



Alcohol Associated Liver Disease

Brian J McMahon MD

Director: Liver Disease and Hepatitis Program

ANTHC





Conflicts of Interest



None

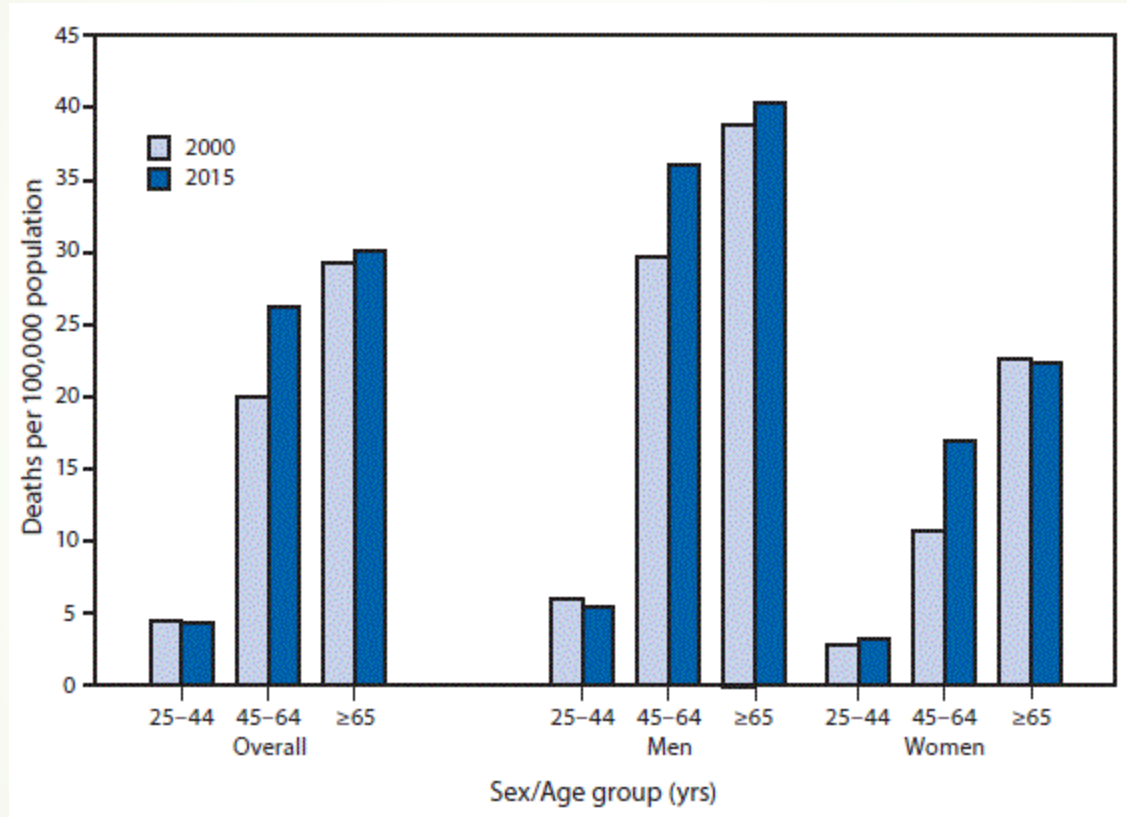




Goals of Presentation

- ▶ Understand purported safe amounts of alcohol and how to screen persons for alcohol history
- ▶ Understand types of alcoholic liver disease
- ▶ Understand diagnosis and treatment of alcohol related hepatitis
- ▶ Understand management of alcohol related cirrhosis
- ▶ Liver transplantation in alcoholic related liver failure

Death Rates* for Chronic Liver Disease and Cirrhosis,[†] by Sex and Age Group — National Vital Statistics System, United States, 2000 and 2015






Death rates for chronic liver disease and cirrhosis: MMWR September 29, 2017 / 66(38);1031 and Alcoholism: Clinical and Experimental Research 2020

- ▶ The number of death certificates mentioning alcohol > doubled 35,914 in 1999 to 72,008 in 2017 (2.6% of all deaths)
 - ▶ 31% due to liver disease
 - ▶ 18% over dose on alcohol with or without other drugs
- ▶ From 2000 to 2015, in the United States increased 31% (from 20.1 per 100,000 to 26.4)
- ▶ Among persons aged 45–64 years. increased 21% for men (from 29.8 to 36.2) and 57% for women (from 10.8 to 17.0).
- ▶ Among persons aged 25–44 years, the death rate for men decreased 10% (from 6.1 to 5.5), and the rate for women increased 18% (from 2.8 to 3.3).
- ▶ Overall, among persons aged ≥ 65 years, rates increased 3% (from 29.4 to 30.2).
- ▶ Death rates for both men and women increased with age.



