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Liver Potpourri

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- Neither myself, nor any of the faculty, planners or individuals in control of the content for this educational activity have any financial relationship(s) to disclose with ineligible companies whose primary business is promoting, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Learning Objectives – at the end of this talk participants should be able to:

1) **Describe the management of common decompensations of liver disease**

2) **Recognize the modern approach to alcohol as it relates to liver transplantation**

3) **Explain the misunderstood coagulopathy of liver disease**

Liver Pearls: Choose Your Own Adventure

- **I've heard NASH is now called MASH. What do I need to know about this?**
- **Is there a mandated 6 month rule of sobriety for patients with alcohol associated liver disease who are being considered for liver transplantation?**
- **When caring for patients with cirrhosis, what medical comorbidities should I address to optimize transplant candidacy?**
- **Is paracentesis safe if a patient with cirrhosis has a high INR?**
- **When should I check a serum ammonia level in patients with hepatic encephalopathy?**
- ***Conclusions***

New Nomenclature

- Fatty Liver Disease (FLD) = Steatotic Liver Disease (SLD)
- Non Alcoholic Fatty Liver Disease (NAFLD) = Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)
- Non-alcoholic Steatohepatitis (NASH) = Metabolic Dysfunction Associated Steatohepatitis (MASH)

Question

- A) I rarely screen my patients for MASLD
- B) I screen all of my patients for MASLD
- C) I specifically screen only patients with type 2 diabetes and central obesity for MASLD
- D) It depends – sometimes I screen patients for MASLD, but without a uniform approach

Why is MASLD important?

- Most common cause of abnormal liver tests in United States
- Approximately 20-30% of the general population estimated to have MASLD

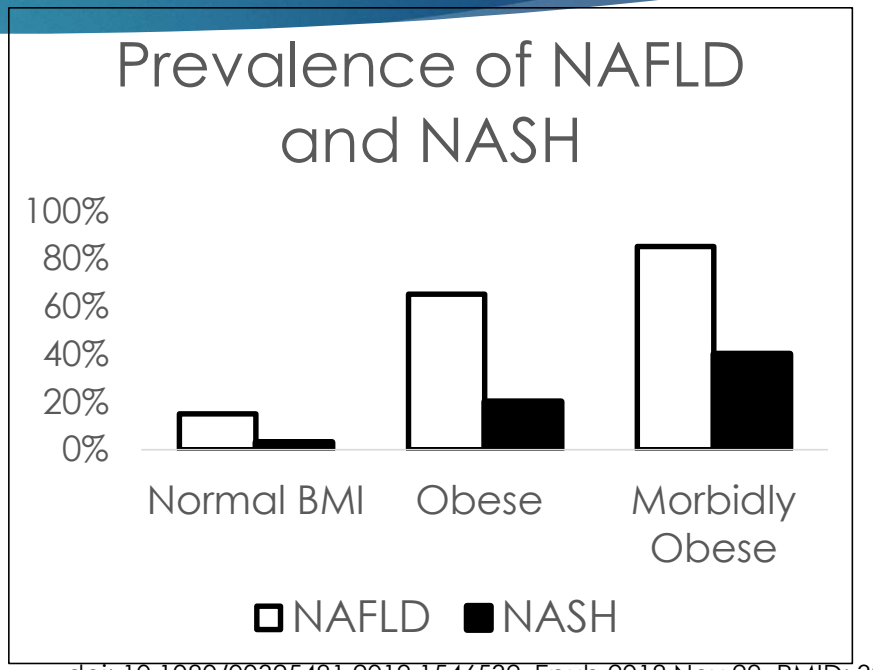
1 in 5 MASLD have MASH

1 in 25 progress to advanced fibrosis/cirrhosis

- MASH (not isolated steatosis) is associated with increased overall mortality

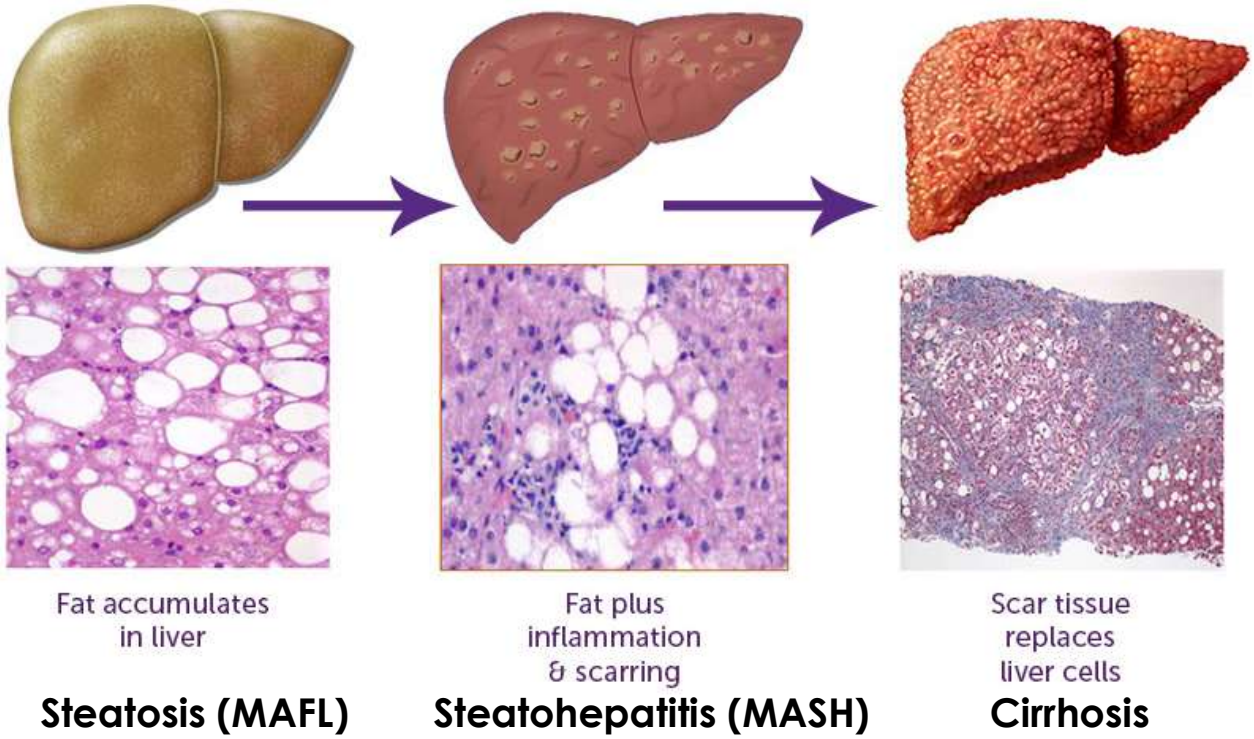
Who is at Risk?

- **Obesity**
- **Diabetes mellitus type 2**
- Hypertension
- Hyperlipidemia
- Hypothyroidism
- Polycystic ovary syndrome
- Obstructive sleep apnea
- Hypopituitarism
- Hypogonadism
- Age, sex, ethnicity



doi: 10.1080/00325481.2019.1546532. Epub 2018 Nov 29. PMID: 30496690.

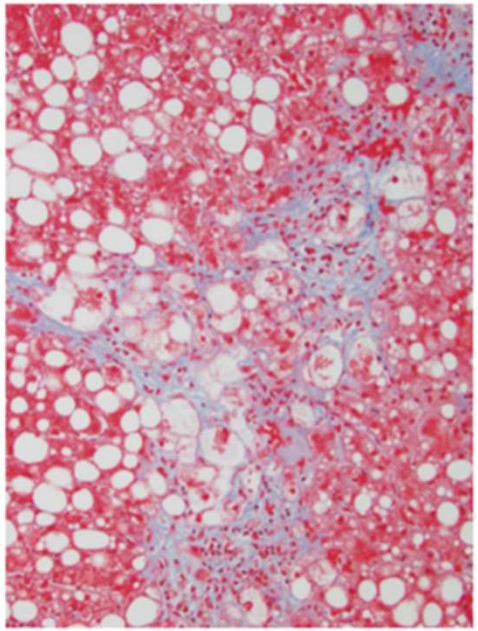
The spectrum of MASLD



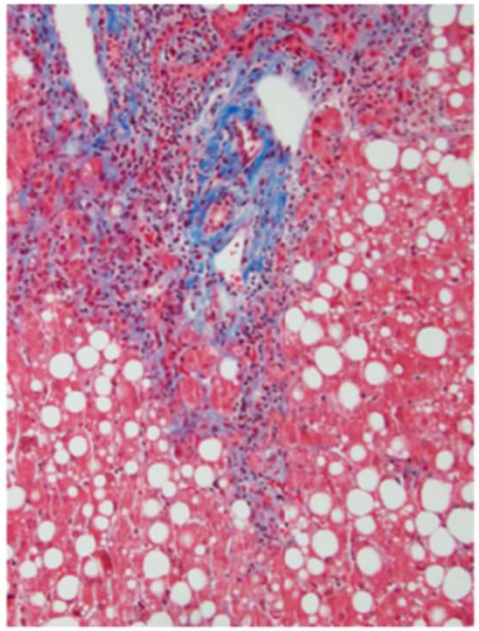
Steatosis (MAFL) **Steatohepatitis (MASH)** **Cirrhosis**

Adapted from doi: 10.1136/bmj.i4428. PMID: 27605111.

MASLD Stage

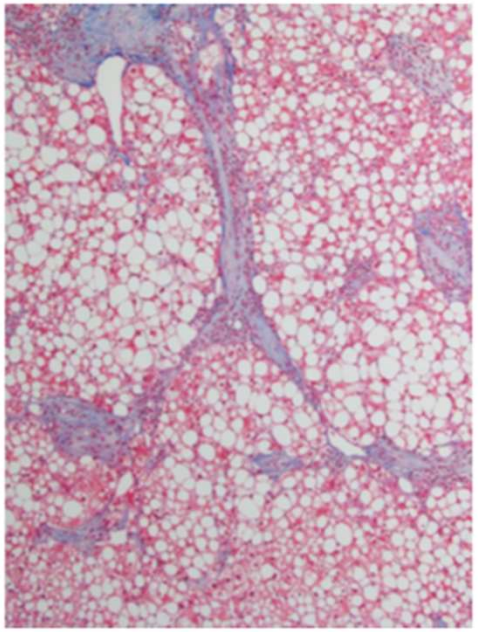


Perisinusoidal fibrosis

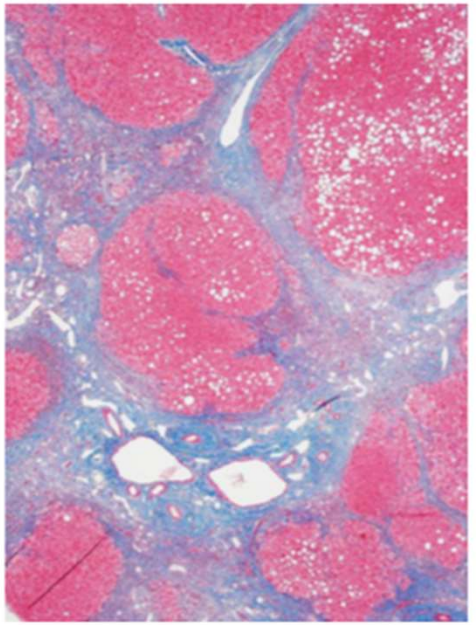


Periportal fibrosis

(Stage 1-2)



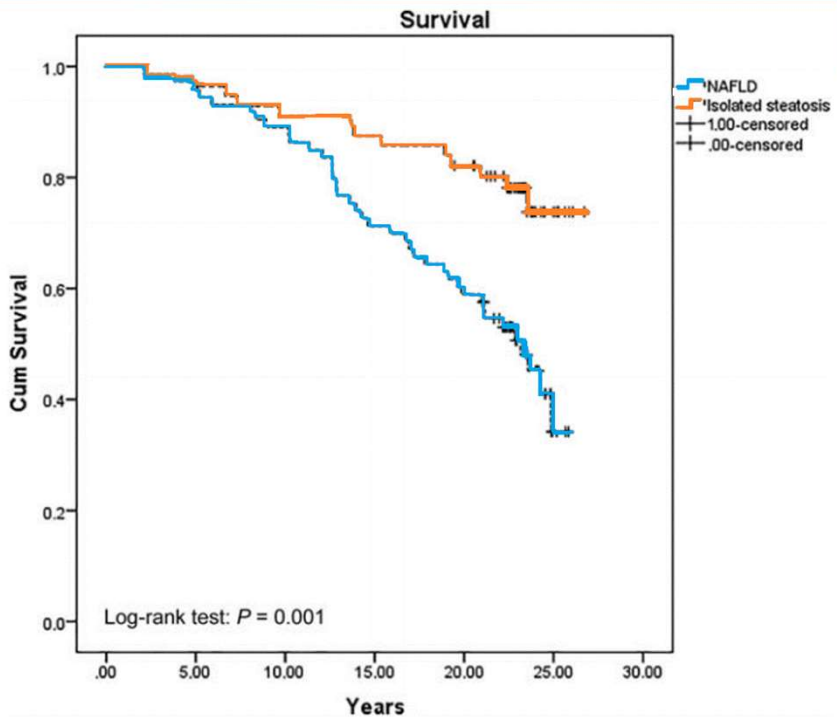
Bridging Fibrosis (Stage 3)



Cirrhosis (Stage 4)

doi: 10.1001/jama.2015.5370. 2015 Oct 13. PMID: 26057287.

