Alcohol Associated Hepatitis

SJ Hashemi MD

Professor of Gastroenterology, Ahvaz Jundishapur university of medical sciences

Agenda

- Definition and presentation of Alcohol-Associated Hepatitis
- Diagnostic approach To The AAH
- Assessment of AAH severity
- Management of AAH
- Follow up after discharge

Public Health Aspects:

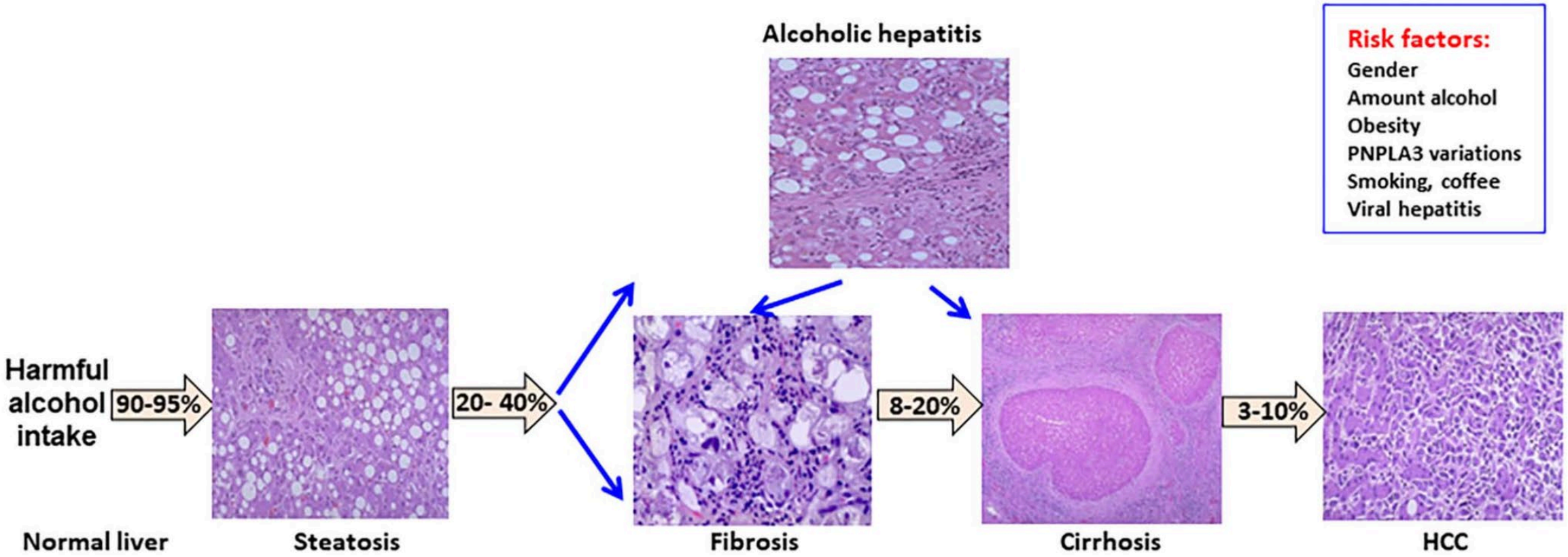
Alcohol-related morbidity and mortality

- Worldwide, harmful use of alcohol is associated with:
  - ~3.3 million deaths every year [1]
    - 5.9% of all deaths overall (7.6% in men, 4.0% in women)[1]
  - ~139 million disability-adjusted life years
    - 5.1% of the global burden of disease and injury
- Alcohol has an impact on over 200 diseases and types of injuries
- Most deaths attributable to alcohol consumption from:
  - Cardiovascular diseases
  - Injuries
  - Gastrointestinal diseases
    - Mainly cirrhosis
  - Cancers
- Alcohol-attributable fraction is highest for liver diseases and foetal alcohol syndrome



1. WHO. Global status report on noncommunicable diseases 2014.
Available at: http://www.who.int/nmh/publications/ncd-status-report-2014/en/. Accessed August 2018;
EASL CPG ALD. J Hepatol 2018;69:154–81

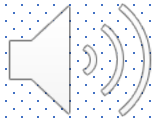
Spectrum of Alcohol-Related Liver disease



Alcohol-associated hepatitis

- AAH is an acute clinical syndrome manifested by the onset of jaundice within the previous 8 wks, ongoing harmful alcohol use and elevated ALT ,AST and total serum bilirubin levels

- Patients with AAH usually have a history of daily heavy alcohol use (>40 g /day for females and >60 g/day for males), usually for at least 6 months but often for >5 years.