Epidemiology of Alcohol-Related Liver Disease

- ▶ Prevalence alcohol use disorder in adults increased by 50% between 2000 and 2013
 - ▶ Marked increase in binge drinking
- ▶ Estimated prevalence in US is ~2% of population
- ▶ Increase in AC mortality between 2008 and 2016
 - ▶ Especially amongst patients between 25-34.



Patterns of Alcohol Usage Suggesting Alcohol Use Disorder

- ▶ Binge drinking: ≥ 5 drinks at a time that occurs monthly or more often
- ▶ Daily alcohol intake:
 - ▶ Men: > 2 drink/day
 - ▶ Women: > 1 drink/day
 - ▶ Alcohol affects women far than men because
 - ▶ Women on average have a lower volume of distribution
 - ▶ Levels of gastric alcohol dehydrogenase are 30%-50% lower in women so less alcohol gets metabolized in the gut and more circulates in the blood
- ▶ For patients with ALD or other liver diseases, in particular NAFLD, NASH, viral hepatitis, and hemochromatosis: there is no safe level of drinking, and they should abstain



Screening for Alcohol Use Disorder

- ▶ All adolescents and adults should be screened by providers for alcohol use disorder
- ▶ Best test is the Alcohol Use Disorders Inventory Test (AUDIT): Its abbreviated version AUDIT-C
 - ▶ This test is widely used, validated and also recommended by the US Preventive Services task Force (USPSTF)
 - ▶ AUDIT-C has only 3 questions and takes < 30 seconds to complete
 - ▶ Scores of ≥ 3 in women and ≥ 4 in men may indicate harmful alcohol use
 - ▶ AUDIT-C performs better than CAGE or other tests
 - ▶ The LDHP program administers AUDIT-C to all patients we see in clinic



AASLD Guidance Recommendations for Screening for Alcohol-Use Disorder

- ▶ All patients in any primary or specialty clinic, ED departments and inpatient should be screened for alcohol use using validated questionnaires.
- ▶ Brief intervention, pharmacotherapy, and referral to treatment should be offered to patients engaged in hazardous drinking (AUDIT-C ≥ 4 , AUDIT > 8 , binge drinkers)

www.AASLD.org/practice guideline



AASLD Guidance 2019

- Referral to AUD treatment professionals is recommended for patients with advanced ALD and/or AUD in order to ensure access to the full range of AUD treatment options.
- Multidisciplinary, integrated management of ALD and AUD is recommended and improves rates of alcohol abstinence amongst ALD patients.
- Based on limited data, the use of acamprosate or baclofen can be considered for the treatment of AUD in patients with ALD



Pharmacotherapy for Alcohol-use Disorder (AUD)

- ▶ Baclofen, a GABA-B receptor agonist, is the only AUD pharmacotherapy that has been tested in a randomized controlled fashion in AC patients with AUD as well as in two small, uncontrolled observational studies.
- ▶ FDA approved medications:
 - ▶ Disulfiram: liver metabolized, not safe in advanced liver disease
 - ▶ Naltrexone: liver metabolized: not safe in advanced liver disease
 - ▶ Acamprosate: not metabolized in liver, safer in cirrhosis. No randomized trials
 - ▶ Other medications with less evidence and not FDA approved: gabapentin, topiramate, ondansetron, and varenicline