MASH is associated with higher mortality

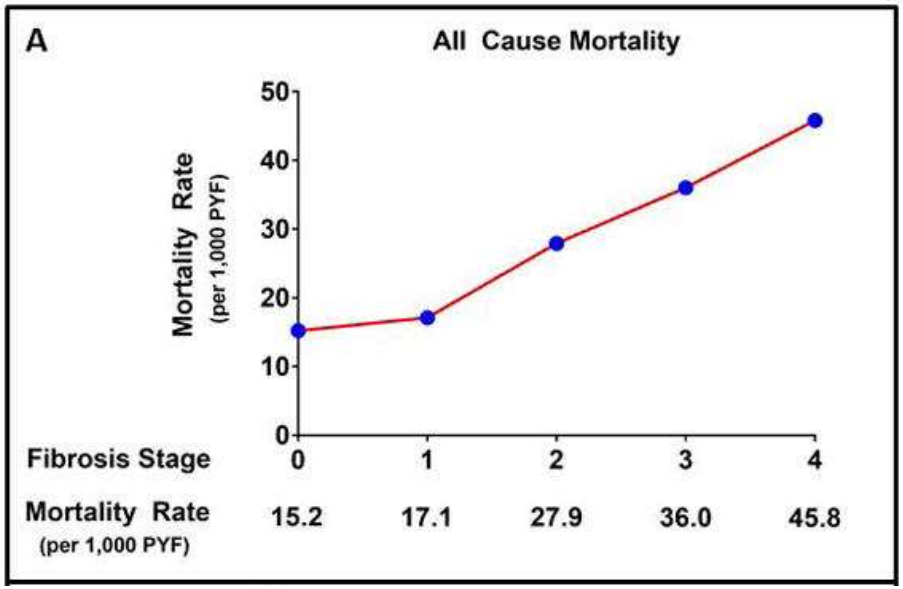


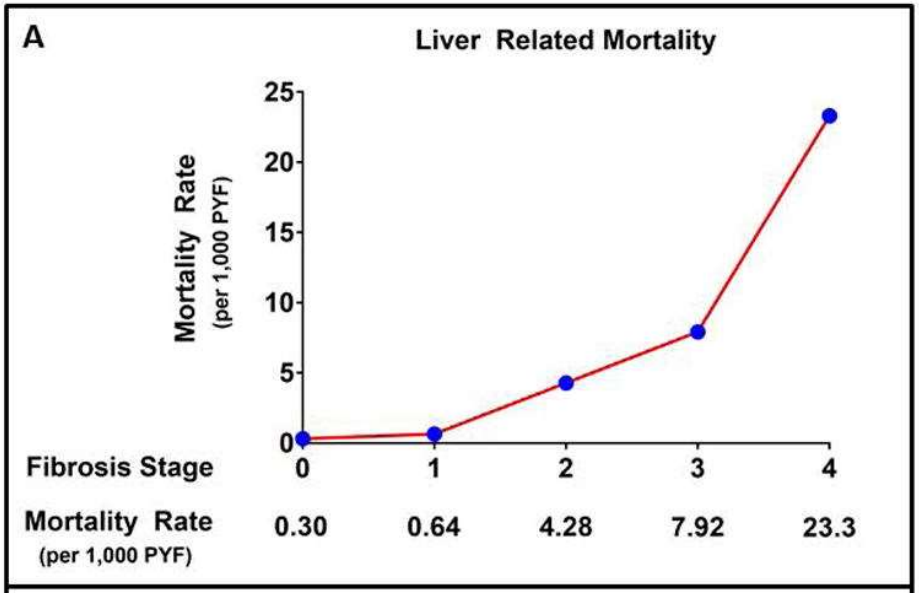
Causes of death in MASH:

1. **Cardiovascular disease (15.5%)**
2. Non-liver malignancy (5.6%)
3. Liver disease (2.8%)

doi: 10.1002/hep.21327. PMID: 17006923.
doi: 10.1002/hep4.1134. PMID: 29404527; PMCID:

MASH with Fibrosis is associated with higher mortality





doi: 10.1002/hep.29085. Epub 2017 Mar 31. PMID: 28130788 .

How to We Approach MASH in 2023?

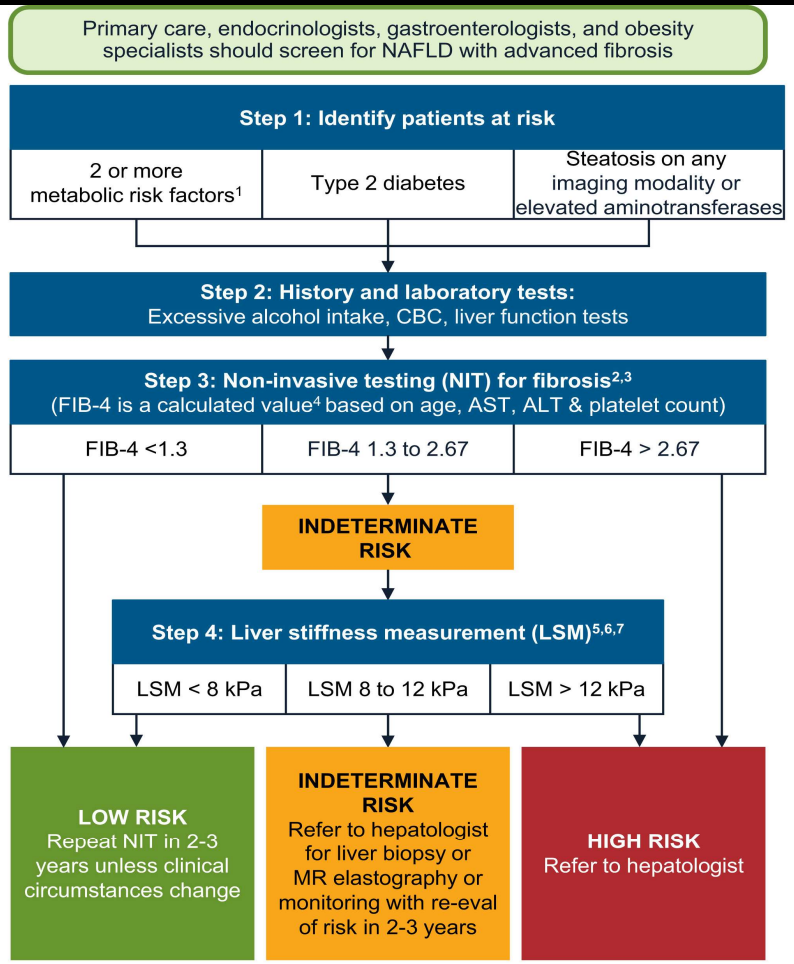
- Massive Problem
- Important health implications
- How do approach this issue?
  - Screen High Risk Groups to low risk vs high risk
  - For high risk
    - Aggressive weight loss
      - Bariatric
      - Pharmacologist

doi: 10.1002/hep.29085. Epub 2017 Mar 31. PMID: 28130788 .

Screening for Advanced Fibrosis: Call-to-Action

- **American Gastroenterological Association (AGA)** assembled a multi-D panel of experts to develop New Clinical Care Pathway published in Nov 2021
- Experts recommend focus be moved toward screening for MASH with fibrosis given the association with both liver and non-liver mortality with fibrosis degree
- Focus on identifying at-risk individuals for MASLD and having simple ways to classify as low, intermediate, and high risk for significant fibrosis

AGA Clinical Care Pathway 2021



Find AGA's NASH Clinical Care Pathway App for iOS and Android mobile devices at nash.gastro.org. Scan this QR code to be taken directly to the website.

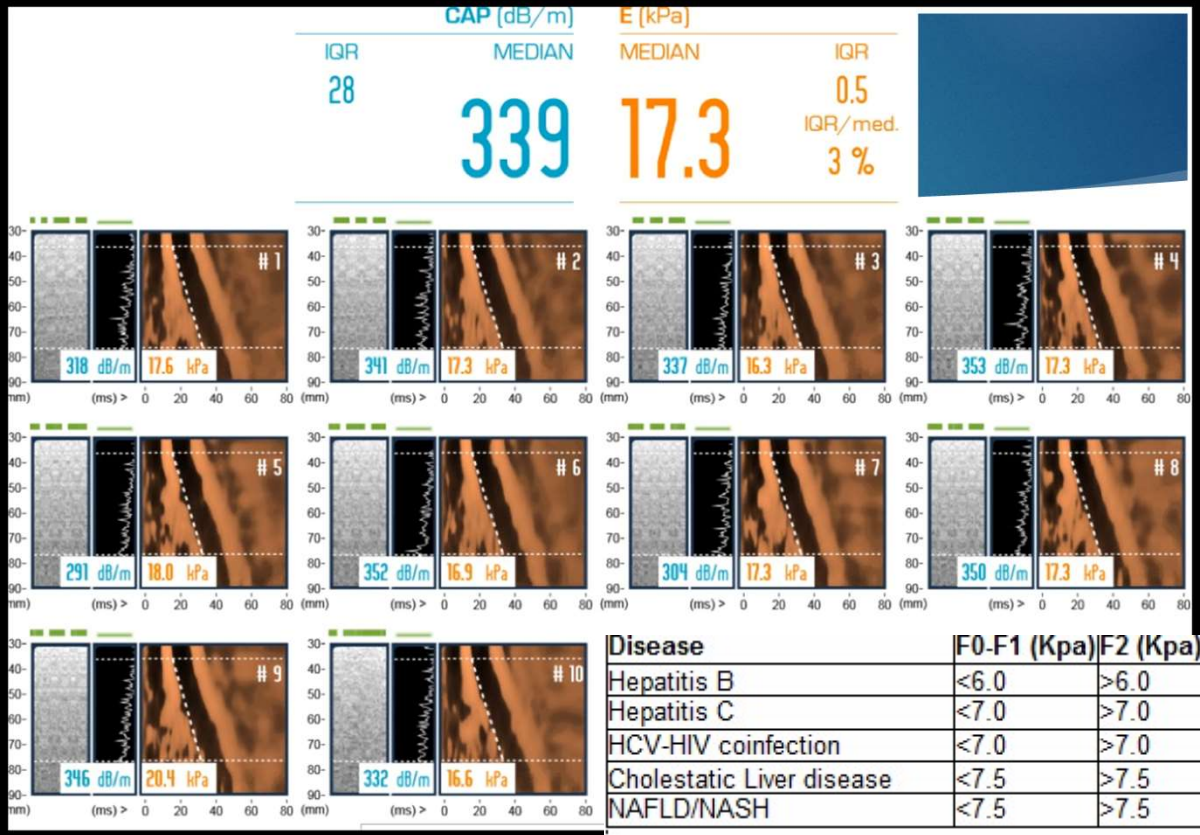
doi: 10.1053/j.gastro.2021.07.049. Nov 2021. PMID: 34602251

Transient Elastography

- FibroScan®is based on patented technology: **V**ibration **C**ontrolled **T**ransient **E**lastography (VCTE™)
- Allows painless and simultaneous measurement of two quantitative parameters:
  - Liver stiffness expressed in kPa
    - ➔ Correlated to liver fibrosis
  - Controlled Attenuation Parameter (CAP™) expressed in dB/meter
    - ➔ Correlated to liver steatosis
- Both quantitative parameters are assessed on the same volume of liver tissue (3cm³)
  - 100 times larger than liver biopsy

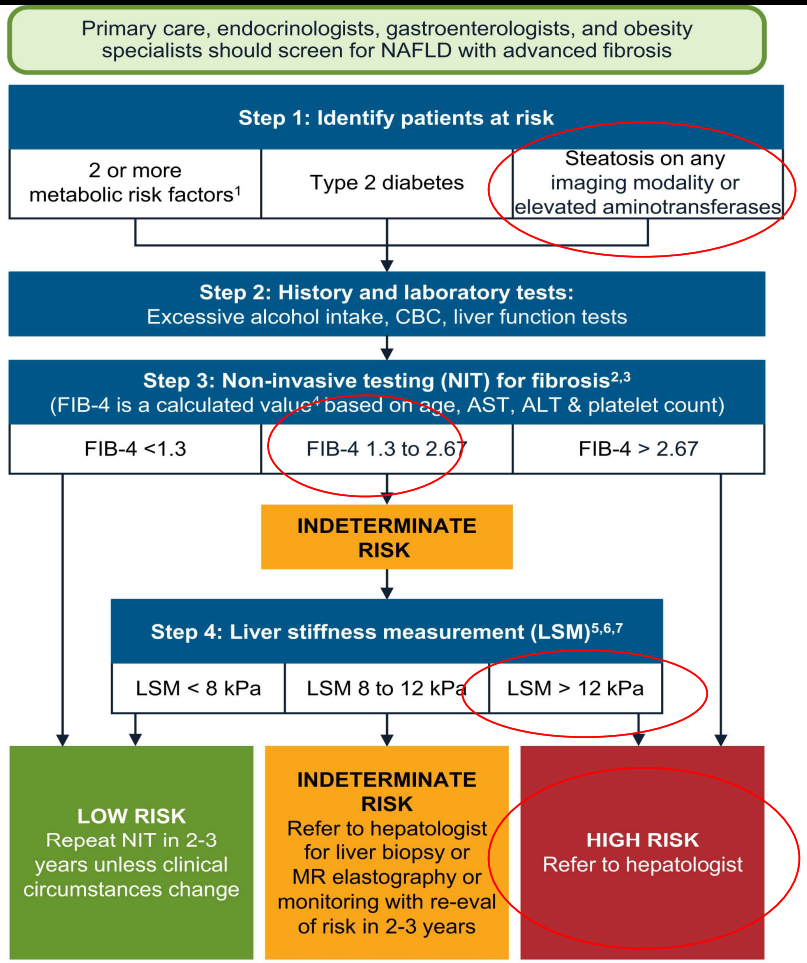
FibroScan® 502 TOUCH

Fibroscan



Disease	F0-F1 (Kpa)	F2 (Kpa)	F3 (Kpa)	F4 (Kpa)
Hepatitis B	<6.0	>6.0	>9.0	>12.0
Hepatitis C	<7.0	>7.0	>9.5	>12.0
HCV-HIV coinfection	<7.0	>7.0	>11.0	>14.0
Cholestatic Liver disease	<7.5	>7.5	>10.0	>17.0
NAFLD/NASH	<7.5	>7.5	>10	>14.0

