

NASH and ASH

Nicole Kershner, MD
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Topics to Be Discussed...

- Prevalence
- Pathogenesis
- Clinical Features/Presentation
- Diagnosis
- Role of Biopsy
- Treatment
- Prognosis
- Transplantation



Fatty Liver Definitions

- Non-Alcoholic Fatty Liver Disease (NAFLD): evidence of hepatic steatosis and no other cause for secondary hepatic fat accumulation
- Non-Alcoholic Steatohepatitis (NASH): presence of steatohepatitis and inflammation with hepatocyte injury with or without fibrosis
- Non-Alcoholic Fatty Liver (NAFL): presence of hepatic steatosis without hepatocellular injury

Prevalence of NAFLD/NASH

- Reported prevalence varies widely depending on the population studied
 - Estimates of worldwide prevalence of NAFLD ranges 6.3%-33% with a median of 20% in the general population
 - The prevalence of NASH is estimated to be between 3-5%
 - Compared to non-Hispanic whites, Hispanic individuals have a higher prevalence of NAFLD and non-Hispanic blacks have a lower prevalence

NAFLD/NASH

- High Risk Groups: Excessive BMI, Visceral Obesity, Type 2 Diabetes Mellitus (Metabolic Syndrome)



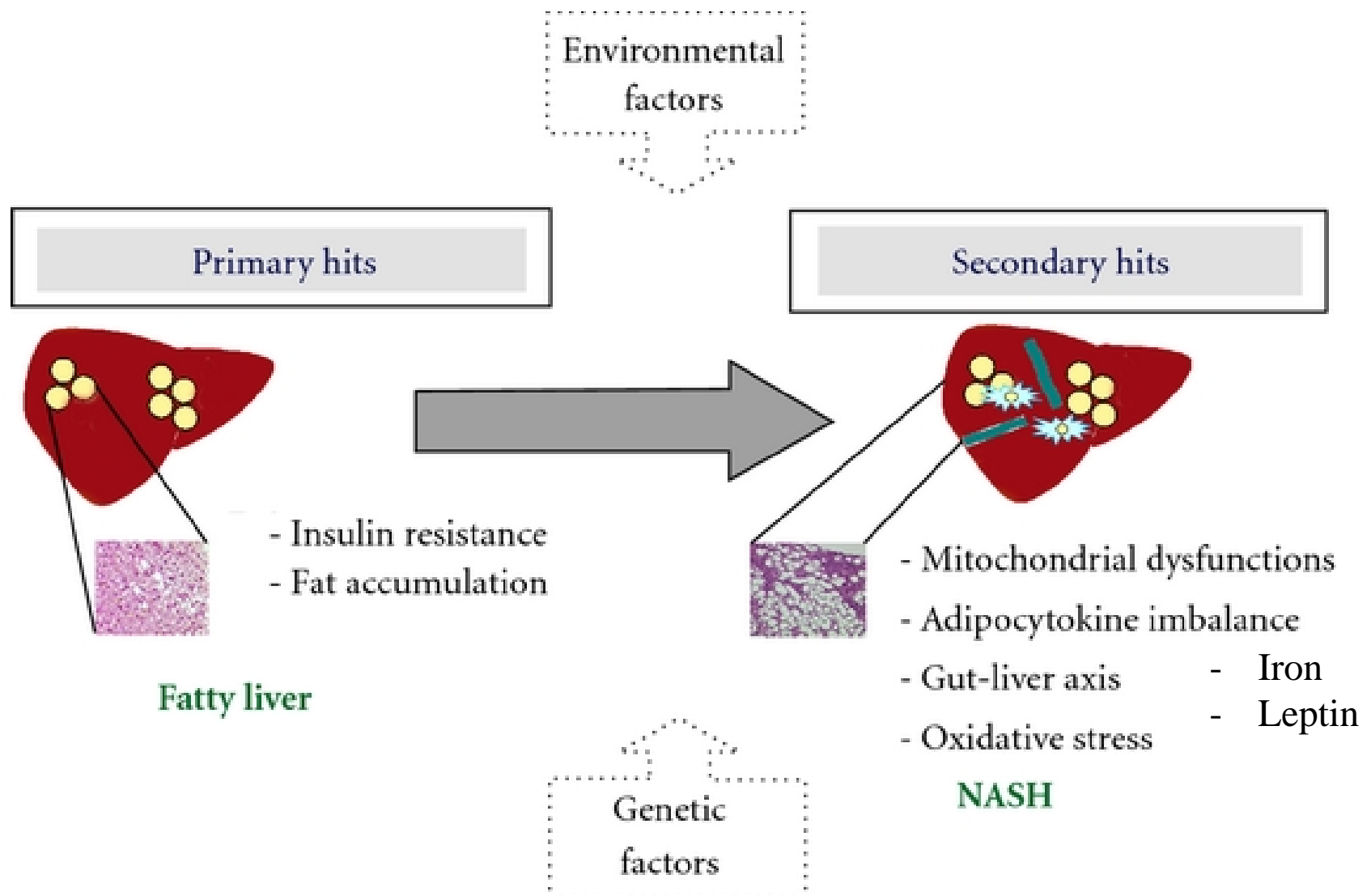
NAFLD/NASH

- In patients with severe obesity undergoing bariatric surgery, prevalence can exceed 95%
- In patients with dyslipidemia, NAFLD was estimated to be 50%
- Conditions with an emerging association with NAFLD: PCOS, Hypothyroidism, OSA, Hypopituitarism, Hypogonadism