Factors Affecting the Risk of Alcohol-Related Liver Disease

Implicated in increasing the risk of alcohol-related liver injury

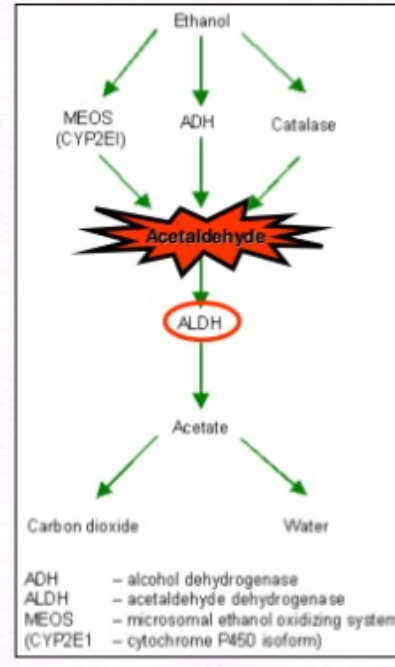
- Alcohol dose above threshold of 1 drink/day (women), 2 drinks/day (men)
- Pattern of consumption: daily drinking; drinking while fasting, binge drinking
- Smoking cigarettes
- Women compared to men
- Genetics*: PNPLA3, TM6SF2, MBOAT7, HSD17B13
- Increased body mass index
- Presence of co-morbid conditions: chronic viral hepatitis, hemochromatosis, NAFLD,

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).





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

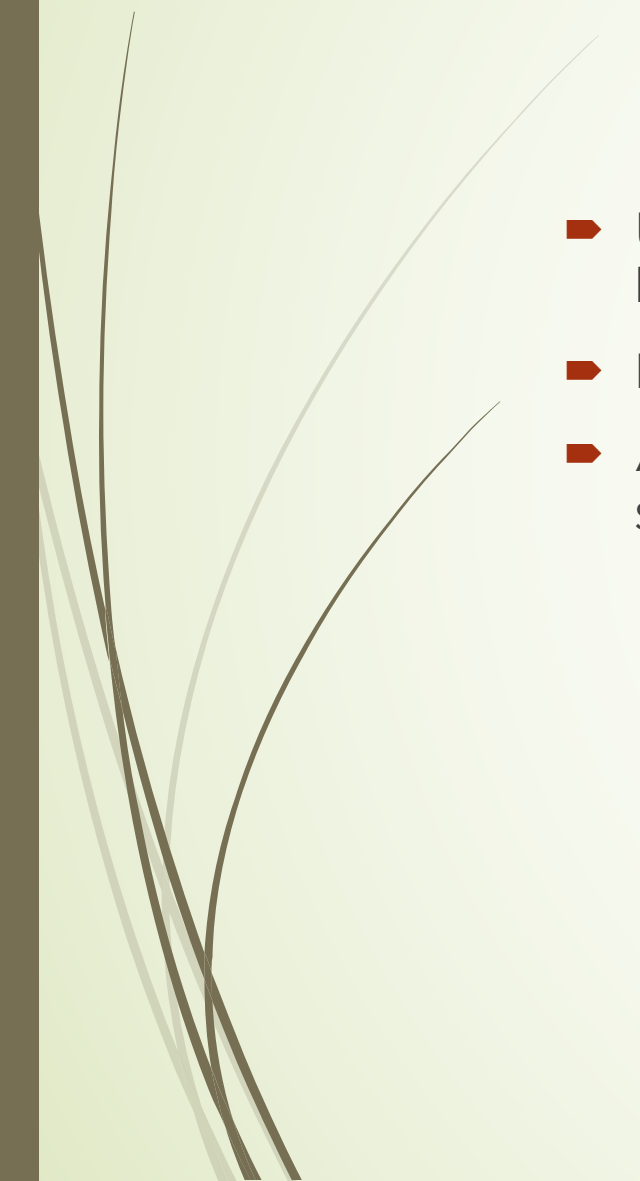


Types of Alcohol-Related Liver Disease

- ▶ Alcohol-related steatosis
 - ▶ Alcoholic hepatitis
 - ▶ Alcoholic-related cirrhosis (AC)
- 