AGA Clinical Care Pathway 2021



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Who not to send to Hepatology

- Incidental steatosis with normal labs with low Fib4 (<1.3)
- Extremely low risk for significant fibrosis – can be reassured these patients are low risk
- Those at risk should get serial non-invasive testing (Fib-4) to monitor risk. If Fib 4 > 1.3 should send for Fibroscan

What to do: Lifestyle Changes

- **Weight loss!**
  - Goal >10%
    - 100% steatosis regression
    - 90% resolution of NASH
    - 81% fibrosis regression
- **Diet**
  - No one specific diet
  - Hypocaloric diet to achieve >5-10% weight reduction
- **Control of metabolic co-morbidities**
  - DMII, HL, HTN, etc
- **Exercise**
- **Limit/avoid alcohol**

doi: 10.1016/j.jhep.2017.05.016. Epub 2017 May 23. PMID:

Points for Emphasis with Lifestyle Changes

- Weight loss is the cornerstone of the treatment of NASH
- Loss of even 5-10% can have meaningful improvements in histology
- Limit simple sugars
- Limit large portion sizes
- The goal is long term healthy habits
- Exercise is important even without weight loss

doi: 10.1016/j.jhep.2017.05.016. Epub 2017 May 23. PMID:

Other considerations

- Bariatric surgery
  - Not an established option to specifically treat NASH
  - AASLD guidance – can be considered in otherwise eligible obese patients
  - Type, safety and efficacy are not established
- **Pharmacologic treatment options**
  - There are no FDA approved treatments for NASH
- Clinical trials

Pharmacologic Treatment Options for MASH

- **There are no FDA approved treatments for MASH**
- Medications with *potential* benefit based on randomized controlled trials:
  - Vitamin E
  - Pioglitazone
  - GLP-1s
  - SGLT2 inhibitors

	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	**INDETERMINATE RISK** FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	**HIGH RISK**[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

doi: 10.1053/j.gastro.2021.07.04
9. Nov 2021. PMID: 34602251

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*

- Phase 2 randomized controlled trial
- 72 weeks Semaglutide (dose 0.1, 0.2, 0.4-mg) vs Placebo in Stage F1, F2, F3 NASH
- Primary end point: Resolution of NASH with no worsening of fibrosis

DOI: 10.1056/NEJMoa2028395

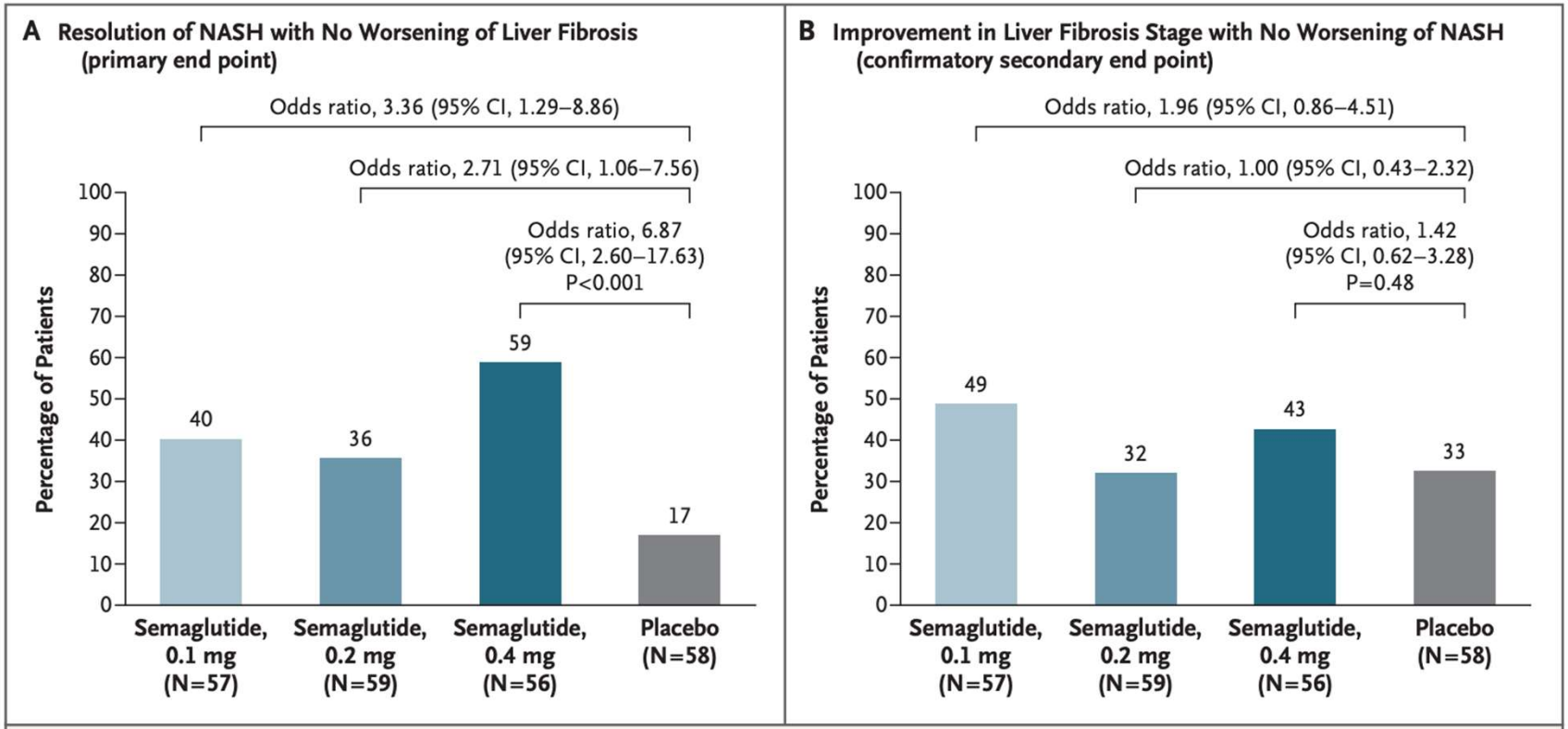


Figure 1. Primary and Secondary Confirmatory End Points.

How to Approach in 2023:

- Assess at risk patients for risk for MASH with significant fibrosis by non-invasive testing (low, intermediate, high) -- **Fib4 >1.3**
- Consider referral for intermediate and high risk patients
- Educate patient on diagnosis and stress impact on overall health
- Multi-disciplinary approach to weight loss
  - Refer to a weight loss program
- Endocrinologist – Use medication with efficacy in NASH: **GLP 1** and Pioglitazone
- Consider clinical trials and referral to bariatric surgery in select cases

Assessment for CVD
ACG 2016 Guidelines

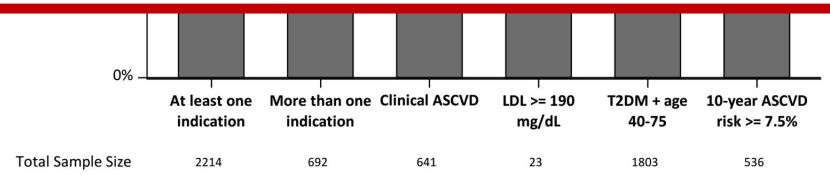
- NAFLD is a predictor of CVD beyond Metabolic Syndrome
  - HR 1.87 [1.2-2.6] for incident CVD
- Screening for CVD ***mandatory*** in NAFLD
  - How to screen remains unclear…
- Statin use is ***NOT*** prohibitive in NAFLD or NASH
  - "…not at higher risk for serious liver injury from statins. Thus, statins can be used to treat dyslipidemia…"
  - Pravastatin in decompensated cirrhotics (***NOT*** CYP3A4)

Targer G et al. NAFLD Is Independently Associated With an Increased Incidence of Cardiovascular Events in Type 2 Diabetic Patients. Diabetes Care 2007

Statins are underutilized in MASLD
ACG 2016 Guidelines

Women have lowest rates of statin

CLINICAL PEARL: Statins prevent CVD in MASLD…,
no contraindication* even in decompensated cirrhosis
(use pravastatin [10mg] or low dose atorvastatin [20mg])



Thomson MJ et al. Prevalence and Factors Associated With Statin Use Among Patients With NAFLD in the TARGET-NASH Study. CGH 2021

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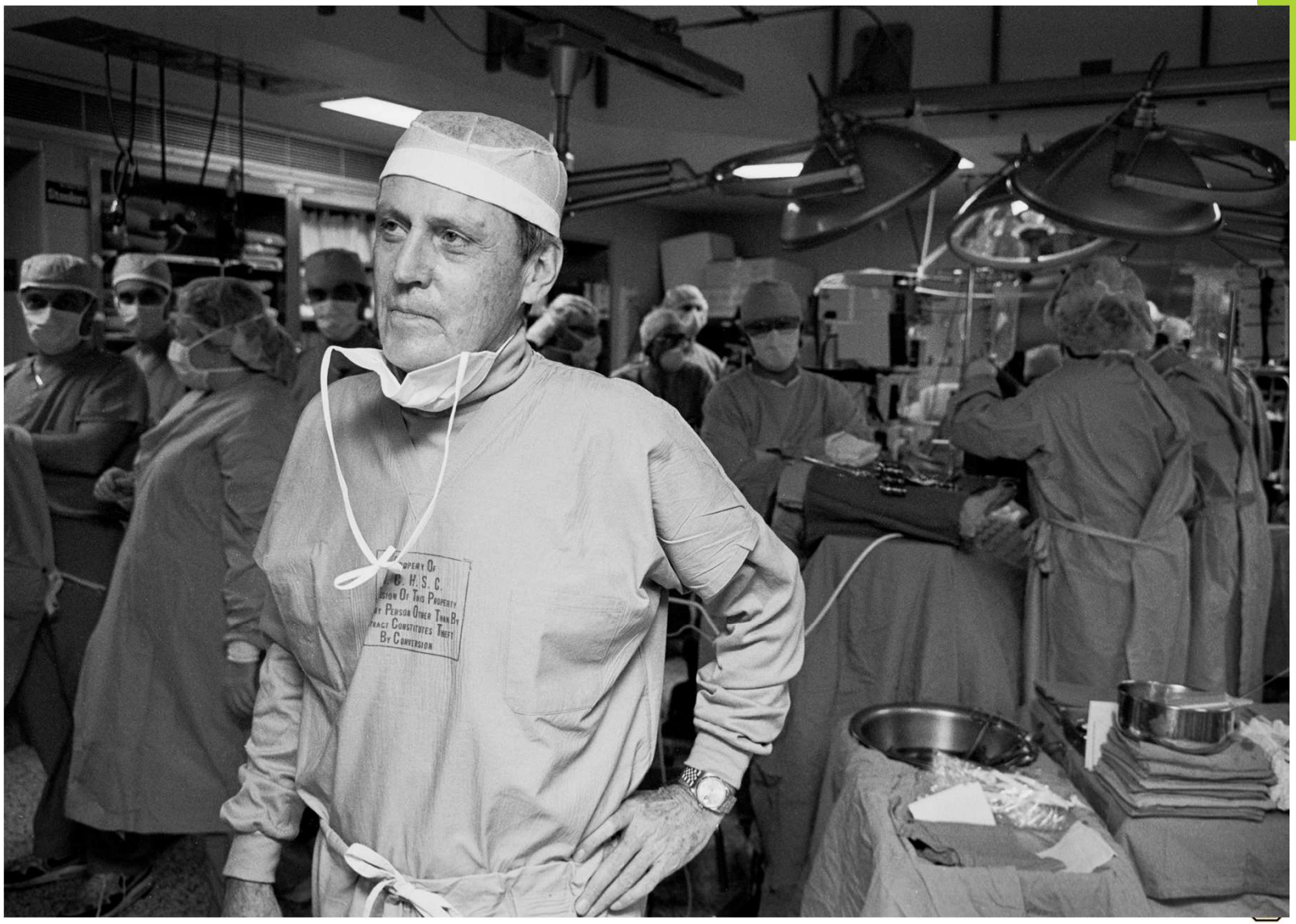
Liver Pearls: Choose Your Own Adventure

- **I've heard NASH is now called MASH. What do I need to know about this?**
- **Is there a mandated 6 month rule of sobriety for patients with alcohol associated liver disease who are being considered for liver transplantation?**
- **When caring for patients with cirrhosis, what medical comorbidities should I address to optimize transplant candidacy?**
- **Is paracentesis safe if a patient with cirrhosis has a high INR?**
- **When should I check a serum ammonia level in patients with hepatic encephalopathy?**
- ***Conclusions***

What is the mandated period of sobriety to qualify for liver transplant?

