fibrosis. In fact, studies have shown that one-third of patients who develop severe alcohol use disorder after LT can develop cirrhosis within as little as 5 years after the procedure. In addition, relapse of harmful drinking has been associated with poor adherence to immunosuppressive medications, which also further impairs graft function.

### G&H What follow-up is required in these LT recipients?

**EM** The long-term health of the LT recipient for ALD requires persistent attention to the management of the allograft, as with all LT recipients; however, careful

attention also needs to be paid to the lifelong disorder of craving and the risk for relapse. Although LT cures the underlying liver disease by providing the patient with a physiologically functioning liver and reverses the complications of end-stage liver disease, it does not cure the alcohol addiction. Therefore, it is not surprising that alcohol relapse after LT is common. However, there are few studies of best practice regarding long-term addiction care in LT recipients for ALD.

As previously mentioned, patients who undergo LT for ALD are at long-term risk for cardiovascular disease, infections, and cancers, and require appropriate and timely screening. Tobacco cessation counseling is often also needed given its frequent concomitant use with alcohol.

### G&H What are the next steps in research in the area of ALD and LT?

**EM** There is an increasing need to develop more uniform and standardized criteria for selection of patients with severe AH for early LT. Further studies are greatly needed to optimize candidate selection by understanding and identifying pre-LT factors that more accurately predict alcohol relapse after LT. Likewise, further studies are needed to aid in developing standardized protocols for posttransplant follow-up and management in LT recipients for ALD.

*Dr Martin has no relevant conflicts of interest to disclose.*

### Suggested Reading

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