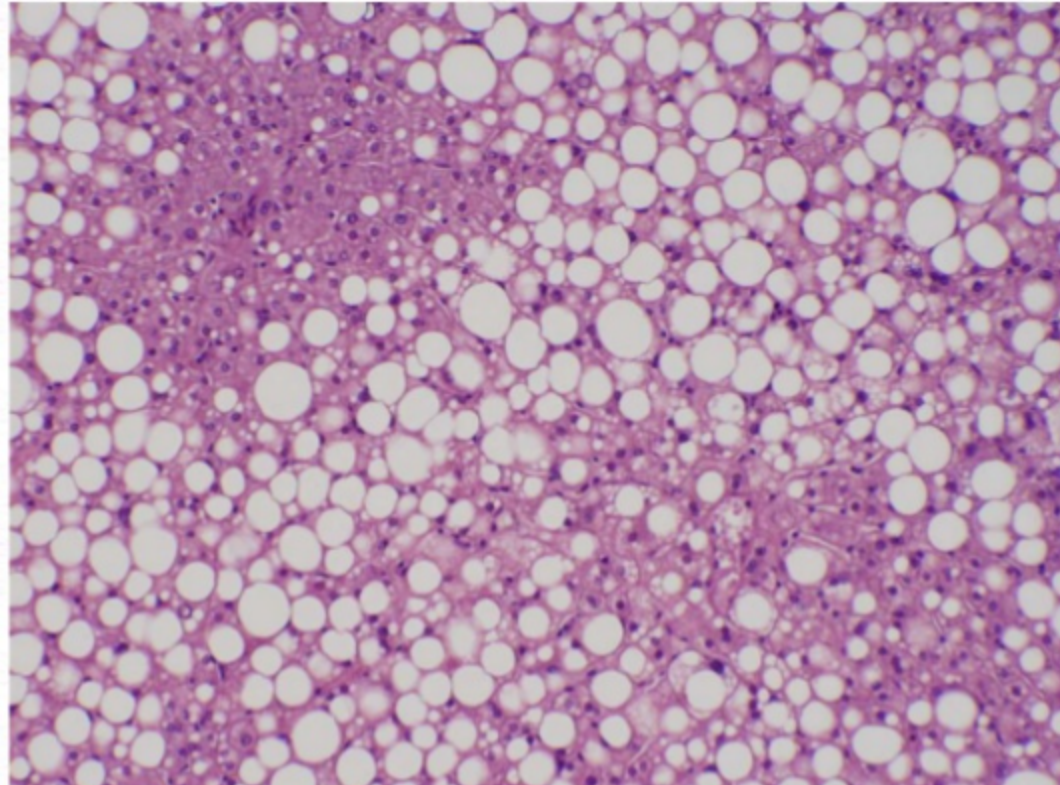
Alcoholic Associated Steatosis


- ▶ Up to 50% of persons with long-time alcohol use disorder (AUD) may only have steatosis in their liver
 - ▶ Patients may have elevated liver enzymes especially GGT
 - ▶ All persons found to have steatosis on ultrasound or liver biopsy should be screened for AUD with AUDIT-C or other test.
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Alcoholic Fatty Liver



Alcoholic Fatty liver:





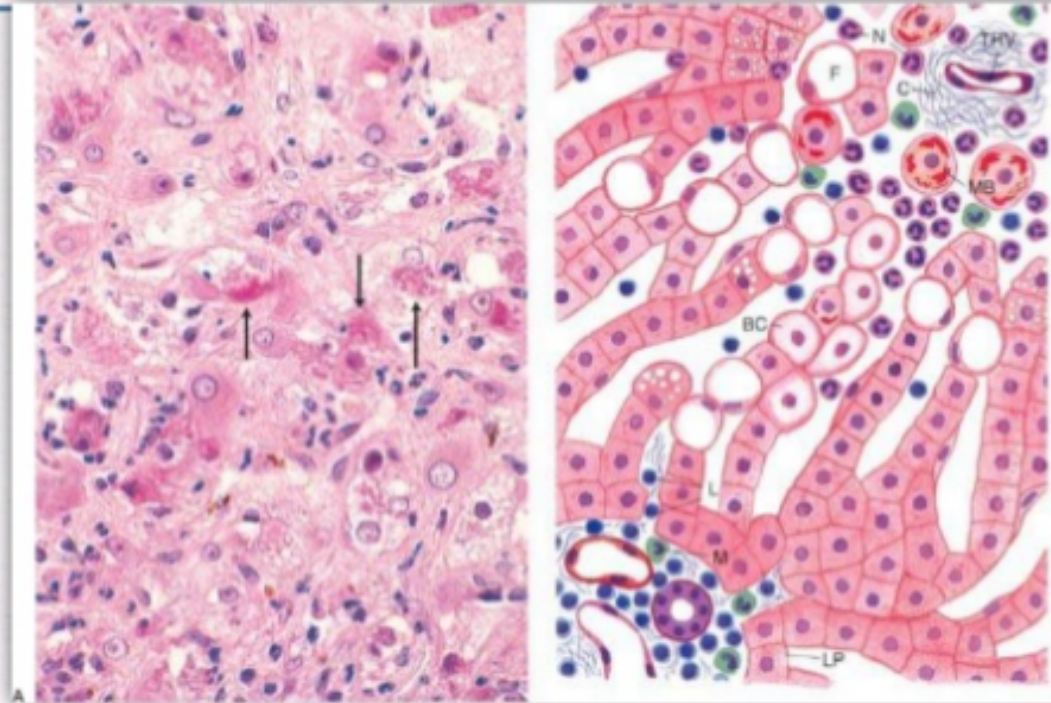
Histologic Findings: Acute Alcoholic Hepatitis