- A) 1 month
- B) 3 months
- C) 6 months
- D) 12 months
- E) There is no mandated period of sobriety



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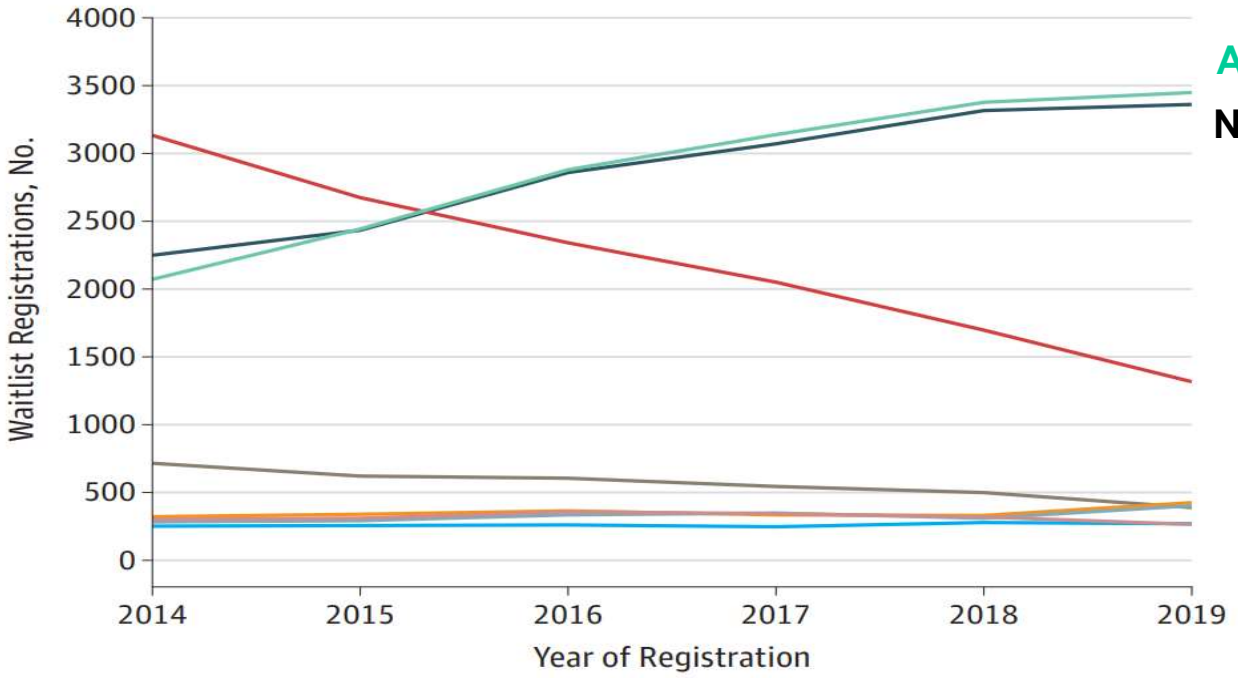
Changing Burden of Liver Disease in Transplant



Wong et al. JAMA Netw Open. 2020.

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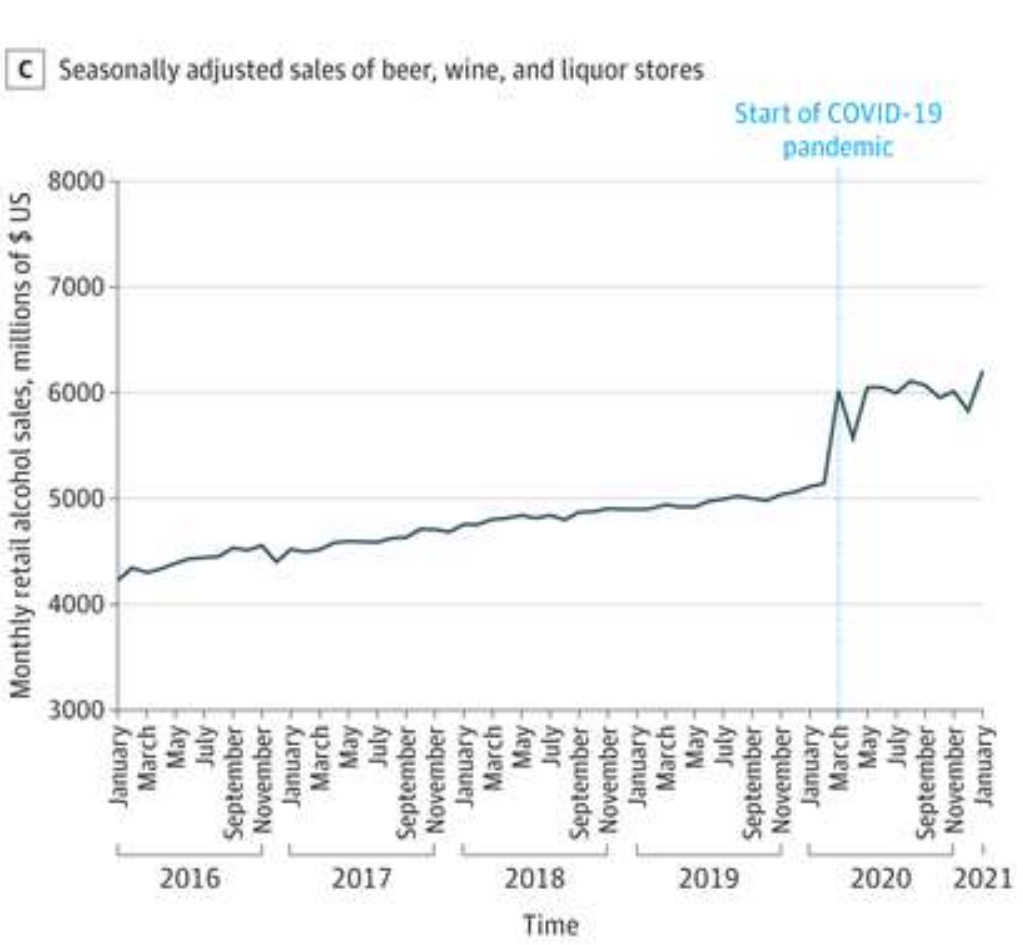
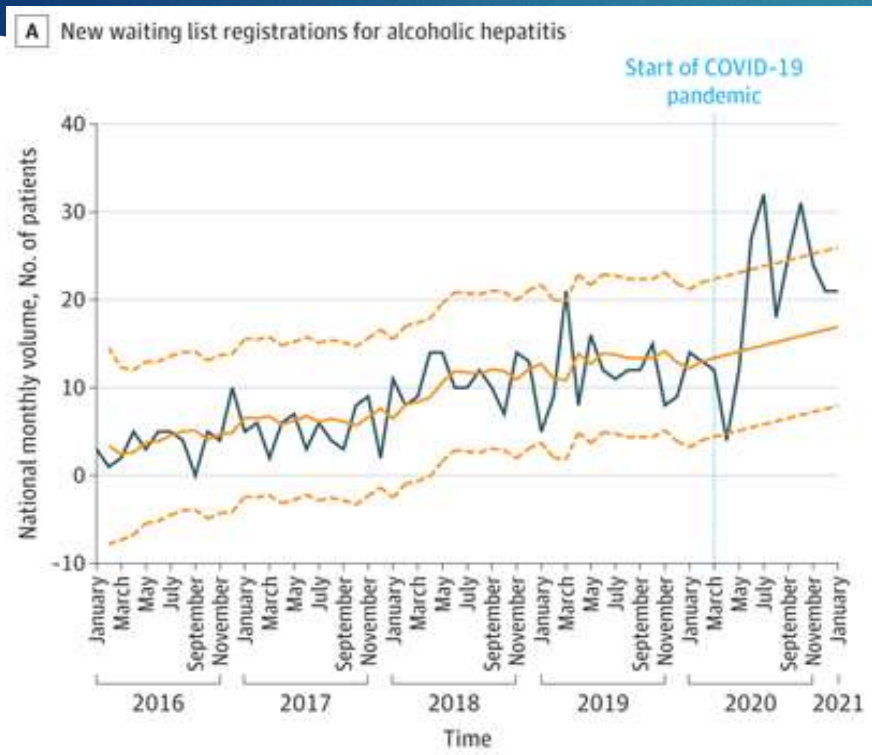
Alcohol Consumption Trends in USA

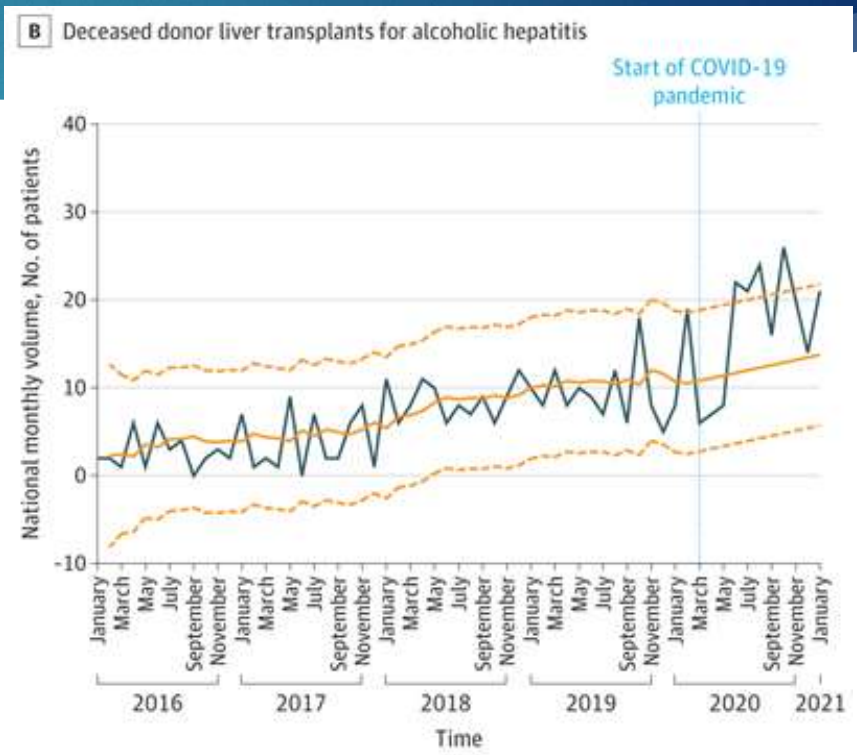
60% of people increased their alcohol consumption since the start of pandemic



Anderson MS, et al. *JAMA Netw Open.*2021;4(10)

Transplant for Alcoholic Hepatitis





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Standard Alcohol Unit

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Did You Know?
The Lines on a Solo Cup are Measurement Marks

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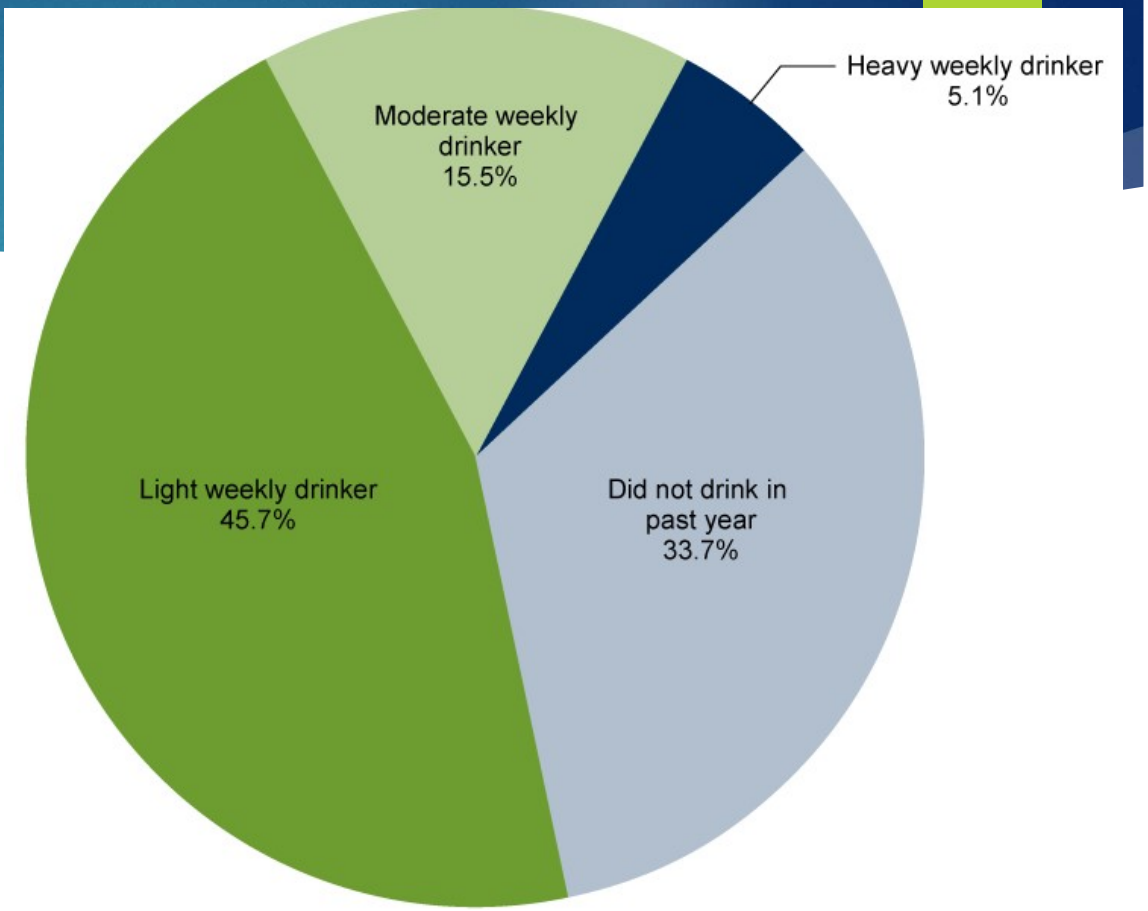
High Risk Alcohol Consumption



Binge Drinking

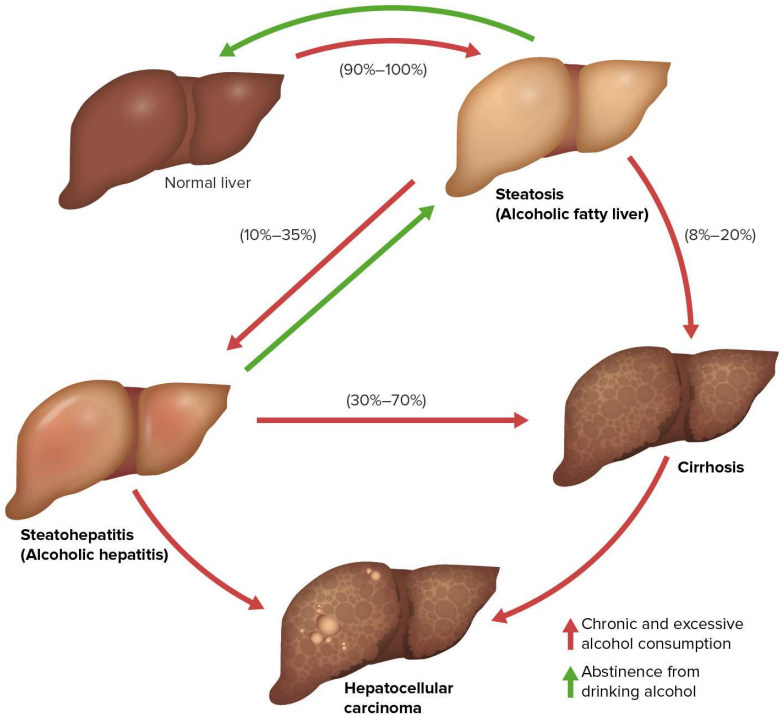
Consuming 5 or more alcoholic drinks for males or 4 or more for females on the same occasion

