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REVIEW ARTICLE

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Alcohol-Associated Hepatitis

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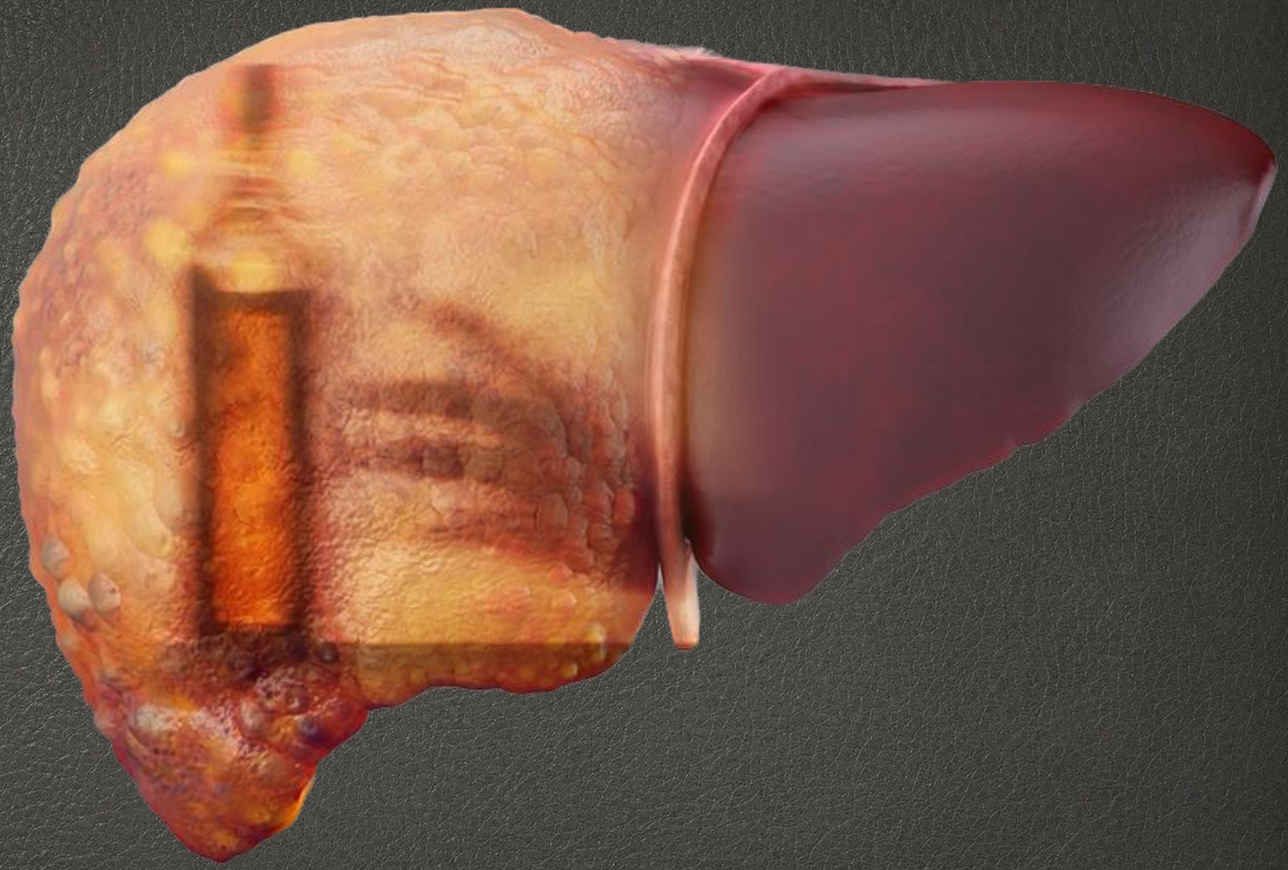
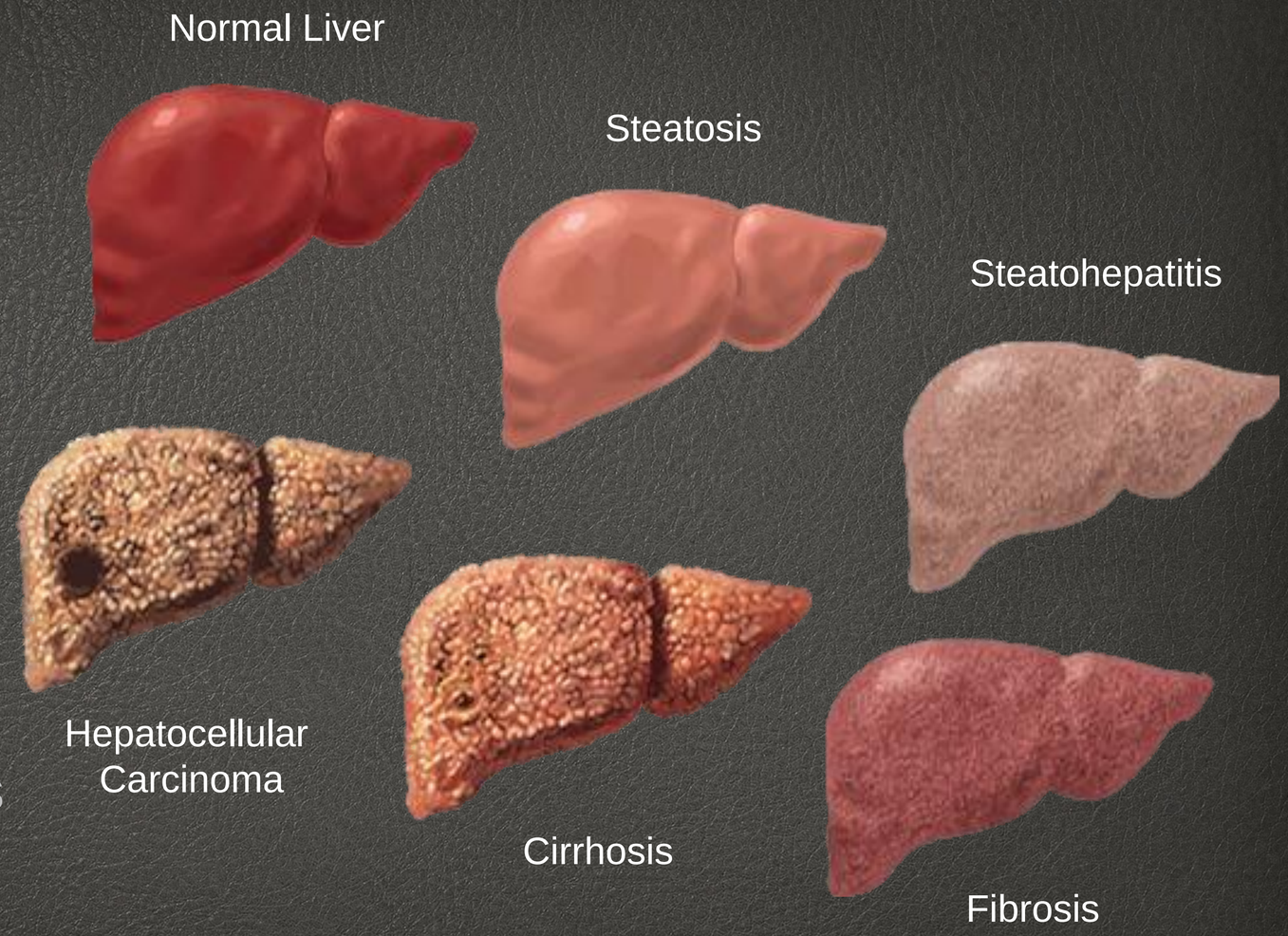


