Acute Alcohol-Induced Hepatitis (AAIH)

To transplant or not

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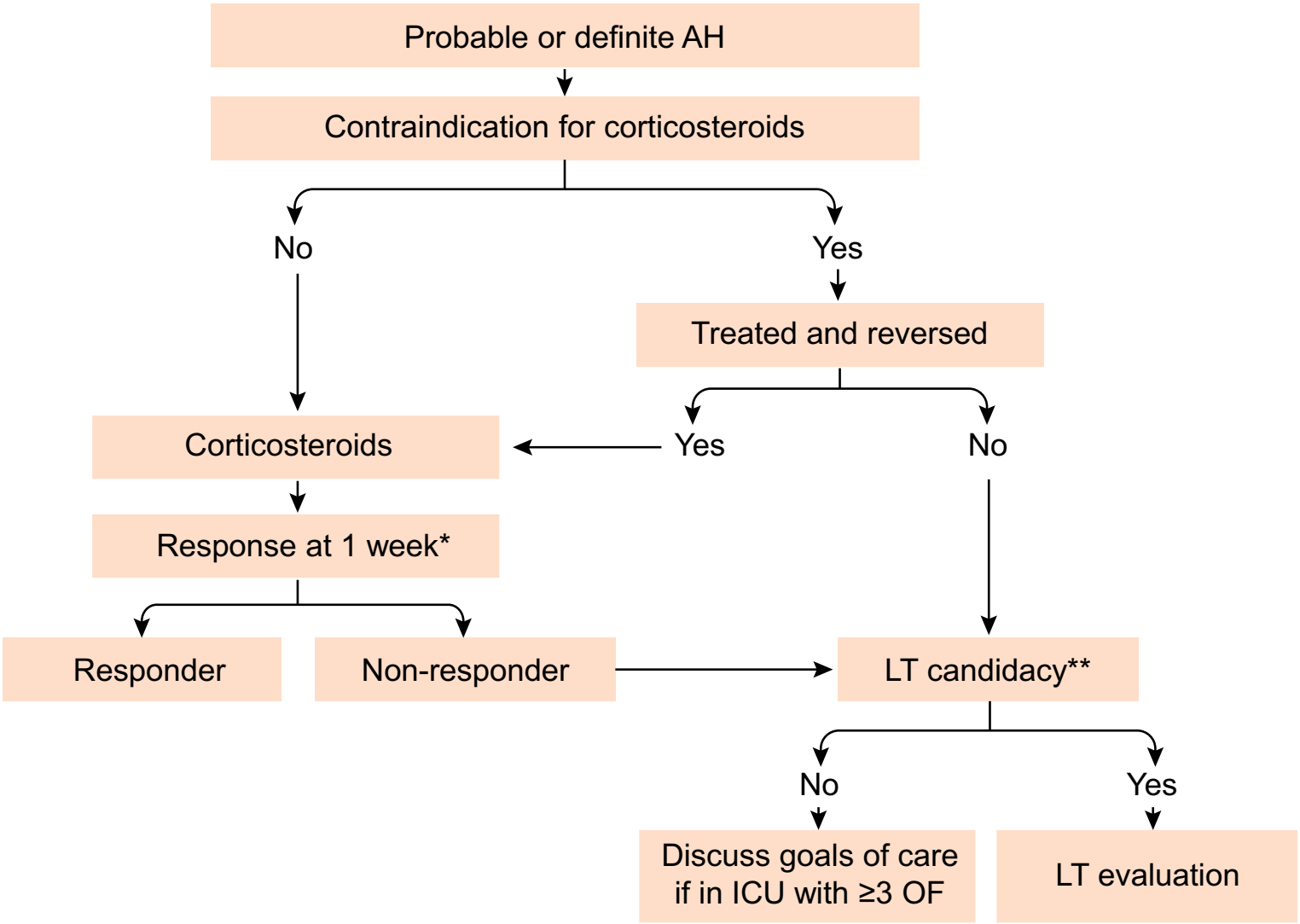
11 May 2019