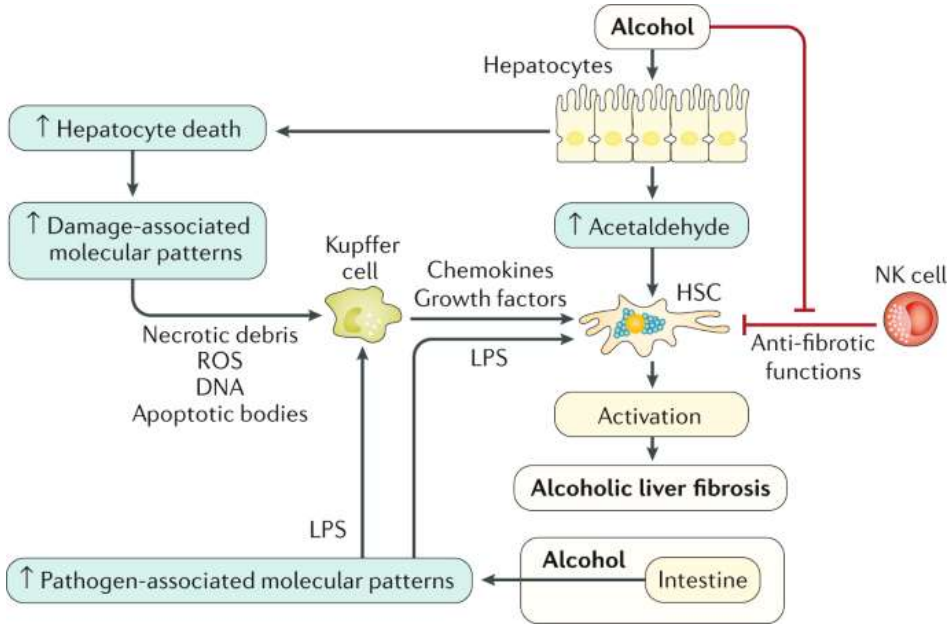
Heavy Drinking

- Men > 4 drinks on any day or more than 14 drinks per week
- Women > 3 drinks on any day or more than 7 drinks per week

arcr.niaaa.nih.gov

Alcohol Associated Liver Disease (ALD)





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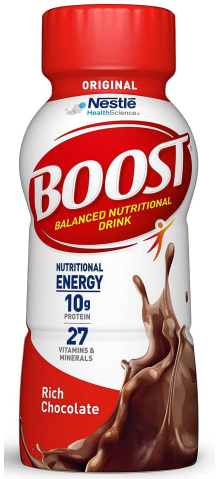
Alcoholic Hepatitis (AH)

- **Diagnosis**
  - Consumption of > 40 (female) or 60 (male) grams of alcohol/day for > 6 months
  - < 60 days of abstinence
  - Onset of jaundice < 8 weeks
  - AST > 50, AST/ALT > 1.5 with both values < 400
  - Bilirubin > 3 mg/dL
- **Management**
  - Nutrition
  - Abstinence
  - Steroids
- **Outcomes**
  - Maddrey Discriminant Function (DF)
  - Lille Score
  - MELD Score

Nutrition in AH

- Total calories
  - ~25–40 Kcal/kg body weight/day
- Protein:
  - ~1.2–1.5 g/kg per day
- Supplement daily oral intake with enteral feedings
- Replace vitamins, minerals, electrolytes as indicated



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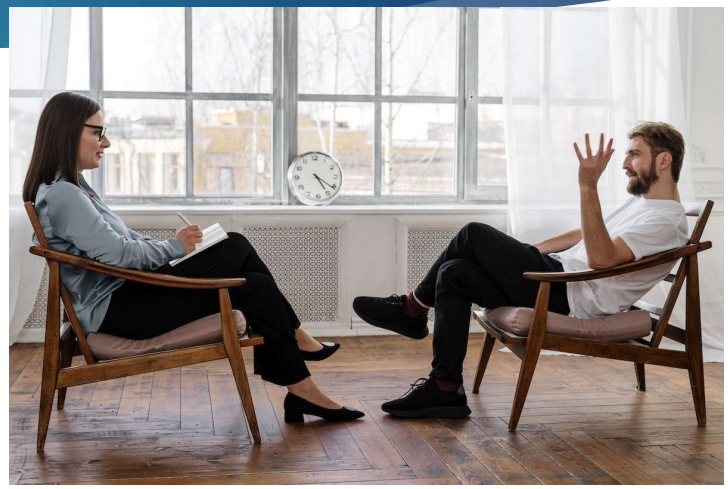
McClain et al Clinical Liver Disease

AUD Counseling

- Types of treatment
  - Inpatient rehabilitation
  - Intensive outpatient therapy (IOP)
  - Group therapies
  - Individual therapy
  - Mutual aid societies (such as AA)
- No modality is consistently superior
- Early alcohol rehabilitation reduces the risk of hospital readmission, relapse, and death
- Integrating AUD treatment and liver care in clinic improves abstinence rates

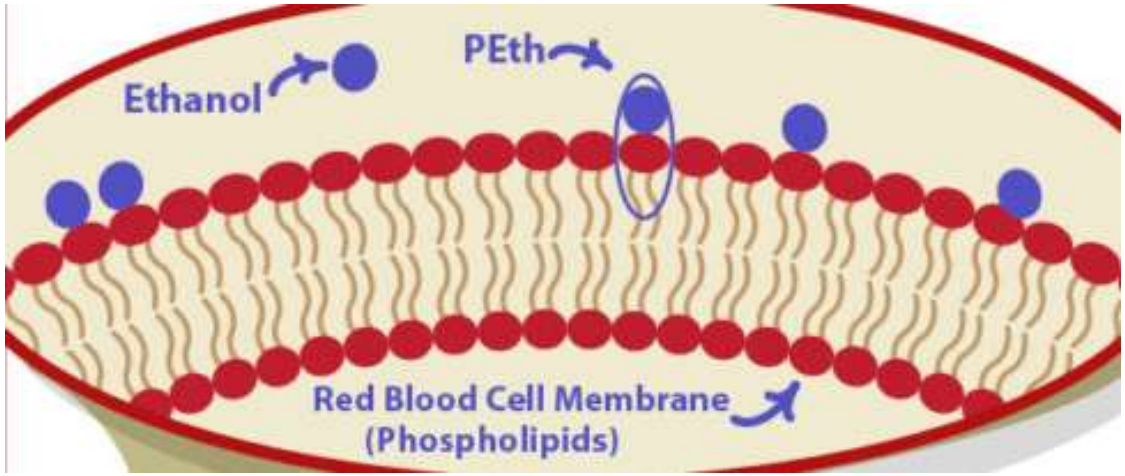


AUD Medical Management

Medication	Dosing	Mechanism of Action	ALD Considerations
Naltrexone	50 mg/d orally or 380 mg monthly SQ	Opioid receptor antagonist	1.Not studied in patients with ALD 2.Hepatotoxicity concerns
Acamprosate	666 mg TID	NMDA receptor antagonist	1.Not studied in patients with ALD 2.No reported instances of hepatotoxicity
Gabapentin	600-1,800 mg/d	Modulates GABA activity through action at presynaptic calcium channels	1.Not studied in patients with ALD 2.Monitor closely for renal dysfunction and worsening mental status/sedation
Baclofen	30-60 mg/d	GABA-B receptor agonist	Single RCT in patients with ALD showed benefit
Topiramate	75-400 mg/d	GABA action augmentation, glutamate antagonism	Not studied in patients with ALD

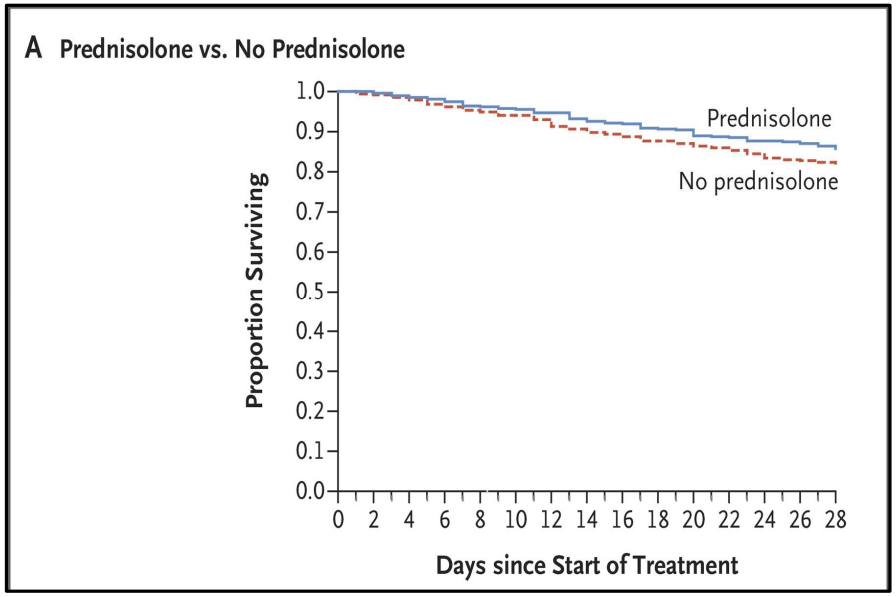
Phosphatidylethanol (PEth)

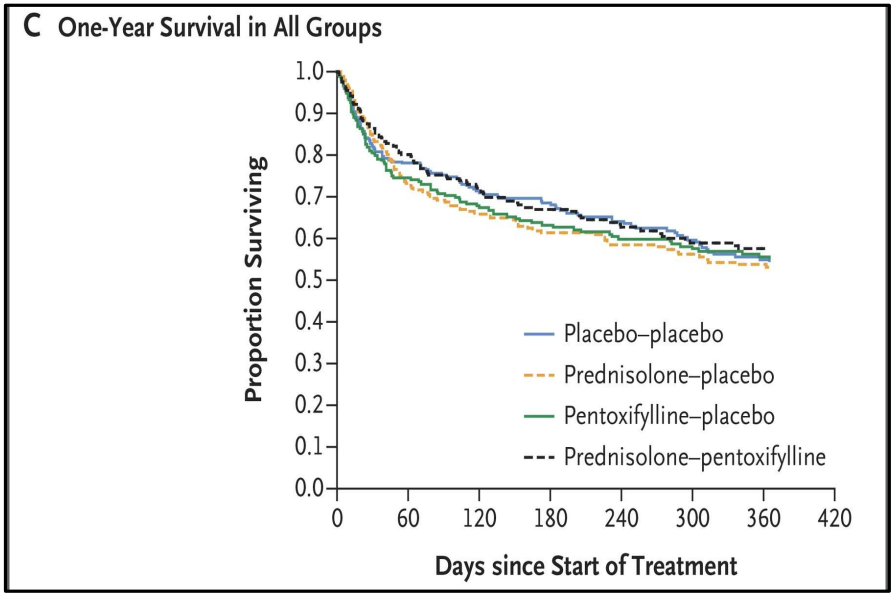
- Phospholipid formed by the reaction of phosphatidylcholine with ethanol in RBC cell membrane
- Half-life ~10-14 days
- Cutoff >20 has a sensitivity of 100% and specificity of 96%
- Blood transfusion can cause false positive (low level)
- Use as a catalyst for discussion rather than to "catch" patient



Steroids for AH

STOPAH Trial





Inclusion: AH + Maddrey Discriminant Function ≥ 32

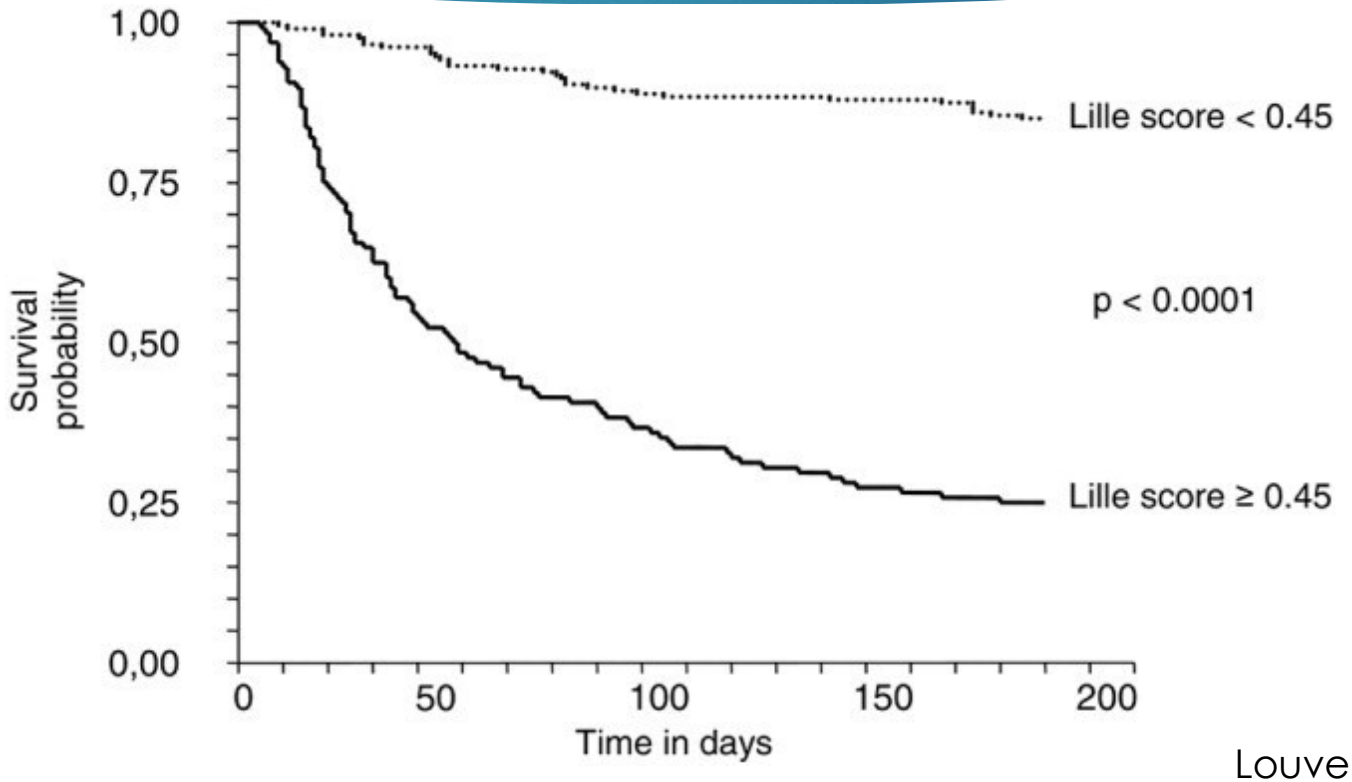
Exclusion: infection, renal failure, GI Bleed

Thursz et al *NEJM* 2015

Steroids for AH

Lille Score

(Day 4 or 7)



Louvet et al *Hepatology* 2

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Refer AH for Transplant?

