

Nonalcoholic Fatty Liver Disease

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Nonalcoholic Fatty Liver Disease (NAFLD)

- The most common form of chronic liver disease.
- Prevalence depends on population studied and method used to make diagnosis.
- Global prevalence: 20 - 30% of adults in the general population.
- Up to 10% of children in some studies may have NAFLD. *due to obesity
junk food*
- ~ 3% of the population has nonalcoholic steatohepatitis (NASH).
- 2nd most common reason for liver transplant.
- 3rd most common cause of HCC in Western countries.
hepatocellular carcinoma

NAFLD

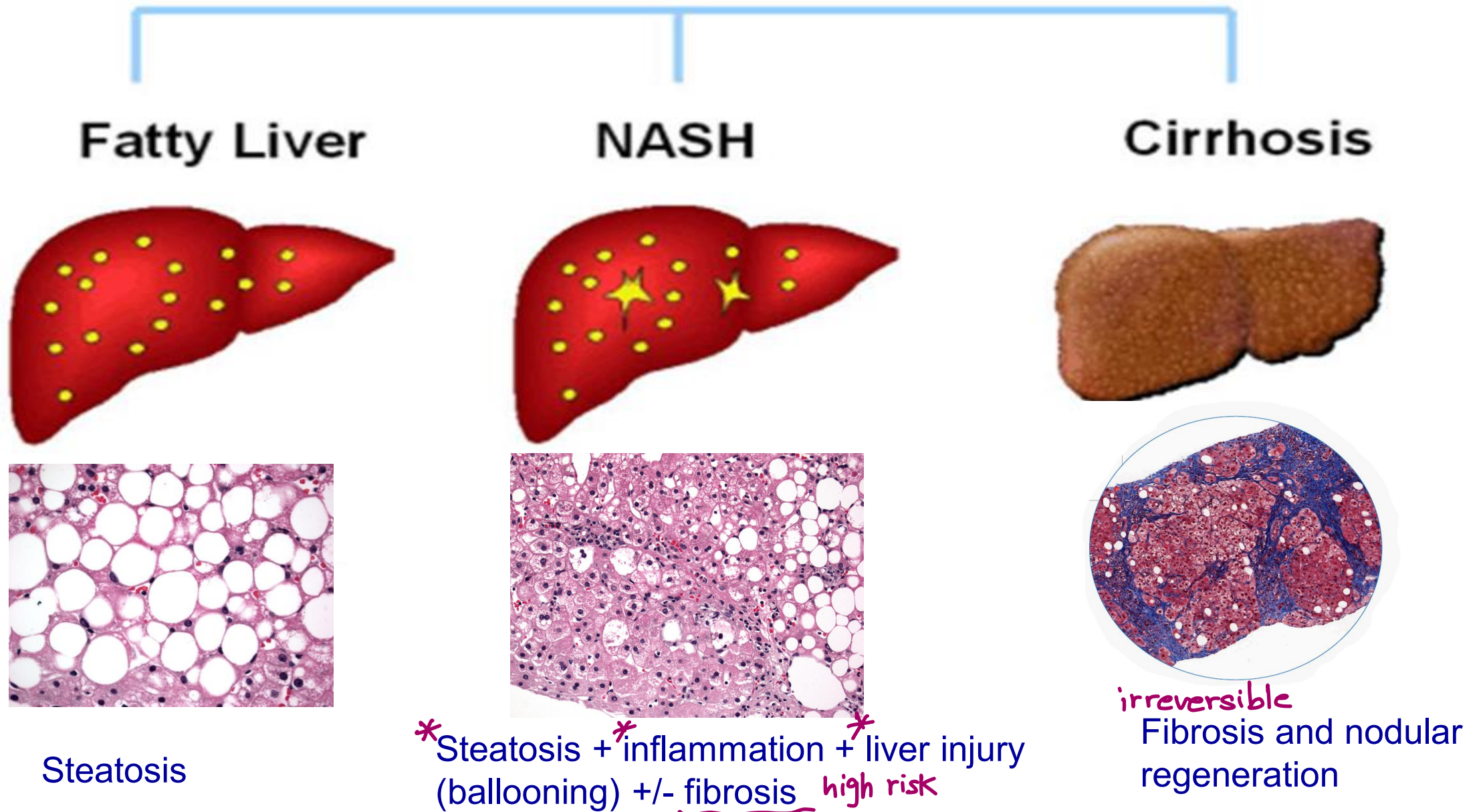
- The hepatic manifestation of metabolic syndrome.
- Incidence of new NAFLD is rising with increasing rates of ^{*}obesity, ^{*}diabetes and ^{*}physical inactivity.
- NAFLD is also present in 7% of normal-weight (lean) individuals.