NASH Pathogenesis

- Underlying reason for liver injury that causes NASH is not fully known – but there are several suspected candidates:
 - Insulin resistance as the key mechanism leading to hepatic steatosis
 - Others propose that a “second hit” of additional oxidative injury is required to manifest the necroinflammatory component of steatohepatitis

NASH Pathogenesis



NASH – Clinical Manifestations

- Silent disease
- May complain of fatigue, malaise, and vague RUQ pain +/- hepatomegaly
- Patients usually feel well in early stages and only begin to have symptoms once the disease becomes more advanced or cirrhosis develops
- Progression of disease can take years, even decades (approximately 20% of patients with NASH progress to cirrhosis)

NASH Presentation

- Usually first suspected in people who have elevations in LFTs during routine blood tests or hepatosteatosis incidentally found on imaging



- Must exclude competing etiologies for steatosis and co-existing common chronic liver disease
- No recommendations on routine screening of adults or high-risk groups

Common Causes of Secondary Hepatic Steatosis

Macrovesicular Steatosis

- Excessive alcohol
- Hepatitis C (Genotype 3)
- Wilson's Disease
- Lipodystrophy
- Parenteral Nutrition
- Severe malnutrition
- Abetalipoproteinemia
- Medications (Amiodarone, Methotrexate, Tamoxifen, Corticosteroids)

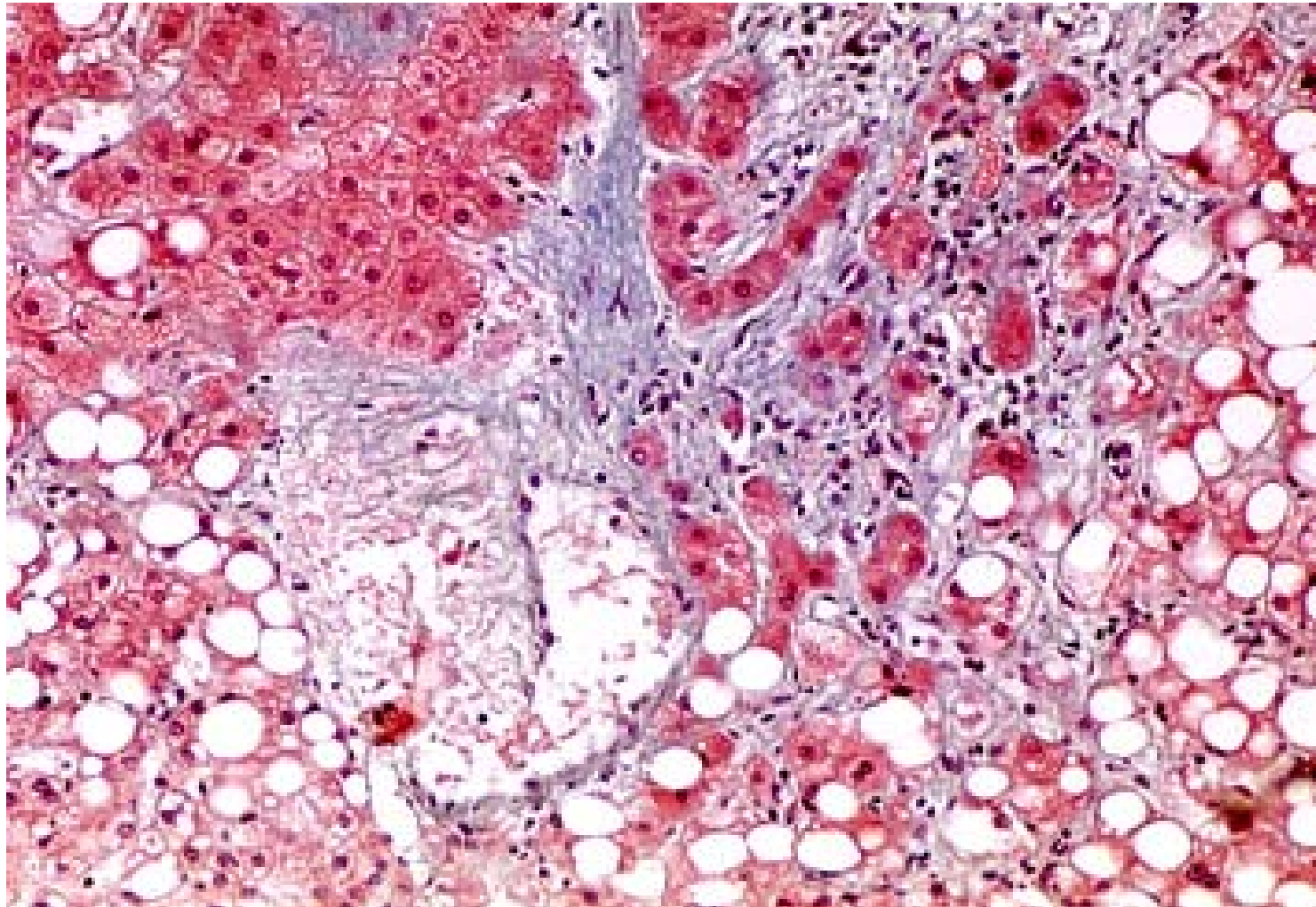
Microvesicular Steatosis

- Reye's Syndrome
- Medications (valproate, anti-retroviral medications)
- Acute fatty liver of pregnancy
- HELLP Syndrome
- Inborn errors of metabolism (LCAT deficiency, cholesterol ester storage disease, Wolman disease)

NAFLD – When to biopsy?

