Acute Alcohol Associated Hepatitis for Liver Disease ECHO 2021

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Disclosures

- None

Goals of Presentation

- Understand diagnosis and treatment of alcohol associated hepatitis

Pre-Test Question

Which test should you use to decide if a patient with alcohol-associated hepatitis should be placed on corticosteroids?

a. **Lille score**
b. **MELD score**
c. **Maddrey DF score**
d. **CTP score**

Clinical Diagnosis of AH

- Onset of jaundice within prior 8 weeks
- Ongoing consumption of alcohol/day of > 40 g/female, >60 g/male
  - Heavy Alcohol usage <60 days of before the onset of jaundice
- AST >50, AST/ALT > 1.5, and both values < 400 IU/L
- Serum total bilirubin >3.0 mg/dl

1 drink = 10-12 g/alcohol, which is:

1 12 oz beer

1 5 oz glass of wine

1 1.5 oz shot of liquor

Clinical diagnosis of AH

- Onset of jaundice within prior 8 weeks
- Ongoing consumption of >40 (female) or 60 (male) g alcohol/day for ≥6 months, with <60 days of abstinence before the onset of jaundice
- AST >50, AST/ALT >1.5, and both values <400 IU/L
- Serum total bilirubin >3.0 mg/dL

Potential confounding factors

- Possible ischemic hepatitis (e.g., severe upper gastrointestinal bleed, hypotension, or cocaine use within 7 days) or metabolic liver disease (Wilson disease, alpha 1 antitrypsin deficiency)
- Possible drug-induced liver disease (suspect drug within 30 days of onset of jaundice)
- Uncertain alcohol use assessment (e.g., patient denies excessive alcohol use)
- Presence of atypical laboratory tests (e.g., AST <50 or >400 IU/L, AST/ALT <1.5), ANA >1:160 or SMA >1:80.

Clinical Manifestations

- Symptoms
  - fatigue, anorexia, weight loss, abdominal pain
  - ascites, encephalopathy, upper GI bleeding
- Findings
  - hepatomegaly, tender RUQ, jaundice, fever
  - splenomegaly, hepatic bruit, collateral vessels
  - ascites, poor nutritional status

Potential Confounding Factors

- Ischemic hepatitis secondary to UGI bleed, hypotension or cocaine use
- Underlying liver disease: HCV, HBV, NAFLD, labs consistent with AIH or other liver diseases
- Drug induced liver disease
- AST < 50 or > 400 IU/ml or AST/ALT ratio <1.5

Laboratory Findings

- Elevated transaminases
  - < 10x upper limit normal or 400 IU/ml
  - AST > ALT
  - levels have no prognostic utility
- Leukocytosis
- Elevated bilirubin and alkaline phosphatase
- Elevated prothrombin time

Pathogenic Mechanisms

- Tumor Necrosis Factor (TNF- α)
  - activates cascades that include cell death
  - can cause fever, neutrophilia, hypotension
  - promoted by uptake of endotoxin from gut
  - increased in alcoholic hepatitis, correlates with mortality

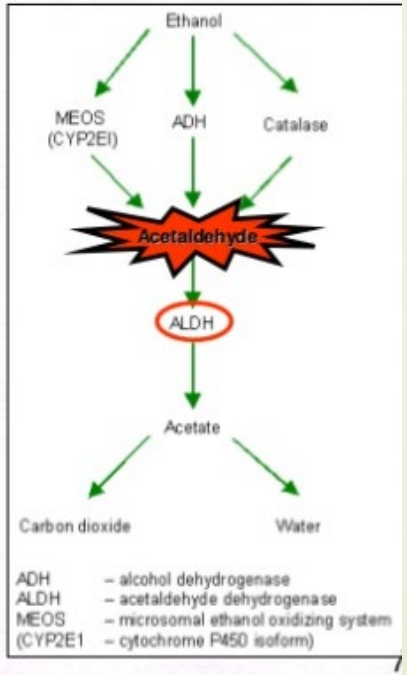
Pathophysiology of ASH

- Oxidative stress
  - contributes to alterations in membrane function
  - ethanol induces cytochrome P450 2E1, which produces toxic oxidants
- Acetaldehyde
  - oxidation product of ethanol via ADH
  - depletes glutathione, a key antioxidant
  - promotes collagen production and fibrosis

