Alcohol Related Liver Disease: 2021 and Beyond

Blaire Burman MD

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Alcohol-related Liver Disease (ALD)

- What is alcohol use disorder (AUD)?
- How does alcohol affect the liver?
- Epidemiology of alcohol use and burden of ALD in the US
  - Change in demographics
- Acute alcohol-related hepatitis
  - Role of steroids?
  - Role of transplant?
- Chronic alcohol-related cirrhosis
  - Management pearls

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How much is too much?

- Standard drink contains 10-14g of alcohol
- Recommendations for safe limits vary worldwide

- Moderate alcohol use is defined (NIAAA) as
  - Up to 1 drink / day for women, < 3 drinks / occasion
  - Up to 2 drinks / day for men, < 4 drinks / occasion

- Binge drinking is defined as > 4 drinks for women or > 5 drinks for men on a single occasion

- Heavy alcohol use has been defined as binge drinking 5+ days over the past month

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Alcohol Use Disorder (AUD)

DSM-5 diagnosis criteria for alcohol use disorder*

1. Alcohol is often taken in larger amounts or over a longer period than was intended
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects
4. Craving or strong desire, or urge to use alcohol
5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use
8. Recurrent alcohol use in situations in which it is physically hazardous
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol
10. Tolerance, as defined by either of the following:

a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect

b. A markedly diminished effect with continued use of the same amount of alcohol

11. Withdrawal or taking alcohol to relieve withdrawal

**(At least of 2 symptoms in past 1 year; mild disorder:2-3; moderate:4-5; severe disorder≥6)*

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Alcohol and the liver

- Spectrum of disease from mild fatty liver to steatohepatitis to cirrhosis
- Dose-response relationship, for the most part
- Disease progression heavily influenced by genetic and environmental factors
- Early stages are more reversible
- Abstinence improves liver function, portal hypertensive complications, and mortality, even in advanced stages

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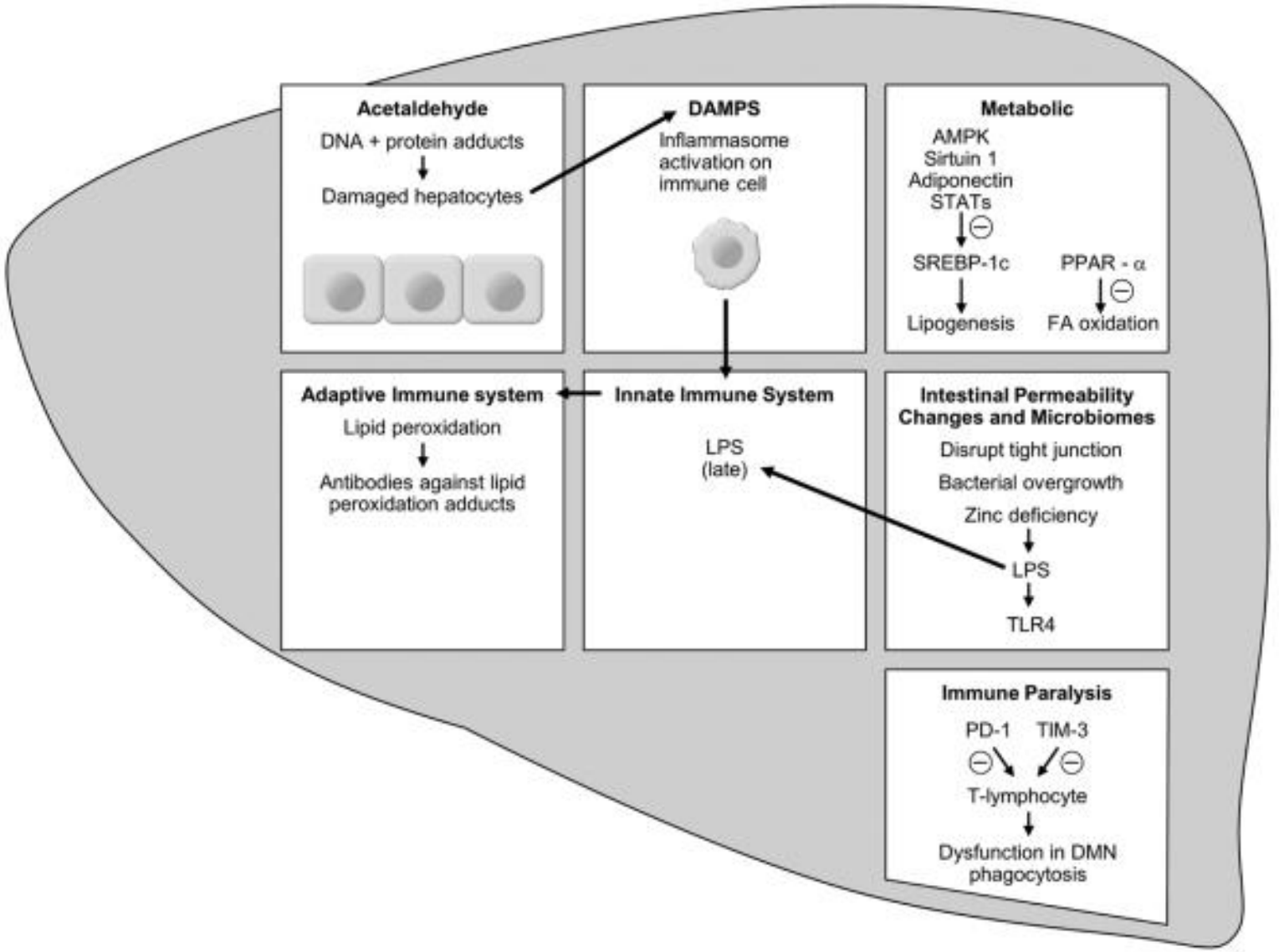
Alcohol and the liver



Multiple Pathways

- Direct toxic effects on hepatocytes
- Inflammatory response
- ↑ lipogenesis and fatty acid oxidation
- Bacterial gut translocation