- Liver biopsy is the “gold standard” used to confirm the presence of NASH and determine the severity
- Consider in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis (may use NAFLD Fibrosis Score)
- Consider in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver disease cannot be excluded without a liver biopsy

NASH – Histologic Findings



Advancements in Diagnosing NASH

- Interest in developing clinical prediction rules and non-invasive biomarkers for identifying steatohepatitis in patients with NAFLD
 - Several studies have demonstrated that serum cytokeratin 18 (CK 18) fragments were markedly increased in patients with NASH compared with patients with simple steatosis or normal biopsies
 - NAFLD Fibrosis Score (variables – age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio), Enhanced Liver Fibrosis (ELF) panel, transient elastography

NASH Treatment

- Lifestyle Interventions:

Weight loss generally reduces hepatic steatosis, achieved by either hypocaloric diet alone or in conjunction with increased physical activity

- Loss of 3-5% of body weight is necessary to improve steatosis, but greater weight loss (up to 10%) may be needed to improve necroinflammation

- Hepatitis A and B vaccinations should be given to patients without serologic evidence of immunity

NASH Treatment

Vitamin E is an anti-oxidant that has been associated with a decrease in aminotransferases in patients with NASH

- It has also been proven to cause histological improvement in steatosis, inflammation, and ballooning and resolution of steatohepatitis in adults with NASH. No effect on hepatic fibrosis.



NASH Treatment

Vitamin E administered at 800IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and should be considered as first-line pharmacotherapy.

Currently, Vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.

NASH Treatment

- Insulin Sensitizing Agents
 - Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in patients with NASH
 - Pioglitazone can be used to treat steatohepatitis in patients with biopsy-proven NASH.
 - It should be noted that patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetics and that long-term safety and efficacy in patients with NASH has not been established.

NASH Treatment

- Premature to recommend omega-3 fatty acids for the specific treatment of NASH. Meta-analysis of 9 studies, treatment with omega-3 fatty acids was associated with improvement in hepatic steatosis and aminotransferase levels. With restriction to RCTs, only benefit demonstrated was improvement in hepatic steatosis.
- Pentoxifylline – inhibits production of TNF- α . Several pilot studies demonstrated biochemical improvement and in some cases, histologic improvement. More studies are needed to further characterize the benefit of PTX in the treatment of NASH.

NASH Treatment

Bariatric surgery is not contraindicated in eligible obese individuals with NAFLD/NASH, but it is premature to consider bariatric surgery as an option to treat NASH



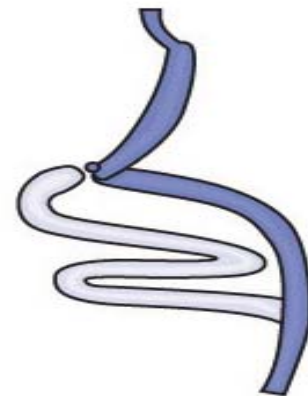
Adjustable
Gastric Band
(AGB)



Roux-en-Y
Gastric Bypass
(RYGB)



Vertical Sleeve
Gastrectomy
(VSG)



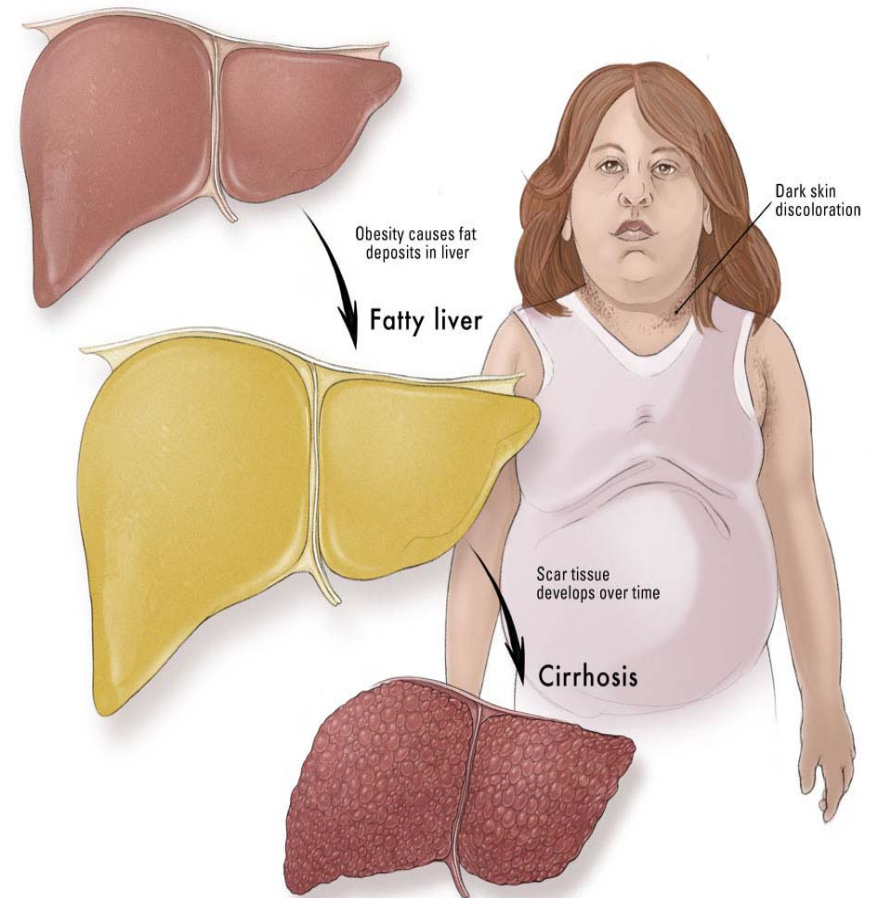
Biliopancreatic
Diversion With a
Duodenal Switch
(BPD-DS)