genetic predisposition

Metabolic Syndrome

- The Adult Treatment Panel III
- Any 3 of the following 5 features:
 1. ^{increased WC} WC $\geq$ 102 cm (40 in) in men or $\geq$ 88 cm (35 in) in women
 2. TG $\geq$ 150 mg/dL ^{hypertriglyceridemia}
 3. HDL $<$ 40 mg/dL in men or $<$ 50 mg/dL in women ^{low HDL}
 4. BP $\geq$ 130/85 mm Hg
 5. FPG $\geq$ 110 mg/dL ^{Fasting plasma glucose (not necessarily diabetic, could be a prediabetic)}

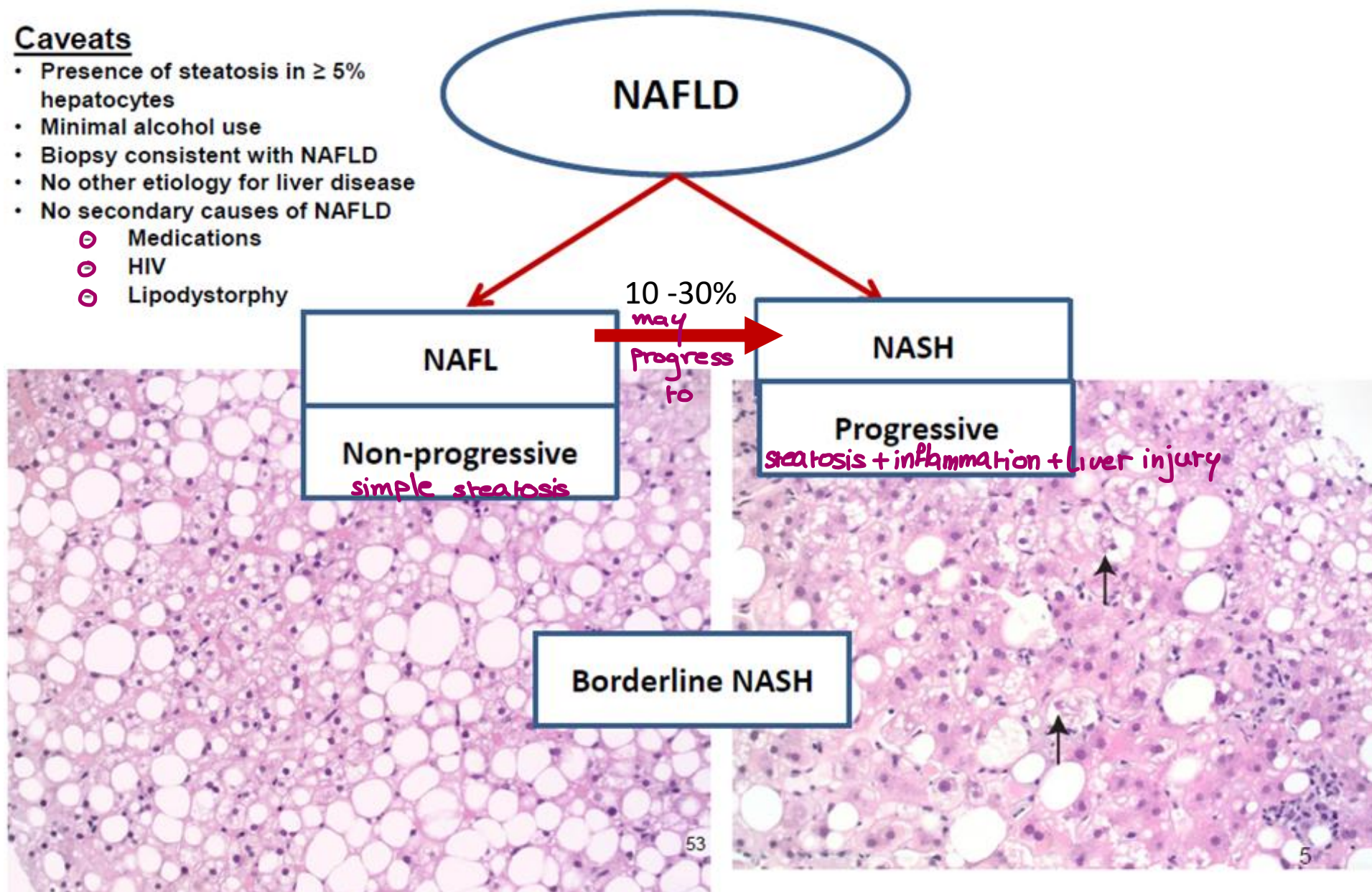
The Spectrum of NAFLD



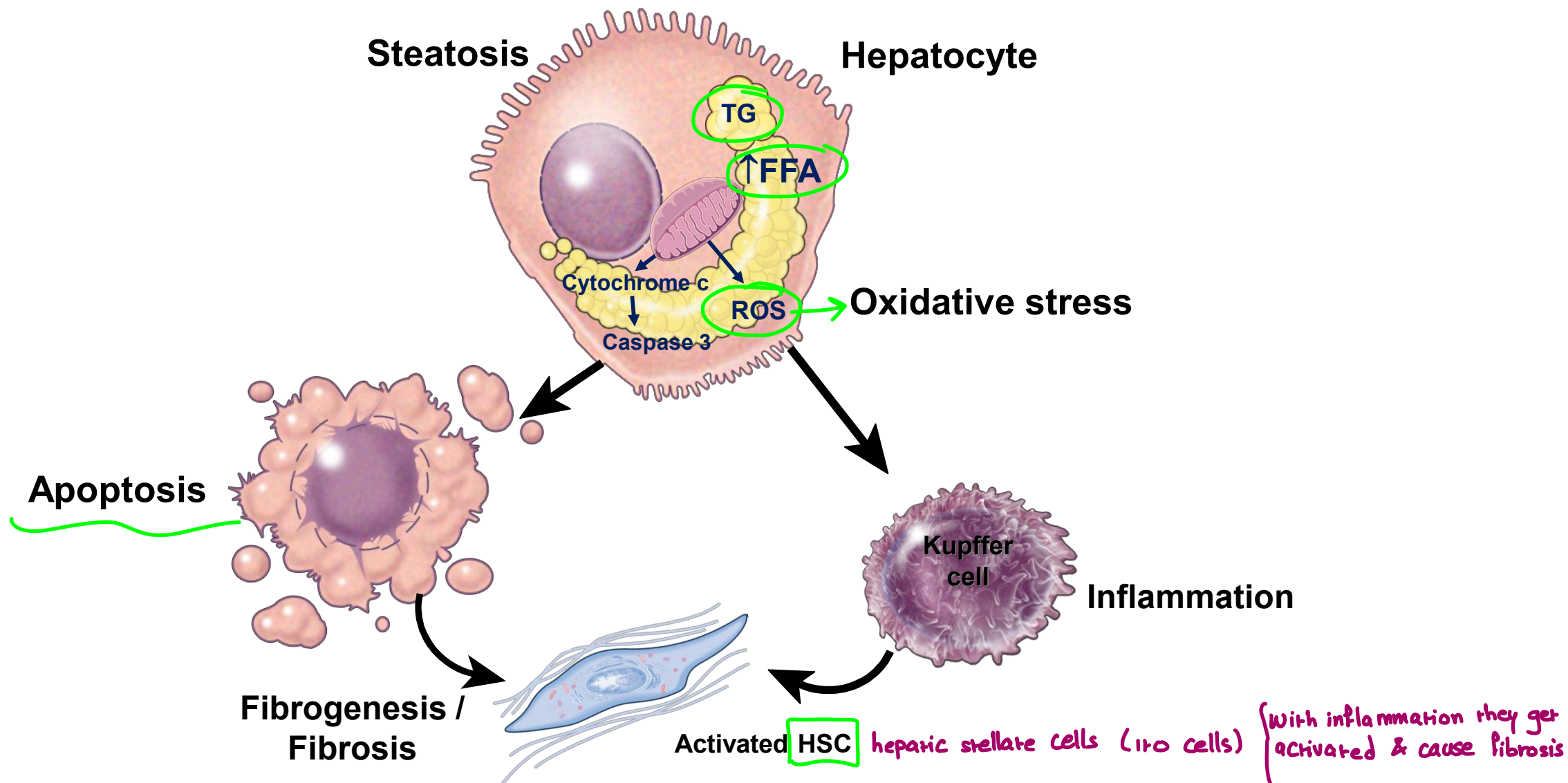
Subtypes of NAFLD

Caveats

- Presence of steatosis in $\geq 5\%$ hepatocytes
- Minimal alcohol use
- Biopsy consistent with NAFLD
- No other etiology for liver disease
- No secondary causes of NAFLD
 - Medications
 - HIV
 - Lipodystrophy