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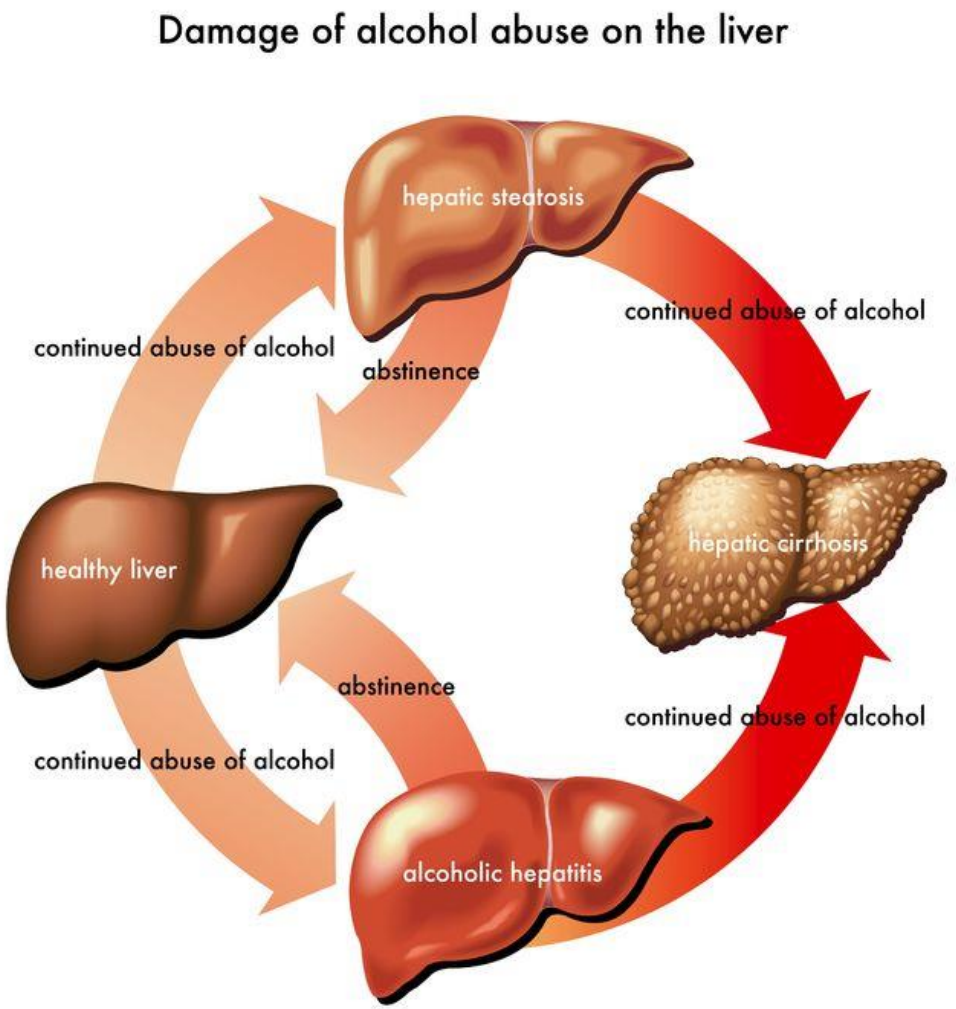
Reversal vs Progression



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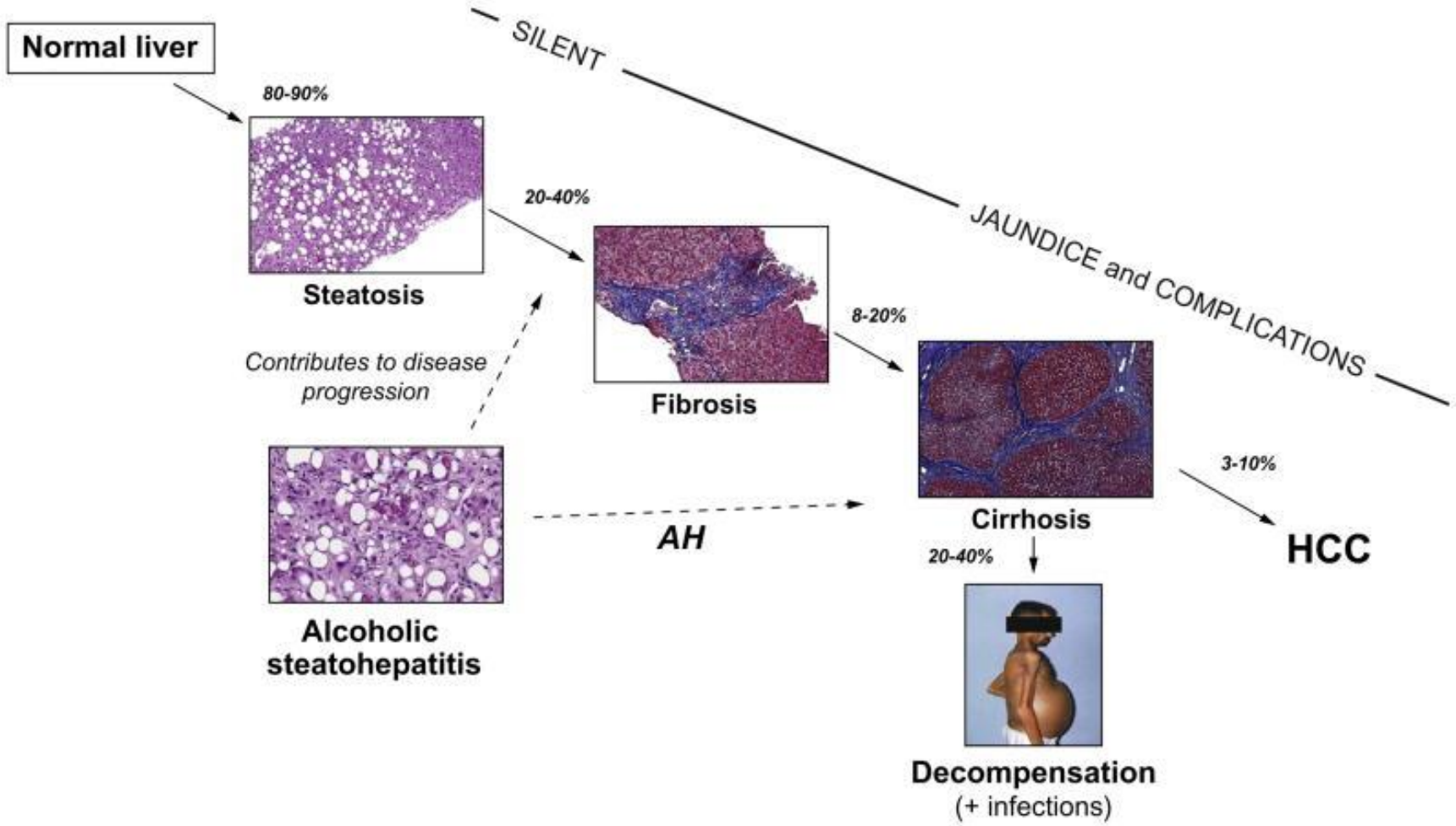
Natural history of alcoholic liver disease: Steatosis to cirrhosis and hepatocellular carcinoma (HCC)



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The Dionysos Project

- Assessed the natural history and prevalence of AC in a large population cohort (6,917) in Northern Italy
- 21% consumed > 30g/day
- Rate of cirrhosis was significantly higher in pts who consumed ≥ 30 g/day (2.2%) than among abstainers or <30 g/day (0.08%)
- Risk of AC increased with the amount consumed
- Subjects who consumed > 120 g/day had the highest risk, with a prevalence of 13.5%

