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Meeting Report: The Dallas consensus conference on liver transplantation for alcohol related hepatitis

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Abstract

Liver transplantation (LT) for alcohol related hepatitis (AH) remains controversial. We convened a consensus conference to examine various aspects of LT for AH. The goal was **not** to unequivocally endorse LT for AH; instead it was to propose recommendations for programs that perform or plan to perform LT for AH. Criteria were established to determine candidacy for LT in the setting of AH and included the following: (1) AH patients presenting for the ***first time*** with decompensated liver disease that are non-responders to medical therapy without severe medical or psychiatric comorbidities (2) A fixed period of abstinence prior to transplantation is not required (3) Assessment with a multidisciplinary psychosocial team including a social worker and a addiction specialist/mental health professional with addiction and transplantation expertise. Supporting factors include lack of repeated unsuccessful attempts at addiction rehabilitation, lack of other substance use/dependency, acceptance of diagnosis/insight with commitment of patient/family to sobriety and formalized agreement to adhere to total alcohol abstinence and counseling. LT should be avoided in AH patients that are likely to spontaneously recover. Short- and long-term survival comparable to other indications for LT must be achieved. There should not be further disparity in LT either by indication, geography, or other sociodemographic factors. Treatment of alcohol use disorders should be incorporated into pre and post-LT care.

The restrictive and focused evaluation process described in the initial LT experience for AH worldwide may not endure as this indication gains wider acceptance at more LT programs. Transparency in selection process is crucial with collection of objective data to assess outcomes and minimize center variation in listing. Oversight of program adherence is important to harmonize listing practices and outcomes.

SUMMARY OF RECOMMENDATIONS

General recommendations: Alcohol related hepatitis

1. There should be efforts to standardize nomenclature and definition of alcohol related hepatitis (AH) with an emphasis on use of less stigmatizing terminology. (***see Table 1 and 2)***

2. Patients with severe AH may be assessed for corticosteroid therapy.
3. Select patients with severe AH that are unresponsive to medical management may be considered for liver transplantation.
4. Predicting response to therapy or pre-LT mortality is best achieved by assessing response over time (change in Model for end stage liver disease (MELD) score, Lille score or a combination of MELD score plus Lille). Mortality is lower for those that have a Lille score <0.45, respond to therapy, have a declining bilirubin, or are abstinent and these patients may not require LT.
5. An inflexible period of abstinence prior to transplantation is not desirable. Acceptance for LT listing should be based upon the severity of liver dysfunction and a comprehensive psychosocial evaluation. ***(see Table 3)***

Recommendations for LT for alcohol related hepatitis ***(see Figure 1 and Table 4)***

A. The goals of LT for AH include:

1. Avoiding LT in patients who will recover without it
2. Avoiding futility and achieving short- and long-term survival comparable to other indications for LT
3. Avoiding creation of further disparity in LT either by indication (versus other indications), geography, sex, race, insurance status or other sociodemographic factors.
4. Identification of LT candidates likely to have long-term abstinence
5. Incorporation treatment of alcohol use disorder (AUD) into pre and post-LT care
6. Consensus of paramedical and medical staff

B. Criteria related to AH

1. First presentation with decompensated alcohol-related liver disease
2. Absence of severe uncontrolled medical or psychiatric comorbidities.
3. Non-response to medical therapy.

C. Criteria related to AUD

1. Establish acceptable risk of relapse by assessment with a multidisciplinary psychosocial team including a social worker and an addiction medicine specialist/ mental health professional with addiction and transplantation expertise.
2. Assessment of coherent patient by addiction specialist (i.e. not intubated or floridly encephalopathic).
3. Lack of repeated unsuccessful attempts at addiction rehabilitation.
4. Lack of current other substance use/dependency.
5. Acceptance of ALD diagnosis with insight.
6. Commitment of patient to lifelong sobriety and support of sober caregivers to assist patient with abstinence goals.
7. Presence of close, supportive family members or caregivers

D. Post LT requirements

1. Pre-LT confirmation of plan for AUD treatment after LT
2. Robust post-transplant monitoring for alcohol slips or relapse during post-LT clinic appointments to include direct interviewing of patient and caregivers about alcohol use.
3. Routine monitoring of alcohol use (e.g. with Phosphatidylethanol (PEth), Urinary ethyl glucuronide) for at least 2 years, with frequency and duration individualized beyond this time period.