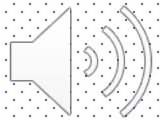
Alcohol -Associated Hepatitis:

Signs and symptoms

- Jaundice :
  Develops or worsens within 8 wks
- General symptoms:
  Anorexia, Fever and malaise.
- Abdominal symptoms :
  RUQ/epigastric pain ,Abdominal distension (ascites).
- Patients with severe AAH may present with hepatic encephalopathy and/or gastrointestinal (variceal) bleeding.
- Symptoms related to undernutrition such as proximal muscle weakness due to muscle wasting.
- Hepatomegaly
- A bruit heard over the liver is also a feature of sever AAH (50%)

Laboratory studies

- Liver tests : ALT , AST , Alkaline phosphatase, total bilirubin, GGT.
- Serum albumin.
- Serum lipid profile.
- Coagulation studies – PT, INR
- Complete blood count with platelets.
- Urine drug testing.
- Serum phosphatidylethanol (PEth) level (a serum marker for detecting chronic alcohol use)
- Serum acetaminophen levels.
- Testing for viral hepatitis: IgM anti HAV ,Hbs Ag ,HBC Ab, HCV ab
- Autoimmune markers : ANA , ASMA , Serum IgG

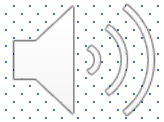


Liver biopsy

❖Limited indications

- Only for patients with AAH if the diagnosis remains:
  - **Atypical laboratory findings**

    A positive autoimmune markers (ANA >1:160 or ASMA >1:80).
  - **Unclear alcohol use assessment**
  - **Risk factor(s) for ischemic hepatitis** (
- Liver biopsy is typically performed using a transjugular approach



Establishing The Diagnosis

- **Alcohol use and pattern:**
  - **Harmful alcohol use** (>280 g /w for females and >420 g /w for males) for at least 6 months
  - **Less than 60 days of abstinence** before the onset of jaundice.
- **Laboratory criteria:**
  - Aspartate aminotransferase (AST) >50 units/L.
  - AST and alanine aminotransferase (ALT) both <400 units/L.
  - AST:ALT ratio ≥1.5:1.
  - Serum bilirubin (total) >3 mg/dL (51 micromol/L).

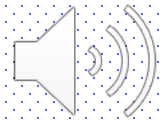


Definition	Criteria
Definite AH	Histological confirmation of features of alcohol-associated hepatitis
Probable AJ	Onset of jaundice within 60 d of heavy alcohol use (more than 50 g/d) for a minimum of 6 mo, serum bilirubin.3 mg/dL, elevated ASTranging from 50 to 400 U/L, an AST:ALT ratio. 1.5, and no other cause of acute hepatitis
Possible AH	Clinical diagnosis uncertain due to another confounding etiology of liver disease or unclear history on alcohol consumption