- ◆ Polymorphonuclear leukocyte infiltration
- ◆ Hepatocyte swelling and degeneration: Ballooning degeneration
- ◆ Macrovesicular & microvesicular steatosis
- ◆ Mallory bodies
- ◆ Pericentral and perisinusoidal fibrosis

Acute Alcoholic Hepatitis

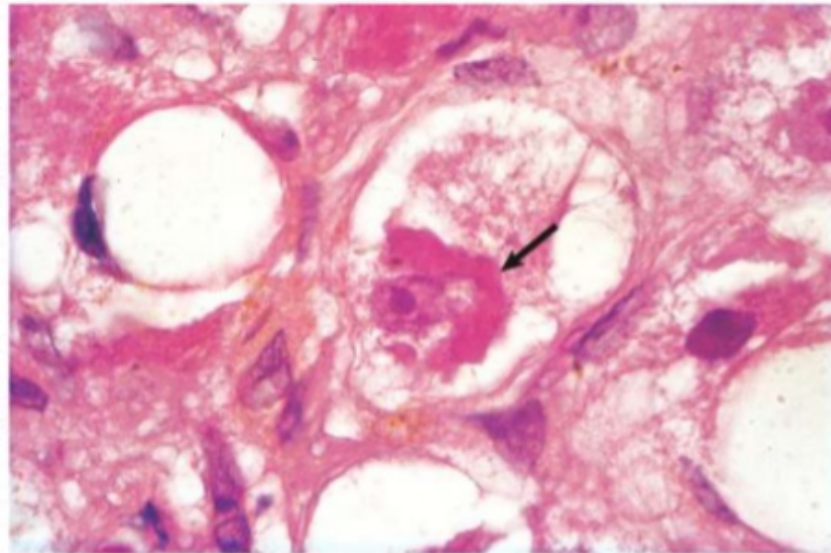


Alcoholic Hepatitis:



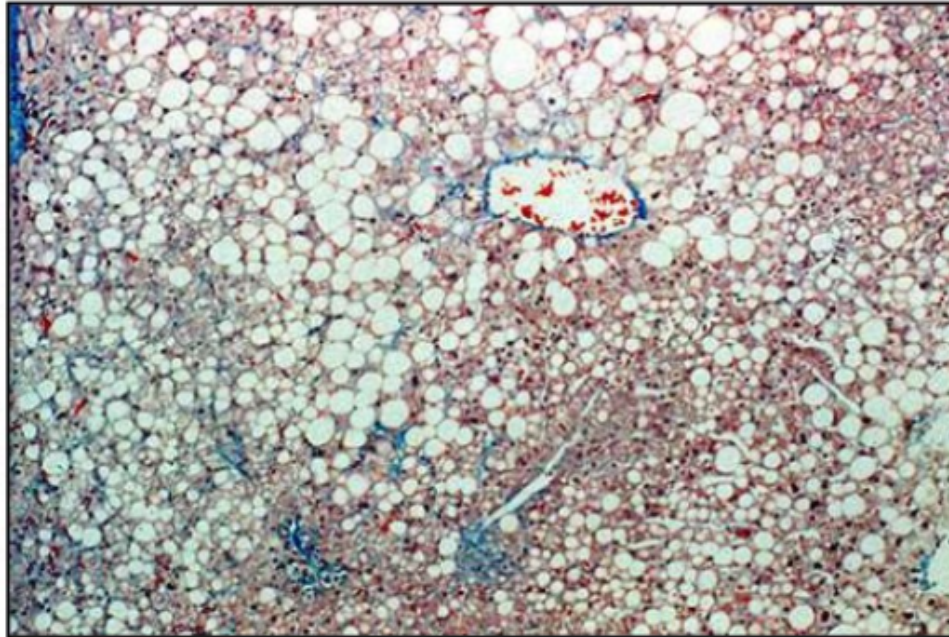
- Centrilobular necrosis. Ballooned degenerating hepatocytes (BC) Mallory bodies (MB) Many Neutrophils, few lymphocytes & Macrophages.
- The central vein(or terminal hepatic venule (THV), is encased in connective tissue (C) (central sclerosis). Fat-laden hepatocytes (F) are evident in the lobule. The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