Disclosures

Acute Alcohol-Induced Hepatitis (AAIH)

- Can develop in abscence or presence of chronic liver disease
- Primary treatment is steroids
- 25-45% of patients will be eligible for steroids
- Non-response in 40%
- 28-day mortality ranging from 30-50%
- 6-month mortality in steroid non-responders (as defined by the Lille score) is 75%

Bangru S, et al. Liver Transpl. 2018 [Epub ahead of print]



Singal A, et al. Journal of Hepatology 2018;69:534–543

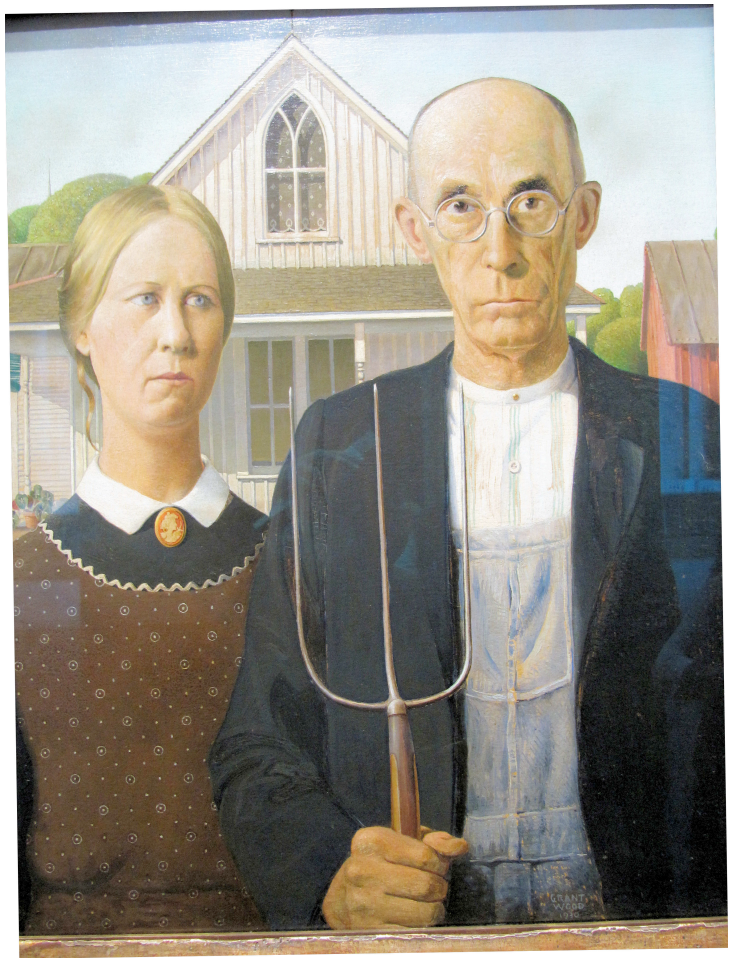
Arguments against

- Recidivism of alcohol abuse
- Post-transplant compliance
- Transplant in self-inflicted conditions
- Reduced organ donation

- Valuable organs should not be given to patients whose liver damage are self-inflicted

- Risk of recidivism is uncontrollably high in patients who have a history of alcohol abuse and an urgent indication for LT

- Homyzygotic opponents
- Heterozygotic opponents



- If you have a problem treating patients with alcoholic liver disease then you shouldn't be a hepatologist/liver surgeon

- Fundamental issue is placing blame for the disease on the patient

Alcohol and transplant

- Alcoholic cirrhosis accounts for up to 48% of cirrhosis associated deaths in the US
- Co-factor in disease progression from other aetiologies of CLD
- In 2015 accounted for 21% of all orthotropic liver transplants

Singal AK, et al. Hepatology. 2012;55:1398-405

The issues

1. Self-inflicted liver damage
2. Outcomes in AAIH Tx
3. Relapse after AAIH Tx
4. Depriving more rewarding patients

“Self-inflicted” liver damage

- Metabolic syndrome NASH-related indications
- Hepatitis B
- Hepatitis C
- Acute paracetamol intoxication