E. Center requirements

1. Transparency in the candidate selection process and structured collection of objective data to assess outcomes ***(see Table 5)***

2. Ongoing support of abstinence that is integrated into post LT care such as concurrent follow-up by addiction specialist/mental health professional with addiction and transplantation expertise.
3. Oversight of program adherence to harmonize listing practices and outcomes.

Introduction

Alcohol is a major cause of liver disease worldwide(1) with alcohol related liver disease (ALD) being one the most frequent indication for liver transplantation (LT) in the US.(2) In addition to complications of cirrhosis and hepatocellular carcinoma, alcohol related hepatitis (AH) remains an important cause of liver related morbidity and mortality. Influenced by small trials showing acceptable outcomes in highly selected patients, transplantation for AH is increasingly performed in the US and elsewhere.(3-8) The percentage of patients transplanted for AH is likely underestimated; in a recent study only 35% of recipients transplanted for AH were accurately identified.(9)

However, LT for AH faces substantial challenges. The medical criteria for AH LT must be carefully defined such that premature use of LT does not occur for patients likely to recover with supportive care. Additionally, in urgent cases of patients with AH, requirements for specific periods of significant sobriety pre-LT may vary. The ability to provide the potential benefits of LT for AH patients must be balanced against the potential for alcohol relapse with resulting morbidity and mortality post-LT. LT for AH may lead to disparities related to selection of candidates with AH for LT (may favor patients with resources) as well as impacting LT rates for other indications. While it is worthy to consider a more compassionate and thoughtful approach to LT for AH patients the shortened time frame for transplant evaluation in urgent AH cases makes it difficult even for experienced teams to accurately capture psychosocial aspects predictive of outcomes after LT in AH. The public and provider perception of LT for ALD continues to evolve and may not be as controversial as previously thought.(10-18) Further, there is a growing recognition that successful outcomes after LT also depend on appropriate treatment of co-existing alcohol use disorder (AUD). These complexities

demand a multidisciplinary team approach to the assessment, selection and post-LT longitudinal care of AH patients.

To address these issues, Baylor University Medical Center in Dallas, Texas organized a two-day consensus conference (April 5-6, 2019) endorsed by International Liver Transplantation Society and American Society of Transplant Surgeons. Overall, 130 participants including 82 physicians and over 60 transplant and non-transplant university and community programs were represented. Of these centers, representatives from 9 out of 12 ACCELERATE AH consortium centers attended. A survey was not taken of which programs currently performed LT for AH, but varied from none to a few cases per year. Participants included addiction counselors, transplant surgeons, hepatologists, psychiatrists, coordinators (living donor, pre transplant, and post-transplant), nurses, program administration, social workers, insurance representatives and other staff. A draft of the manuscript was sent to all attendees for their collective input and comments.

There were several contentious points that were raised and a balanced discussion is presented in the submission. This included pros and cons of LT for AH, mandatory requirements for center reporting as well discussions regarding financial aspects. The goal was **not** to unequivocally endorse LT for AH; instead was to bring together a multidisciplinary group to discuss AH related practices at their centers and consider how clinical assessment, care, and selection for LT could be improved by the collective experiences. The consensus conference expanded on recent recommendations that "Liver transplantation may be considered in carefully selected patients with favorable psychosocial profiles in severe AH not responding to medical therapy."(19)

General considerations: Alcohol related hepatitis

Definition: Defining AH requires consideration of the pattern of alcohol use, clinical and laboratory presentation and exclusion of other etiologies of liver dysfunction. Guidance is provided by a recent consensus statement on behalf of National Institute on Alcohol Abuse and Alcoholism (NIAAA) though this definition focuses on bringing

uniformity to clinical trials and does not address LT.(20) **(Table 1 and 2)** Liver biopsy should be pursued in cases where the diagnosis of AH is unclear and/or if any alternative diagnosis may affect the treatment plan, especially with regards to eligibility for LT. Considering LT for AH does not obviate program requirements for chronic liver disease/cirrhosis related to alcohol which may follow a separate center specific pathway.

Incidence and mortality*:* Population based estimates in the US confirm an increase in the incidence of AH mirroring a global increase in ALD. (1, 21-23) There has been an increase among young adults, minorities and women. (21, 24-26) In national data, the age and gender standardized rate of ALD related mortality has increased by 3-fold in persons aged 25-34 (CDC accessed March 2019).