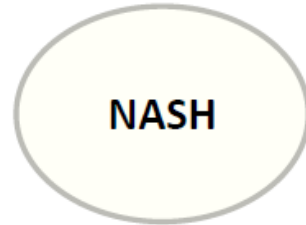


Pathogenesis

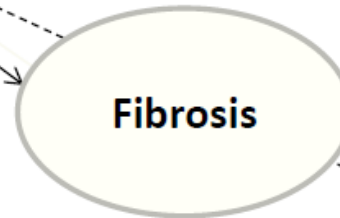


Natural History of NASH

3-12% of population



40-50%



15-20%

Risk of death in NASH

- * 1st CVD *metabolic syndrome*
- 2nd Cancer
- 3rd Liver

Fibrosis progression rate in NASH: 1 stage per 7 year

20% of patients are fast progressors: progress to cirrhosis in 10 years

Cirrhosis

2-3%/yr

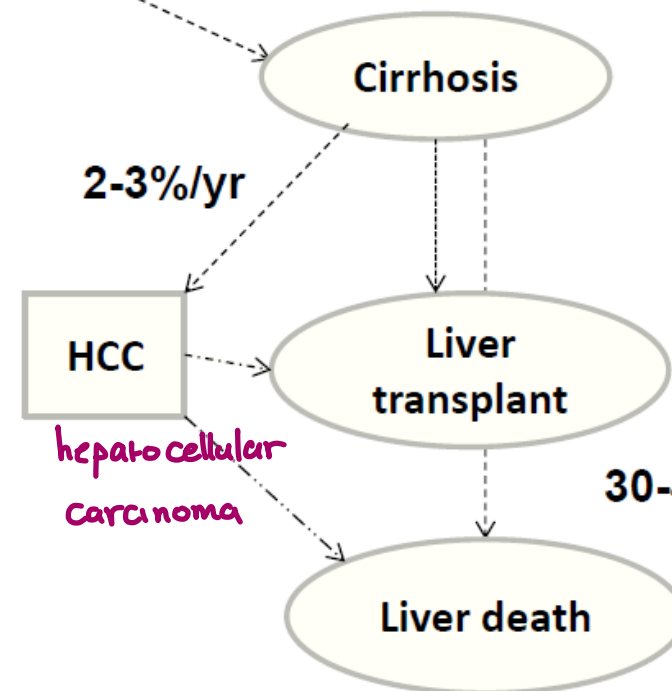
HCC

hepatocellular carcinoma

Liver transplant

30-40%

Liver death



Risk Factors for Progression in NAFLD

- Central obesity
 - Hypertension
 - Type 2 Diabetes
 - Dyslipidemia
 - Metabolic syndrome
 - Advancing age
-
- ALT is not a reliable indicator of disease severity.

Diagnosis of NAFLD: Presentation

- usually asymptomatic (45- 100%)
- minimal / non-specific symptoms:
 - fatigue (20- 73%)
 - RUQ discomfort (15- 48%)
- hepatomegaly may be detected (60- 80%)

- often an “incidental” finding:
 - incidental elevated aminotransferase levels
 - incidental fatty liver on radiographic studies
 - incidental hepatomegaly

Diagnosis of NAFLD/NASH

- Liver tests
- Non-invasive markers
- Imaging
- Liver Biopsy

Biochemical Findings

Parameter	Finding
AST and ALT	↑ 2 – 5 fold <i>mild to moderate elevation</i>
AST/ALT ratio	< 1 (in 65 – 90% of pts)
Alkaline phosphatase	↑ 2 – 3 fold (< 50% pts)
Albumin, Bilirubin , INR	Normal (unless cirrhosis has developed) → <i>hypoalbuminemia</i> ↑ INR ↑ bilirubin
Serum Ferritin	↑ ^{ed} ~ 50 % of pts

- AST increases more than ALT with disease progression *even if NAFLD*
↳ *more fibrosis*
- AST/ALT ratio > 1 → advanced fibrotic form of NAFLD
- ratio almost never > 2

Fibrosis Assessment for Patients With NAFLD

Category	Blood Tests Assessing Fibrosis Stage in NAFLD	
“Simple” lab/clinical indices	▪ NAFLD fibrosis score ▪ FIB-4 score ▪ Ferritin levels ▪ IgA levels	▪ AST/ALT ratio ▪ BARD ▪ APRI ▪ BAAT
“Expanded” lab indices	▪ FibroTest[†] ▪ FibroMeter	
Direct fibrosis markers	▪ ELF test[*] ▪ PIIINP	

*Assays HA, PIIINP, and TIMP-1; F3/4 fibrosis, AUC: 0.90 (95% CI: 0.84-0.96).