NASH/NAFLD Prognosis

- Overall, increased mortality compared to general population
- Most common cause of death patients with NAFLD, NAFL, and NASH is cardiovascular disease
- Increased liver-related mortality in patients with NASH (not NAFL)
- Up to 20% of patients with NASH go on to develop cirrhosis
- Increased risk of hepatocellular carcinoma (limited to those with advanced fibrosis and cirrhosis) – ultrasound Q6 months

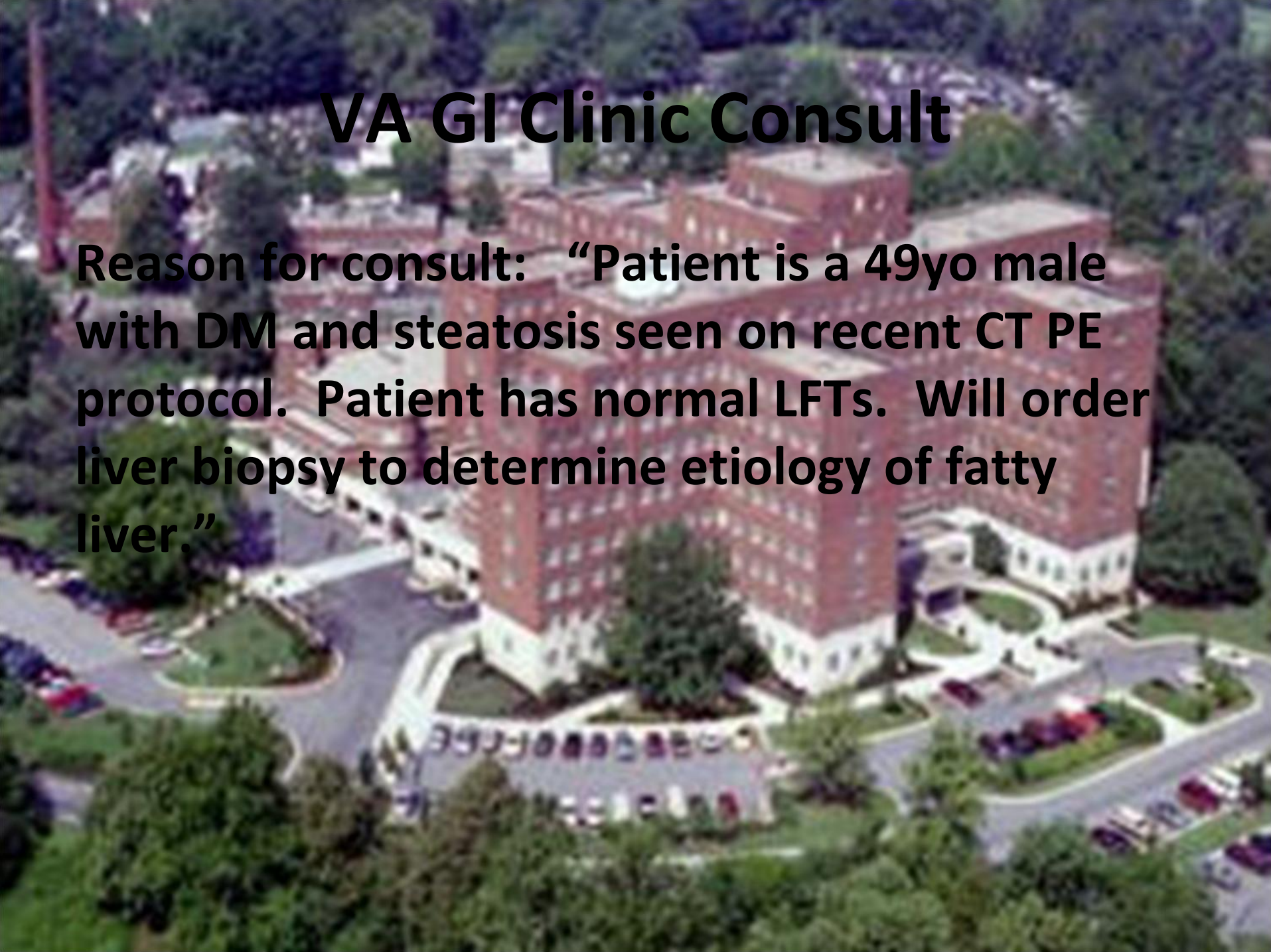
NASH and Cryptogenic Cirrhosis

- Cryptogenic cirrhosis is the presence of cirrhosis with no obvious etiology
- Patients have disproportionately high prevalence of metabolic risk factors typical of patients with NAFLD (up to 70%), their biopsies frequently show one or more features of NASH
- Studies have shown that histologic features of NASH are lost with the development of cirrhosis



VA GI Clinic Consult

Reason for consult: “Patient is a 49yo male with DM and steatosis seen on recent CT PE protocol. Patient has normal LFTs. Will order liver biopsy to determine etiology of fatty liver.”