INTRODUCTION:

Alcohol abuse is a major cause of advanced liver disease and liver-related hospitalisation and death worldwide. Globally, 50% of all deaths related to liver disease are due to alcohol.

Various forms of alcohol-associated liver disease (ALD) will develop in approximately 35% of patients with alcohol use disorder.

The clinical and histopathological forms of ALD range from isolated steatosis > progressive steatohepatitis > fibrosis > cirrhosis >hepatocellular carcinoma.



In this review article, the following aspects are discussed:

- New concepts in the diagnosis and prognosis of alcohol associated hepatitis
- Current methods in the treatment of these patients
- Ongoing clinical trials testing new targets for therapy
- Selection criteria for early liver transplantation

Predisposing factors

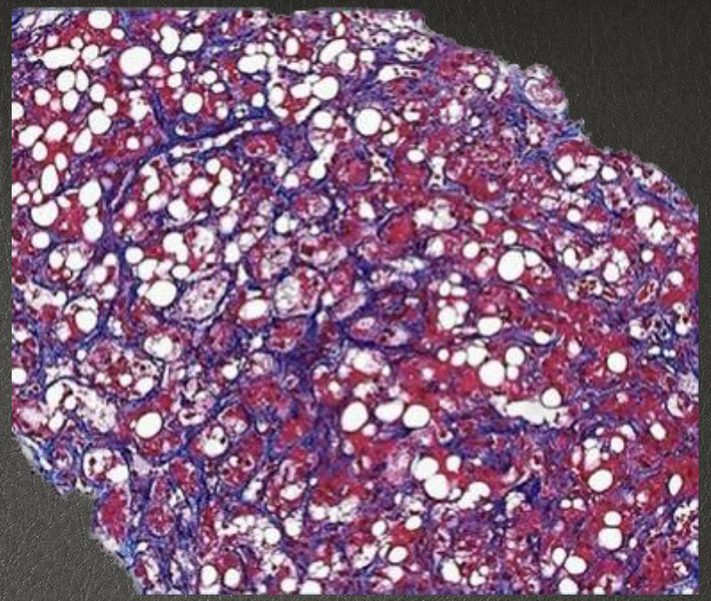
- The factors underlying the development of the abrupt form of liver failure that defines alcohol-associated hepatitis are largely unknown and probably include environmental, genetic, and epigenetic factors. Although most patients presenting with alcohol-associated hepatitis have a history of prolonged and heavy alcohol use, whether the total amount or pattern of alcohol consumption plays a role remains unknown
- Sex differences have been observed in alcohol-associated hepatitis, both in the manifestations and severity of liver disease.Women are more susceptible to alcohol injury and cirrhosis.
- Female sex is independently associated with ALD- related burden and alcohol-related acute-on- chronic liver failure in the United States.
- Influencing factors: genetic factors such as variations in the gene encoding patatin-like phospholipase domain– containing protein 3 (*PNAPL3*) influence disease severity
- Protective factors: Some factors such as coffee con- sumption and polymorphism in the gene encoding hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*) have shown a protective role.

Pathogenesis 1

- The pathogenesis of alcohol-associated hepatitis is incompletely understood
- The liver is the main site to metabolise alcohol into acetaldehyde > DNA adducts (DNA segment binds to acetaldehyde) > promotes innate immune response, glutathione depletion, lipid peroxidation, & mitochondrial damage.
- Injured hepatocytes release DAMPs eg; HMGP(1) > activate inflammsome-caspase-1 complex > activates IL-1β & IL-18

Pathogenesis 2

- Excessive alcohol consumption disrupts the intestinal tight junctions > increases gut permeability > changes in the microbiome such as increased pathogenic bacteria eg: E. faecalis exotoxin & LPS promote alcohol induced liver injury via PAMPs > inflammation > hepatocyte death > fibrotic response.
- CXC chemokines, macrophage migration inhibitory factor, and complement factors > hepatocellular injury.
- These processes activate fibrogenic cell types which cause the accumulation of extracellular matrix around hepatocytes and sinusoidal cells > chicken wire pattern (a network of collagen strands surrounding damaged hepatocytes) > development of portal hypertension.