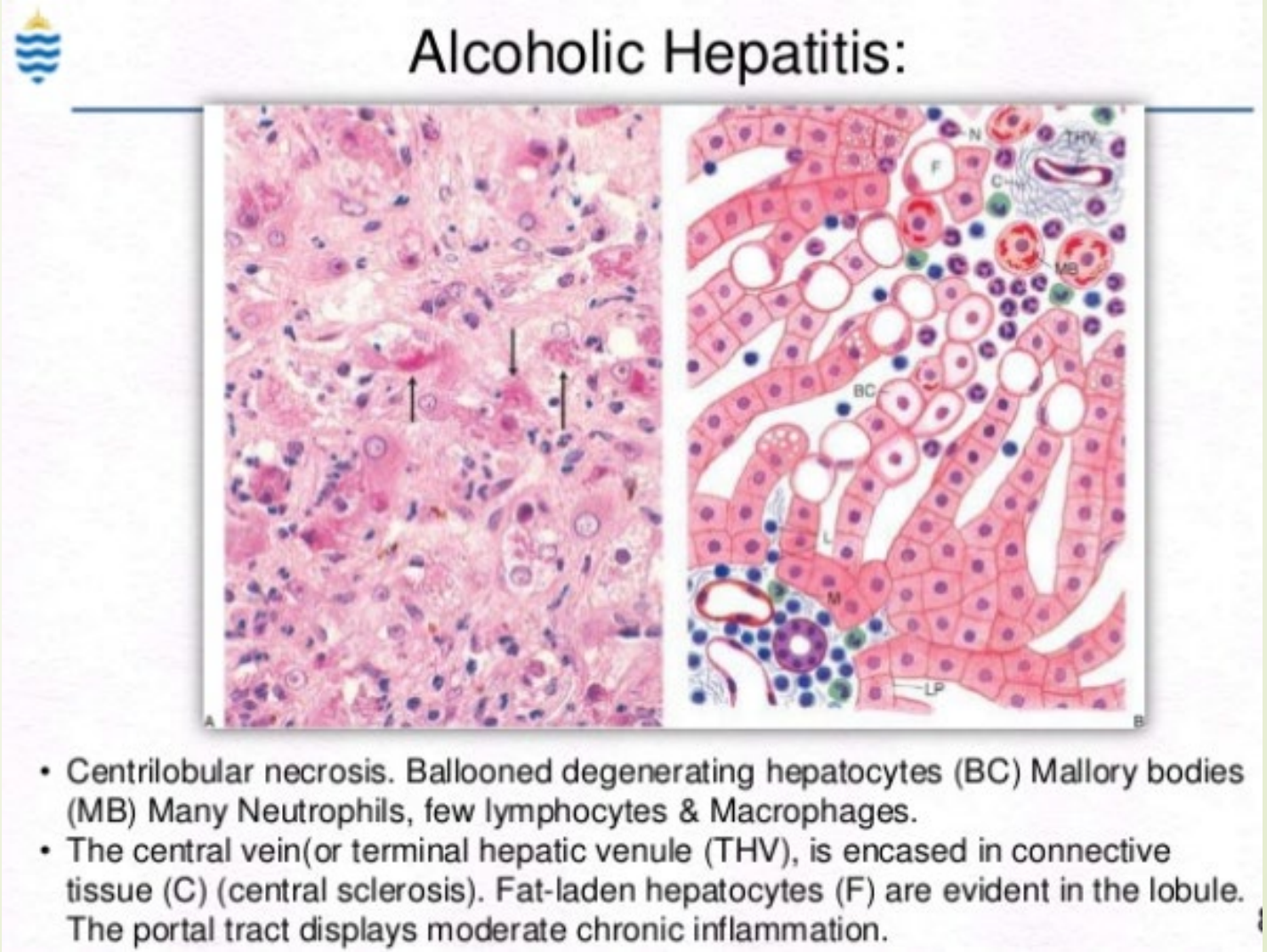
Pathogenesis

Alcoholic Liver Injury: Pathogenesis

- Diversion of fat metabolism to alcohol – fat storage.
- Acetaldehyde – hepatotoxic – denatures Proteins
- Increased peripheral release of fatty acids.
- Alcohol stimulates collagen synthesis
- Mutant ALDH2 gene with low activity enzyme is observed in Caucasians but is found in some 40% of Orientals (autosomal dominant).