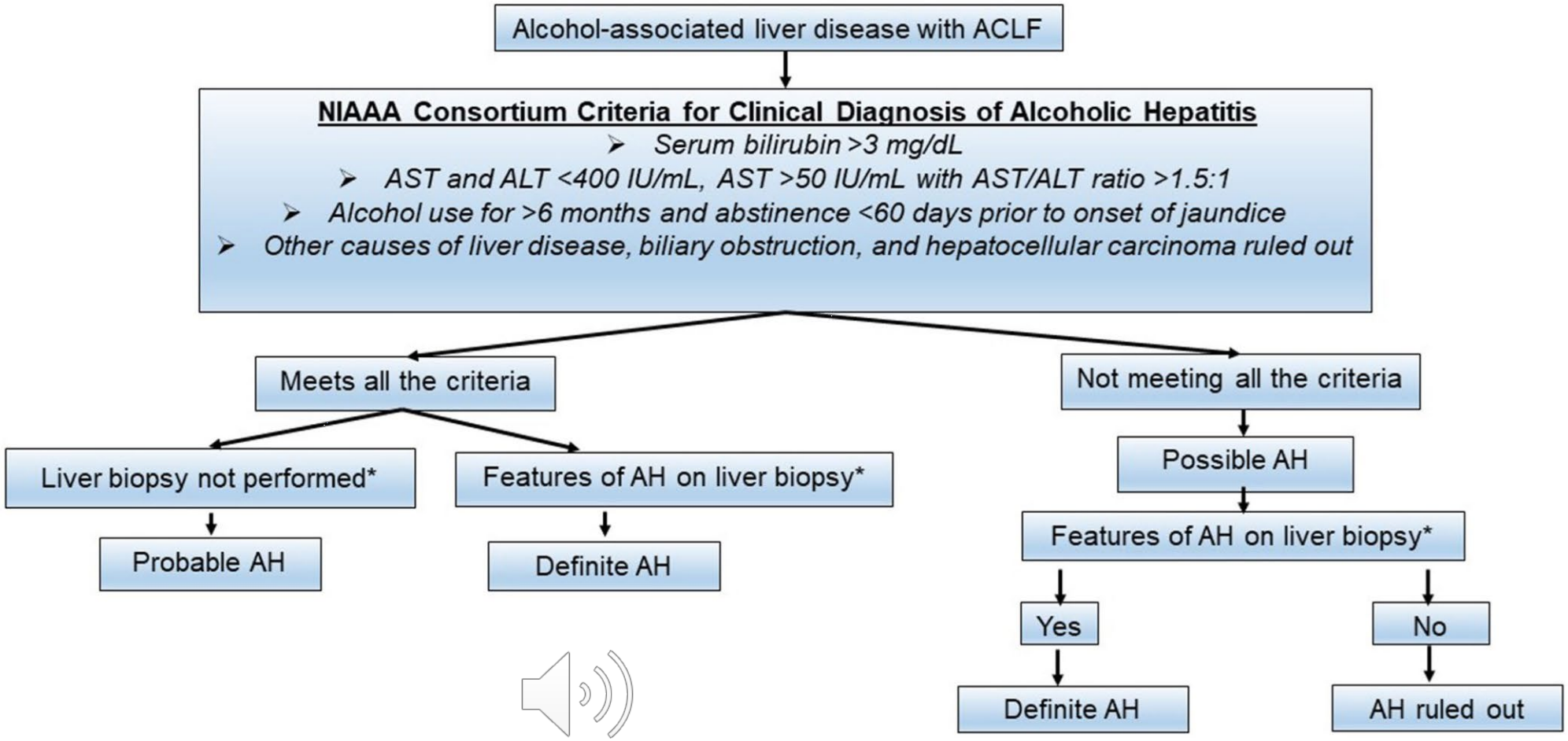
NIAAA, National Institute of Alcoholism and Alcohol Abuse. AGA Guidline 2024

Exclude DDx

- Acute viral hepatitis
- Autoimmune hepatitis
- Biliary obstruction
- Budd-Chiari syndrome
- Drug-induced liver injury
- Ischemic hepatitis
- Wilson disease

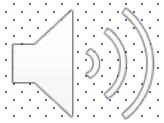


Alcohol-Associated Hepatitis



Jophlin, & Singal, A. K. (n.d.). Journal of Clinical and Experimental Hepatology., 12(2), 544–550.

Management of Alcohol-Associated Hepatitis



Evaluation of severity

- Different prognostic models aim to identify patients at high risk of early death
  - Often incorporate the same variables and have similar efficacy in predicting short-term survival

Score	Bilirubin	PT/INR	Creatinine/ urea	Leucocytes	Age	Albumin	Change in bilirubin (Day 0 to 7)
Maddrey DF*	↟	↟	=	=	=	=	=
MELD	↟	↟	↟	=	=	=	=
GAHS	↟	↟	↟	↟	↟	▬	▬
ABIC	↟	↟	↟	▬	↟	↟	=
Lille	↟	↟	↟	▬	↟	↟	↟

- *Modified version (mDF) cut-off value of 32 identifies patients with severe AH and is usually the threshold used for initiating specific therapy
- EASL CPG ALD. J Hepatol 2018;69:154–81

Evaluation of severity

- Different prognostic models aim to identify patients at high risk of early death
  - Often incorporate the same variables and have similar efficacy in predicting short-term survival

Score	Bilirubin	PT/INR	Creatinine/ urea	Leucocytes	Age	Albumin	Change in bilirubin (Day 0 to 7)
Maddrey DF*	First score and still most widely used DF = 4.6 X (PT- Control_PT) + Bilirubin						
MELD	+	+	+	–	–	–	–
GAHS	+	+	+	+	+	–	–
ABIC	+	+	+	–	+	+	–
Lille	+	+	+	–	+	+	+