- Who:
  - Severe steroid refractory (or intolerant) alcoholic hepatitis
  - No previous knowledge of their liver disease
  - No concomitant substance use disorder
  - Favorable "psychosocial profile"
- When?

"6-month Rule"

- Provides time to determine if liver function could improve and avoid transplant
- 6 months of sobriety is a poor predictor of alcohol relapse
  - Encourages dishonesty
  - Does not encourage AUD treatment
- Unrealistic barrier to transplant
  - 75-90% of deaths occur within the first 2 months

Predictors of Alcohol Relapse

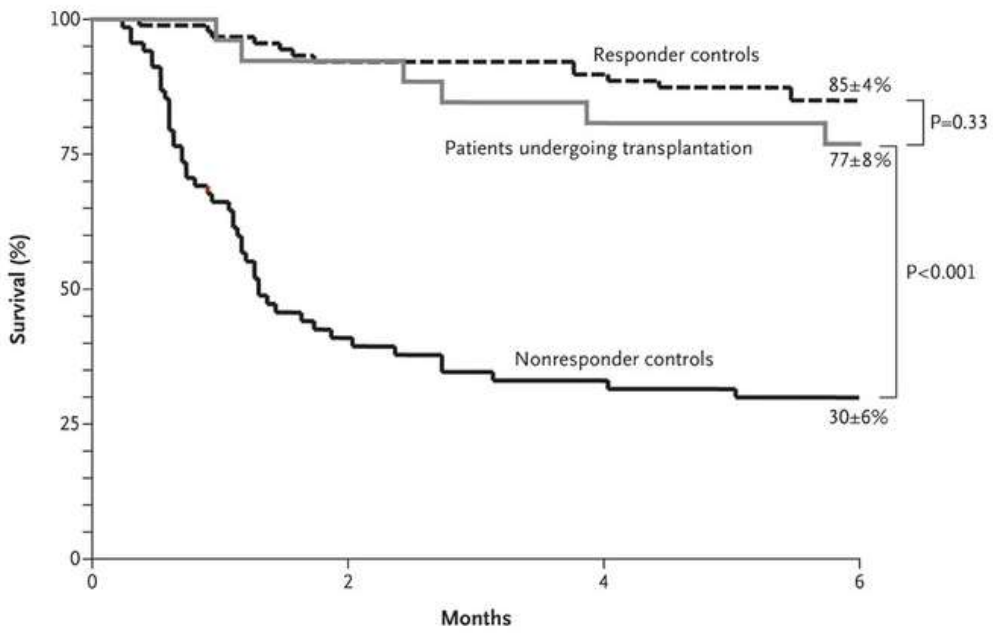
Protective Factors

- Insight to their addiction
- Social support
- Substitute activities
- Improved self-esteem or hope
- Perception of negative consequences of alcohol use

Negative Factors

- Psychotic disorders
- Personality disorders
- Family history of alcoholism
- Alcohol dependence diagnosis
- Repeated attempts at rehabilitation
- Unremitting substance abuse despite physical and social consequences
- Social isolation

Early Liver Transplant for AH



- 26 patients
- Inclusion
  - Severe AH, non-response to treatment
  - First liver decompensation
  - +Close support
  - Absence of severe coexisting psychiatric disorder
  - Universal agreement among providers
  - < 2% of patients screened were transplanted
- 6-month survival
  - LT recipients: 77%
  - Non-LT recipients: 23%

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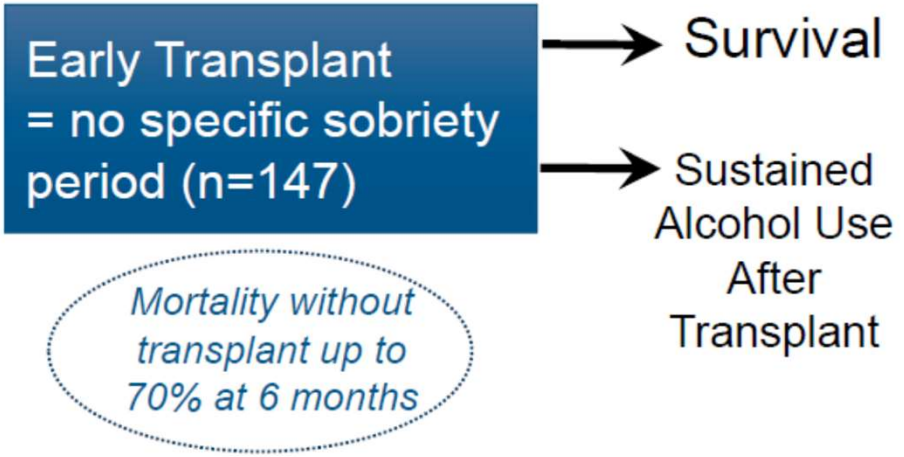
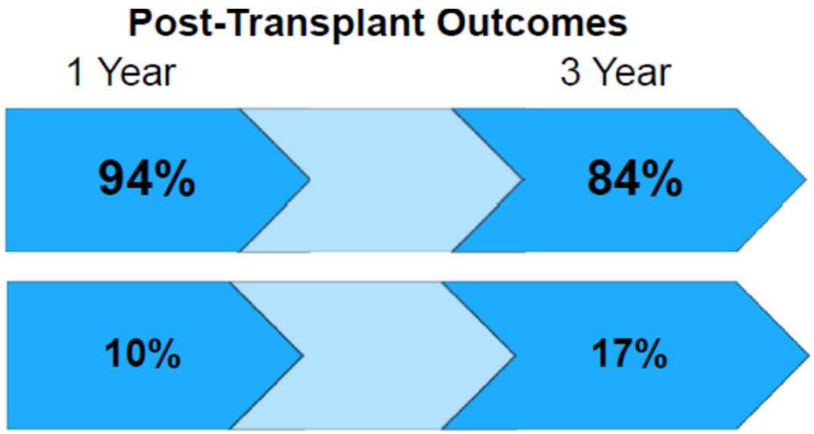
ACCELERATE AH

- 147 patients from 12 US centers (2006-2017) transplanted for steroid refractory autoimmune hepatitis
- Median duration of alcohol abstinence prior to transplant was 55 days
- Median MELD-Na was 39





LT Requirements for AH (UCH)

- Candidates must admit alcohol use:
  - Patients denying significant alcohol use either don't have ALD or are in denial
  - Demonstrate insight & commitment to lifelong abstinence
  - Agree to and believe that treatment will be helpful
- Lack of untreated co-existing major psychiatric disorder or other untreated addiction
- Able/willing to engage in the evaluation process
  - No grade 3-4 encephalopathy or too sick to engage with our psychosocial team
  - Leave the hospital to initiate alcohol counseling and screening or be a candidate for "alcohol high risk pathway"
- Strong social support, housing & compliance
- No other contraindications to transplant

"High-Risk" Alcohol Pathway

- "High-risk" patients that do not have time/ability to complete requirements prior to transplant
  - No sobriety time limits
  - Signed agreement for counseling after transplant
  - Post-transplant
    - Monthly visits with transplant team
    - Monthly PEth tests for 1 year
- ~90% sobriety at 1 year

Requirements

- No major psychiatric conditions
- No prior relapses
- No prior major complication of AUD
- First hepatic decompensating event
- Must acknowledge role of EtOH in ALD
- No prohibitive hepatic encephalopathy
- Unanimous agreement by transplant selection committee
- Support of advocating hepatologist

What Can You Do?

- Screen for AUD
- Get detailed alcohol history
  - Document protective/negative factors
- Discuss AUD like a medical diagnosis
  - There is no safe amount
  - Offer resources & referrals for addiction medicine & counseling
- Check baseline and then monthly Peth
- Initiate early nutrition intervention
- Start steroids in appropriate patients & only continue when indicated
- Early referral for transplant if patient has indications and is motivated to remain sober

Referral Considerations

- There is no 6 month rule
- Patients need to demonstrate insight and commitment to abstinence
- The patient can't be so sick that they cannot engage with our psychosocial team

Liver Pearls: Choose Your Own Adventure

- **I've heard NASH is now called MASH. What do I need to know about this?**
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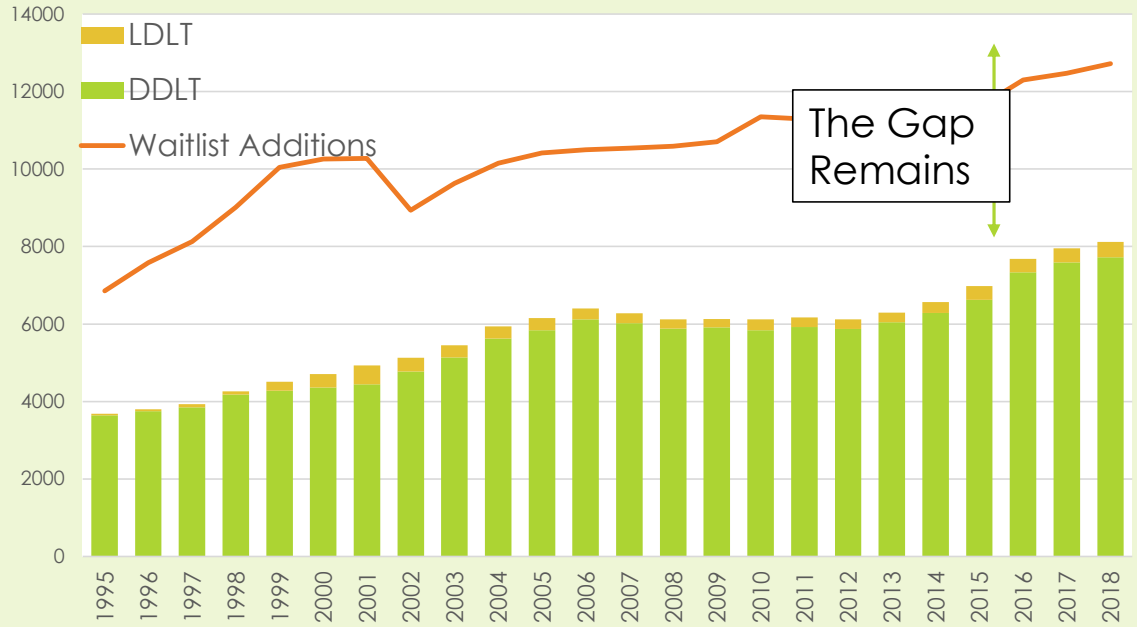
- **When caring for patients with cirrhosis, what medical comorbidities should I address to optimize transplant candidacy?**
- **Is paracentesis safe if a patient with cirrhosis has a high INR?**
- **When should I check a serum ammonia level in patients with hepatic encephalopathy?**
- ***Conclusions***

Protein recommendations for patients with cirrhosis?

- A) 0.5-0.8 g/kg of protein daily
- B) 1.2-1.5 g/kg of protein daily
- C) Discourage a high-protein diet due to the risk of precipitating hepatic encephalopathy

Despite Increasing Number of Transplants, the Waitlist Reflects a Limited Resource



2017 Annual Data Report. SRTR. OPTN. http://optn.transplant.hrsa.gov. Accessed 3/1/2019.

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The Evaluation Process

Financial screening	Secure approval for evaluation
Hepatology evaluation	Assess disease severity and prognosis, confirm diagnosis and optimize management
Surgical evaluation	Confirm need for transplant, identify technical challenges (e.g. prior abdominal surgery, portal vein thrombosis etc.), discuss donor options (deceased, living, extended)
Laboratory testing	Assess hepatic synthetic function, serum electrolytes, renal function, viral serologies, markers of other causes of liver disease, tumor markers, ABO-Rh blood typing, creatinine clearance, urinalysis and urine drug screen
Cardiac evaluation	Initial non-invasive evaluation with echocardiography. Noninvasive stress testing and cardiology evaluation if cardiac risk factors are present (hyperlipidemia, hypertension, diabetes, cigarette consumption, age >60 years)

Martin et al. AASLD Practice Guideline 2003.