[†]Includes total bilirubin, GGT, α_2 -macroglobulin, ApoA1, and haptoglobin, corrected for age and sex; F3/4 fibrosis, AUC: 0.88 (95% CI: 0.82-0.92).

Routine liver tests do not differentiate NAFL vs NASH or accurately stage fibrosis

NAFLD Fibrosis Score and FIB-4 Assessing Presence of F3/4 Fibrosis

**NAFLD
Fibrosis
Score**

NAFLD Fibrosis Score ^[1]	Effect	NPV or PPV, %
< -1.455	Rules out fibrosis	88 to 93
> 0.676	Predicts fibrosis	82 to 90

Parameter

Age
AST
ALT
Platelet count
BMI
Albumin
Impaired fasting glucose/diabetes?

**FIB-4
Score**

FIB-4 Score ^[2,3]	Effect	NPV or PPV, %
< 1.3	Rules out fibrosis	95
> 3.25	Predicts fibrosis	75

1. Angulo P, et al. Hepatology. 2007;45:846-854. 2. Sterling RK, et al. Hepatology. 2006;43:1317-1325. 3. McPherson S, et al. Gut. 2010;59:1265-1269.

Imaging Modalities in NAFLD

- Ultrasound
- CT scan
- Transient elastography
- MR technologies

Imaging Findings

U/S



- Increased echogenicity *light color*
- Hepatomegaly

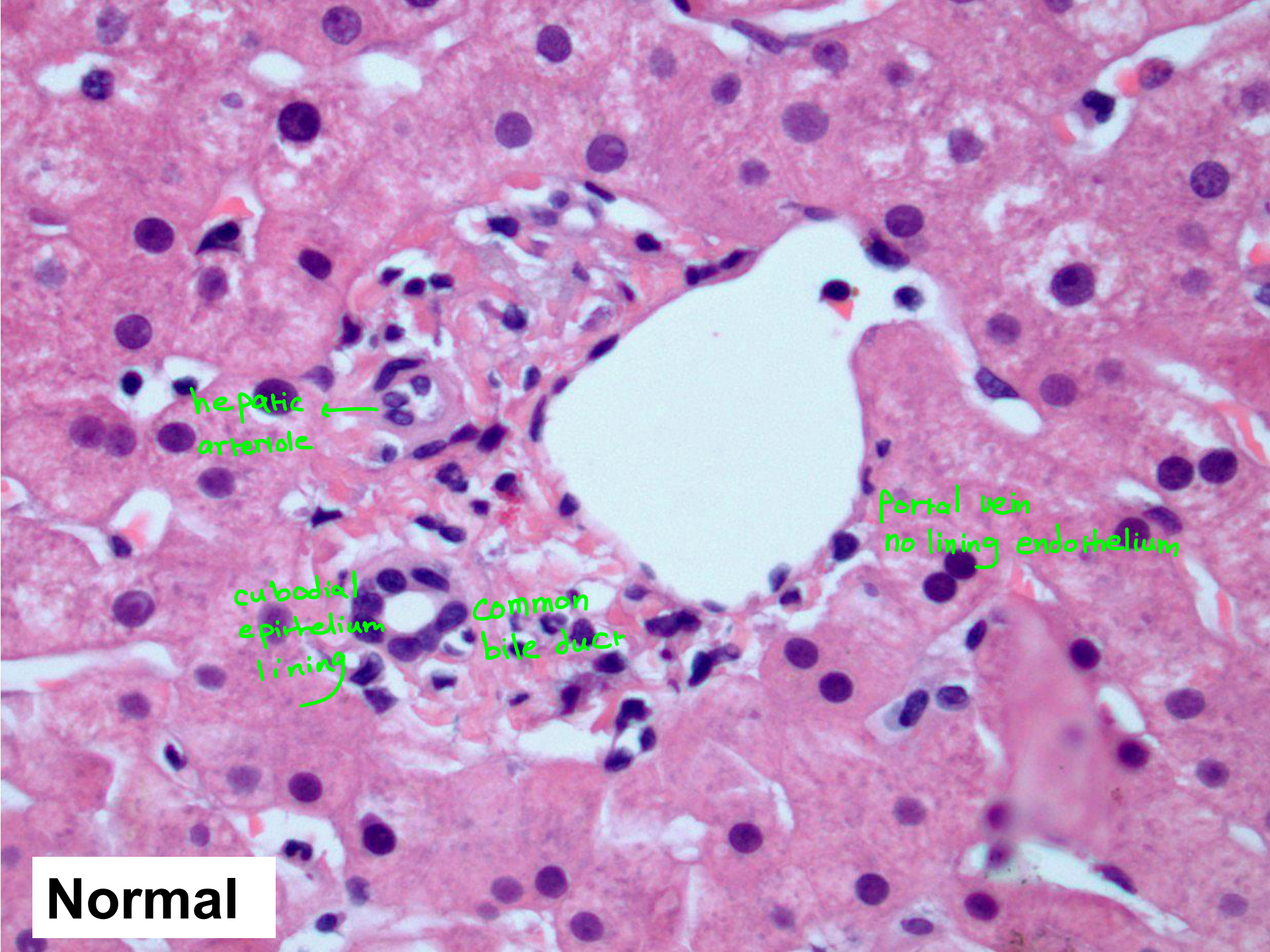
CT scan



- Low attenuation compared with the spleen

Liver Biopsy

- The gold standard for diagnosis
 - To assess severity of hepatic steatosis *mild / moderate / severe > 66%*
 - To differentiate simple steatosis from NASH
 - To stage fibrosis
- Histological criteria for NASH :
 - Steatosis ($\geq 5\%$ of hepatic parenchyma) AND
 - Mixed lobular inflammation AND
 - Hepatocellular ballooning