Medical Therapy*:* The proposed treatment algorithm in AH differentiates management based on disease severity.(27) Treatment for AH includes supportive medical therapy in addition to abstinence from alcohol, management of withdrawal symptoms, nutritional support and consideration of corticosteroid therapy for definite and probable AH. There is a need to accurately identify patients that are candidates for corticosteroid therapy, those ineligible for corticosteroids or non-responders to therapy as early as possible. If corticosteroids are used, absence of response as defined by the Lille score should lead to their discontinuation. Several investigational compounds are under evaluation for patients with AH but their role in AH remains to be established.(28)

Predictive models: Several predictive models assess treatment response and predict mortality within 1-6 months after diagnosis of AH (29-34). Most models have high negative predictive value (predict those that will do well) and not necessarily identify all that will not survive. A model combining a static component (MELD) with a dynamic model (Lille) may be useful to identify non-responders to medical therapy and/or patients unlikely to recover (35). Extra hepatic complications most notably serious infection and renal failure profoundly affect outcomes.(2, 36-38)

Liver transplantation for alcohol related hepatitis

Figure 1, Table 3 and 4 summarize recommendations from the consensus conference. The following sections discuss specific recommendations in more detail.

Ethical Considerations: Liver transplantation balances three principles of justice: urgency, utility, and equity. Urgency demands that organs go to the "sickest first." AH typically have high MELD scores with 75% mortality at 6 months in those not responding to prednisolone.(33) Utility demands that organs be given to patients in whom post-transplant outcomes will be acceptable. Medically, AH patients compare favorably to other diagnoses, with acceptable post LT patient and graft survival rates.(5, 39) Equity mandates that we adopt principles of liver transplant allocation that are applied similarly to all liver diseases. Where behaviors are responsible for primary liver disease requiring transplant or for graft loss (such as non-adherence) after transplant, allocation decisions should be made in a similar manner and not applied in a more stringent manner only to those with ALD or AH.(40)

***European and US Experience in LT for AH**:* The initial experience in early "rescue" liver transplant in AH was the French/Belgian trial.(6) Non-responders to medical therapy, defined as a Lille model of ≥ 0.45 or a worsening of MELD score at day 7 of therapy, were considered for rescue LT. Candidates were selected using the following criteria: nonresponse to medical therapy, severe AH as the first liver-decompensating event, presence of close supportive family members, absence of severe coexisting or psychiatric disorders, and agreement to adhere to lifelong total alcohol abstinence. Complete consensus was required among four provider "circles" involved in patient care for LT approval. Ultimately, 26 medical non-responders underwent LT. A significant survival benefit at 6 months was observed (76.9% versus 23.1% for matched non-transplanted patients). Survival after transplant was similar to random responder controls (85%). Relapse rate was low; 10% overall had return to harmful drinking. (6, 41). These results supported future evaluation in selected patients with severe AH failing medical therapy (42).

Studies in the US were subsequently pursued (3-8) As compared to the European experience where a prospective protocol was followed, the US experience was a mix of center specific experience and established protocols. In one study, 20/94 patients (21.2%) with severe AH refractory to medical therapy were approved for LT and 9 ultimately underwent LT (3). Eight of the 9 patients (89%) survived more than 6 months compared to 30% of the patients that did not undergo LT. Two patients had alcohol relapse, neither leading to adverse outcomes. A second pilot study compared the outcomes of LT for AH and alcohol associated cirrhosis (AC). At a median follow-up of 532 days (IQR 281-998 days), rates of alcohol use and harmful drinking post-LT were similar for AH and AC at 28% and 24%, respectively (p=0.80).(7) ACCELERATE-AH, the largest US experience in LT for AH, was a retrospective review from 12 centers, including the two centers that had published the pilot studies.(5) Each center had their own "protocol" and while there were some differences between sites in terms of inclusion/exclusion criteria, there were many similarities.(5) Of the 432 patients evaluated, 155 (35.9%) were accepted as candidates with rates ranging from 13-100% across centers.(5) Psychosocial concerns were the predominant reason for denial of listing for LT. Overall survival after LT for AH was excellent with 1 and 3-year survival rates of 94% (95% CI, 89-97%) and 84 % (95% CI, 75-90%), respectively. In patients surviving to discharge, 28% resumed alcohol use with 11% returning to harmful drinking. Alcohol relapse post-LT had an adverse impact on survival at 3 years when compared with abstainers (75% vs. 97%, respectively, p=0.03) and 7 of the 9 deaths that occurred after one-year were alcohol related. More than 10 drinks per day, non-THC substance use, prior alcohol related legal difficulties , and more than 1 failed alcohol treatment attempt were associated with sustained alcohol use after LT.(43) No long-term follow-up data are available.