Bellantani et al, Gut 1997; Bellantani et al, Hepatology 2004

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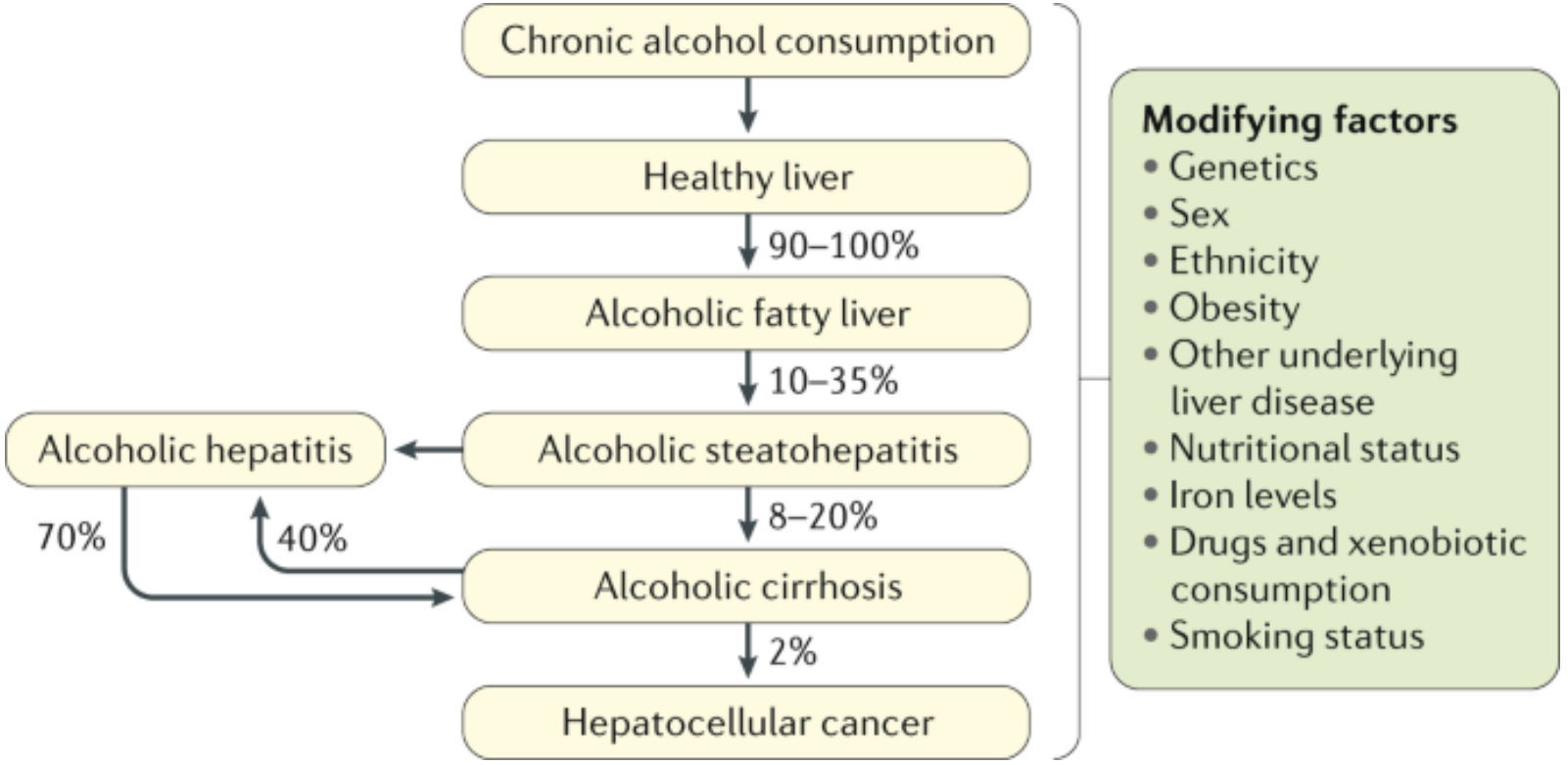
What impacts risk of ALD?

- PNPLA3 variations (G allele)
- Female sex
- Ethnicity (Hispanic >While > AA)
- Obesity
- Nutritional status
- Concomitant liver disease
- Smoking



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Epidemiology of Alcohol Use in US

- Increased prevalence of high risk drinking over past 2 decades
- 12-mo prevalence high-risk drinking increased 30% from 9.7% to 12.6%
- 50% increase in AUD during this time from 8.5% to 12.7%
  - representing now 30 million Americans
- Alarming increases in high-risk drinking and AUD among women (57.9% and 83.7%, respectively) relative to men (15.5 and 34.7%)
- Increases in alcohol use, high-risk drinking, and AUD generally much greater among minorities than white individuals

Grant et al, JAMA Psychiatry 2017

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Complications of AUD

- Alcohol is responsible for nearly half of liver-related mortality
- Having remained stable for > 3 decades, the number of alcohol-related cirrhosis (AC) deaths are rising
  - Increase most pronounced among young adults 24-35 yrs
- Alcohol accounts for 37% of cirrhosis cases
  - May be underestimate as synergistic with other etiologies (ie: HCV)
- Alcohol-related liver disease (ALD) is now the leading indication for liver transplantation in the US

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High Burden of Alcoholic Cirrhosis

- Mellinger et al looked at the prevalence, health care use, and cost of AC among privately insured persons in the US (>100 million enrollees)
- Prevalence of cirrhosis increased 20% while prevalence of AC increased 42%
- Higher rate of increase for women (50%) vs men (30%)
- Compared to non-alcoholic cirrhosis, AC patients were more likely to:
  - Be disproportionately sicker
  - Have portal hypertensive complications at diagnosis
  - Higher rate of admissions and re-admissions
  - Have 2x increased per-person costs (in 1st year of diagnosis)

Mellinger et al, Hepatology 2018

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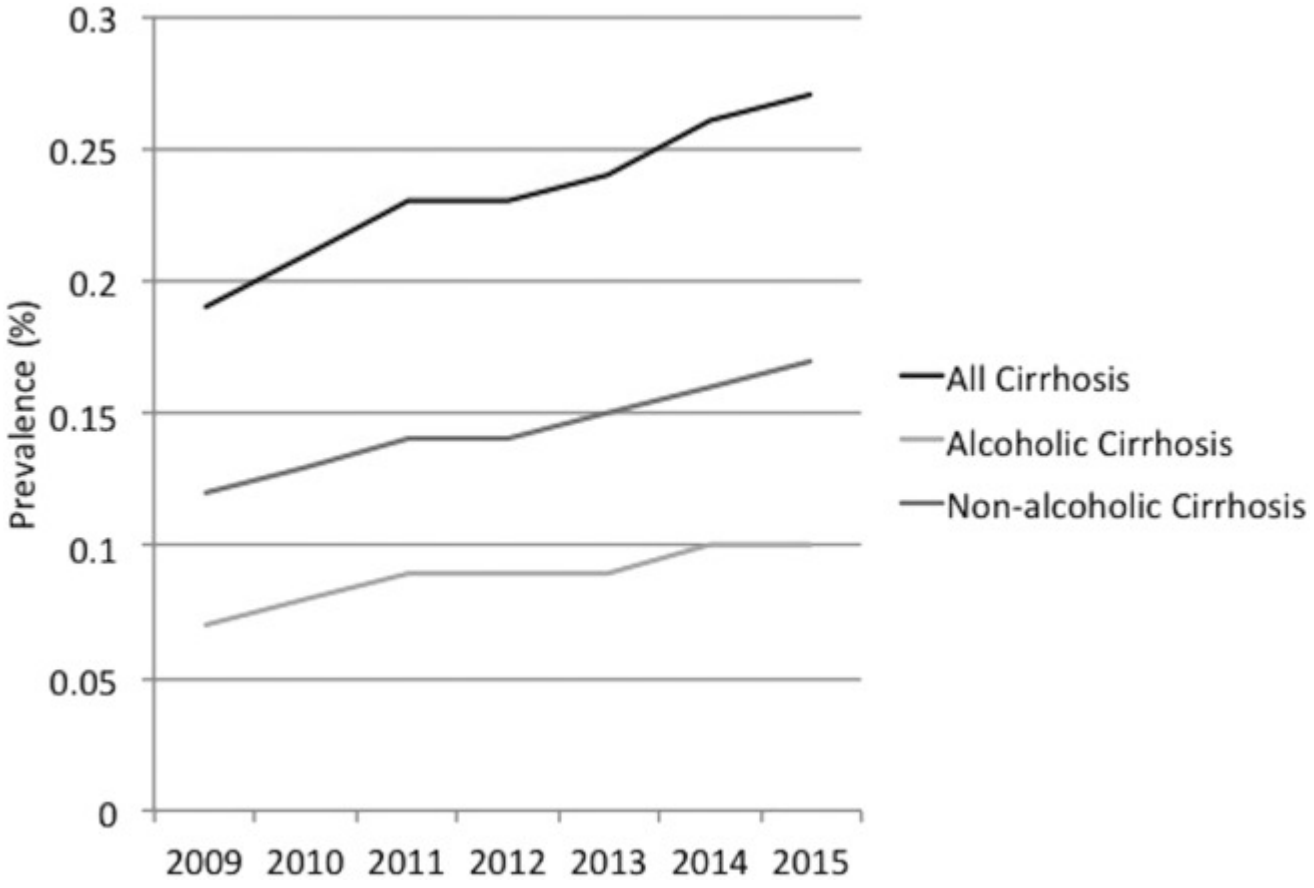
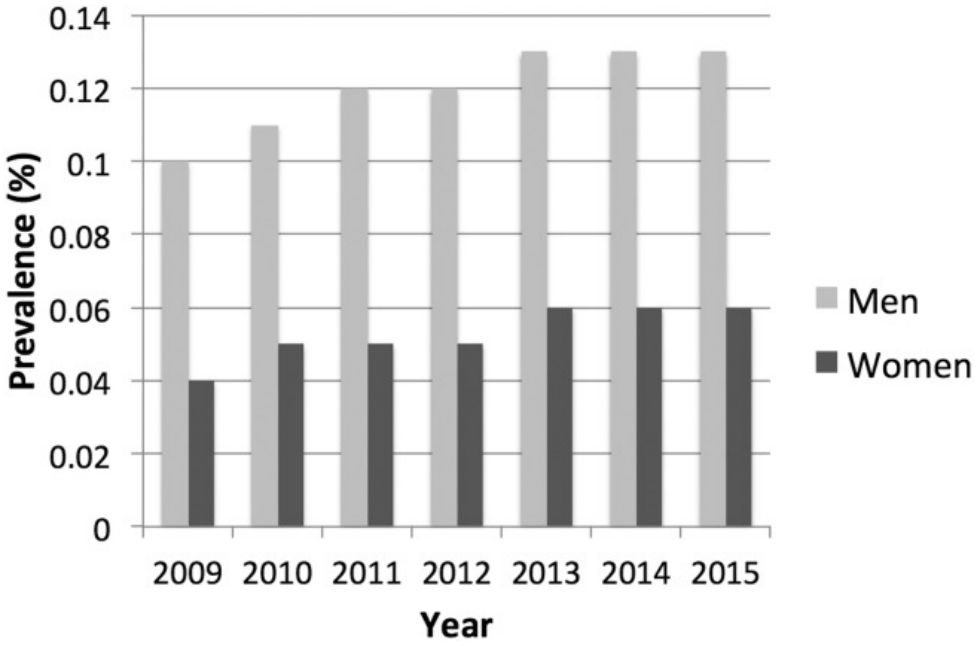
High Burden of Alcoholic Cirrhosis