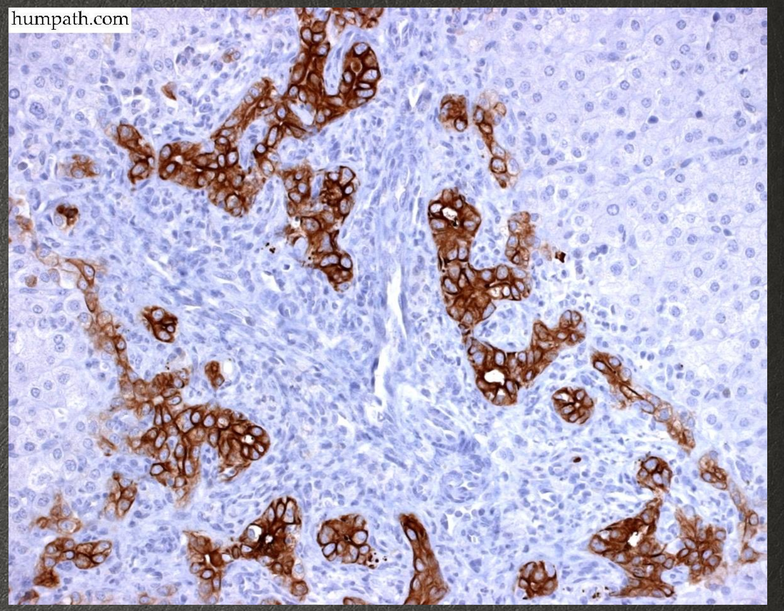


Chicken wire patten in liver pathology

Real chicken wire

Pathogenesis 3

- Pro-fibrogenic mediators such as TGFβ1 > hepatocyte regeneration impairment and hepatocyte dedifferentiation > synthetic dysfunction & failure of metabolic liver functions (defective bilirubin transport, clotting factor synthesis, glucose metabolisation). This failure of differentiation results in a massive expansion of liver progenitor cells (ductular reaction) = futile attempt at liver regeneration. This effect is mainly caused by inefficient activation of HNF4α and YAP.
- SIRS and immune dysfunction often develop > bacterial infections & acute on chronic liver failure + multi organ failure.
- In severe cases, the liver is characterised by massive ductular reaction and hepatic dedifferentiation into a cholangiocyte-like phenotype



Ductular reaction: proliferation of reactive bile ducts by liver injury ie; **bile duct hyperplasia**

Diagnosis

Initial Evaluation

Clinical presentation:
- Prolonged alcohol intake (>60 g/day for men or >40 g/day for women) until <8 wk before presentation, recent-onset jaundice, malaise, ascites or edema, fever (in 30–50% of patients), tender hepatomegaly, confusion, and asterixis (in 50%)

Laboratory markers:
- Abrupt rise in total bilirubin (>3 mg/dl), AST>ALT (>2× ULN), AST <400 IU/liter, GGT >100 U/liter, albumin <3.0 g/liter, INR >1.5, platelet count <150,000/mm^3; in some cases, nonimmune hemolytic anemia

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Rule Out Other Reasons for Jaundice

Mechanical obstruction:
- HCC, biliary obstruction, or Budd–Chiari syndrome
- Perform Doppler abdominal ultrasonography and, if indicated, CT or MRI-MRCP

Drug-induced liver injury:
- Review detailed history of medications, supplements, and pharmacy records
- Check http://livertox.nih.gov

Viral hepatitis:
- Acute hepatitis A, B, C, or E, especially if first episode, or high clinical suspicion

Autoimmune hepatitis:
- Severe autoimmune hepatitis if first episode, clinical suspicion (ANA, ASMA, IgG), or both

Ischemic hepatitis:
- Presence of hypotension, septic shock, massive bleeding, or recent cocaine use

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Role for Transjugular Liver Biopsy

- Atypical presentation, laboratory tests (e.g., AST or ALT >400 IU/liter), or both
- Uncertain alcohol assessment
- Use of any potential hepatotoxic substance in the past 3 mo
- High suspicion of autoimmune hepatitis

All negative → Probable alcohol-associated hepatitis, clinically diagnosed

Any positive → Transjugular liver biopsy recommended

Histologic confirmation → Definite alcohol-associated hepatitis, biopsy-proven

Not available → Possible alcohol-associated hepatitis, clinically suspected

Figure 2. Algorithm for the Diagnosis of Alcohol-Associated Hepatitis.

To convert the value for bilirubin to micromoles per liter, multiply by 17.1. ALT denotes alanine aminotransferase, ANA antinuclear antibodies, ASMA α–smooth-muscle actin antibodies, AST aspartate aminotransferase, CT computerized tomography, GGT γ-glutamyltransferase, HCC hepatocellular carcinoma, INR international normalized ratio, MRI-MRCP magnetic resonance imaging–magnetic resonance cholangiopancreatography, and ULN upper limit of the normal range.

Prognosis

Bad prognosis

- Presence of fully developeed cirrhosis
- Hepatic encephalopathy
- In-hospital incident infections, often caused by multi drug-resistant bacteria (often lead to AKI and acute on chronic liver failure
- Infection in patients receiving glucocorticoids
- Presence of SIRS (predicts multi organ failure and acute on chronic liver failure

The main factor influencing long-term prognosis after an episode of alcohol-associated hepatitis is prolonged alcohol abstinence.