portal tract
↳ hepatic artery
↳ portal vein
↳ bile duct

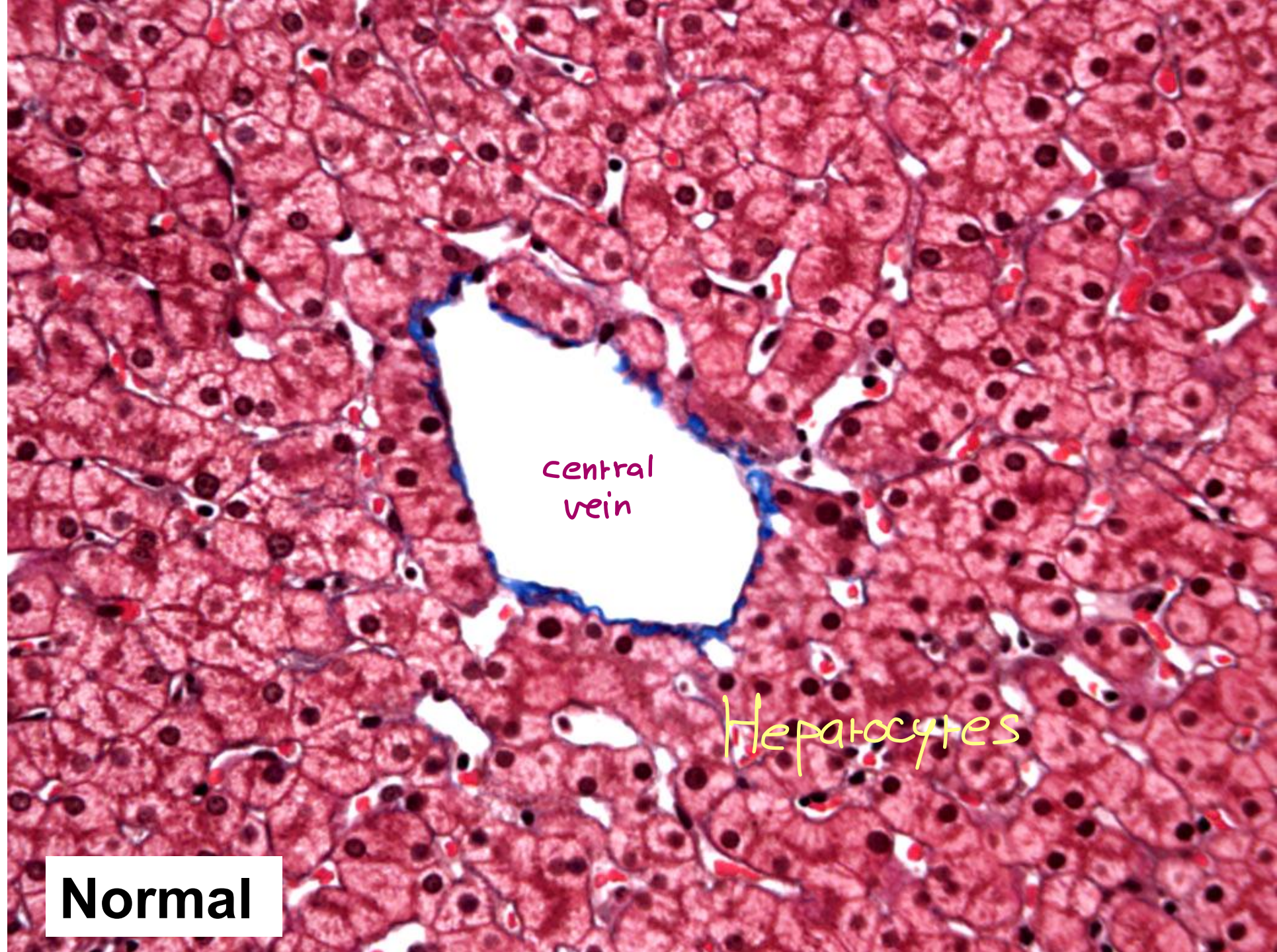
hepatic