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Liver Transplantation for Severe Alcoholic Hepatitis

- Multicenter study (seven centers)
- Inclusion cirteria
  - no prior hepatitis
  - Lille score ≥ 0.45 or higher or rapid worsening LFTs
  - supportive family members
  - no severe coexisting conditions
  - commitment to alcohol abstinence
  - several meetings between four medical team circles
    - 1st – Nurses, resident, fellow
    - 2nd – Specialist in addiction
    - 3rd Senior hepatologist
    - 4th – Anesthetist & surgeon
  - complete consensus on selection

- Survival was compared between transplantated patients and a matched cohort

Mathurin P, et al. N Engl J Med. 2011;10:1790-800

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Liver Transplantation for Severe Alcoholic Hepatitis

Results

- 26 patients
- median Lille score 0.88

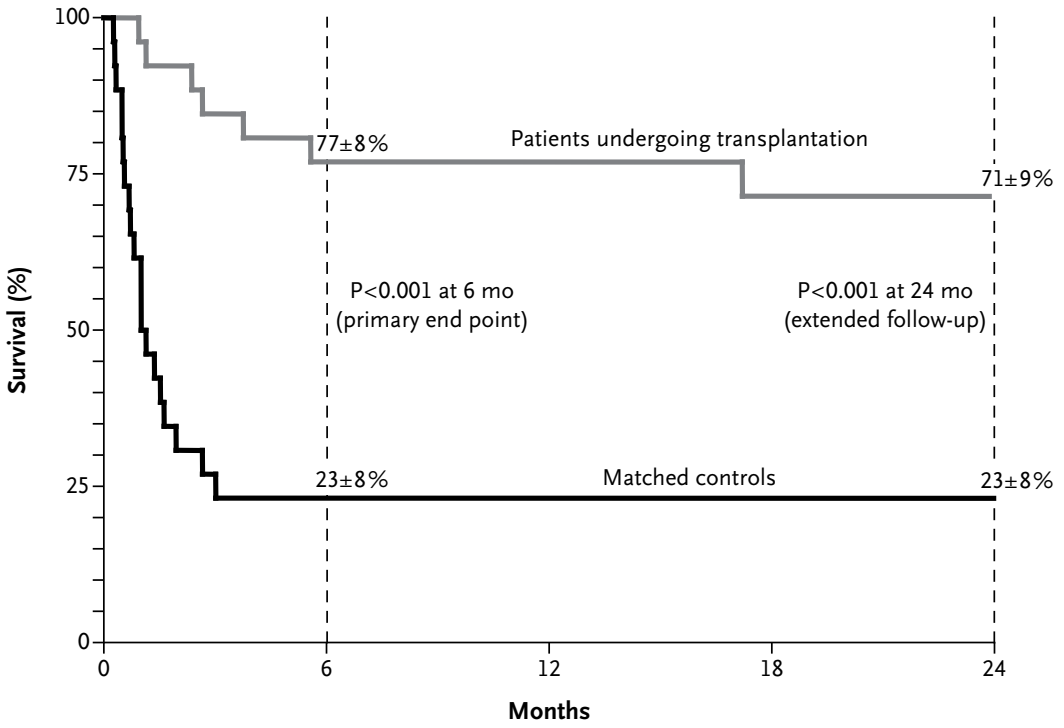


Figure 1. Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

Mathurin P, et al. N Engl J Med. 2011;10:1790-800

RESEARCH ARTICLE

Liver transplantation for alcoholic hepatitis: A systematic review with meta-analysis

Astrid Marot[1], Margaux Dubois[1], Eric Trépo[2,3], Christophe Moreno[2,3], Pierre Deltenre[1,2]*

- Meta-analysis including 11 studies
- 325 patients (240 clinical; 85 on explant)
- Endpoints
  - Survival
  - Alcohol relapse