*Modified version (mDF) cut-off value of 32 identifies patients with severe AH and is usually the threshold used for initiating specific therapy

EASL CPG ALD. J Hepatol 2018;69:154–81

Evaluation of severity

- Different prognostic models aim to identify patients at high risk of early death
  - Often incorporate the same variables and have similar efficacy in predicting short-term survival

Score	Bilirubin	PT/INR	Creatinine/ urea	Leucocytes	Age	Albumin	Change in bilirubin (Day 0 to 7)
Maddrey DF*	+	+	–	–	–	–	–
MELD	Score >20: high risk of 90-day mortality						
GAHS	+	+	+	+	+	–	–
ABIC	+	+	+	–	+	+	–
Lille	+	+	+	–	+	+	+

*Modified version (mDF) cut-off value of 32 identifies patients with severe AH and is usually the threshold used for initiating specific therapy

EASL CPG ALD. J Hepatol 2018;69:154–81

Evaluation of severity

- Different prognostic models aim to identify patients at high risk of early death
  - Often incorporate the same variables and have similar efficacy in predicting short-term survival

Score	Bilirubin	PT/INR	Creatinine/ urea	Leucocytes	Age	Albumin	Change in bilirubin (Day 0 to 7)
Maddrey DF*	+	+	–	–	–	–	–
MELD	+	+	+	–	–	–	–
GAHS	Score ≥9 + mDF ≥32: poor prognosis and survival benefit with corticosteroids						
ABIC	+	+	+	–	+	+	–
Lille	+	+	+	–	+	+	+

*Modified version (mDF) cut-off value of 32 identifies patients with severe AH and is usually the threshold used for initiating specific therapy

EASL CPG ALD. J Hepatol 2018;69:154–81

Evaluation of severity

- Different prognostic models aim to identify patients at high risk of early death
  - Often incorporate the same variables and have similar efficacy in predicting short-term survival

Score	Bilirubin	PT/INR	Creatinine/ urea	Leucocytes	Age	Albumin	Change in bilirubin (Day 0 to 7)
Maddrey DF*	+	+	–	–	–	–	–
MELD	+	+	+	–	–	–	–
GAHS	+	+	+	+	+	–	–
ABIC	Classification according to low, medium, and high risk of death at 90 days						
Lille	+	+	+	–	+	+	+

*Modified version (mDF) cut-off value of 32 identifies patients with severe AH and is usually the threshold used for initiating specific therapy

EASL CPG ALD. J Hepatol 2018;69:154–81

Evaluation of severity

- Different prognostic models aim to identify patients at high risk of early death
  - Often incorporate the same variables and have similar efficacy in predicting short-term survival
- **Lille model** can predict pattern of response to corticosteroid treatment
  - Based on pre-treatment data plus the response of serum bilirubin

Score	Bilirubin	PT/INR	Creatinine/ urea	Leucocytes	Age	Albumin	Change in bilirubin (Day 0 to 7)
Maddrey DF*	+	+	–	–	–	–	–
MELD	+	+	+	–	–	–	–
GAHS	+	+	+	+	+	–	–
ABIC	+	+	+	–	+	+	–
Lille	Score is 0–1; a score of ≥0.45 indicates non-response to corticosteroids†						

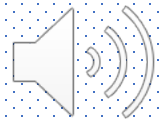
*Modified version (mDF) cut-off value of 32 identifies patients with severe AH and is usually the threshold used for initiating specific therapy;
†In a subsequent analysis <0.16, 0.16–<0.56 and ≥0.56 indicated complete, partial, and null response, respectively
EASL CPG ALD. J Hepatol 2018;69:154–81

Assess risk of infection

Infections were common in patients with AAH .