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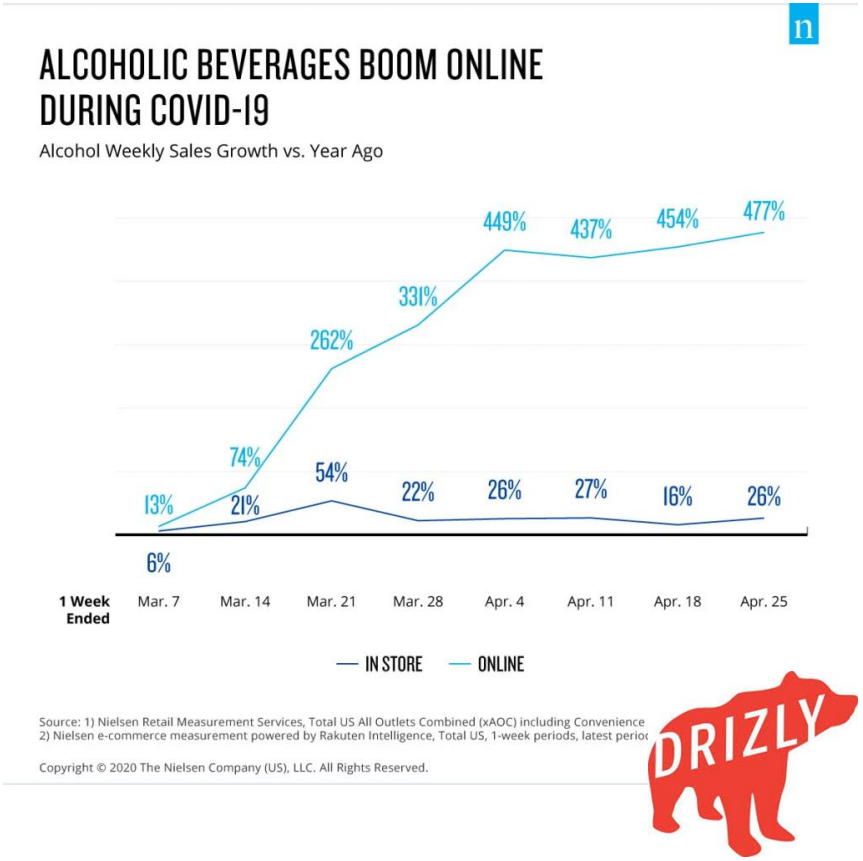
Impact of Covid on Alcohol Use

- Prior to Covid, incidence of AUD and ALD had already been rising
- First month of pandemic: 55% increase in store alcohol sales, 300% rise online sales
- Increased purchasing more pronounced among younger adults, households with children < 18, and minorities
- Impact of economic and interpersonal stress, lockdowns, social isolation, childcare → shift to at-home drinking, and more of it



Moon et al, Hep Communications, 2021; Lee at al, Ann Int Med, 2021; Bloomberg.com

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Impact of Covid on Alcohol Use and ALD

- In US, frequency of alcohol consumption increased 15-20%
- Disproportionately high increases among **women** in terms of frequency (17 vs 11% for men), days of heavy drinking (41 vs 7%), and alcohol related consequences
- 39% increase in AUD diagnoses among women
- Risk of developing ALD is higher in women across all levels of consumption
    - At less alcohol, earlier onset, and more severe presentation

Moon et al, Hep Communications, 2021; Lee at al, Ann Int Med,e2021; Pollard et al, JAMA, 2021

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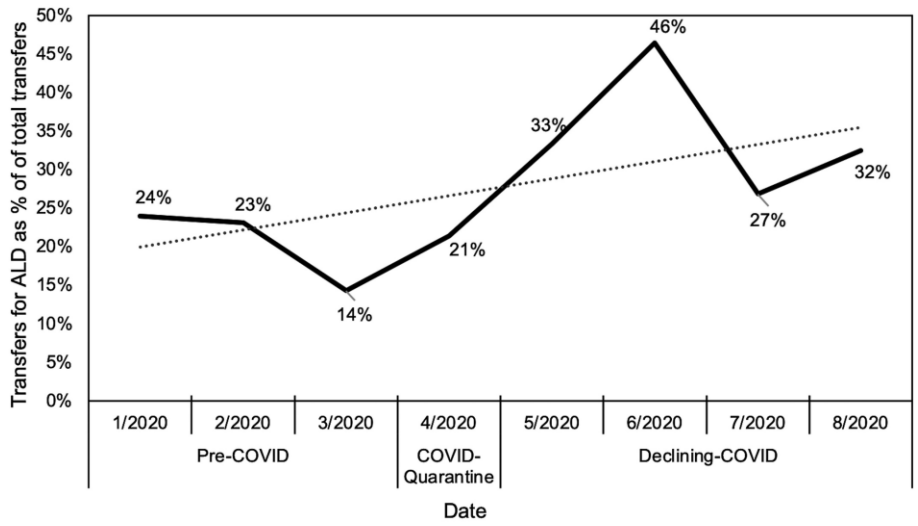
Downstream Effects