Arguments in favor of LT for AH*:* First, LT for ALD has been performed since the 1960s.(44) LT for appropriately selected AH prevents premature mortality. In severe AH, failure of medical therapy can be predicted early in the patient's course and is associated with a 6-month survival around 30%. (33) As most deaths occur within 2 months, early LT is life saving. Second, there are effective treatments for AUDs that

patients can participate in following LT. Given the stringent criteria used to select AH LT candidates thus far, relapse rates after LT are similar for patients transplanted for AH versus ALD with cirrhosis.(45-49) Third, LT for those with AH ensures equity of access to life-saving transplant, as in other liver diseases. As an example, LT is offered to obese individuals with NASH even without demonstration of weight loss pre-LT and is also offered to carefully selected patients with acute liver failure following a suicide attempt due to medication overdoses with uncontrolled psychiatric disease. Finally, concern that early LT for AH may decrease organ donation is contrary to a survey showing that most potential organ donors were supportive or neutral with regard to this new indication (16).

***Concerns about LT for AH**:* First, criteria advocated for LT for AH may not be uniformly adhered to at all centers. There may be a disconnect between the restrictive and focused evaluation process described in the initial experience with LT for AH and its wider acceptance elsewhere across LT programs.(6) There is already wide variation in acceptance of AH for LT and clarity on what criteria are necessary to ensure good outcomes is lacking. Second, relevant outcomes after LT may be inadequately captured. Although survival rates were acceptable, deaths due to fungal infection were frequent in the European experience with most deaths due to infection within 2 weeks after LT. Survival at 6 months for recipients (77%) was much lower than that for ALD reported to UNOS (94%). Variation in medical management (e.g. steroid use) among centers may play a role. Third, the cumulative probability of any alcohol use after LT was 25%, 30% and 34% at 1, 2 and 3 year.(5) Patterns of alcohol use were worrisome with median time to first drink of 160 days (79-346), sustained alcohol use in 38%, and binge or frequent drinking in 42%. Hence, there is an obvious need for predictive tools to identify patients at high risk of relapse especially those with harmful drinking patterns (42). Fourth, high MELD score at LT, common among those presenting with AH, may tilt the balance toward “bending the rules” to transplant these recipients. It is unavoidable that competition between programs will loosen acceptance criteria. The requirements for acceptance should be the same for all patients, regardless of social or financial status. As an example, increasingly women present with AH, though the percent of

women undergoing LT for AH is low (5). Hence there may be unrecognized barriers to LT for certain subgroups.

Psychosocial perspective in LT for AH (Table 3)

In addition to being responsible stewards and "gatekeepers," psychosocial assessors of transplant candidates often create intervention or treatment plans to mitigate risk for potentially poor outcomes. For patients with an AUD and short duration of sobriety this commonly involves engaging the patient in addiction rehabilitation. However, in the urgent AH scenario because there is no time to provide pre-LT rehabilitation, LT teams rely on more stringent selection criteria for AH candidates in hope of preventing poor outcomes post-LT.

Challenges in Evaluation of AUD in an urgent setting: Evaluation and treatment of AUD that coexists in patients with AH is crucial. During an expedited evaluation, AUD may be inadequately addressed, (2) assessment and selection occurs in a limited and expedited time and (3) treatment for AUD, a chronic disorder with need for ongoing management, is often not accorded priority. In a life-threatening medical condition, it is difficult to expect a patient to contemplate hypotheticals (e.g. lifelong abstinence, willingness to attend addiction rehabilitation, adherence to transplant directives) with no/little evidence they will/can do so. In addition, there is no opportunity to reassess a candidate's response after addiction treatment initiation. Patients and families may try to manage impressions about or minimize their alcohol use history. Patients may be difficult to interview due to being in denial or feeling ashamed, guilty, overwhelmed, scared, or in pain. In this context, establishment of an effective therapeutic relationship to management AUD can be challenging.