Incidental Discovery of Hepatic Steatosis

- If patient has symptoms or signs attributable to liver disease or abnormal LFTs, they should be evaluated as though they have suspected NAFLD and worked up accordingly
- If patient lacks any liver-related symptoms or signs and have normal LFTs, it is reasonable to assess for metabolic risk factors and alternate causes for hepatic steatosis. Liver biopsy is not recommended.

VA GI E-Consult

- **“Patient with CAD and hyperlipidemia who was recently diagnosed with mildly elevated LFTs secondary to NAFLD. I have discontinued his Crestor. Please make recommendations regarding anti-lipid therapy.”**

Statin therapy and NASH

- Patients with NAFLD/NASH are at increased risk of CV disease
- Statins are important agents to treat dyslipidemia yet there is continued reluctance to use them in patients with suspected or established liver disease
- Given lack of evidence to show that patients with NAFLD and NASH are at increased risk for serious drug-induced liver injury from statins, statins can be used to treat dyslipidemia in patients with NAFLD and NASH

VA GI E-Consult

- “I have a patient with NASH continues to drink a glass of wine with dinner. He is refusing to attend Substance Abuse counseling - do you have any recommendations?”

Alcohol Consumption and NAFLD/NASH

- NAFLD/NASH indicates the lack of any evidence of ongoing or recent consumption of alcohol
- Definition of significant alcohol consumption has been inconsistent (ranging from > 1 alcoholic drink per day to > 4 alcoholic drinks per day)
- Current AASLD Guidelines state that ongoing or recent alcohol consumption of >21 drinks/week in men and >14 drinks/week in women is a reasonable definition for significant alcohol consumption

Benefit of Alcohol in patients with NASH?

- Of course, patients should not consume heavy amounts of alcohol
 - National Institute on Alcohol Abuse and Alcoholism defines heavy drinking as more than 4 drinks on any day or more than 14 drinks/week in men and more than 3 drinks on any day or 7 drinks/week in women
- Currently no recommendations regarding non-heavy consumption of alcohol in individuals with NAFLD.
 - Several recent studies suggest a beneficial effect of light alcohol consumption (less than one drink/day) on the presence and severity of NAFLD





ICE
(TO COOL BEER)

ICE BEER

QUEBEC CIDER

BUD LIGHT

BOURBON

CORONA

TEQUILA

CUBA LIBRE

CURACAO

RUM

PISCO

**FLAMING
SPIRITS**

MEAD

**SCOTCH
WHISKEY**

BEER

**COGNAC
WINE**

BRANDY

ABSINTHE

OUZO

RELIGION

DESERT

THIRSTY

NO BEER

VODKA

RICE WINE

SOJU

SAKE

PALM WINE

SNAKE LIQUOR

RICE WINE

BEER

**PACIFIC DAWN
SHEEP**

The World and Alcohol

Quantity of Alcohol in a Standard Drink

Region	Amount	Range
•USA	12 g	9.3–13.2 g
•Canada	13.6 g	13.6 g
•UK	9.5 g	8–10 g
•Europe	9.8 g	8.7–10.0 g
•Australia /New Zealand	9.2 g	6.0–11.0 g
•Japan	23.5 g	21.2–28.0 g

Alcoholic Steatohepatitis

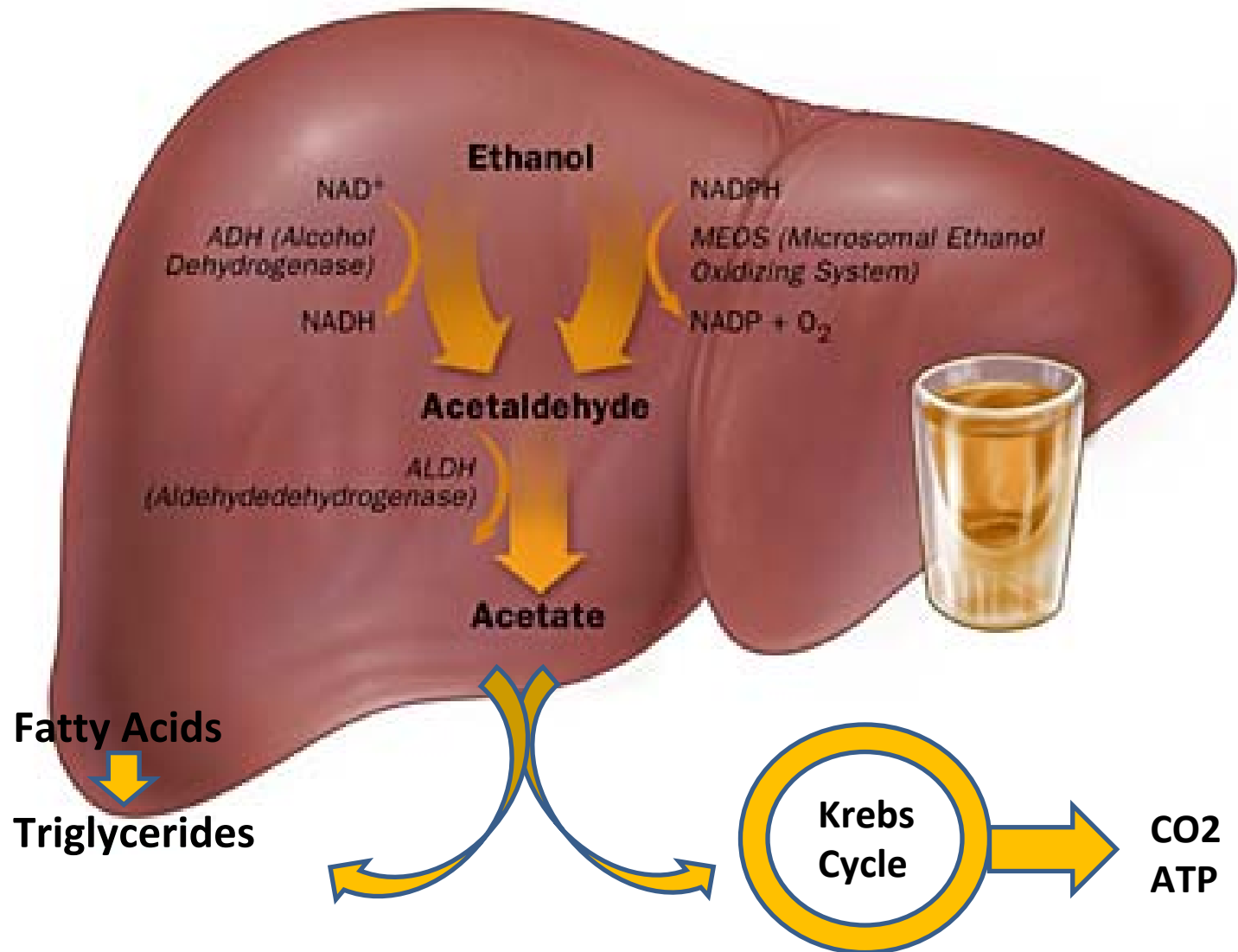
- 14 million adult Americans meet diagnostic criteria for alcohol use disorder
- Steatosis develops in approximately 90% of individuals who drink more than 60gm/day of alcohol, but may occur in individuals who drink less
- Signs, symptoms, and severity of liver disease vary significantly among individuals with alcoholic hepatitis