- 6-month survival for AAIH and AC were similar (OR = 2.00, 95% CI = 0.95–4.23, p = 0.07, *I2* = 0%)

Marot A, et al. PLoS One. 2018;13:e0190823

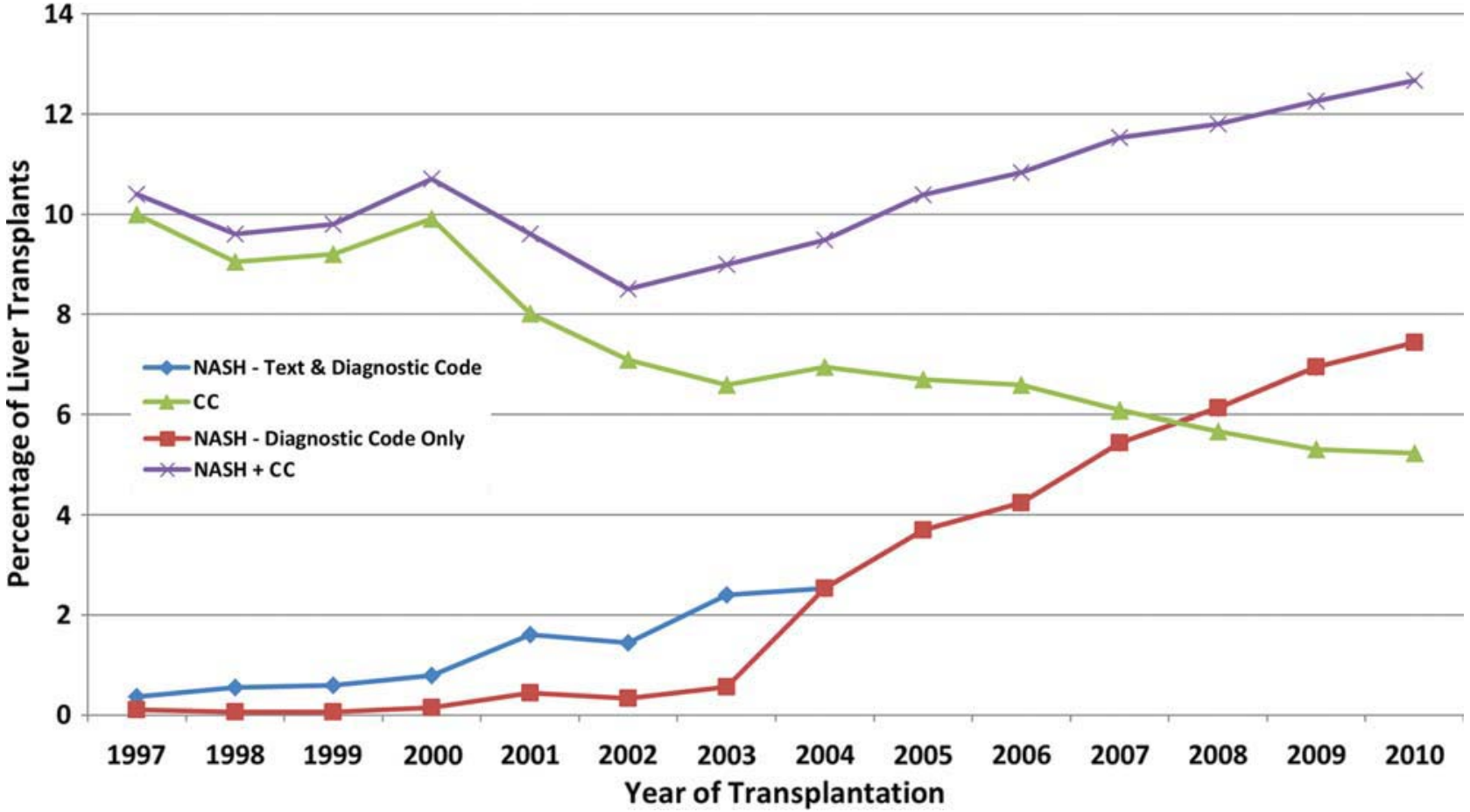
Study	Number of LT for AH	Age*	Male	Abstinence prior to LT*	MELD at time of LT*	1-year patient Survival
Mathurin[21]	26	47	58%	<90 days	34	77%
Im[25]	9	41	56%	33 days	39	89%
Weeks[27]	46	50	72%	50.5 days	33	97%
Lee[28]	147	43	73%	55 days	38	94%