Necessary Components of the psychosocial assessment: Optimally the patient should be directly interviewed by the social work and mental health and/or addiction professionals. Thus, the request for these evaluations should occur early in the hospital course prior to the development of encephalopathy. The composition of the mental health/social work team and competencies matter and may dictate the quality and

strength of recommendations. Transplant centers considering AH transplant should have in place a multidisciplinary psychosocial team composed, at a minimum, of a transplant social worker and a mental health professional preferably with addiction and transplant experience. An addiction specialist may be helpful in ensuring AH patients receive the full spectrum of AUD care. Psychometric scales and instruments can be used to aid the collection and integration of data but should not be used to determine candidacy. Scales may be helpful for tracking treatment response and anticipating further treatment needs. Collateral information should be sought from family members, LT team members and other clinical care providers to provide a comprehensive picture of the patient's history. Active family or caregiver support is paramount for current and future care. Biochemical markers may also be needed to corroborate drinking history. Patients with AUDs often have other psychiatric co-morbidities. In circumstances where an AH candidate has a co-morbid other psychiatric disorder additional evaluation by a psychiatrist is indicated. That may be a decision taking place at the program level based on (1) the comfort and psych expertise of the referring team and social worker, (2) potential meeting of a threshold on a standardized scale (e.g. SIPAT) and (3) resource availability.

Factors associated with risk for post-LT alcohol use: Until a larger experience is developed with AH alcohol use outcomes, the LT field draws on the substantial experience of predictors of relapse for ALD LT and from the general non-LT population of AUD patients. It is critical to recognize that the presence of a factor associated with alcohol use means the likelihood of alcohol use is greater, not that it is certain.(5, 7, 50-53) Whether a single criterion or cumulative factors are used to determine AH LT candidacy is not settled. Proposed criteria or risk scores have high negative predictive value and predict those who will not return to harmful patters of alcohol use rather than identify those that will.(54)

Duration of sobriety: Aside from allowing a period of observation to ensure an AH patient has adequate time to respond to medical therapy avoiding preemptive LT, the notion of waiting a specific number of days or months of abstinence to demonstrate the

patient's ability to maintain sobriety is ill-conceived. In AH such a mandated wait could allow the patient to deteriorate increasing the surgical risk, but each month sober only incrementally reduces risk. There is limited support for a specific 6-month cut point(51) Further, in the natural history of AUD, stable abstinence is measured in years not months. Recently, expert guidelines no longer recommend a fixed period of abstinence prior to transplantation (27, 55) and have stopped listing AH as an absolute contraindication (55) to LT contrary to the recommendations from the preceding decade (56).

Post transplantation needs: After transplantation, the AH LT recipient should be assisted in beginning addiction treatment as soon as medically feasible. This critical requirement should not be lost among the other post-LT care needs. Psychosocial evaluation and treatment should be integrated in the flow of post LT care and should be mandated by center. There should be agreement of LT team to facilitate post-LT participation in addiction treatment and rigorous collection of alcohol use outcome data. To improve adherence, treatment and monitoring expectations should be developed prior to LT. LT teams may need significant assistance from their social work and behavioral health providers to overcome potential barriers to addiction treatment; lack of local care, lack of adequate or appropriate resources, lack of monitoring (biochemical or collateral) and insurance issues.

Living donor transplantation for AH

AH patients listed for deceased donor liver transplantation may also be considered candidates for living donor liver transplantation. The medical risks to the donor are the same regardless of recipient etiology of disease. However, there may be increased psychological risks to donors for recipients with AH related to relapse and graft loss especially long term once routine follow up ends. Adherence to autonomy for both the donor and recipient through the process of informed consent and disclosure is equally important. With AH, the recipient's etiology of disease and potential for relapse might affect the donor candidate's decision about donation so centers must have a policy in place regarding disclosure of issues unique to LT for AH. The transplant program

must ensure that the urgency of need is not interfering with information disclosure, processing, or the ultimate decisions of donors. The informed consent process also requires voluntariness in decision-making. Voluntariness is defined as the absence of coercion, unwarranted persuasion or undue manipulation. Potential living donors for AH recipients may be victims of unwarranted persuasion because they are asked to decide in a time pressured manner to help a loved one who is at imminent risk of dying. All transplant centers are required to provide an independent living donor advocate for living donor evaluation. For individuals considering living donation to AH recipients, the independent living donor advocate, along with the rest of the donor evaluation team, must ensure that the decision meets the standards of voluntariness.