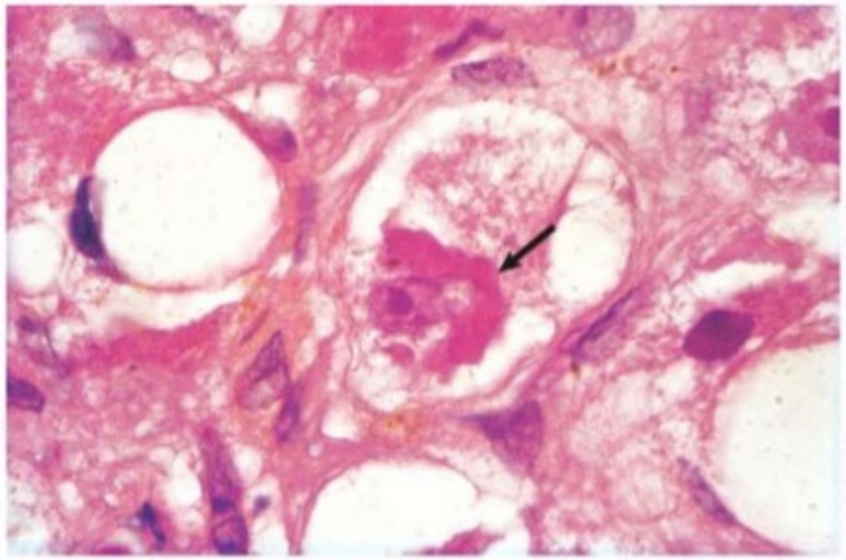


Acute Alcoholic Hepatitis

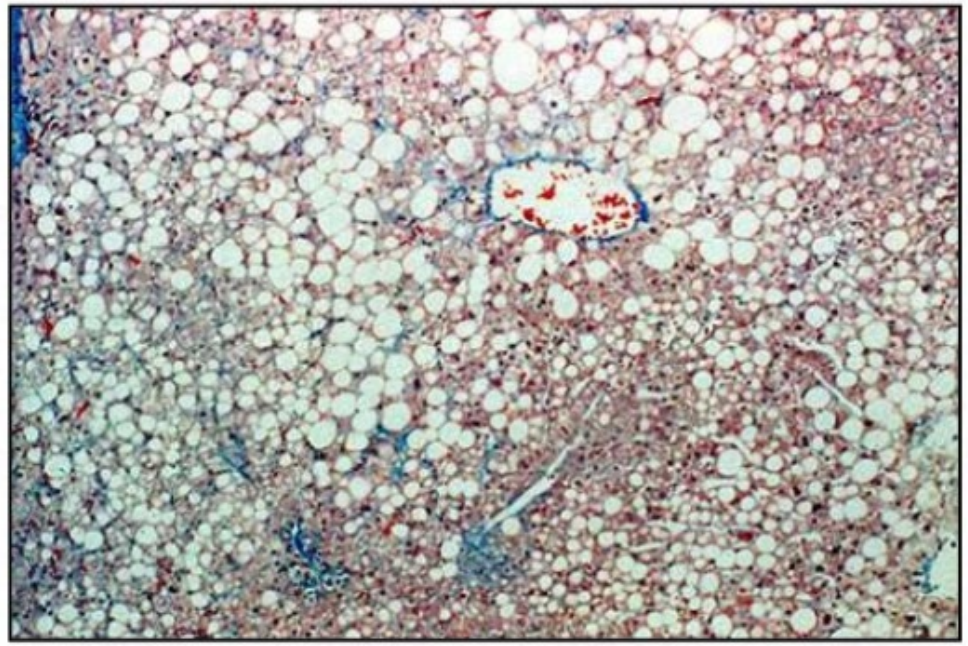


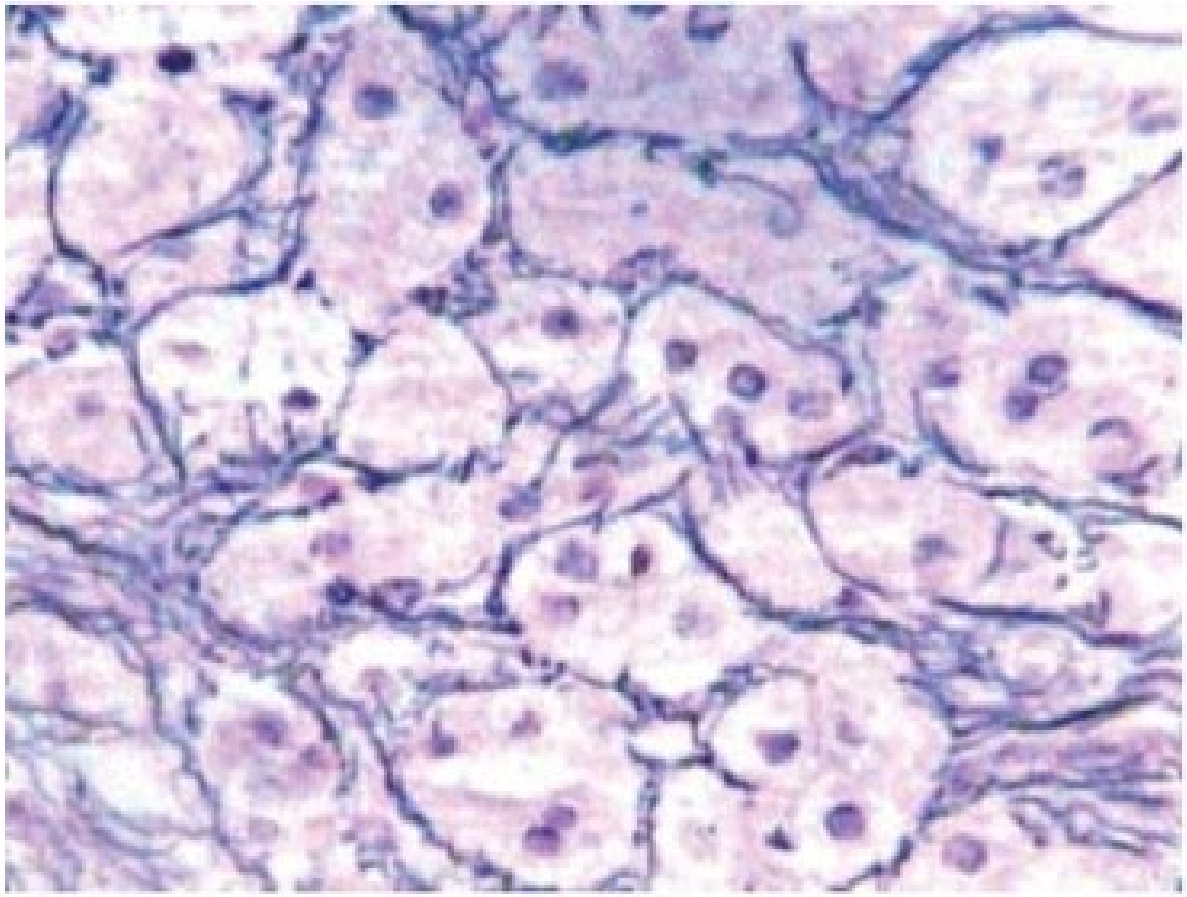
- Centrilobular necrosis. Ballooned degenerating hepatocytes (BC) Mallory bodies (MB) Many Neutrophils, few lymphocytes & Macrophages.
- The central vein(or terminal hepatic venule (THV), is encased in connective tissue (C) (central sclerosis). Fat-laden hepatocytes (F) are evident in the lobule. The portal tract displays moderate chronic inflammation.