AH, alcoholic hepatitis; LT, liver transplantation; MELD, model for end-stage liver disease.
* Data reported as median.

Im GY, et al. Journal of Hepatology 2019;70:328–334

Relapse after liver transplant

Excellent Posttransplant Survival for Patients with Nonalcoholic Steatohepatitis in the United States



Afzali A, et al. Liver Transpl 2012;18:29-37

Recurrent Disease Following Liver Transplantation for Nonalcoholic Steatohepatitis Cirrhosis

Shahid M. Malik,[1] Michael E. deVera,[2] Paulo Fontes,[2] Obaid Shaikh,[1] Eizaburo Sasatomi,[3] and Jawad Ahmad[1]

[1]*Division of Gastroenterology, Hepatology, and Nutrition,* [2]*Thomas E. Starzl Transplantation Institute, and* [3]*Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA*

- 98 NASH Tx
- 79 biopsied

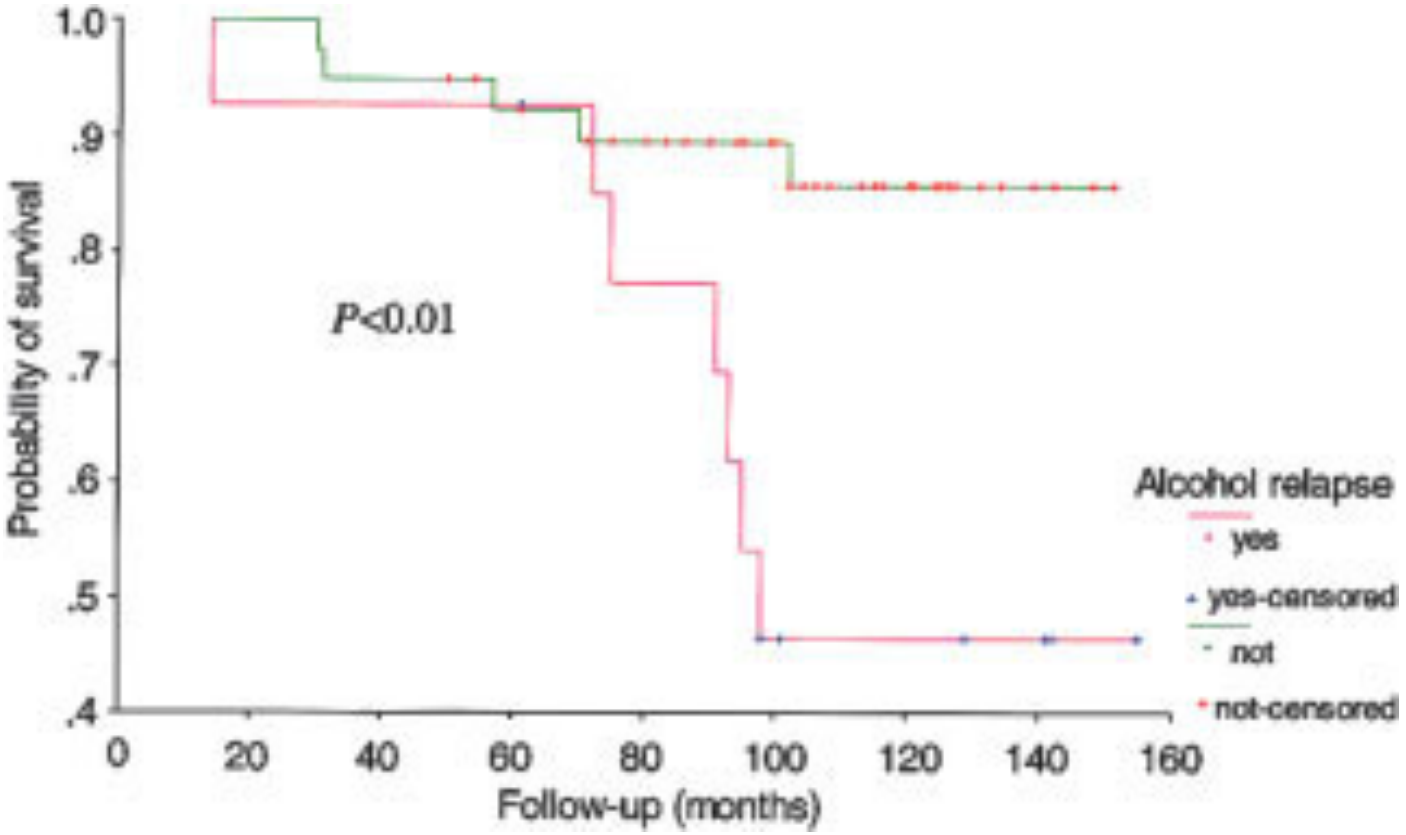
Mean follow-up 18 months

- 10 normal
- 36 (45%) bland steatosis
- 19 (24%) NASH
- 14 (18%) fibrosis ≥ stage 2

Malik S, et al. Liver Transpl 2009;15:1843-1851

Alcohol Recidivism Impairs Long-Term Patient Survival After Orthotopic Liver Transplantation for Alcoholic Liver Disease

Antonio Cuadrado, Emilio Fábrega, Fernando Casafont, and Fernando Pons-Romero



Survival curves for patients with or without alcohol recidivism

Cuadrado A, et al. Liver Transpl 2005;11:420–6