Risk Factors of ASH

- Amount of alcohol ingested is the most important risk factor
- Type of alcohol consumed may influence the risk (beer and spirits are more likely to be associated with liver disease than drinking wine)
- Drinking pattern (drinking outside of mealtime or binge drinking)
- Gender (female > male)
- Race (Hispanics and African Americans > Caucasians)
- Excessive body weight



ASH Pathogenesis

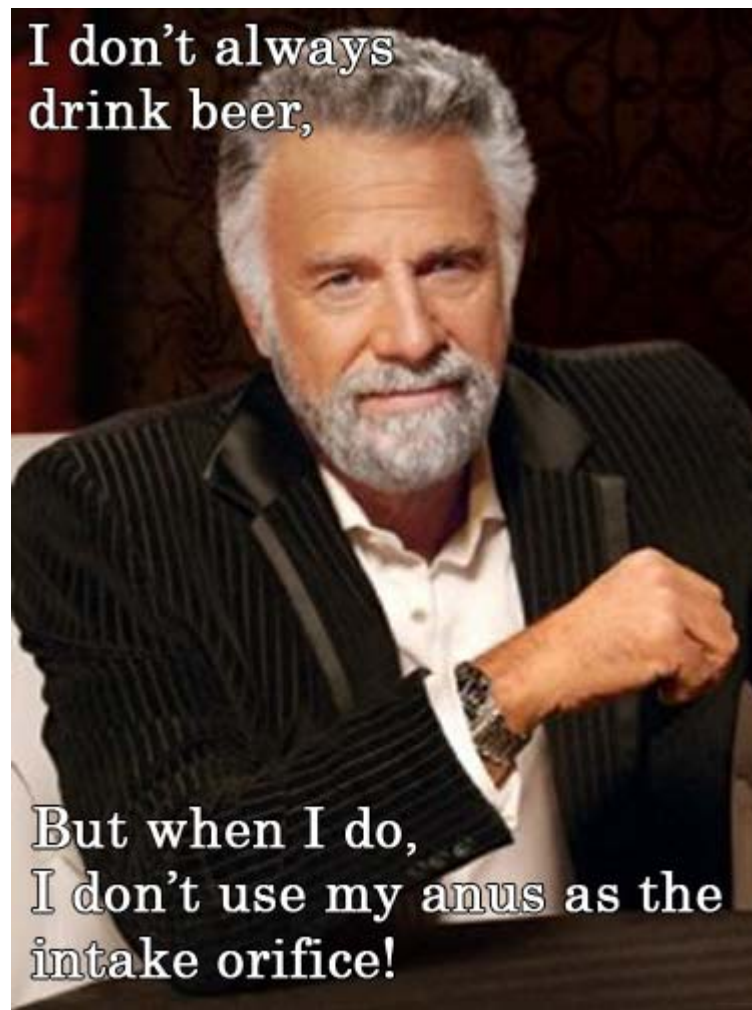




ASH – Diagnosis

- Based on compatible history, clinical presentation and disease severity
- Difficult to diagnose alcohol abuse / dependence due to patient reluctance to openly share a drinking history if it may be viewed as excessive or problematic.

Would this guy be reluctant to share
his drinking habits with you?



ASH - Diagnosis

- Other causes of liver disease should be excluded, as alcoholic liver disease commonly coexists with and aggravates liver injury caused by other liver diseases
- Search for biomarkers is ongoing: Elevated GGT, MCV, and mitochondrial aspartate transaminase (mAST)/total aspartate transaminase (AST) ratios have been studied as possible measures of excessive alcohol consumption

ASH - Clinical Features



Patients with alcoholic hepatitis may be asymptomatic, have only hepatomegaly, or have full-blown alcoholic hepatitis with tender hepatomegaly, jaundice, fever, ascites, and encephalopathy.