Payer coverage

The 6-month rule has been enforced and reflected in medical policy set forth by most payers. With recent data and a more definitive set of professional statements and modification of specific institutional criteria referring the 6-month rule, changes in payer coverage policies must follow. This would result in a coverage that better reflects evolving standard of care. A commitment by payers for addiction counseling post transplantation is equally important. From a resource allocation standpoint advocating for insurance payer coverage for AUD treatment is crucial. In addition, centers may experiment with unique ways of bridging coverage gaps, resource deficits, and insurance disparities. These may include telemedicine, provider-to-provider consultation models, collaborative care models, cross-disciplinary training, and community outreach efforts. Programs need to invest not only in coordinators and nutrition specialists for medical management but also addiction specialists.

Payer limitation of coverage continues to be an issue. There has been increased attention to mental health benefits as there continues to be concern about the adequacy of coverage under most health plans. The Mental Health Parity Act (MHPA) of 1996 aimed to prevent group health plans and health insurance issuers that provide mental health or substance use disorder (MH/SUD) benefits from imposing less favorable benefit limitations on MH/SUD benefits than on medical/surgical benefits. Mental Health Parity and Addiction Equity Act of 2008 (MHPAEA) preserves the MHPA protections

and adds significant new protections, such as extending the parity requirements to substance use disorders. It was amended by the Health Care and Education Reconciliation Act of 2010 (collectively referred to as the "Affordable Care Act") to also apply to individual health insurance coverage. A concerted effort by national liver societies and patient advocacy groups may be needed to harmonize this coverage across centers.

Role of the transplant center

LT centers are likely only seeing the tip of the iceberg' with many AH patients never being evaluated or even discussed with LT centers. Transparency in center practices and oversight is paramount. Oversight of structural components of the program are needed. This includes presence of adequate psychosocial and addiction personnel at centers undergoing LT for AH, monitoring of pre/post-transplant outcomes and structured data collection. The transplant community needs to consider mandated collection of AH specific elements and centers be open to sharing center specific practices to improve outcomes. (**Table 5**) Local or regional review boards may need to be involved to assure transparency and third party adjudication or oversight, such as that provided by UNOS may be needed.

The need to streamline processes and the anticipated burden to the system (psychosocial assessments, expansion of team, increased hospital volume) is clear. Centers need to invest and ensure having mental health professionals/addiction specialists available not only for pre transplant evaluation, but also for post-transplant assessment and active follow up after discharge. Provider team frustration and burnout may feature prominently as more patients with AH are evaluated. This will require teams to monitor and address the mental health, burnout, and cynicism of their providers and staff. Teams need to insist on and expect psychosocial providers to meet frequently and thoroughly collaborate among themselves.

Expansion of LT for AH will affect center activity. Issues may arise about the number of donor offers, offers accepted for AH candidates but transplanted in other patients and

how LT for AH might impact LT for other indications, particularly within the new acuity circle policy. There may be financial gain in transplanting patients with AH; a high MELD patient with AH may inherently have better short-term outcomes than high MELD patients without AH though further data is needed. This could be partially mitigated by requiring centers to meet 2 year survival criterion for AH, as relapse to harmful alcohol use typically leads to deaths beyond the 1st year.

Competition between centers for these patients is a concern. Within a region, there may be market pressures for other centers to follow suit. Hence, failure to offer transplant for patients with AH may reduce referrals for this and other indications. In addition, referral physicians often view an "active plan" such as transplant as a better option than a "passive plan," i.e., supportive care. So, the perception of the transplant center within the community as an "aggressive" or "forward thinking" or "cutting edge" center plays heavily on the treatment plan for these patients. There is a clear need for community education on this topic so that limited LT center resources can be optimally used and to limit patient dissatisfaction and associated provider burnout/cynicism.
It needs to be reiterated that only a very small number of patients is expected to fulfill this very strict criteria.

Conclusion

LT for ALD has evolved over the last 40 years, starting from an absolute contraindication to an accepted routine reason for LT. Following in its footsteps, LT for AH remains contentious. With a measured approach that collectively considers and respects the perspectives of all stakeholders in the transplant process, consensus and progress is possible to improve the outcomes of our sickest waitlisted patients, regardless of etiology.