Medical Management

Treat Liver-Related Complications and Alcohol Use Disorder

Liver-related complications and AKI:
- Administer diuretics for ascites or edema, albumin with or without terlipressin or norepinephrine if AKI-HRS
- If GI bleeding, administer endoscopic and pharmacologic therapy
- If HE, administer lactulose and rifaximin and treat precipitant

Nutritional support:
- Administer parenteral vitamin K, vitamin B complex, vitamin D if levels are low
- Administer enteral nutrition if calorie intake <21.5 kcal/kg/day with goal of 35–40 kcal/kg/day

Infection:
- Perform extensive workup for infection (cultures, ascitic fluid analysis, chest radiography, urinalysis)
- If suspicion of infection, administer early broad-spectrum antibiotics

Management of alcohol use disorder:
- Prevent with chlormethiazole; if withdrawal, CIWA protocol, benzodiazepines (chlordiazepoxide preferred)
- Consult addiction specialist
- Consider baclofen or acamprosate (if not AKI) at discharge

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MELD score >20 (maximum benefit, MELD score of 25–39)
Alternative: calculate serum bilirubin trajectory

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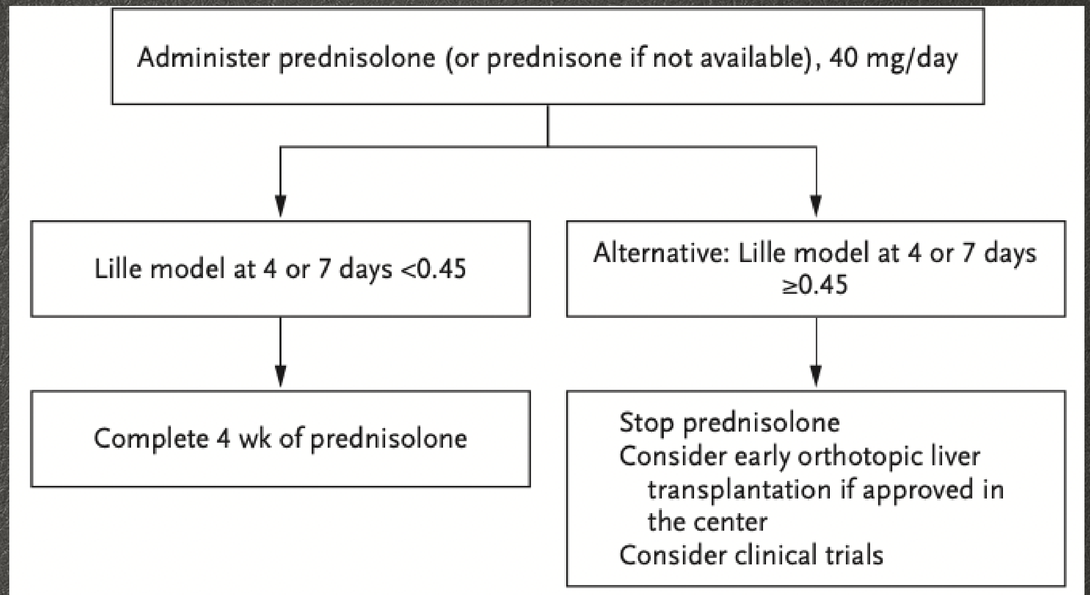