RESEARCH ARTICLE

Liver transplantation for alcoholic hepatitis: A systematic review with meta-analysis

Astrid Marot[1], Margaux Dubois[1], Eric Trépo[2,3], Christophe Moreno[2,3], Pierre Deltenre[1,2]*

- Meta-analysis including 11 studies
- 325 patients (240 clinical; 85 on explant)

Relapse

- pooled estimate 0.22 (95% CI = 0.12–0.36)
- non-significant difference comparing AAID/AC (OR = 2.28, 95% CI = 0.98–5.29, p = 0.055),

Marot A, et al. PLoS One. 2018;13:e0190823

Study	Number of LT for AH	Age*	Male	Abstinence prior to LT*	MELD at time of LT*	1-year patient Survival	Return to harmful drinking
Mathurin[21]	26	47	58%	<90 days	34	77%	10%
Im[25]	9	41	56%	33 days	39	89%	12.5%
Weeks[27]	46	50	72%	50.5 days	33	97%	17%
Lee[28]	147	43	73%	55 days	38	94%	11%

AH, alcoholic hepatitis; LT, liver transplantation; MELD, model for end-stage liver disease.
* Data reported as median.

The six month rule

- Hope that liver function will improve
- Fear of recurrent alcohol consumption after Tx
- Liver Tx in self-inflicted disease could cause problems in:
  - graft allocation
  - public opinion
  - funding from healthcare providers

*Bangru S, et al. Liver Transpl. 2018 [Epub ahead of print]

The six month rule

- An absolute interval of abstinence?