Hepatic imaging	Ultrasonography with Doppler to document portal vein patency, triple-phase computed tomography or gadolinium magnetic resonance imaging for tumor diagnosis and staging
General health assessment	Chest film, Pap smear and mammogram (women), colonoscopy if patient is age 50 years or older or has primary sclerosing cholangitis
Dental assessment	Identify dental caries, buried roots and dental abscesses. Coordinate dental extractions if necessary with hepatology
Anesthesia evaluation	Required if unusually high operative risk, i.e., patient has portopulmonary hypertension, hypertrophic obstructive cardiomyopathy, previous anesthesia complications
Psychiatry, psychology or mental health professional consultation	Determine if history of substance abuse, psychiatric illness, or adjustment difficulties (e.g. behavioral or adherence problems)
Social work evaluation	Address potential psychosocial issues, adequacy of support, and possible effect of transplantation on patient's personal and social system
Financial and insurance counseling	Itemize costs of transplantation and posttransplantation care, review insurance coverage, help develop financial management plans
Nutritional evaluation	Assess nutritional status and patient education
Infectious disease	Identify infectious processes that require intervention prior to transplant (e.g. latent TB or posttransplant e.g. CMV naïve recipient)

Martin et al. AASLD Practice Guideline 2003.

Tobacco

- Cigarette smoking: implicated in a number of adverse outcomes in LT recipients (cardiovascular mortality; increased incidence of hepatic artery thrombosis)
- Oropharyngeal and other neoplasms following LT are also linked to cigarette smoking
- Some transplant programs make cigarette cessation a condition for listing for LT and require negative serial nicotine screens for documenting tobacco cessation

Leithead et al. Liver Transpl 2008

Nutrition

- Cirrhosis is a catabolic chronic illness often accompanied by reduced appetite
- Malnutrition leads to poorer outcomes following LT with a BMI <18.5
- Severity of muscle wasting can be masked by ascites and obesity
- Misconception re: protein intake: No need to limit protein intake for patients with chronic liver disease

Tsiaousi et al. J Gastroenterol Hepatol 2008

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD GUIDANCE | HEPATOLOGY, VOL. 74, NO. 3, 2021

Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases

Jennifer C. Lai ,[1*] Puneeta Tandon,[2*] William Bernal,[3] Elliot B. Tapper ,[4] Udeme Ekong ,[5] Srinivasan Dasarathy,[6] and Elizabeth J. Carey[7]

Malnutrition: What is it?

- Clinical syndrome: results from "imbalance (deficiency or excess) of nutrients that causes measurable adverse effects on tissue/body form (body shape, size, composition) or function, and/or clinical outcome"
- Recognize: **malnutrition represents spectrum** of nutritional disorders across entire range BMI —from underweight to obese
- Leads to adverse physical effects: commonly manifested phenotypically as frailty or sarcopenia

Lai et al. AASLD Practice Guidelines 2021.

LIVER TRANSPLANTATION 21:1286–1294, 2015

ORIGINAL ARTICLE

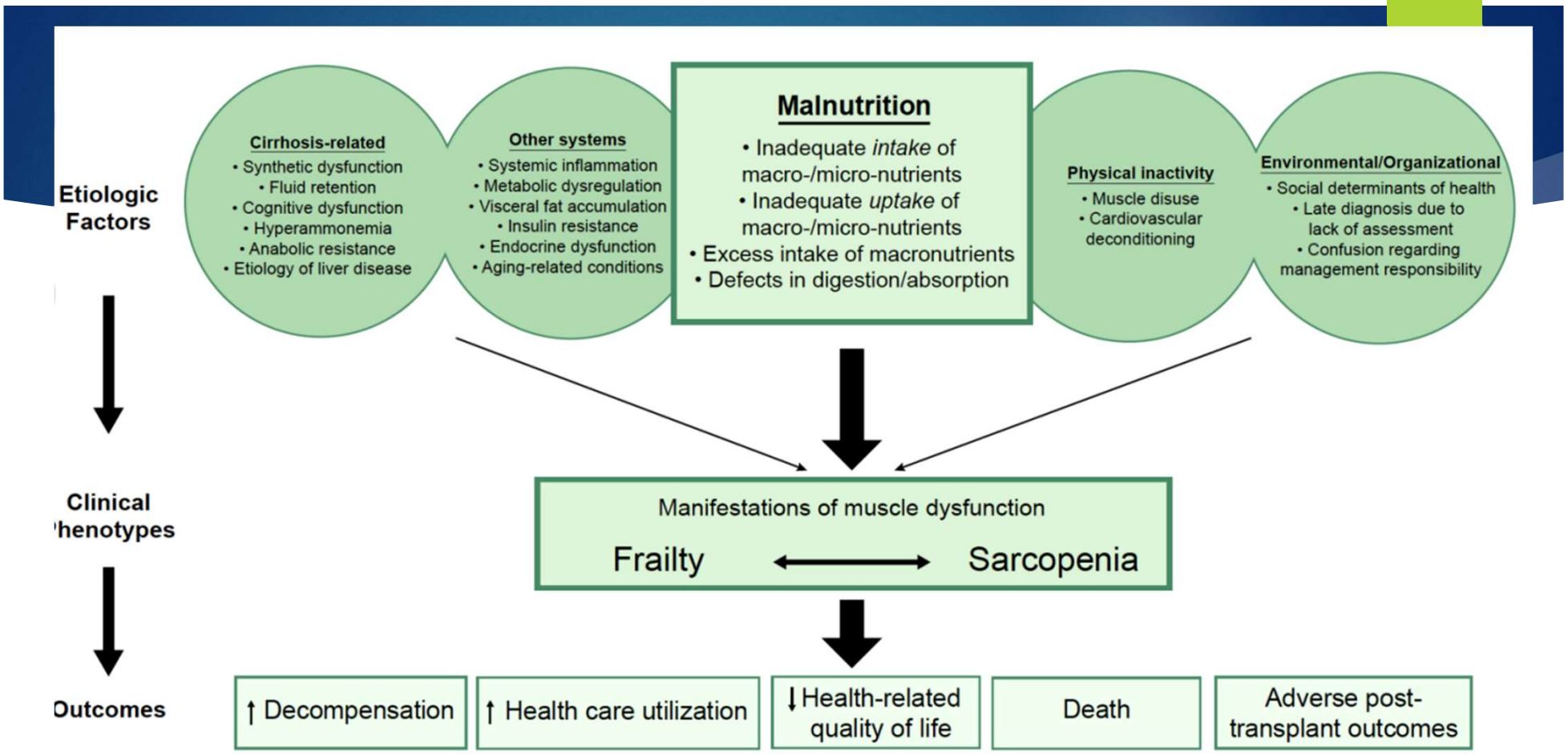
Low, Rather than High, Body Mass Index Confers Increased Risk for Post-Liver Transplant Death and Graft Loss: Risk Modulated by Model for End-Stage Liver Disease

Kiran M. Bambha,[1] Jennifer L. Dodge,[3] Jane Gralla,[2] David Sprague,[1] and Scott W. Biggins[1]
[1]Division of Gastroenterology and Hepatology, [2]Department of Pediatrics, University of Colorado Denver, Aurora, CO; and [3]Division of Transplant Surgery, University of California, San Francisco, CA

Frailty: What is it?

- Broad term classically used in the medical literature by geriatricians
- **Clinical state of decreased reserve and ability to endure health stressors**
- Operational definition of frailty for patients with cirrhosis: physical frailty, the manifestations and consequences of the loss of muscle function
- **Present in over 30 percent of patients listed for liver transplantation**
  - Strongly linked to increased waitlist mortality, decreased quality of life in patients awaiting LT, and increased hospitalizations independent of liver disease severity
  - Frailty also worsens longitudinally without intervention and may persist even following LT

Lai et al. AASLD Practice Guidelines 2021.
Aby et al. Clinical Liver Disease 2019.



Lai et al. AASLD Practice Guidelines 2021.

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Frailty: Why is it so common?

- **Malnutrition**: Impaired intake and uptake of both macronutrients and micronutrients (e.g. zinc, folate, thiamine, Vit D)
  - Reduced oral intake related to symptoms and disease processes
  - Malabsorption (e.g. cholestatic liver disease)
  - Altered metabolic processes, including increased catabolism
- **Cirrhosis:** impaired hepatic ammonia clearance, leading to mitochrondrial oxidative dysfunction and myotoxic damage
- **Systemic inflammation and endotoxemia**
- **Physical inactivity**
- **Social determinants of health**

Lai et al. AASLD Practice Guideline
Aby et al. Clinical Liver Disease 201

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Social Determinants of Health

- Many patients with cirrhosis: **limited knowledge** about disease self-management, including nutrition therapy
- Inadequate food knowledge/preparation skills and **food insecurity** (owing to social factors such as poverty, isolation or limited access to nutritious food) can impact dietary intake—through either reduced or excess intake—across the spectrum of nutritional disorders from undernutrition to obesity
- **Financial strain** → limits caregiver presence → limited monitoring, limited supervision for physical activity, and less attentive management of cirrhosis complications (e.g. timely lactulose therapy)

Lai et al. AASLD Practice Guidelines 2021.
Aby et al. Clinical Liver Disease 2019.

Frailty and Malnutrition: Why do we care?

- Frailty: strongly linked with mortality in both the ambulatory and acute care settings as well as the posttransplant setting.

- AASLD: "All patients with cirrhosis should be assessed for frailty with a standardized tool both at baseline and longitudinally"

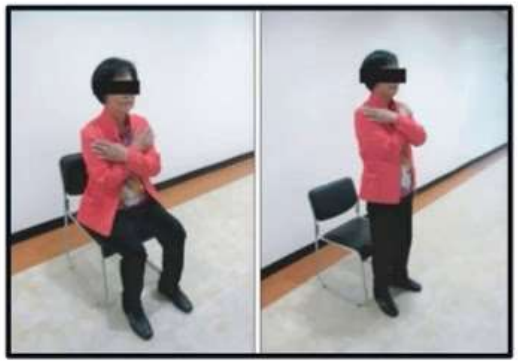
- Frailty, by the **Liver Frailty Index:** associated with a nearly 2-fold increased adjusted risk of death in a study of >1,000 ambulatory patients with cirrhosis awaiting liver transplantation at 9 U.S. centers (subhazard ratio, 1.82; 95% CI, 1.31-2.52).

Lai et al. AASLD Practice Guidelines

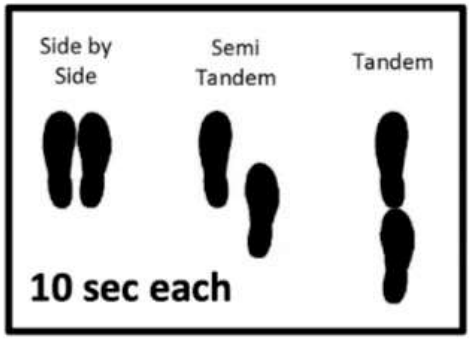
The Liver Frailty Index
liverfrailtyindex.ucsf.edu

Grip + **Chair stands** + **Balance**

Nutrition



Muscle strength



Neuromotor coordination

Lai *et al*. Hepatology 2017.

Frailty and Malnutrition: Why do we care?

- Frailty, as measured by the Liver Frailty Index, **improved in only 16%** of 1,093 patients with cirrhosis awaiting liver transplantation during a median follow-up time of 10.6 months on the waitlist.
- At 3, 6, and 12 months after liver transplantation, Liver Frailty Index scores worsened from pretransplant values in 59%, 41%, and 32% of patients, respectively.
- Only 20% of patients achieved functional "robustness" as defined by a Liver Frailty Index score of ≤ 3.2 by 1 year after liver transplantation.

Lai et al. AASLD Practice Guidelines

Practical Interventions: Assessment

- The Liver Frailty Index has established cut-points to define:
  - **Robust** (Liver Frailty Index < 3.2)
  - **Prefrail** (Liver Frailty Index 3.2-4.3)
  - **Frail** (Liver Frailty Index ≥ 4.4)
- Each 0.1 unit change in the Liver Frailty Index over 3 months: associated with a 2-fold increased hazard of waitlist mortality (HR, 2.04; 95% CI, 1.35-3.09), independent of baseline frailty and MELD

Lai et al. AASLD Practice Guidelines

Practical Interventions: Nutrition

- Protein intake of 1.2 – 1.5 g/kg/day for adults with cirrhosis
  - Maintains a positive protein balance and importantly does not worsen hepatic encephalopathy
- Prolonged fasting should be avoided to limit exacerbation of catabolism in cirrhosis
  - Evidence supports: early morning breakfast or late evening snack
- Enteral supplementation should be considered, particularly for patients awaiting LT who have failed oral supplementation
  - **In patients who are critically ill with cirrhosis, a higher protein target of 1.2-2.0 g/kg ideal body weight/day is recommended**

Lai et al. AASLD Practice Guidelines

Vanilla

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Practical Interventions: Nutrition

- Personalize calorie needs
- Energy expenditure in patients with cirrhosis: total energy expenditure ranges from 28 to 38 kcal/kg/day
- Current nutrition guidelines for patients with chronic liver diseases and/or cirrhosis: weight-based daily caloric intake of **at least 35 kcal/kg/day**

Lai et al. AASLD Practice Guidelines

Practical Interventions: Physical Activity

- Create a physical activity plan consisting of a combination of aerobic and resistance training for **150 minutes a week**
  - **Particularly important in the "sarcopenic obese" phenotype**
  - Tailored to the patient's baseline frailty and functional status
  - **Particular caution should be applied to prescribing weight loss in a patient with decompensated cirrhosis**.

- Utilize modern technology such as fitness trackers or smartphone applications to provide real-time objective tracking data and to identify areas for improvement.

Lai et al. AASLD Practice Guidelines

Bone disease

- Osteoporosis is frequent in patients with cirrhosis (up to 55%)
- Reflects common risk factors, e.g. inactivity, inadequate nutritional status, hypogonadism, chronic **cholestasis**, and alcohol excess
- Bone densitometry is indicated pre-LT, given the frequency of osteoporosis in cirrhosis as well as determining vitamin D and calcium levels.
- Bone mass diminishes in the initial 3 months following transplant due to high-dose steroids, which in turn increases fracture risk.

Collier et al. Hepatology 2007.