- Spring of 2020 – signs that pts with cirrhosis were delaying care
  - Patients admitted had higher MELD, higher rate of ICU admissions
  - Only sickest were coming in for care
- Reopening phase - significant increase in alcohol-associated hospitalizations
  - 60% increase in proportion of inpatient consults alcohol-related GI and liver dz
  - 53% increase in severe alcoholic hepatitis
  - Higher in-hospital mortality



Chung et al, Abstract 436 DDW 2021

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Summary: Epidemiology of ALD

- Rates of AUD are rising
- Rates of ALD are rising, disproportionately among women, young adults, rural and minorities
- Rising rates of alcoholic cirrhosis and associated mortality
- Patients with ALD tend to be sicker and more costly
- Covid made this worse

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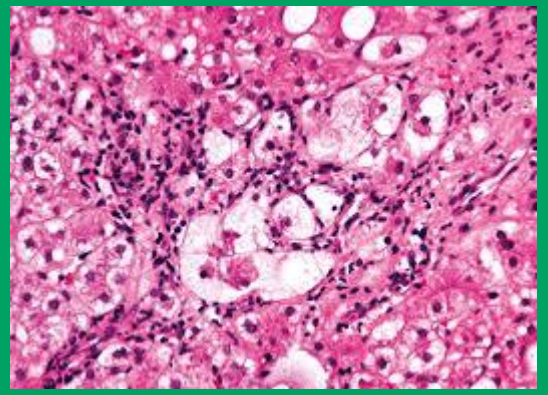
Acute Alcoholic Hepatitis



Alcoholic hepatitis, defined

- Serious form of acute decompensation of ALD that develops in heavy drinkers
  - Usually within 2-4 weeks of heavy regular consumption, dose dependent risk
  - Serum bilirubin > 3; AST elevated (but < 400), AST:ALT > 1.5
  - No obvious other cause for hepatitis
- Rapid onset of jaundice, malaise, anorexia, tender hepatomegaly, and features of SIRS
- Patients are *systemically ill* with high risk of nutritional deficiency, infection, renal failure, multi-organ system failure
- Underlying cirrhosis present in vast majority (90%) of severe AH cases

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AH Diagnosis

- Clinical diagnosis
- Detailed history of alcohol consumption
- Lab markers
  - GGT, MCV, AST>ALT, ferritin
- Alcohol biomarkers
  - Ethyl glucuronide, etc
- Liver biopsy is underutilized
  - In US, only used in limited cases of diagnostic uncertainty; standard globally
  - 10-15% of clinical AH diagnoses do *not* have characteristic histologic features
  - Recent studies indicate certain histologic features predict worse **prognosis**

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Alcohol Biomarkers

Test	Detection Time	Cutoff Values	Sensitivity	Specificity	PPV	NPV
Urine ethyl glucuronide	3-5 days	500 ng/mL	76-89%	93-99%	81-90%	91-99%
Hair ethyl glucuronide	2-3 months	30 pg/mg	81-100%	83-98%	65-95%	86-100%
Urine ethyl sulfate	3 days	75 ng/mL	82%	86%	70%	93%
Phosphatidyl-ethanol (blood)	2-3 weeks	20 ng/mL	97-100%	66-96%	85%	100%

- Hair EtG is costly, requires significant sample, limited availability
- EtS often used to confirm +EtG
- PEth more costly than urine EtG

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AH: Assessment of Disease Severity

- Maddrey discriminant function (mDF)
  - 4.6 x (patient's PT – control PT) + bilirubin
  - Severe disease > **32**
- MELD Score
  - Composite of sodium, creatinine, bilirubin, INR
  - Severe disease > **20**
- Lille Score
  - Age, albumin PT, baseline bilirubin, and Δ bilirubin at 7 days
  - Severe disease **> 0.45**, predicts nonresponse to steroids, assoc with 75% mortality at 6 months
  - *Best* predictor of prognosis

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AH Management

- Abstinence, duh
- Monitor and manage withdrawal
- Hospitalize
  - if severe AH, infection, GI bleeding, AKI, encephalopathy
- Enteral nutrition
  - Maintains gut mucosal integrity, lowers risk of bacterial translocation
  - 1.2-1.5 g protein & 30-40 kcal/kg daily; consider tube feeds
  - Supplement B vitamins, thiamine, folic acid
- Vigilant surveillance for infection, worsening renal function
- High rates of GI bleeding

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Patient Case

37 yo Mexican American man with hx of DMII and social alcohol, here with jaundice and RUQ discomfort

Bilirubin 3.0, AST 116, ALT 54, INR 1.2

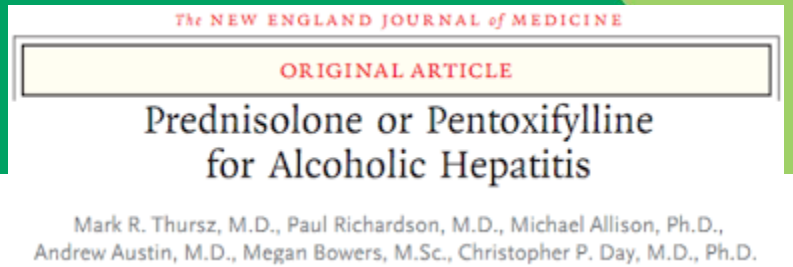
How do we know if this is ASH or NASH?

Patient Case

Biopsy shows steatohepatitis and cirrhosis →
Abstinent x 6 months, returns feeling 'ill' with bilirubin 32, INR 2.2

What is the diagnosis?
What are treatment options?

STOPAH Trial



Largest multicenter RCT out of the UK enrolled 1,103 severe AH (DF ≥32) patients and randomized then to four arms: placebo, prednisolone, pentoxifylline, or both

- No biopsy required
- Per provider treatment clinical care otherwise
- Placebo arm mortality rate was much lower than for all other trials to date

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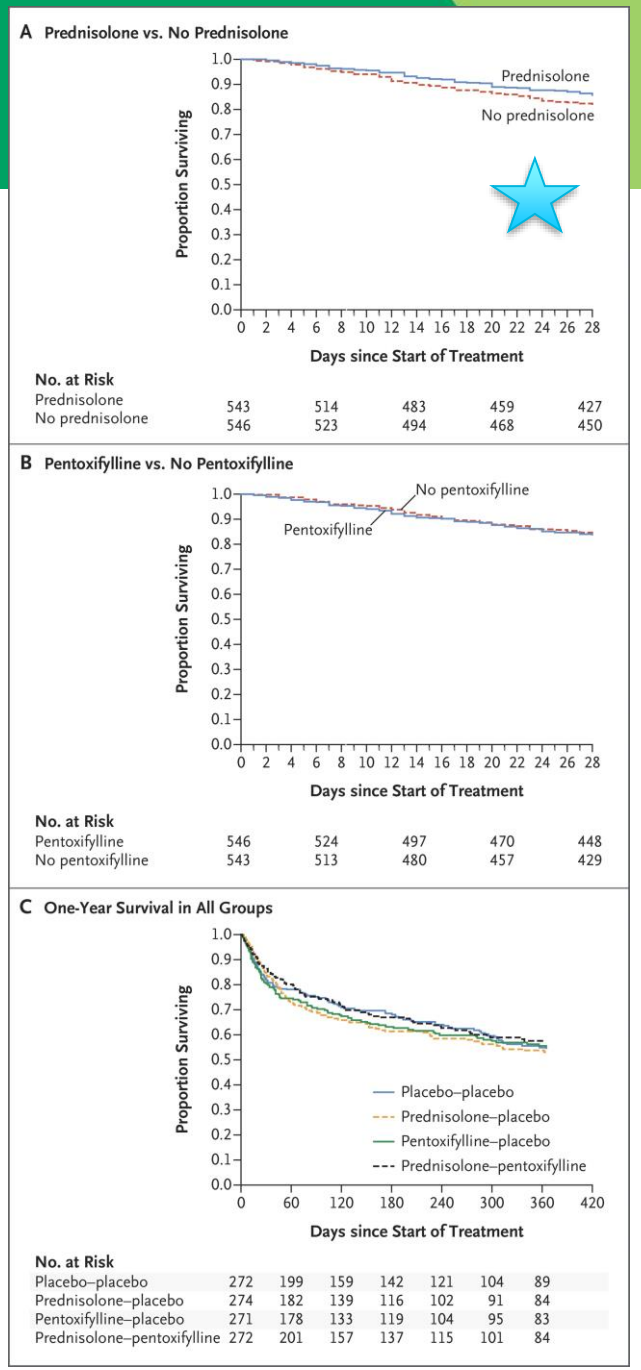
STOPAH Trial