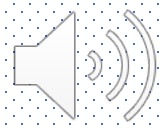
In a meta-analysis of 12 studies including over 1000 patients with severe alcohol-associated hepatitis, the overall rate of infection was 20 percent

- **Should be requested for All patients**
  - Blood cultures (aerobic and anaerobic)
  - Urine culture
  - Chest radiograph
- **Should be requested in special conditions :**
  - **Ascites fluid aspiration and culture**
  - **Sputum exam &culture**
  - **Lumbar puncture**



Assess the need for critical care support

- Admission to ICU may be necessary for patients with:
  - Hemodynamic instability
  - uncooperative
  - Acute alcohol intoxication
  - Hepatic encephalopathy
  - Sepsis



Management of Alcohol-Associated Hepatitis
General measures

- Alcohol abstinence is the cornerstone of therapy
  - Early management of AUD is recommended in all patients with AH
- Considering the potential risk of Wernicke's encephalopathy, supplementation with B-complex vitamins is recommended
- Other general approaches include:
  - Treatment of hepatic encephalopathy (lactulose, rifaximin)
  - Treatment of ascites (salt restriction)
  - Prevention of renal failure in patients with severe AH
    - Avoidance of diuretics and nephrotoxic drugs
    - Volume expansion if needed
    - Use of beta-blockers may increase the risk of AKI



EASL CPG ALD. J Hepatol 2018;69:154–81

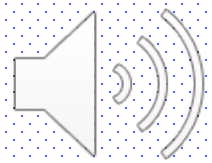
Nutrition

- All patients with ALD are assessed for nutritional deficiencies including protein calorie malnutrition and deficiencies of vitamins, minerals, and trace elements.
- The general nutrition requirements :
  - Eating multiple meals per day, including a nighttime snack, to achieve the following:
    - Total daily energy intake of 35 kcal/kg of body weight
    - Total daily protein intake 1.2 to 1.5 g/kg of body weight
  - Oral ingestion is the preferred method of delivery, although tube feedings (nasogastric or nasoduodenal) are used when oral intake does not meet daily requirements.



Pharmacologic Therapy

- Glucocorticoids
- Acetylcysteine (N-acetylcysteine)

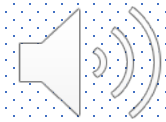


Glucocorticoids

- **Indications and precautions** :
  - severe alcohol-associated hepatitis: (MDF>32 , MELD >20)
  - who are not at high risk for glucocorticoid-related adverse events:
    - (Infection, GI bleeding , Renal failure :Cr>2.5)
    - Its better to be start at 3rd day of admission
- **Dosing and administration** :

  Methylprednisolone, 32 mg / day IV or oral prednisolone 40 mg/day.

  Duration of oral glucocorticoid therapy : 28 days then taper over 2 wks.



Pharmacologic Therapy

Liver Fellow Network
Evidence Corner
@AlexSVogel

Should we treat patients with alcohol-associated hepatitis with N-Acetylcysteine in addition to prednisolone?

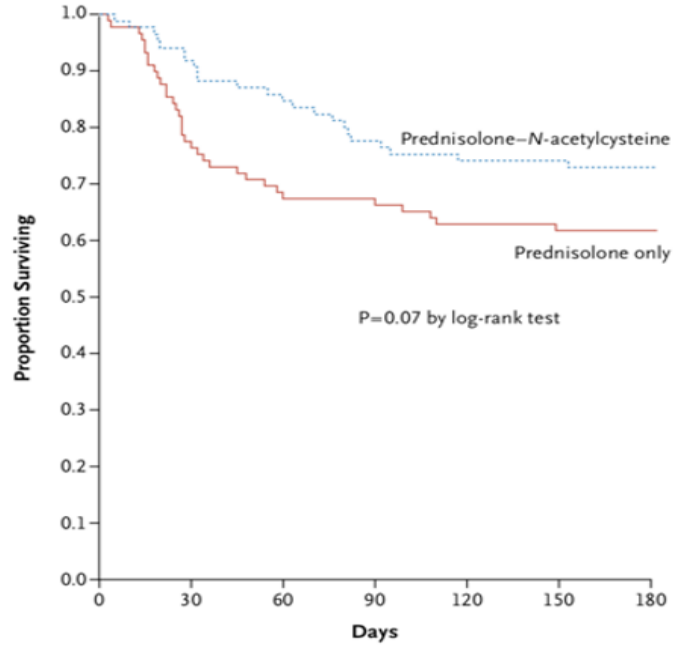
Context: Even when treated with glucocorticoids, patients with severe alcohol-associated hepatitis (AH) have high mortality rates

Article Title: Glucocorticoids plus N-Acetylcysteine in Severe Alcoholic Hepatitis
Authors: Eric Nguyen-Khac, et al.
Journal: New England Journal of Medicine
Year: 2011 **PMID:** 22070475
Study type: multi-center, randomized control trial