ASH - Clinical Features

- Almost all patients have elevated liver enzymes with an AST:ALT ratio usually >2
- Patients with ASH will often have leukocytosis and thrombocytopenia
- Elevated bilirubin, hypoalbuminemia, and prolonged PT are markers of more severe ASH
- Imaging studies can be used for evaluation of hepatic parenchymal changes, but not to confirm the presence of alcoholic liver disease.

Alcoholic Steatohepatitis - Prognosis

- Model for End-Stage Liver Disease (MELD):
score based on serum bilirubin, creatinine and INR. Predicts 90 day mortality and is routinely used for organ allocation in the US
- Maddrey's Discriminant Function:
 - Discriminant function = $(4.6 \times [\text{prothrombin time} - \text{control PT}]) + (\text{serum bilirubin})$
 - Value greater than 32 is associated with high short-term mortality

Alcoholic Steatohepatitis - Prognosis

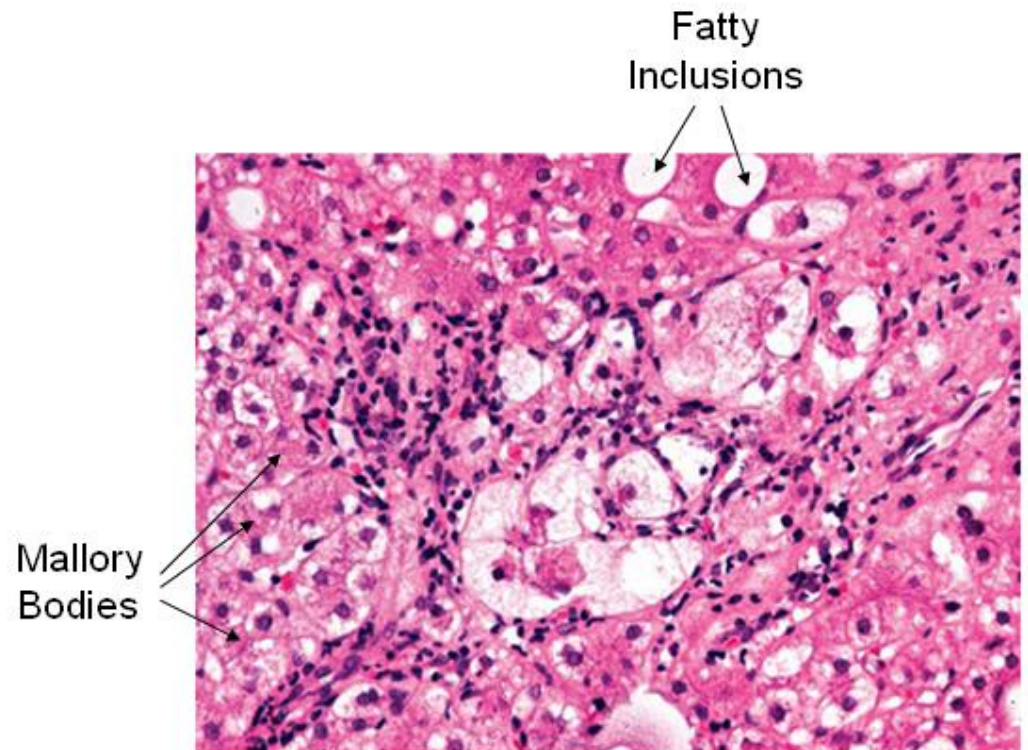
- Evidence that cytokines such as TNF α , interleukin-6, and interleukin-8 correlate with mortality in patients with alcoholic hepatitis has been demonstrated, but levels of these cytokines are not determined in routine clinical practice.

Alcoholic Steatohepatitis – Role for Biopsy?