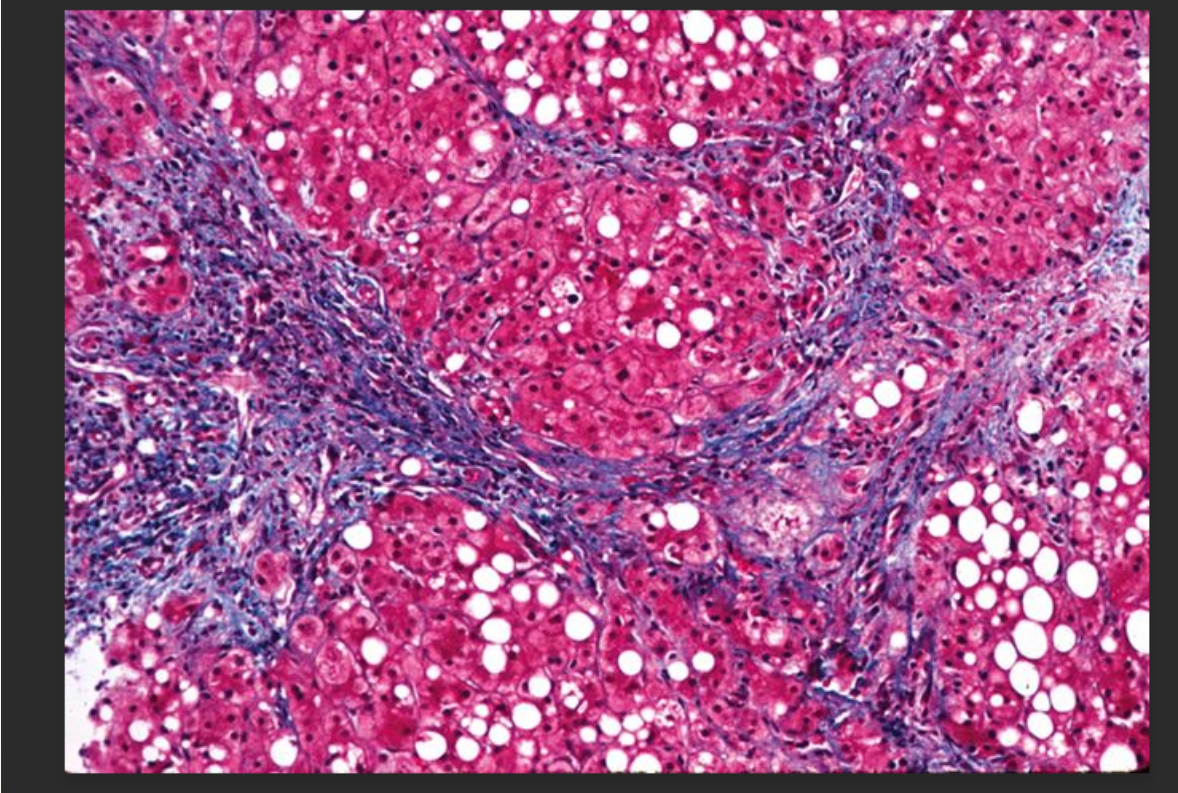
Alcoholic hepatitis & Mallory Hyalin:

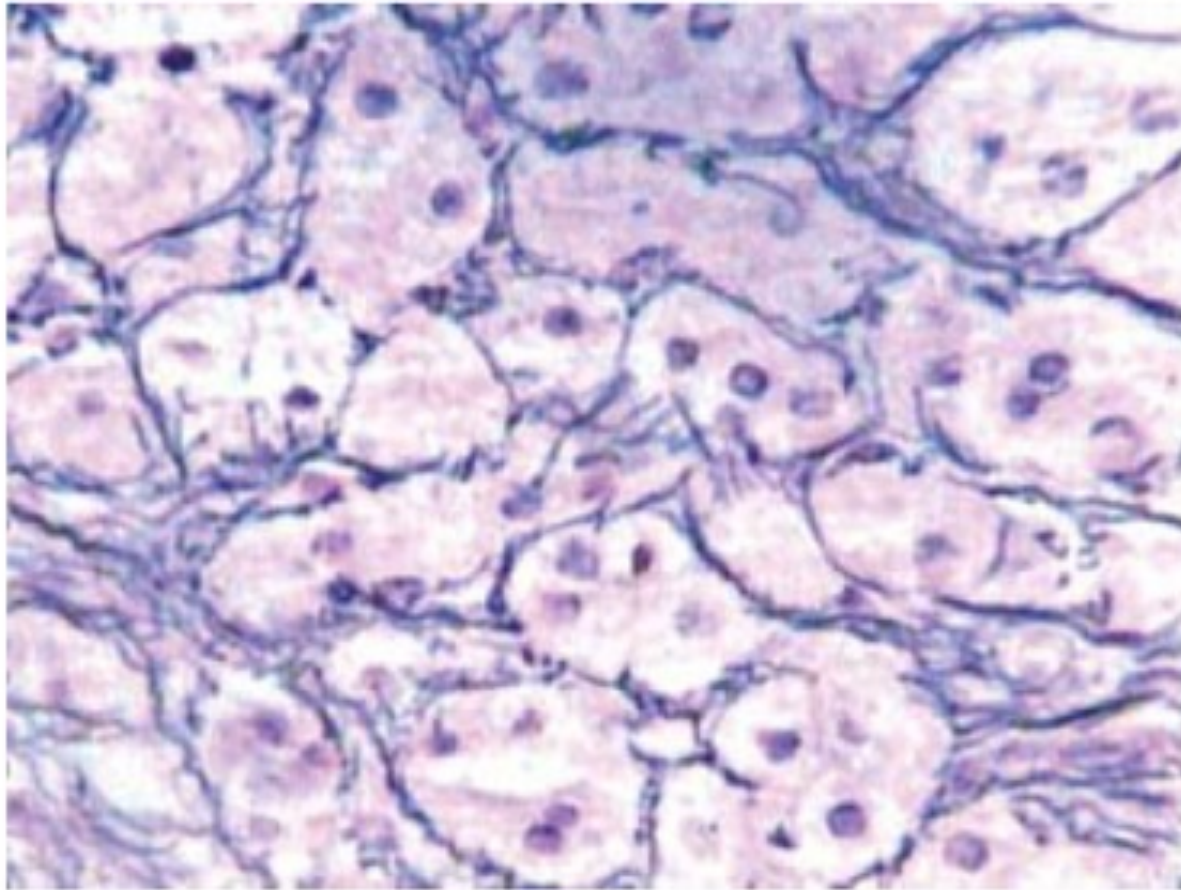


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Alcoholic Fatty Liver - collagen stain









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

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 Diagnosis of AIH

- ▶ Onset of jaundice within prior 8 weeks
- ▶ Ongoing consumption of alcohol/day of > 40 g/female, >60 g/male
 - ▶ Within <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

1 beer, 1 glass of wine, 1 shot of hard liquor + 10-12 g/alcohol



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



Quintuple Therapy for AIH

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



Not Effective for AH

- ▶ Vitamins other than B vitamins and antioxidants
- ▶ Pentoxifylline
- ▶ TNF inhibitors
- ▶ Insulin and glucagon,
- ▶ propylthiouracil
- ▶ JoJo juice, liver cleanse and herbals: Avoid like the plague!