P: In patients with severe alcohol-associated hepatitis receiving prednisolone for 28 days
I: does the addition of 5 days of IV N-Acetylcysteine (NAC)
C: as compared to placebo
O: lead to improved survival at 6 months

Who was in it?
174 patients (85 prednisolone + N-Acetylcysteine, 89 prednisolone + placebo) with an MDF ≥32 and biopsy consistent with AH.
Excluded if patient with: hepatorenal syndrome, HCC, uncontrolled bacterial infection, GI bleed (in last 4 days), HCV, HBV, HIV, AIH, HH, Wilson's, AAT, acetaminophen-induced hepatitis, cancer, allergy to N-Acetylcysteine, serious cardiac, respiratory or neuro disease.

What did it show?
In the prednisolone + N-Acetylcysteine arm there was:
- Significantly lower 1-month mortality (8% vs 24%, p=0.006)
- Trend towards lower 3-month (22 vs 34%, p=0.06) and 6-month (27 vs 38%, p=0.07) mortality
- Lower mortality from HRS at 6-months (9 vs 22%, p=0.02
- ** less frequent infections (19% vs 42%, p=0.001)



Strengths

- Multicenter, randomized, placebo controlled trial with intention-to-treat analysis
- AH was biopsy proven

Weaknesses

- May have been underpowered for primary outcome
- Unclear if alternative dosing/duration of NAC would have been superior

Take away:
In patients with severe AH receiving prednisolone, addition of N-Acetylcysteine can be considered and may help decrease risk of infection and short-term mortality

Acetylcysteine (N-acetylcysteine)