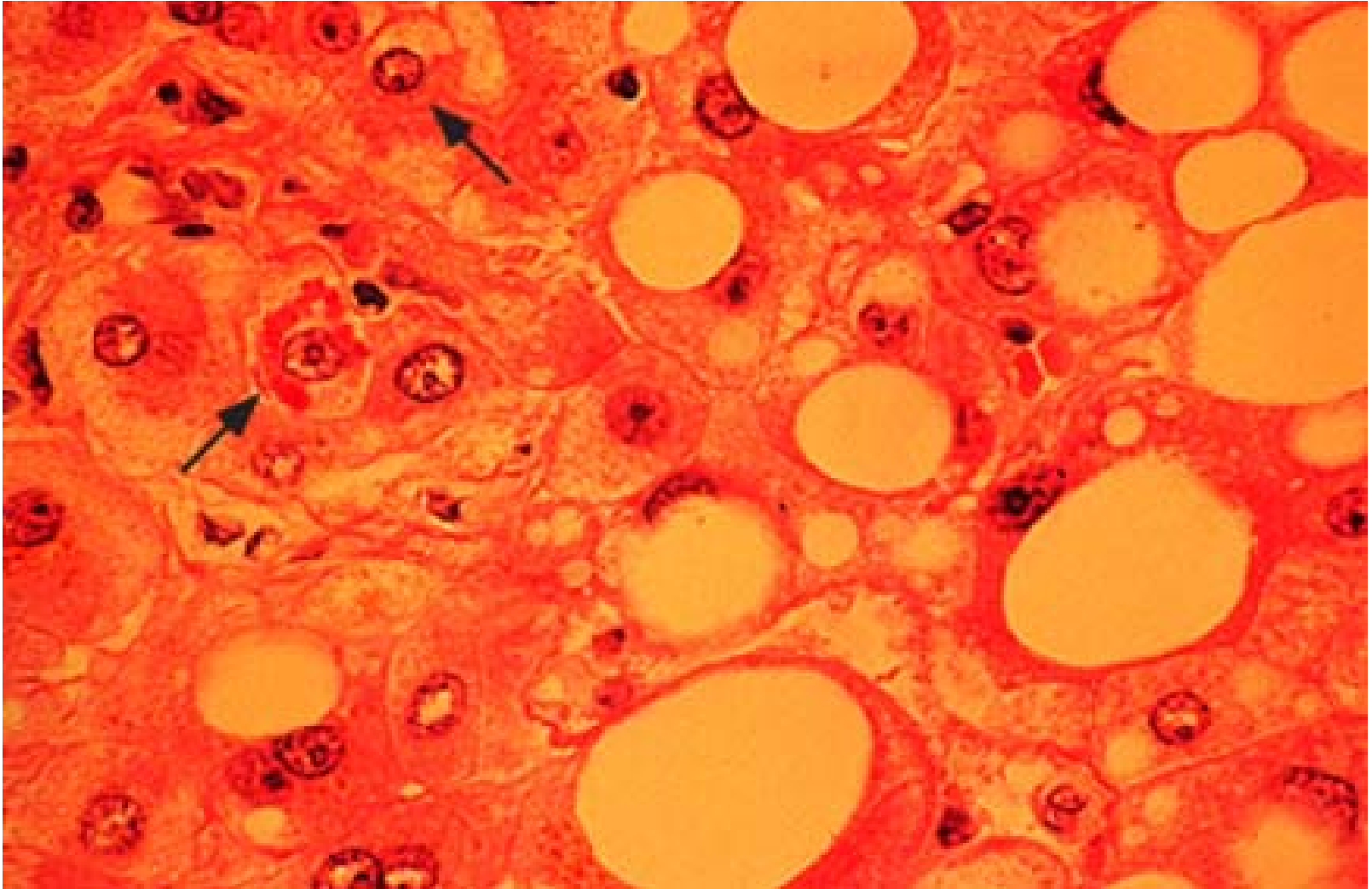
- Not indicated in the diagnosis of alcoholic steatohepatitis
- Liver biopsy is mainly used to clarify atypical cases, to better define the contribution of alcohol in patients with possible non-alcohol-related coexisting conditions, and to determine severity of disease

Alcoholic Steatohepatitis

Macrovesicular steatosis, mixed lobular inflammation, ballooning degeneration of hepatocytes, Mallory bodies and fibrosis represent a collection of pathologic findings indicative of steatohepatitis.



Alcoholic Hepatitis Histology



ASH Treatment

- Simple, uncomplicated fatty liver secondary to alcohol is usually self-limited and may be completely reversible with abstinence of alcohol after 4-6 weeks
- Several studies have suggested that progression to fibrosis and cirrhosis occurs in 5-15% of people despite abstinence



ASH Treatment – Lifestyle Changes



- Abstinence of alcohol
 - Medications to facilitate abstinence → naltrexone and acamprosate have been shown to be effective in chronic alcoholics. Disulfiram is widely used, but less clearly supported in clinical trials.
- Cigarette smoking causes oxidative stress, which may be a factor leading to accelerated liver disease
- Obesity has been proven to be an independent risk factor for the development of ALD

ASH Treatment – Nutritional Support

- These patients are malnourished:
 - decreased caloric intake
 - decreased intestinal absorption/digestion of nutrients
 - decreased processing and storage of nutrients
- Current guidelines recommend: 1.2-1.5 g/kg for protein and 35 to 40 kcal/kg per day in patients with alcoholic liver disease

Severe ASH – Pharmacologic Therapy

- Corticosteroids:
 - The most extensively studied form of therapy for alcoholic hepatitis, but they have a limited role
 - Rationale for use = decrease the immune response and the pro-inflammatory cytokine response
 - Side effects: increased risk of infection, thus a major disadvantage is that they cannot be used in patients with alcoholic hepatitis
 - Most investigators agree that if they are to be used, they should be reserved for patients with severe liver disease (DF >32) and possibly those with PSE

Severe ASH – Pharmacologic Therapy

- Pentoxifylline is thought to improve outcomes in alcoholic hepatitis via down regulation of pro-inflammatory cytokines (TNF α)
 - Shown to have anti-fibrotic effects through attenuation of procollagen I and profibrogenic cytokine expression
 - Reduces mortality and renal failure
 - Studies have demonstrated an advantage of PTX over prednisolone in terms of survival (thought to be attributed to the reduction of HRS and lower occurrence of GI bleeding)
- Dose of Pentoxifylline : 400mg PO TID

Severe ASH – Pharmacologic Therapy

- Specific anti-TNF therapies (infliximab, entercept) have not shown benefit and have been associated with an increased risk of severe infections
- At this time, there is no proven benefit with using antioxidant therapy, Vitamin E, SAME, anabolic steroids, PTU, Colchicine, Lecithin, Silymarin (Milk Thistle)
- Additional studies are needing in regards to the benefit of NAC

Liver Transplant?

- Despite a clear benefit from OLT, issue to transplantation in alcoholics remains controversial
- Concerns regarding risk of recidivism, public opinion, poor compliance with post-op care, and the use of transplantation in patients with what is perceived as a self-inflicted disease