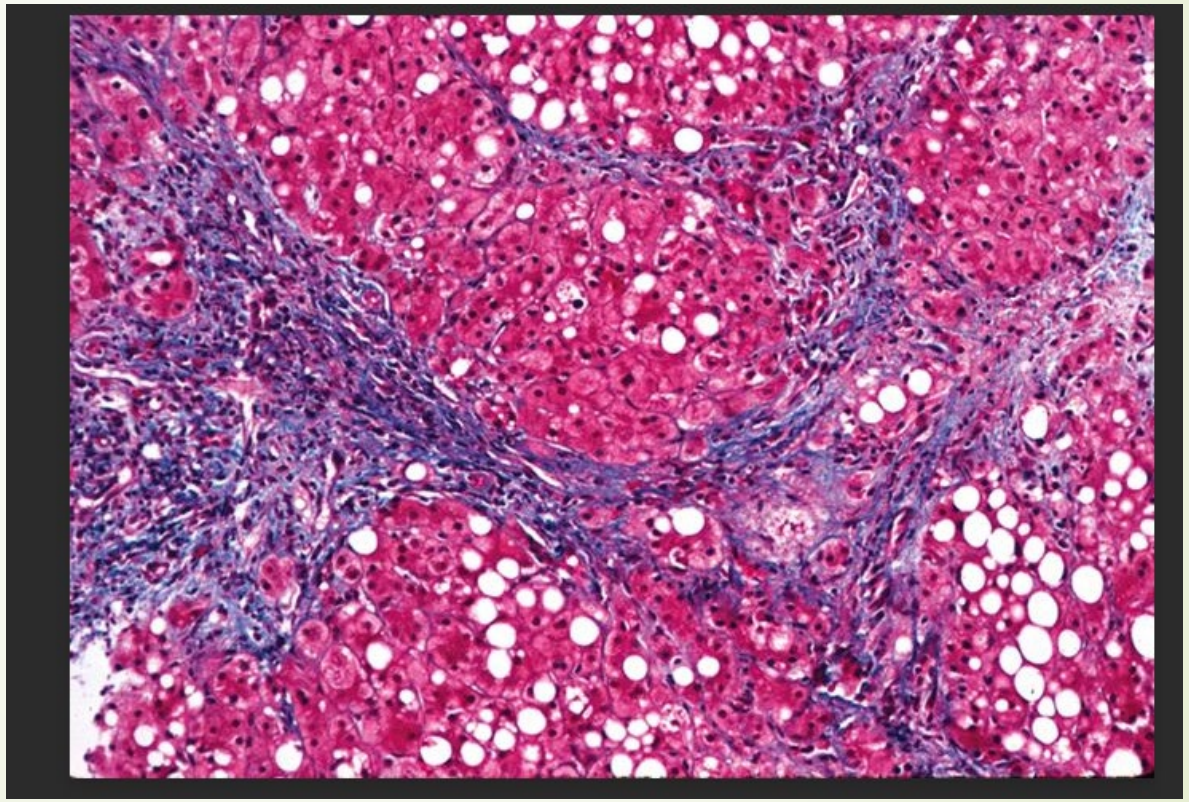
Alcoholic hepatitis & Mallory Hyalin:



Alcoholic Fatty Liver - collagen stain







Prognostic Factors in Acute Alcoholic Hepatitis

- Modified Maddrey Discriminant Function
  - [4.6 x (Prothrombin time – Control or normal) + T. Bilirubin
  - Mortality 50% if modified DF $\geq$ 32 (original DF > 93): initiate corticosteroids
- MELD score ABIC (albumin, bilirubin, INR, creatinine):
  - >20 suggests need for corticosteroids
  - Rising MELD score indicates poor prognosis
- Glasgow Alcoholic Hepatitis Score: may be better at predicting 28 day mortality
- Lille Score: incorporates change in bilirubin at 7 days after starting corticosteroids to assess early treatment response and utility of continuation.