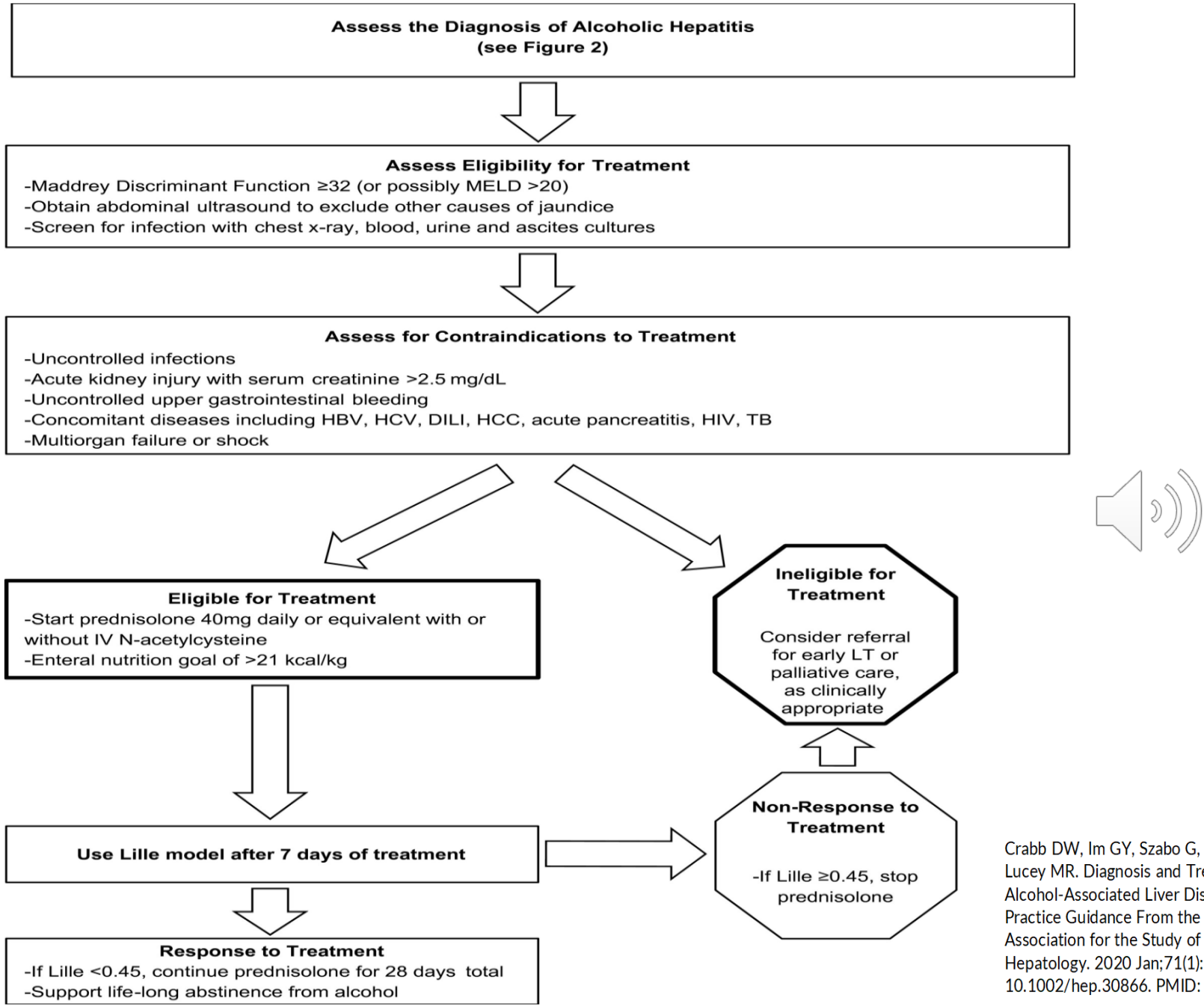
First DAY

- Loading dose: **IV:** 150 mg/kg (max: 15 **g**) in 250 mL of 5% dextrose infused over 30 min.
- Second dose: **IV:** 50 mg/kg (max: 5 **g**) 500 mL of 5% dextrose infused over 4 hours.
- Third dose: **IV:** 100 mg/kg (maxi: 10 **g**) 1000 mL of 5% dextrose infused over 16 hours.

2nd DAY through 5th :

- 100 mg/kg in 1 L of 5 percent dextrose infused over 24 hours;
  Repeat daily for four days.

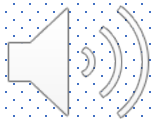




Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases. Hepatology. 2020 Jan;71(1):306-333. doi: 10.1002/hep.30866. PMID: 31314133.

ACG Clinical Guideline 2024

18. We recommend against the use of PTX for individuals with severe AH (strong recommendation, moderate level of evidence).
19. There are insufficient data to determine the role of granulocyte colony-stimulating factor (G-CSF) and microbiome-based therapies in the treatment of severe AH (conditional recommendation, moderate level of evidence).
20. We recommend use of IV N-acetylcysteine as an adjuvant to corticosteroids in patients with severe AH (strong recommendation, moderate level of evidence).



MANAGEMENT OF ALD

- Patients with ALD are suffering from 2 disorders,
  - **Alcohol-associated liver disease (ALD)**
  - **Alcohol use disorder (AUD)**
- The most effective therapy to attenuate the clinical course of ALD and even reverse liver damage is prolonged alcohol abstinence
- Integrated care with a hepatologist and an addiction specialist is more effective than the absence of one



ACG Clinical Guideline

9. In patients with compensated ALD, we recommend use of baclofen as an option for treatment of AUD (strong recommendation, moderate level of evidence).
10. In patients with compensated ALD, we suggest use of acamprosate or naltrexone as an option for treatment of AUD (conditional recommendation, very low level of evidence).
11. In patients with compensated ALD, we suggest use of gabapentin or topiramate as an option for treatment of AUD (conditional recommendation, very low level of evidence).
12. Disulfiram should not be used in the treatment of AUD along any spectrum of ALD (conditional recommendation, very low level of evidence).