  80% of units 3-6 months; 20% 7-9 months*
- Arbitrary threshold - has never been shown to affect survival, sobriety, or other outcomes
- Senseless to apply it in a patient cohort with a 6 month mortality rate of up to 75%
- AASLD & EASL guidelines state that a 6 month period of abstinence should no longer be an absolute rule

*Bangru S, et al. Liver Transpl. 2018 [Epub ahead of print]

Depriving more rewarding patients

CME

A Critical Review of Candidacy for Orthotopic Liver Transplantation in Alcoholic Liver Disease

- 100 000 patients/year - Estimated number of patients with decompensated cirrhosis in the US
- 10 000 (10%) referred for transplant assessment
- 3673 (4%) listed for transplant
- 1200 (1.2%) transplanted

Kotlyar D, et al. Am J Gastroenterol 2008;103:734–743

Transplant for AAID

	Patients assessed	% Tx	% of total Tx
Mathurin et al.	233	<1%	2.9%
Im et al.	94	9%	3%

Mathurin P, et al. N Engl J Med. 2011;10:1790-800
Im GY, et al. Am J Transplant 2016;16:841-849

Current situation

Impact of a First Study of Early Transplantation in Acute Alcoholic Hepatitis: Results of a Nationwide Survey in French Liver Transplantation Programs

	Yes	No
Regarding AAH, were there any changes to its management after 2011?	88%	12%
Since 2011, have you considered AAH to be a potential indication for LT?	97%	3%
Regarding AAH, have there been any changes to the management of LT for alcoholic cirrhosis since 2011?	88%	12%
Did you perform LT for AAH in your center before 2011?	35%	65%
Have you performed LT for AAH in your center since 2011?	71%	29%
Are alcoholic patients with cirrhosis systematically evaluated by an addiction specialist during the pretransplant workup (before and after 2011)?	76%/100%	24%/0%

Antonini TM, et al. Liver Transpl. 2018;24:841-844

Underestimation of Liver Transplantation for Alcoholic Hepatitis in the National Transplant Database

Brian P. Lee [1], Gene Y. Im [2], John P. Rice,[3] Ethan Weinberg,[4] Christine Hsu,[5] Oren K. Fix,[6] George Therapondos [7], Hyosun Han,[8] David W. Victor,[9] Sheila Eswaran,[10] Haripriya Maddur,[11] and Norah A. Terrault[8]

- Adult patients with clinically severe acute AH
- Chronic and recent alcohol use
- No prior diagnosis of chronic liver disease / episodes of AH
- LT without a minimum prescribed period of abstinence

- Compared to the diagnosis listed in UNOS database

Lee BP, et al. Liver Transpl. 2019;25:706-711

- 124 patients with clinically AAIH

- UNOS database diagnosis
  - AAIH – 43/124 (35%)
  - Alcoholic cirrhosis – 80/124 (64%)
  - Fulminant hepatic necrosis – 1/124 (1%)

Lee BP, et al. Liver Transpl. 2019;25:706-711

Reasons for discrepancy

Why was this patient not coded as AH in UNOS?

- 1 = coordinator was not aware there was a separate AH listing code in UNOS
- 2 = there was uncertainty at the time of listing about the diagnosis of AH versus alcoholic cirrhosis, and the coordinator chose alcoholic cirrhosis for the UNOS entry
- 3 = there was a data entry error in UNOS
- 4 = given the controversy for this LT indication and the heated atmosphere, there was a reluctance to publicly reveal LT for AH
- 5 = there was some other reason

Lee BP, et al. Liver Transpl. 2019;25:706-711

Reasons for discrepancy

Why was this patient not coded as AH in UNOS?

- 1 = coordinator was not aware there was a separate AH listing code in UNOS **54%**
- 2 = there was uncertainty at the time of listing about the diagnosis of AH versus alcoholic cirrhosis, and the coordinator chose alcoholic cirrhosis for the UNOS entry **31%**
- 3 = there was a data entry error in UNOS **15%**
- 4 = given the controversy for this LT indication and the heated atmosphere, there was a reluctance to publicly reveal LT for AH **0%**
- 5 = there was some other reason

Lee BP, et al. Liver Transpl. 2019;25:706-711

Conclusions

- AAIH have good outcomes when transplanted
- Complex etiology – needs further research
- The 6 month rule is an unethical experiment in the natural course of AAIH
- Patient-specific pre-operative evaluation and post-transplant care
- Social prejudice and bias should not influence organ allocation for liver transplantation