Mayo Clinic End Stage Liver Disease Score: MELD Score

- https://www.thecalculator.co/health/MELD-Calculator-421.html
- Gives 1, 3 and 6 month mortality
- Prognosis is guarded if admission score is >20

Lille Score

- The Lille score differs as a dynamic score by incorporating the change in bilirubin at 7 days after starting corticosteroids to assess early treatment response and the utility of its continuation for 28-days.
- Nonresponse defined by the Lille score >0.45 predicts poor prognosis, supports cessation of corticosteroids
- Joint-effect model of MELD plus Lille outperformed other combinations such that for a patient with MELD >21and Lille >0.45 had a 1.9-fold higher risk of death at 2 months than one with MELD <21 and Lille 0.16 (23.7% vs 12.5%).*

https://www.mdcalc.com/lille-model-alcoholic-hepatitis

*Louvet A et al, Gastroenterology. 2015;149(2):398-406

Lille model

- Proposed for predicting mortality in patients with severe alcoholic hepatitis who have been treated with corticosteroids .

- Combines six variables
  - age
  - Renal insufficiency (Cr >1.3 or creatinine clearance <40)
  - Albumin
  - Prothrombin time
  - Bilirubin and
  - evolution of bilirubin at day 7 .

- Performed better than the Child-Pugh score, discriminant function, or Glasgow score in predicting survival at six months.

Who to Treat

- Supportive Care:
  - Maddrey Discriminant Factor <32
  - MELD ≤ 20
- Treatment:
  - Maddrey Discriminant Factor ≥32
  - MELD >20

Treatment

- Supportive care
- Corticosteroids: If Maddrey criteria met and no contraindications
- N-Acetylcysteine: consider if patient fails Lille Score
- Pentoxifylline: currently in the “dog house”
- Nutritional Therapy
- Zinc
- Early intervention from Behavioral Health!
  - Do it on admission. Don’t wait until discharge

Supportive Care

- Abstinence from alcohol most important
  - One study showed 63% survival if abstinent, 40% if continued drinking
  - Study of 61 patients with AH on biopsy showed 18% progression to cirrhosis if abstinent, 38% if not
  - Continued clinical & lab improvement x6 and even 12 months.
- Replacement of fluid, electrolytes, including Mg, PO4
- Treat DTs, replace thiamine and other B vitamins as needed
- Protein: Promotes regeneration and corrects malnutrition and sarcopenia
- Zinc
- Coffee

Corticosteroid Therapy

- 12 randomized controlled trials (RCTs), 3 placebo controlled, double blind
  - Inconsistent result
- 3 meta analyses support corticosteroids
- Recent STOPAH trial with 1103 patients with AH found modest support for prednisolone but not pentoxifylline*
- Dose: prednisolone 40 mg for 28 days

*Thursz MR et al. N Engl J Med. 2015;372(17):1619-1628.

N-Acetylcysteine

- Randomized controlled trial in France, co-administration of intravenous N-acetylcysteine(NAC)with corticosteroids reduced some early complications (infection, hepatorenal syndrome) compared to corticosteroids alone
- Prednisolone plus NAC arm improved 1-month mortality compared with prednisolone plus placebo (8% vs 24%; P=.006)
- Benefit not seen at 3 or 6 months
- IV Dose is the same as used for acetaminophen toxicity

Nguyen-Khac E et al. N Engl J Med.2011;365(19):1781–1789

Zinc

- Most patients with chronic alcohol abuse and AH are zinc deficient.
- Zinc has been shown to contribute to improving gut mucosal barrier integrity in animal models of ALD and in small pilot human clinical trials.
- Because of the established role of gut-derived pathogen-associated danger molecules in AH, use of therapeutic doses of zinc should be considered in moderate and severe AH