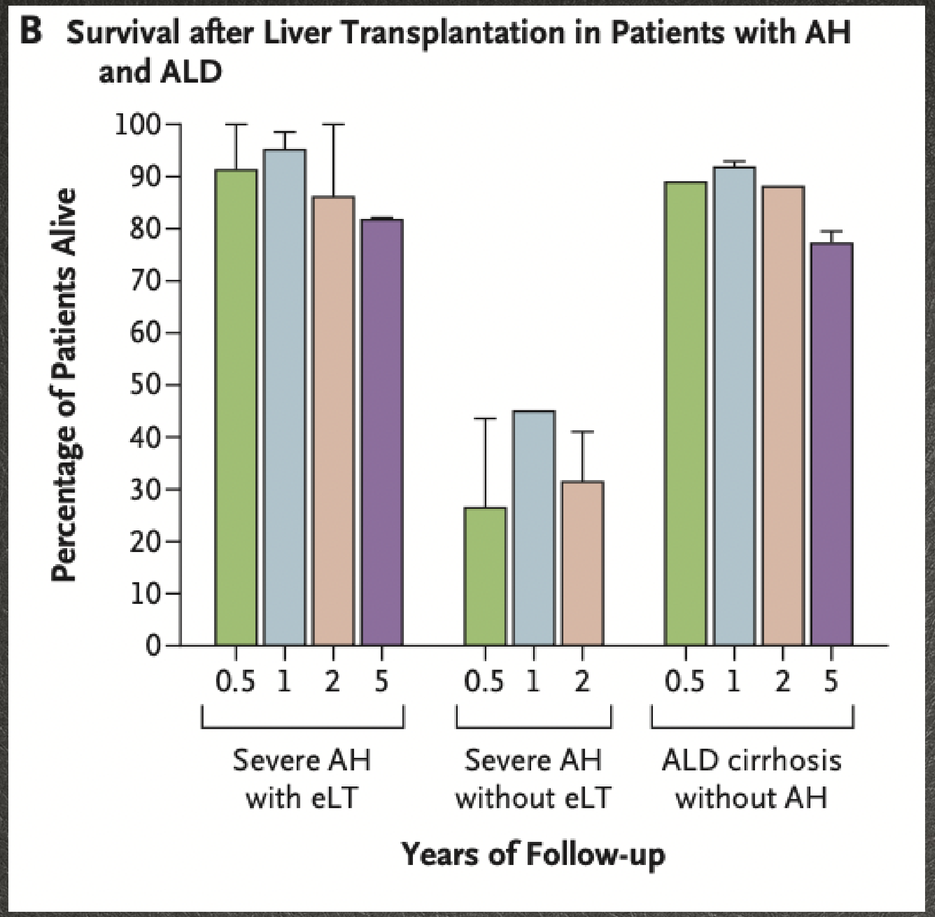
Figure 3. Algorithm for the Management of Alcohol-Associated Hepatitis.

Model for End-Stage Liver Disease (MELD) scores range from 6 to 40, with higher scores indicating a higher risk of death at 3 months. AKI denotes acute kidney injury, AKI-HRS AKI–hepatorenal syndrome, CIWA Clinical Institute Withdrawal Assessment for Alcohol, GI gastrointestinal, and HE hepatic encephalopathy.

Early liver transplantation

A Characteristics of the Studies

Study	Inclusion Criteria	Primary End Point	Location
Mathurin et al., 2011[21]	Severe AH not responding to glucocorticoids or rapid worsening of liver function No previous episodes of AH, supportive family members, no severe psychiatric conditions, commitment to alcohol abstinence	Survival at 6 mo	France Belgium
Im et al., 2016[85]	Severe AH not responding to medical therapy	Survival at 6 mo	United States
Lee et al., 2017[86]	Severe AH as first liver decompensation	Survival at 6 mo	United States
Lee et al., 2018[87]	Severe AH and no previous diagnosis of liver disease or episodes of AH	Survival and AUD after liver transplantation	United States
Cotter et al., 2021[88]	Severe AH and no previous diagnosis of liver disease or episodes of AH	Survival at 1 and 5 yr	United States
Lee et al., 2022[89]	Retrospective analysis of UNOS database of patients undergoing liver transplantation for AH	Survival at 1 and 5 yr	United States
Louvet et al., 2022[90]	Patients with severe AH who did not have a response to medical treatment and were eligible for eLT according to social and addiction evaluation	Alcohol relapse and survival at 2 yr	France Belgium
Germani et al., 2022[91]	Severe AH according to NIAAA criteria, not responding to medical therapy	Survival at 6, 12, and 24 mo	Italy