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



Work-up and Treatment of Complications

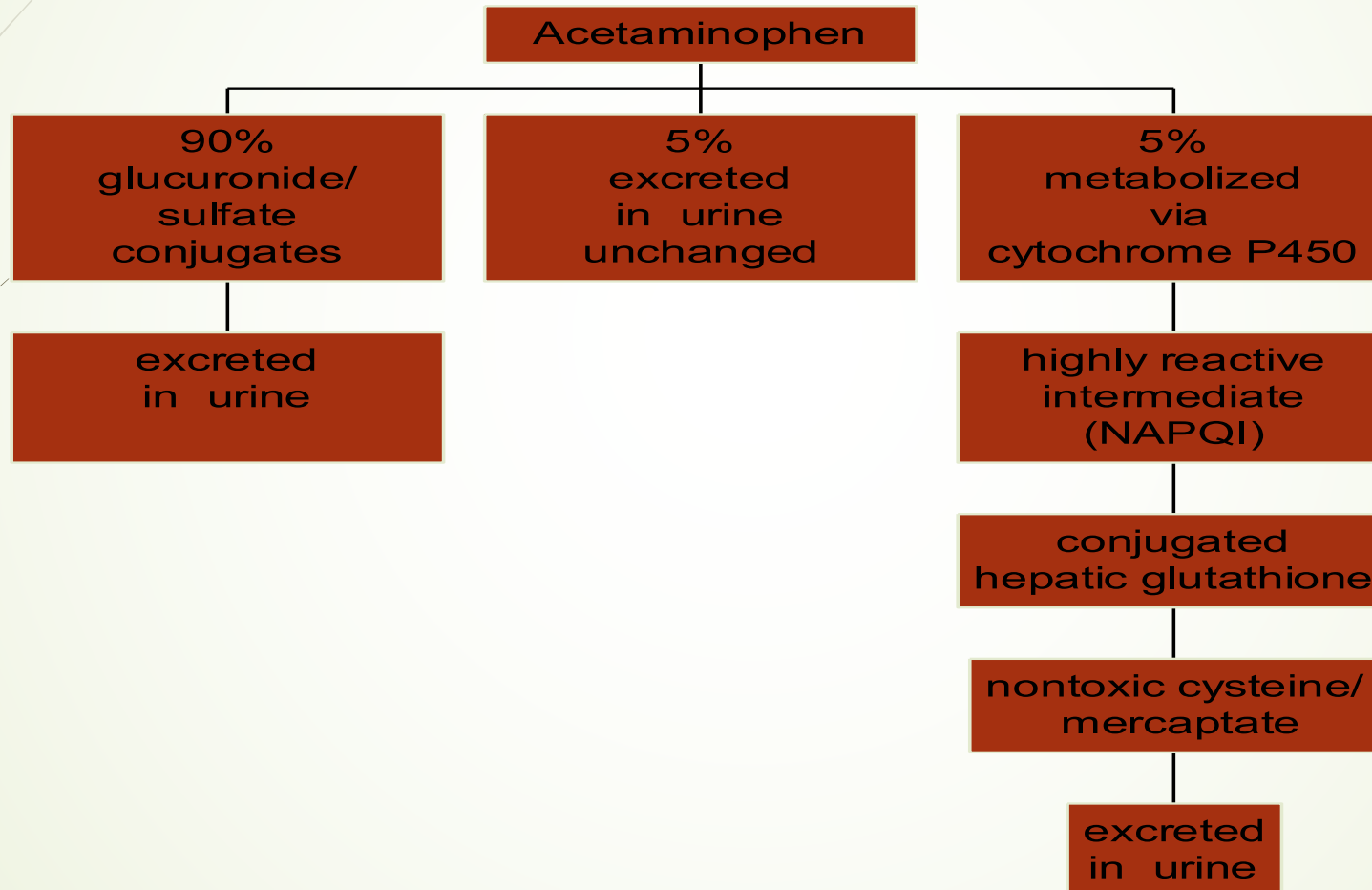
- ◆ Ascites -- diagnostic paracentesis for every patient on admission and repeat if any change in status such as fever, onset encephalopathy etc.
 - ◆ Diuretics
- ◆ Renal Failure (corticosteroids contraindicated)
- ◆ Encephalopathy – lactulose, Rifaximin
- ◆ GI bleeding – EGD for etiology, varices address, prophylactic antibiotics
- ◆ Hepatorenal syndrome
- ◆ Alcohol withdrawal



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

Acetaminophen Metabolism





Acetaminophen Toxicity in Chronic Alcoholism

- Depletion of glutathione stores due to chronic alcohol ingestion or malnutrition.
- Chronic Alcohol induces CYP2E1
- Results in enhanced generation of NAPQI.



Acetaminophen Use in Alcohol Use Disorder

- ▶ Therapeutic doses may cause severe acute fulminant hepatitis
- ▶ Severe hepatitis has been reported in patients with AUD with 2gms/day or less
- ▶ Best to avoid Acetaminophen in persons with AUD
- ▶ NSAIDS should be used with caution in persons with AUD and not at all if ascites present or creatinine elevated
- ▶ Therapeutic doses of acetaminophen (< 3 gms/day) and NSAID okay in those with liver diseases, including ALD without cirrhosis or with compensated cirrhosis IF THEY ARE ABSTAINING FROM ALCOHOL



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 Factor, MELD) and stopping (Lille score after 1 week of corticosteroids) are available on line
 - ▶ Supportive drugs to consider adding on are N-acetylcysteine and Zinc
 - ▶ 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 event if they have no liver disease