Quintuple Therapy for Acute Alcoholic Hepatitis if Circumstances Warrant

- Prednisolone
- Zinc
- Fluids, electrolyte and Mg replacement
- N-acetylcysteine
- Protein and other nutrients
- Coffee: Caffeinated or Decaf

Outcome in Alcohol Associated Hepatitis

- Three possible outcomes can generally be divided into thirds
  1. Full recovery within 6 months
  2. Mortality within 90 days
  3. Improvement but liver failure remains after 4 to 6 months
     1. Half of these patients have high MELD scores above 20 and are candidates for liver transplantation
     2. Half end up in "MELD Hell" with MELD scores 10 to 17, not high enough to qualify for transplant but have debilitating conditions such as ascites, encephalopathy, sarcopenia and fatigue
     3. Living donor transplant is a potential option for these patients in MELD Hell

Other treatment in study

- Drugs in trial for NASH
- Drugs that target leaky gut barrier and endotoxin
- Immune active drugs and other compounds that effect liver cell death and collagen generation

Liver Transplant (LT)

- ALD is now a leading indication for patients undergoing LT in the US
- 1 year survival for ALD after LT is among highest of all indications
- Relapse use of ETOH to > 20g/d women, 30 g/day men about 20% during first 5-years
- 6-month sobriety rule is being relaxed in some centers
- Few centers are now transplanting young patients with severe acute alcoholic hepatitis but criteria are very strict
  - 1-year post LT survival 77% vs. 23% overall,
  - Patients with no previous episode of AH 1-year survival 94%, 3-year 84%
  - Return to sustained alcohol use: 10% at 1-year and 17% at 3-years post LT

Does Treatment for Alcohol Use Disorder affect Outcomes after Diagnosis of Cirrhosis?

- Large Retrospective cohort study from VA in patients with cirrhosis and alcohol use: 35,682 patients of whom 5,088 received AUD treatment in the first 180 days after diagnosis
  - 4,461 received behavioral therapy alone
  - 159 pharmacotherapy alone
  - 468 received both behavioral and pharmacotherapy
- In adjusted analysis, behavioral and/or pharmacotherapy significantly reduced the incidence of hepatic decompensation (6.5% vs. 11.6% adjusted odds ratio {AOR) 0.63; 95% CI 0.52-0.76)
- Extended beyond 180 days any AUD treatment significantly reduced mortality (AOR, 0.87, 95% CI 0.80-0.96)
  - Persons who received baclofen had significantly lower Audit-C scores at last f/u
  - Audit-C scores were associated with death (AOR/point 1.06; 95%CI 1.04, 1.09)

Rogal S et al. Hepatology 2020;71:2080-2092

Conclusions

- Overall alcohol use has increased dramatically in all ethnic and racial groups in the USA
  - Binge drinking rates have increased in young people including those in high school and college
- Alcohol associated deaths have more than doubled in the past 2 decades
- Screening all teenagers and adults for alcohol use should be done at each visit
  - Audit-C test or equivalent is recommended
- Effective drugs to decrease alcohol craving are available
  - Baclofen can be used safely in persons with cirrhosis

Conclusions Continued

- The mainstay of treatment for alcoholic hepatitis is corticosteroids
  - Criteria for starting (Maddrey DF, MELD) and stopping (Lille score after 1 week of corticosteroids) are available on line
  - Add Zinc for all persons with AH
  - Supportive drugs to consider adding on are N-acetylcysteine
  - Replacing electrolytes, fluids are critical
  - Nutritional support with a high protein diet is important
  - Coffee can be a welcome adjuvant to therapy
  - Acetaminophen should be avoided in anyone who drinks heavily even if they have no liver disease

Post-Test Question

Which test should you use to decide if a patient with alcohol-associated hepatitis should be placed on corticosteroids?

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