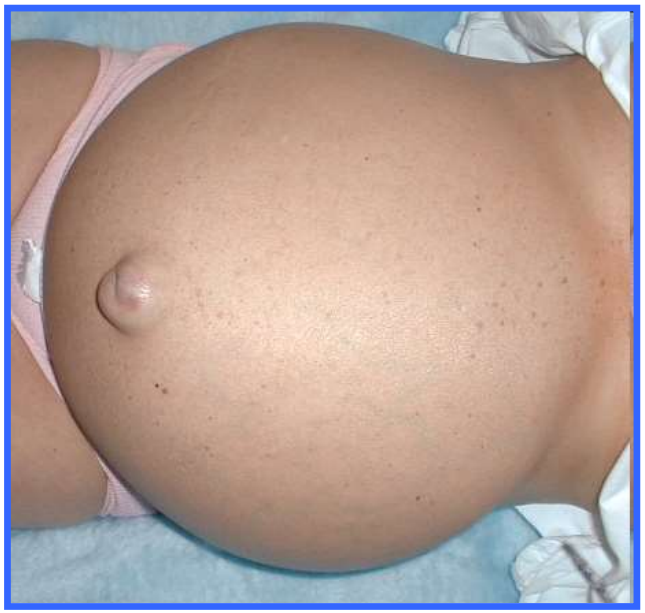
Liver Pearls: Choose Your Own Adventure

- **I've heard NASH is now called MASH. What do I need to know about this?**
- **Is there a mandated 6 month rule of sobriety for patients with alcohol associated liver disease who are being considered for liver transplantation?**
- **When caring for patients with cirrhosis, what medical comorbidities should I address to optimize transplant candidacy?**
- **Is paracentesis safe if a patient with cirrhosis has a high INR?**
- **When should I check a serum ammonia level in patients with hepatic encephalopathy?**
- ***Conclusions***

What is the generally accepted INR cutoff for a patient with cirrhosis undergoing paracentesis?

- A) 1.5
- B) 2.0
- C) 2.5
- D) 3.0
- E) There is no INR cutoff

Is paracentesis safe?



Safety of Paracentesis

- 85% of ascites in US is from cirrhosis
  - 71% have abnormal prothrombin time[1]
- Coagulation tests don't reflect risk in cirrhotics
  - Balanced deficiency of procoagulants and anticoagulants[2]
- Serious complications are unusual (<1/1000)[1]
- No data-supported cutoff of coagulation parameters

[1]Hepatology 2009;49:2087.
[2]N Engl J Med 2011;365;147.

The Misunderstood Coagulopathy

- INR, a ratio of the patient's PT as compared to a laboratory normative PT value, was designed as a method of **monitoring individual patient responses to anticoagulation therapy with a vitamin-K antagonist such as warfarin**

[1]Hepatology 2009;49:2087.
[2]N Engl J Med 2011;365;147.

The Misunderstood Coagulopathy

- The liver is responsible for the synthesis of many of the procoagulant and anticoagulant proteins responsible for maintaining hemostasis
- In most cases, a "rebalancing" occurs and the vast majority of chronic liver disease patients achieve a hemostatic equilibrium
- No data to support that an "INR < 1.5" is safe for a procedure despite wide acceptance

[1]Hepatology 2009;49:2087.
[2]N Engl J Med 2011;365;147.

The Misunderstood Coagulopathy

- Prophylactic transfusions may expose the patient to increased risk of adverse events (e.g., transfusion reactions including transfusion-related acute lung injury [TRALI] and exacerbation of portal hypertension) as a result of the transfusion

- … while providing no protective effects.

Harrison. West J Emerg Med.2018.

The Misunderstood Coagulopathy

- Despite the notion of "auto-anticoagulation," patients with hepatic dysfunction are not protected against the occurrence of venous thromboembolism or other thrombotic events merely by the presence of an elevated PT and INR

- At risk for portal vein thrombosis, DVT despite "high INR"

Harrison. West J Emerg Med.2018.

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- ***Conclusions***

Serum ammonia levels…

- A) Should be used to diagnose hepatic encephalopathy
- B) Are useful to titrate medications such as lactulose or rifaximin in patients with hepatic encephalopathy
- C) Are useful for prognosis in patients with hepatic encephalopathy
- D) Add no diagnostic or prognostic value for patients with hepatic encephalopathy, and should not be used for management.

Hepatic Encephalopathy

- Broadly defined as brain dysfunction caused by liver insufficiency and/or portal-systemic shunting

- Manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma

Rose et al. Journal of Hepatology 2020.

Hepatic Encephalopathy

- Widely considered to be reversible following liver transplantation (LT)

- However… numerous studies have demonstrated that neuroinflammation and neuronal cell death (features of overt HE episodes) can lead to irreversibility and persistent neurologic complications following LT

Rose et al. Journal of Hepatology 2020.

Hepatic Encephalopathy

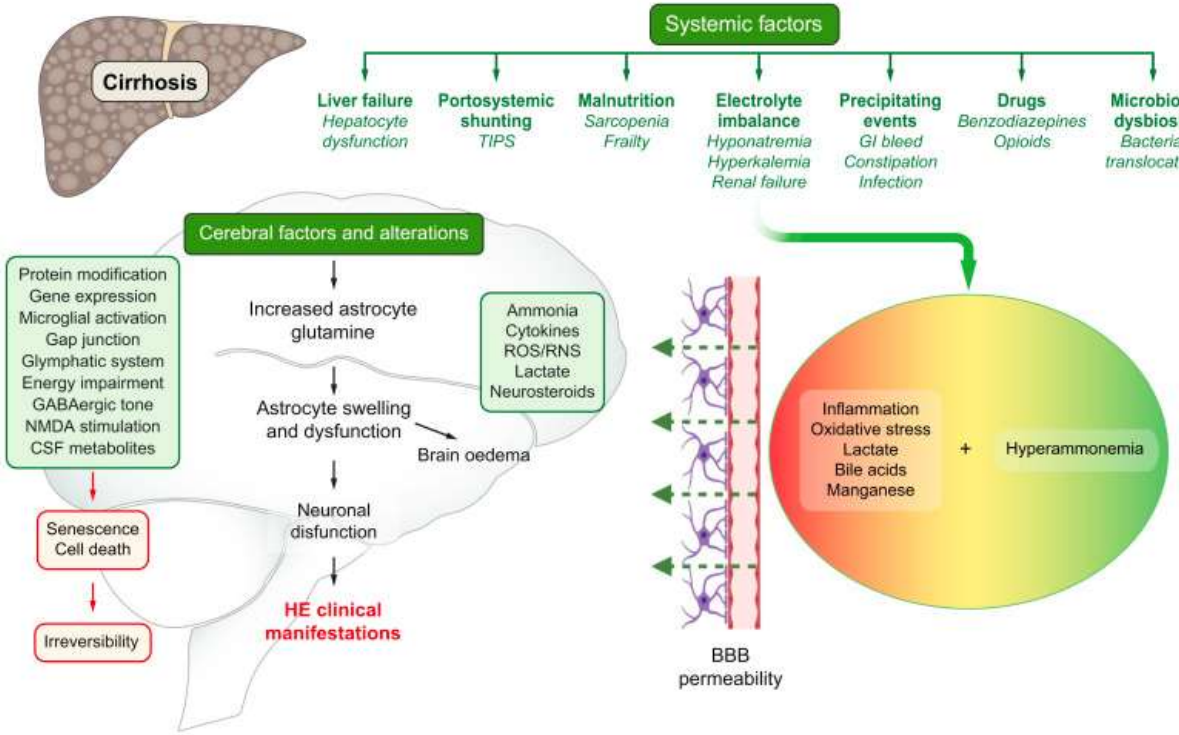
- Prevalence of overt HE:
  - At the time of diagnosis of cirrhosis: 10-14%
  - In decompensated cirrhosis: 16-21%
  - In patients who have had a TIPS inserted: 10-50%
- Prevalence of minimal HE: 20-80%
- Patients with a previous episode of overt HE: 42% risk of recurrence at 1 year
- Patients with recurrent overt HE: 46% risk of another episode within 6 months (despite receiving standard care)

Rose et al. Journal of Hepatology 2020.

Hepatic Encephalopathy

- HE has traditionally been graded into:
  - Overt HE (clinically manifest neurological-psychiatric abnormalities)
  - Minimal HE (abnormalities on neuropsychological or electrophysiological tests without clinically detectable neurological-psychiatric abnormalities)

Rose et al. Journal of Hepatology 2020.

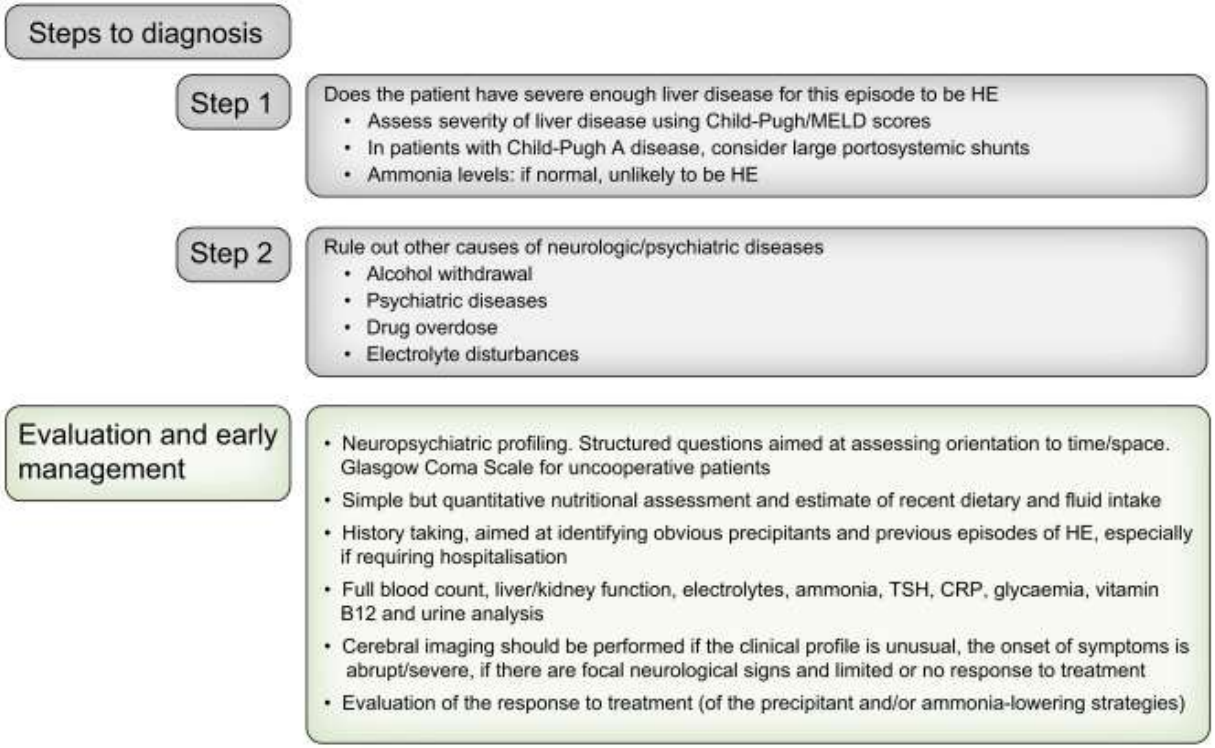


Rose et al. Journal of Hepatology 2020

Ammonia

- Ammonia remains at the core of HE pathogenesis
- Ammonia is primarily produced in the gut, as an end product of protein digestion, amino acid deamination and bacterial urease activity
  - A healthy liver, with an intact urea cycle, regulates the concentration of ammonia in the systemic circulation

Rose et al. Journal of Hepatology 2020.



Rose et al. Journal of Hepatology 2020

Hepatic Encephalopathy

- Early management focuses on correcting the predisposing condition, which will improve mental status in up to 80% of patients with encephalopathy.
- Evaluate for infection (SBP, UTI), GI bleed, electrolyte abnormalities (hypokalemia decreases ammonia excretion), and constipation.
- **No role for checking a serum ammonia level in patients with chronic liver disease and hepatic encephalopathy**

Vilstrup et al. AASLD Practice Guidelines 2014.

Hepatic Encephalopathy

ARTICLE

Ammonia Levels Do Not Guide Clinical Management of Patients With Hepatic Encephalopathy Caused by Cirrhosis

Haj, Mona MD[1]; Rockey, Don C. MD[1]

Author Information

The American Journal of Gastroenterology: May 2020 - Volume 115 - Issue 5 - p 723-728
doi: 10.14309/ajg.0000000000000343

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Hepatic Encephalopathy

- 1200 adult patients with cirrhosis and diagnoses of HE
- Ammonia levels were drawn for 46% of patients; 60% of tested patients had elevated levels.
- Amount of lactulose given in the first 48 hours of HE management was similar in the tested and untested groups.
- **No correlation between lactulose dose and ammonia level**

Haj et al. American Journal of Gastroenterology 2020.

Ammonia

- Best evidence for the prognostic role of ammonia and its relationship with severity of HE is observed in patients with **acute liver failure**.
- Ammonia level of >120 µmol/L identifies patients at high risk of developing intracranial hypertension and cerebral edema.
- In patients with cirrhosis: although the level of ammonia does not follow the severity of HE, more severe HE is generally associated with higher ammonia level
  - Underscores that ammonia is central to pathophysiology… but there is no need to check it on lab work!

Rose et al. Journal of Hepatology 2020.

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- ***Conclusions***

UC Health University of Colorado Liver Transplant Program

- Doc-Line (24/7 Attending Hepatologist): 720-848-2828
- Hepatology clinic referrals including **outreach**:
  - Phone: 720-848-2245 Fax: 720-848-2246
  - Current outreach clinics: Loveland CO, **Lone Tree CO**, Colorado Springs CO, **Albuquerque NM, Billings MT**. Coming soon: **Grand Junction CO.**
- Avash Kalra, MD
  - Cell: 937-305-6130
  - Email: Avash.Kalra@CUAnschutz.edu

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Questions?

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