- Prednisolone arm showed a *trend* toward improving 28-day survival (odds ratio **0.72**, 95% CI 0.52-1.01)
- When adjusting for baseline determinants of prognosis, showed significant benefit of prednisolone with respect to 28-day mortality
- No significant survival benefit for any therapy at 90-day or 1 year → Abstinence matters most
- No benefit to combination therapy
- Any reduction in mortality attributable to pentoxifylline was related to lower risk of renal disease



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STOPAH Trial

- Abstinence at 90 days after enrollment was the *only* factor associated with survival at 1 year
- Any alcohol use at all at day 90, including less than 2 drinks/day, was associated with a 2- to 3-fold increase in mortality
- Involve social work, addiction counselors, family

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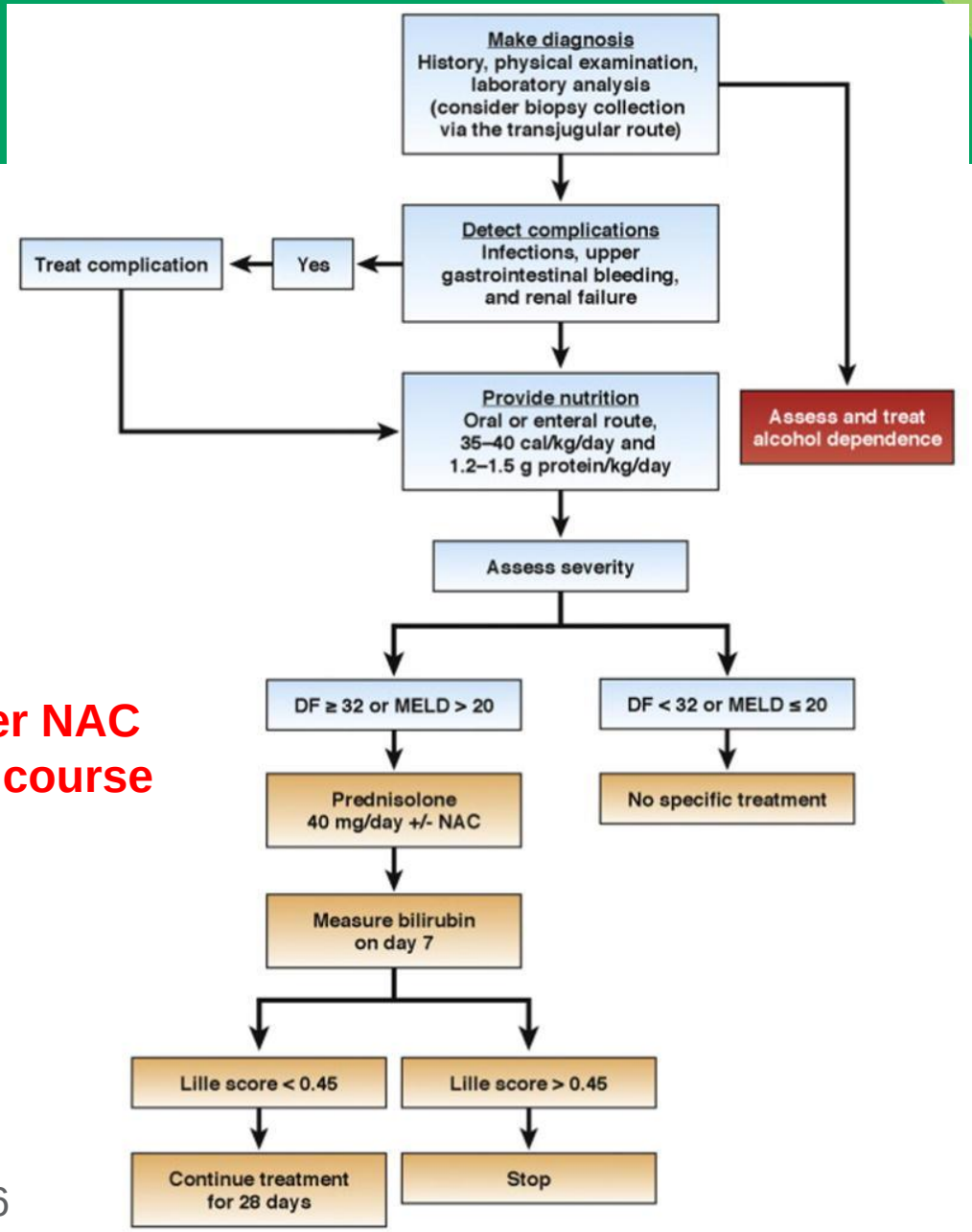
Treatment Algorithm



Consider NAC early in course

M. Thursz, Treatment of Severe Alcoholic Hepatitis, Gastro 2016

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Extremely poor prognosis

6-month mortality of 75% for severe AH refractory to steroids

75-90% of deaths occur within the first 2 months.

What do we offer these patients?

- Pentoxifylline
- Palliative care
- Transplant? How is this patient going to make it 6 months??

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Patient Case

MELD of 45, new AKI, worsening encephalopathy
Transfer patient to UW to consider transplant
Hair ethyl glucuronide comes back strongly positive, pt discharged on hospice

If the French are doing it…

In 2011, Mathurin et al conducted a landmark pilot study of OLT for highly selected AH patients

- 26 patients with severe AH and steroid failure were transplanted
- 77±8% survived for 6 months (similar to matched group of steroid responders, Lille score <0.45, 85%±4%) and significantly better than matched group of steroid non-responders who did not receive liver transplants (23±8%)
- 3 of 26 returned to drinking
- Of all patients with severe AH, <2% received a liver transplant, and only 3% of liver grafts were used for AH transplantation

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ACCELERATE-AH

- Retrospective study of (147) consecutive patients diagnosed with severe AH and no prior dx of ALD who underwent OLT <6 months of abstinence between 2006-17 at 12 US centers
- Median duration of abstinence 55 days
- 54% received steroids, mean Lille score 0.82, mean MELD 39
- Survival rates of 94% at 1 year, 84% at 3 years
- Sustained alcohol use post-transplant in 11%
  - Associated with younger age, male gender
  - Return to drinking assoc with rapid graft loss and death

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ACCELERATE- AH

American Consortium of Early Liver Transplantation for Alcoholic Hepatitis: ACCELERATE-AH