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Figure 1: Listing criteria and program components for LT for AH
AH: alcohol related hepatitis; AUD: Alcohol use disorder; PEth: Phosphatidylethanol; ETG: Urinary ethyl glucuronide

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Table 1: Suggested changes in nomenclature

Suggested	Current
Alcohol related liver disease	Alcoholic liver disease
Relapse	Recidivism
Alcohol related hepatitis	Alcoholic hepatitis
Alcohol use disorder	Alcoholic

Table 2: Defining alcohol related hepatitis, modified from NIAAA AH clinical trial definition (Crabb et al Gastroenterology 2016)

Definition	Clinical entity with rapid onset of jaundice with elevated AST in background of heavy alcohol use.
Pattern of alcohol use	Heavy alcohol use for >6 months, <60 days of abstinence before onset of jaundice.
Supporting features	
Biopsy	steatohepatitis, cholestasis, severe fibrosis
Presentation	malaise, tender hepatomegaly, decompensation
Labs	Bilirubin>3, AST/ALT ratio 1.5, AST<400

Exclude	Drug induced liver injury, biliary obstruction, viral hepatitis, autoimmune liver disease, Wilson disease
Spectrum	AH versus acute on chronic liver failure Presence of cirrhosis
Definite	Clinical and biopsy proven
Probable	Clinical and exclude competing
Possible *Biopsy recommended*	Clinically diagnosed but with potential confounding factors (e.g. pt denies alcohol)
Associated other diagnoses?	E.g. Viral hepatitis

Table 3: Psychosocial domains to be assessed in AH transplant candidates.
Most of these predictors are for sustained or harmful relapse (not slips).

Domain Assessed/Questions Asked	Factors that May Predict Relapse
1. Alcohol Use History	
• Length of use over time, when did use start, consumption patterns,	• Younger age at onset of drinking • >10 drinks per day at time of

context of use, periods of abstinence • Diagnostic criteria for alcohol use disorder (reference DSM-V) • Problems with cravings/urges to drink • Sobriety attempts- voluntary and mandated • Alcohol use treatment history- types of treatment tried, sobriety duration after treatment, experiences with treatment, successes and failures. • Attitudes towards alcohol use: assess insight and acceptance of alcohol as problem, readiness for change, commitment to sobriety and alcohol treatment • Recent changes in alcohol use in relation to life stressors with assessment of potential modifiable behaviors and situations.	transplant consideration • Multiple failed rehab attempts • History of legal problems due to alcohol use • Shorter pre-transplant abstinence • Lack of insight into alcohol use problems • Lack of acceptance of alcohol use as a problem • Lack of candor and/or deceptive behavior with respect to transplant team • Severe AUD
2. Other Substance Use History	
• Length of use over time, onset of use, consumption patterns, context of use • Diagnostic criteria for substance use disorder • Treatment history (as above)	• Active, untreated polysubstance use (except marijuana) • Comorbid tobacco use, relapse to tobacco use
3. Mental Health History	
• History of psychiatric diagnoses • Presence of suicide attempts	• Active, untreated mental health diagnosis

• History of any mental health treatment, including inpatient treatment • Response to mental health treatment	• Recent suicide attempt
4. Treatment Adherence History	
• Past and current adherence to medical and mental health treatment plan • Ability to understand and adhere to transplant treatment plan	• History of extensive nonadherence to medical or mental health treatment
5. Social Criteria	
• Sober support system • Number of support persons, relationship to patient, ability to dedicate time/resources to medical and mental health care	• Lack of sober support network • Only 1 sober support person

Optimal Assessment Criteria
1. Awake, alert patient (not comatose, altered, or intubated), able to be directly interviewed
2. Psychosocial team assess patient first to obtain unbiased evaluation of above factors.
3. Consistent history and commitment verbalized by patient
4. Multiple assessments over time
5. Active involvement and sober support by family/caregivers
6. Corroboration of history from patient collaterals

Table 4: Listing criteria and program components for LT for AH

	Primary criteria	Secondary considerations
Alcohol related hepatitis assessment	First presentation with decompensated AH	No prior liver related hospitalization
	Absence of severe medical comorbidities	• Frailty, debility and multiorgan failure • No other contraindications to LT
	Non-response to medical therapy.	• Contraindications: disease severity, multi organ failure, infection, renal failure and low likelihood for response • Consider non-responders using Lille score >=0.45 or worsening of liver function by d4 or d7 • Monitor for signs of recovery after listing.
Alcohol use disorder assessment	Establish acceptable risk of relapse as assessed by a multidisciplinary psychosocial team composed of a social worker and at least one addiction specialist.	• Not intubated • Consider independent team of specialists in addiction, social workers, and mental health providers • Ideally first member of LT team to evaluate • Consider independent mechanisms