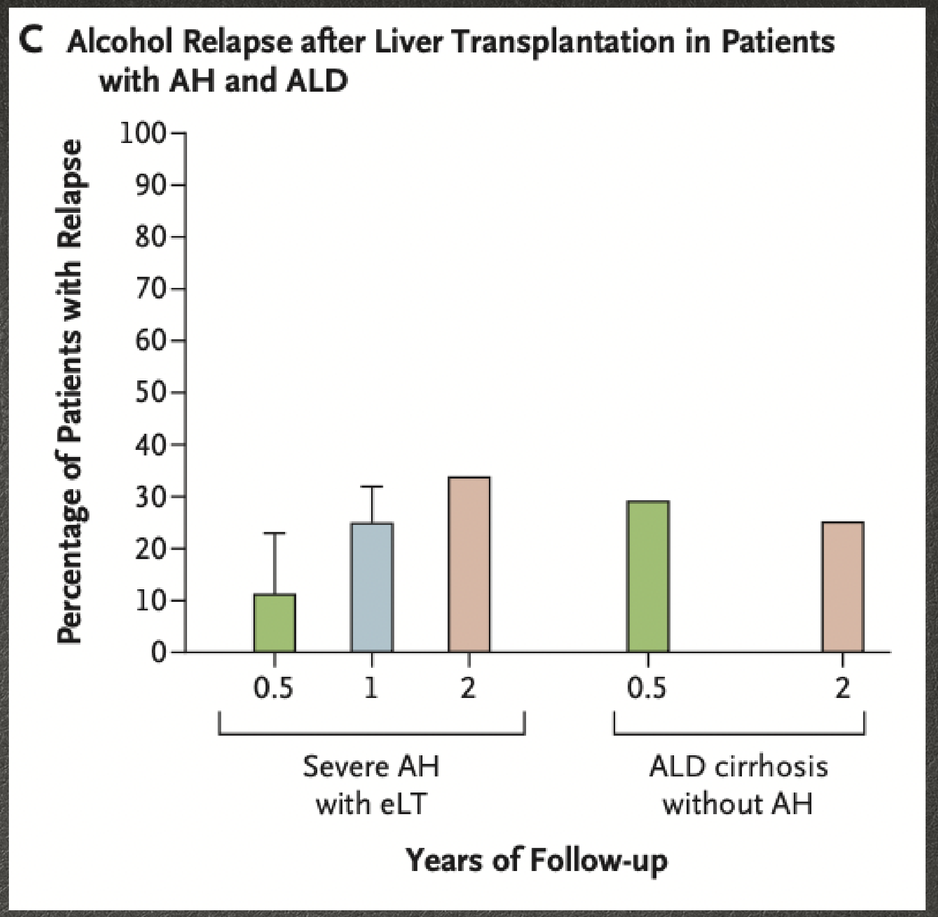


Figure 4. Summary of Studies Assessing Early Liver Transplantation (eLT) for Severe Alcohol-Associated Hepatitis (AH).
In Panels B and C, I bars indicate standard deviations. ALD denotes alcohol-associated liver disease, AUD alcohol use disorder, NIAAA National Institute on Alcohol Abuse and Alcoholism, and UNOS United Network for Organ Sharing.

Emerging Therapies

- A pilot study of a recombinant fusion protein of human interleukin-22, an antiinflammatory and pro-regenerative cytokine, showed favorable out- comes as determined by Lille and MELD scores, a reduction in markers of inflammation, and increased expression of markers of hepatic regeneration
- Two open-label, randomized trials comparing (G-CSF) plus standard medical therapy with standard medical therapy alone in patients with severe alcohol-associated hepatitis showed an improvement in 3- and 6-month survival and a lower incidence of bacterial infections. **A more recent European study, however, failed to show a benefit with G-CSF in patients with severe alcohol-associated hepatitis**
- A pilot study showed that faecal microbiome transplantation from healthy donors was associated with lower mortality than in a historical cohort
- A study of IL-1 inhibition by anakinra, pentoxifylline, and zinc showed an acceptable side-effect profile, but 180-day survival did not differ sig-nificantly between the combination therapy and glucocorticoid therapy.
- Several clinical trials are now examining the role of probiotics, rifaxi-min, and faecal microbiome transplantation
- Other clinical trials are testing the use of

A. anti inflammatory drugs
B. drugs targeting gut-liver axis dysfunction and dysbiosis
C. antioxidants
D. drugs targeting apoptosis
E. phage therapy and supplemental nutrition strategies

Future Directions

To reduce the burden of ALD several method have been proposed

- increasing taxes or raising the price of alcohol
- Assess the determinants of the increasing prevalence of ALD
- Development of new prognostic biomarkers of alcohol associated hepatitis
- Identify molecular subtypes for personalised medicine and response to therapy
- Development of human based experimental models to test new therapies
- Better definition of indications for early liver transplantation in patients who do not respond to medical therapy
- Multidisciplinary approaches to treat the underlying cause of alcohol abuse and promote alcohol abstinence

Questions?
Thank you for your attention