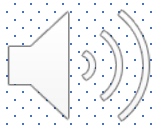
Th



Am J Gastroenterol 2024;119:30–54

Patients who do not respond to therapy

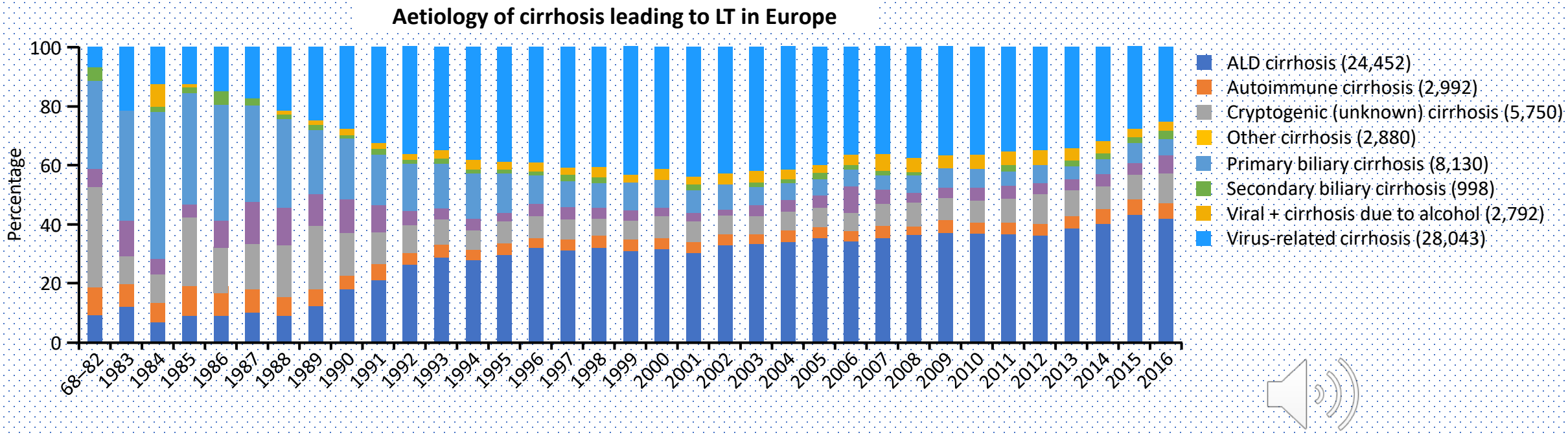
- Continued supportive care (eg, nutrition),
- Evaluation for liver transplantation
  - Liver transplantation may be the only treatment option for patients with severe alcohol-associated hepatitis
- Transition to palliative care.



Liver transplantation

Trends in liver transplantation of ALD

- LT is the most effective therapeutic option for patients with ESLD
  - 1-year post-transplant patient and graft survival is ~80–85%
- Liver outcomes after LT in patients with AUD have improved
  - Graft and patient survival now similar to after LT for other aetiologies
- Alcohol-related cirrhosis represents an increasing proportion of LTs in Europe[1]



1. Data from European Liver Transplant Registry; EASL CPG ALD. J Hepatol 2018;69:154–81

Liver transplantation: Selection of patients for LT

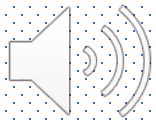
A multidisciplinary approach evaluating medical and psychological suitability for LT is essential

Psychological assessments

- Psychosocial to establish likelihood of long-term abstinence post-LT
  - Limited evidence to support use of the 6-month abstinence rule alone
- Psychiatric evaluation in cases of personality disorder, depression, anxiety, poly-substance abuse or other psychiatric disorders
- Laboratory tests for abstinence may be used in patients on the transplant waiting list

Medical assessments

- Pancreatic function
- Renal function
- Nutritional status
- Central and peripheral neuropathy
- Myopathy and cardiomyopathy
- Encephalopathy/alcohol-related dementia
- Atherosclerosis and ischaemic heart disease
- Neoplastic or pre-neoplastic disease*



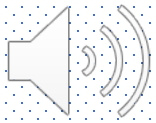
*Particularly URT and GI

EASL CPG ALD. J Hepatol 2018;69:154–81

DISEASE COURSE

Mortality

- Severe hepatitis :
  - longer-term (≥1 year) :35 -70%
  - Short-term (1Mo)10 to 45 %
- Nonsevere hepatitis :
  - one year :2 to 20 percent



Risk factors for increased mortality include

- Older age
- Acute kidney injury
- Persistently elevated bilirubin level
- Elevated INR
- Leukocytosis
- Ongoing alcohol use
- Infection
- Hepatic encephalopathy
- Upper gastrointestinal bleeding
- Systemic inflammatory response syndrome

Summary

- Alcoholic use disorder is a multisystemic disorder
- Alcohol associated hepatitis is a common & serious condition
- Abstinence is the most effective therapy
- Before treatment severity assessment and R/O infection is essential
- Corticosteroid is the most recommended pharmacologic treatment for AH
- LT is the most effective therapeutic option for patients with sever AAH.
- Integrated Multidisciplinary Management is the best approach for advance ALD



Thank you for your attention



(Chogha-Zanbil) Ziggurat : Khuzestan , Shoosh