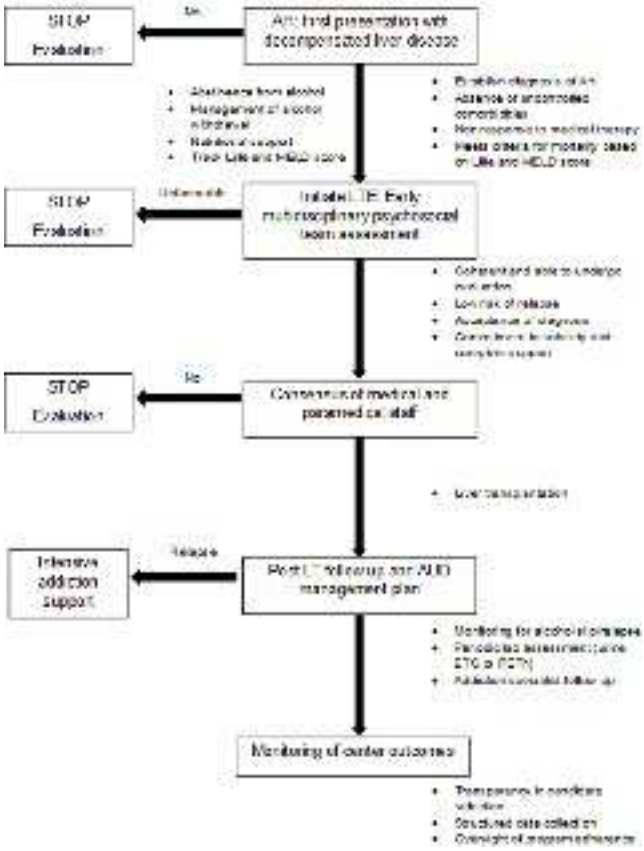
		for regional or local review
	Direct assessment of patient possible by addiction specialist	• i.e. not intubated or floridly encephalopathic.
	A maximum of 1 prior failed attempt at rehabilitation.	
	Lack of other active substance use/dependency or active untreated psychiatric disorder	
	Acceptance of diagnosis/insight	
	Commitment of patient/family to sobriety and formalized agreement to adhere to lifelong total alcohol abstinence	Establish contract and participation in addiction rehabilitation following transplant
	Presence of close, supportive family members or caregivers	
Committee Decision making	Consensus of paramedical and medical staff	Consider blinded voting in committee deliberations Consider absolute consensus
Program components	Transparency in selection process	• Creation of internal policies / procedures consistently followed by the transplant program • Willingness to share, publish or have policies/procedures reviewed by outside agents • Documentation of transplant program

		experiences with AH in CONSORT flow diagram including those assessed for eligibility, excluded and reasons, treatment responders, transplant outcomes, and elements of selection criteria • Enhanced reproducibility by use of standard definitions and common data elements • Consistent and timely structured data reporting
	Independent psychosocial assessment	• Mental health professional with addiction background/training • Mental health professional familiar with transplant process
	Structured Post LT follow up mechanism in place	• Documentation of AUD management plan pre and post-LT • Dedicated addiction specialist/mental health professional for longitudinal management • Commitment for regular monitoring for alcohol use Phosphatidylethanol (PEth), Urinary ethyl glucuronide • Structured monitoring program for post-transplant alcohol relapse and, in the event of alcohol relapse, provide resources to assist the patient in recovery
	Team mental health	• Consider formal addiction education for transplant staff

Table 5: Data collection in programs performing LT for AH

Timing	Main component	Sub component
Pretransplant	AH	definite, probable, possible
	Number with AH	
	Number evaluated	
	Number listed	
	Medical and psychosocial Characteristics of evaluated not listed vs listed	Gender, race, MELD, insurance
	Medical treatment	Steroids, other
	Contraindication or ineligible for steroids	Disease severity Multiorgan failure
	Accurate coding for AH	
	AUD diagnosis	Mild, moderate, severe
	Prior AUD treatment	Types of AUD treatment previously used
	Explant and Biopsy characteristics	
	Comorbid psychiatric and/or substance use disorders	

	Other substance use	
Transplant	Multidisciplinary Team assessment	Addiction specialist Social Worker mental health professional
	Routine Testing	Alcohol biomarker testing: Phosphatidylethanol (PEth), Urinary ethyl glucuronide
	Pattern of alcohol use	Slip, relapse, heavy
Post LT	Documentation of AUD management plan pre and post-LT required	
	Documentation of EtG or PEtH testing	



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