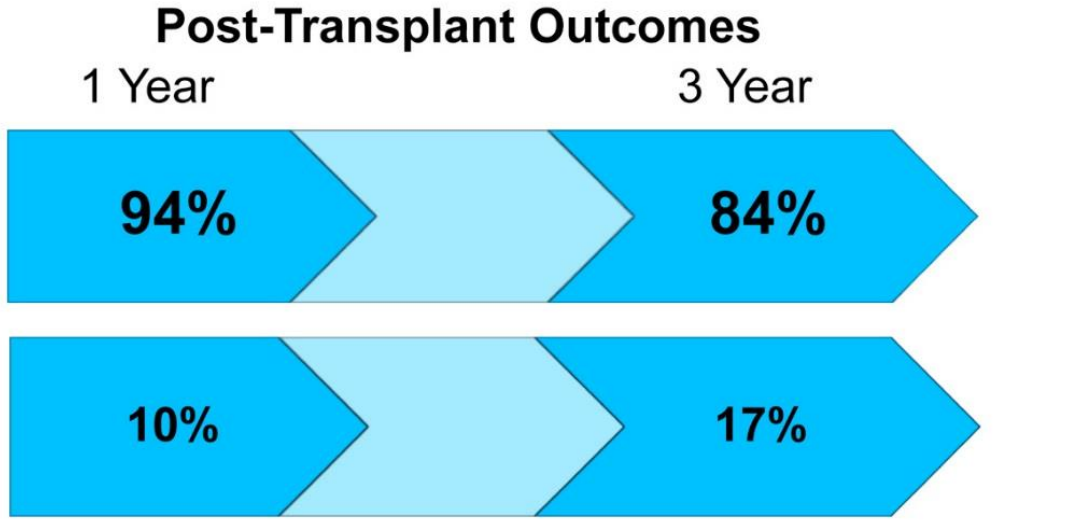
12 centers in 8 UNOS regions

Early Transplant = no specific sobriety period (n=147)

Mortality without transplant up to 70% at 6 months

→ Survival

→ Sustained Alcohol Use After Transplant



Gastroenterology

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Liver Transplantation for AH

- Majority of US centers now consider transplant for AH with abstinence < 6 months
- Patients with severe AH and high MELD, good insight, and adequate social support should be referred for transplant evaluation, given exceedingly high 90-day mortality
- The decision on LT evaluation should not be based solely on minimum 6 months of alcohol abstinence, and other criteria should be taken into consideration

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ALD and Liver Transplant

- Highest survival rates for any LT indication
- 20%-25% of ALD recipients return to drinking within 5 yr
  - NOT well predicted by duration of sobriety
- Most centers moving away from fixed interval of abstinence
- Patients with ALD who fail to improve after 3 months of abstinence (particularly Child C) should be referred for LT
- Patients with severe AH, adequate social support, lower recidivism risk*, should be referred ASAP

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Back to our patient…
Would you recommend liver transplant?

Polling Question

Impact of Covid on Liver Transplant

- Over 40% of listings in Covid era were due to ALD
  - For the first time, ALD accounted for more listings than HCV and NASH *combined*
- MELD-NA score at listing and transplant was significantly higher
  - 15% increased in listing with MELD>30
  - Rate of high MELD listings rose in states with longer stay-at-home orders
- Notable shift in demographics toward younger age and Medicaid insurance
- Early transplant for severe AH doubled since July 2020
- Analyses suggest impact of ALD will be felt for years to come…

Cholankeril et al, Hepatology 2021; Weerakoon et al, Am J Drug Alcohol Abuse 2021; Bloom and Fontana, Hepatology 2021

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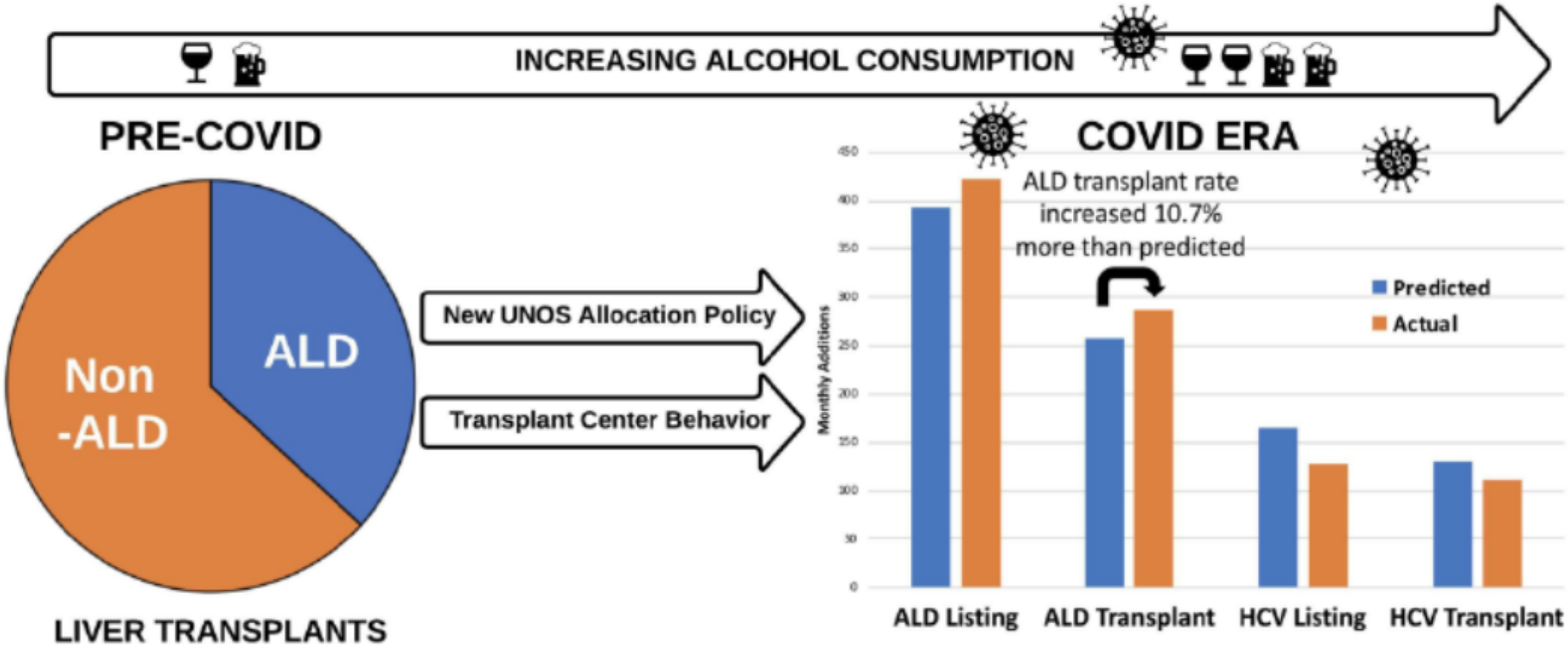
Liver Transplant in the Covid Era



Bloom and Fontana, Hepatology 2021

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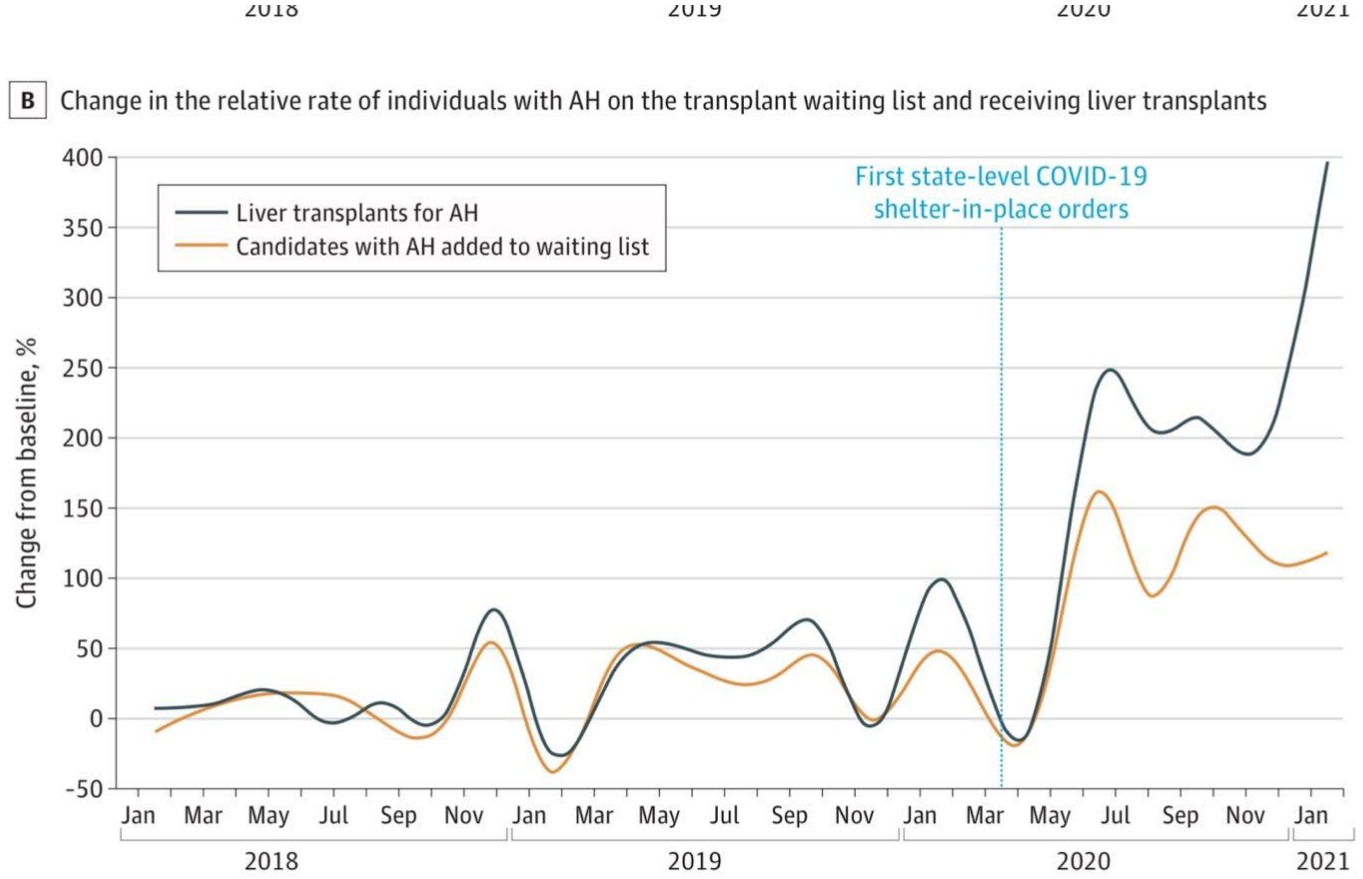
Relative Increase in AH Transplants



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Cause for Concern?

- Increased transplant for ALD will likely continue
- Wider differences in transplant center politics and practices
- Resource allocation concern: pts with severe ALT could outstrip the entire national supply of donor organs
  - Impact on other wait listed groups?
- Prognostic utility of MELD score less reliable in ALD
  - High ALD-MELD may have comparable mortality to non-ALT with lower MELD scores

Bloom and Fontana, Hep 2021; Cholankeril et al, Hep 2021

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In Summary…

- Risky alcohol use is on the rise
- Increased burden of ALD
- Treatment for severe AH is limited
- Early liver transplant is an increasingly available option for select patients
- What will the impact of ALD be on our health care system in years to come?

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Chronic Alcohol Related Cirrhosis

- Continued drinking is associated with eventual development of cirrhosis in ~20%
- Two-thirds present with decompensated disease
- 15-20% lifetime risk of HCC
- Excess mortality both in relation to liver disease and to other complications of alcohol abuse
- Five-year mortality rates:
  - Child A: 34%
  - Child B: 50%
  - Child C: 75%

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Transplant for Alcoholic Cirrhosis

- Survival benefit if MELD consistently > 15
- Most programs require an (arbitrary) 6 month period of abstinence
  - Allow for potential regression and allow for ample time for counseling to prevent relapse
- Rate of relapse after transplant varies among studies ranging from 10 to 50% depending on definition
  - Any alcohol or heavy alcohol?
- No difference in proportion of alcohol vs non-alcohol LT recipients who drank after transplant (17 vs 16% at 12 mo), however AC patients were more likely to drink excessively post-transplant

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Multi-systemic Effects of Chronic Alcohol

- Malnutrition
- Vitamin deficiencies
- Non-immune hemolytic anemia
- Peripheral and central nervous system abnormalities
- Depression and anxiety
- Nephropathy
- Alcoholic myopathy and muscle wasting

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Malnutrition in Alcoholic Cirrhosis

- Up to 90% of patients with AC are clinically malnourished
- Disproportionately worse nutritional status compared to other cirrhosis
- Underlying mechanisms include:
  - Poor dietary intake – anorexia, altered taste, nausea
  - Maldigestion due to pancreatic insufficiency
  - Malabsorption due to bile acid deficiency
  - Impaired motility and bacterial overgrowth
  - Loss of proteins 2/2 portal hypertension, hypermetabolic state, insulin resistance, and impaired protein synthesis

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Malnutrition in Alcoholic Cirrhosis

- Correlates with higher rates of complications: variceal bleeding, ascites, encephalopathy, infections, and HRS
- Correlates with mortality, including post-transplant
  - Recent study on 363 AH patients, reporting a one year mortality of 14% and 76% in those with mild or severe malnutrition
- Sarcopenia a risk for more severe encephalopathy - as skeletal muscle is a major non-hepatic organ for ammonia disposal

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Malnutrition and Sarcopenia

Management of Malnutrition
Step 1: Abstinence from alcohol
Step 2: Nutritional support: increased protein/caloric intake Oral or enteral supplementation • 2000 kcal daily • 1.5 g/kg/day protein Frequent small meals Avoid fasting, eat before bed and upon awakening Amino acid supplementation Micronutrient replacement • Zinc, vitamin D, thiamine, folate, cyanocobalamin, and selenium
Step 3: Increase physical activity

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Abstinence Support

- Rehab and inpatient treatment is best
- AA works, but consider alternatives
- Pharmacotherapy
  - Acomprosate (Campral)
  - Naltrexone (Revia, Vivitrol)
  - Disulfram (Antabuse)
  - Gabapentin
  - Sertrialine
  - Topiramate

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ALD and Women

- Women develop ALD with lower amounts (approx. 50% male counterparts)
- Women develop ALD on average 3 years earlier
- Women are more likely to present with *severe* alcoholic hepatitis without prior dx of ALD
- We are seeing epidemic rates of ALD among younger, rural, minority women
- Need a high index of suspicion to diagnose ALD early enough to be reversible – women underreport, don't ask for help
- Covid has been hard on women and moms…

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Thank You!

blaire.burman@commonspirit.org
Clinic: 206-223-2319
Cell: 646-306-7143