arteriole

portal vein
no lining endothelium

cuboidal
epithelium
lining

common
bile duct

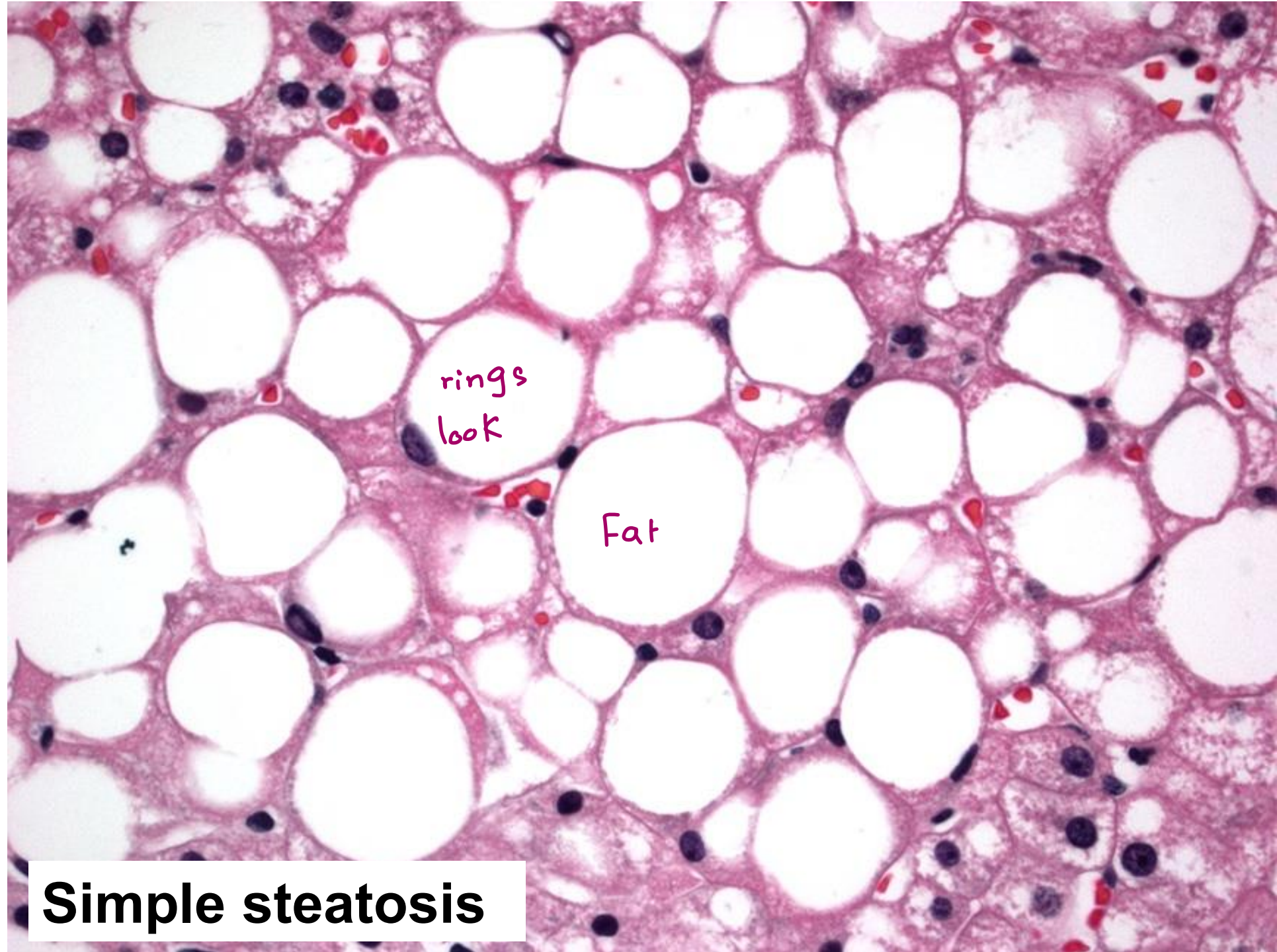
Normal



central
vein

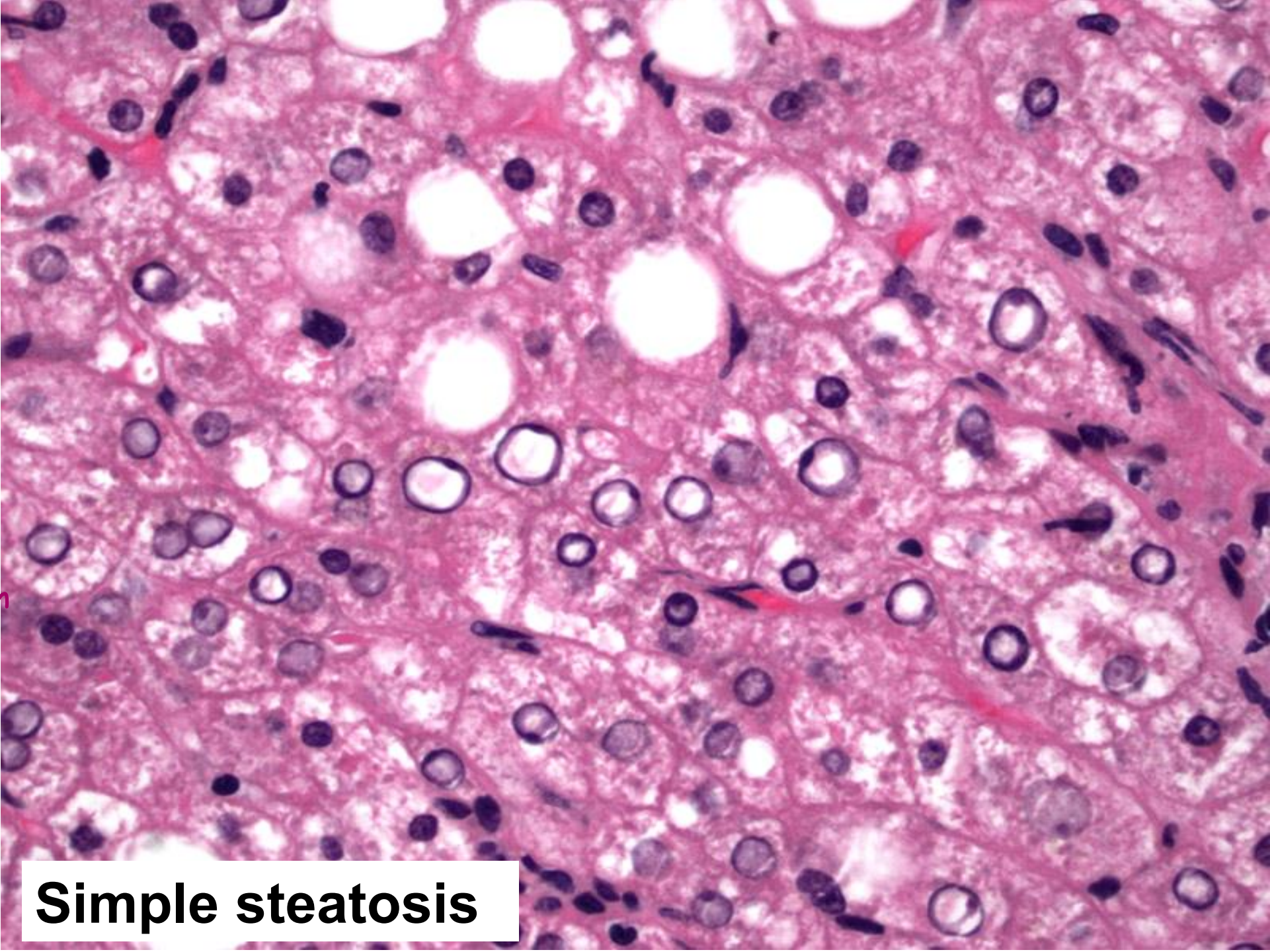
Hepatocytes

Normal



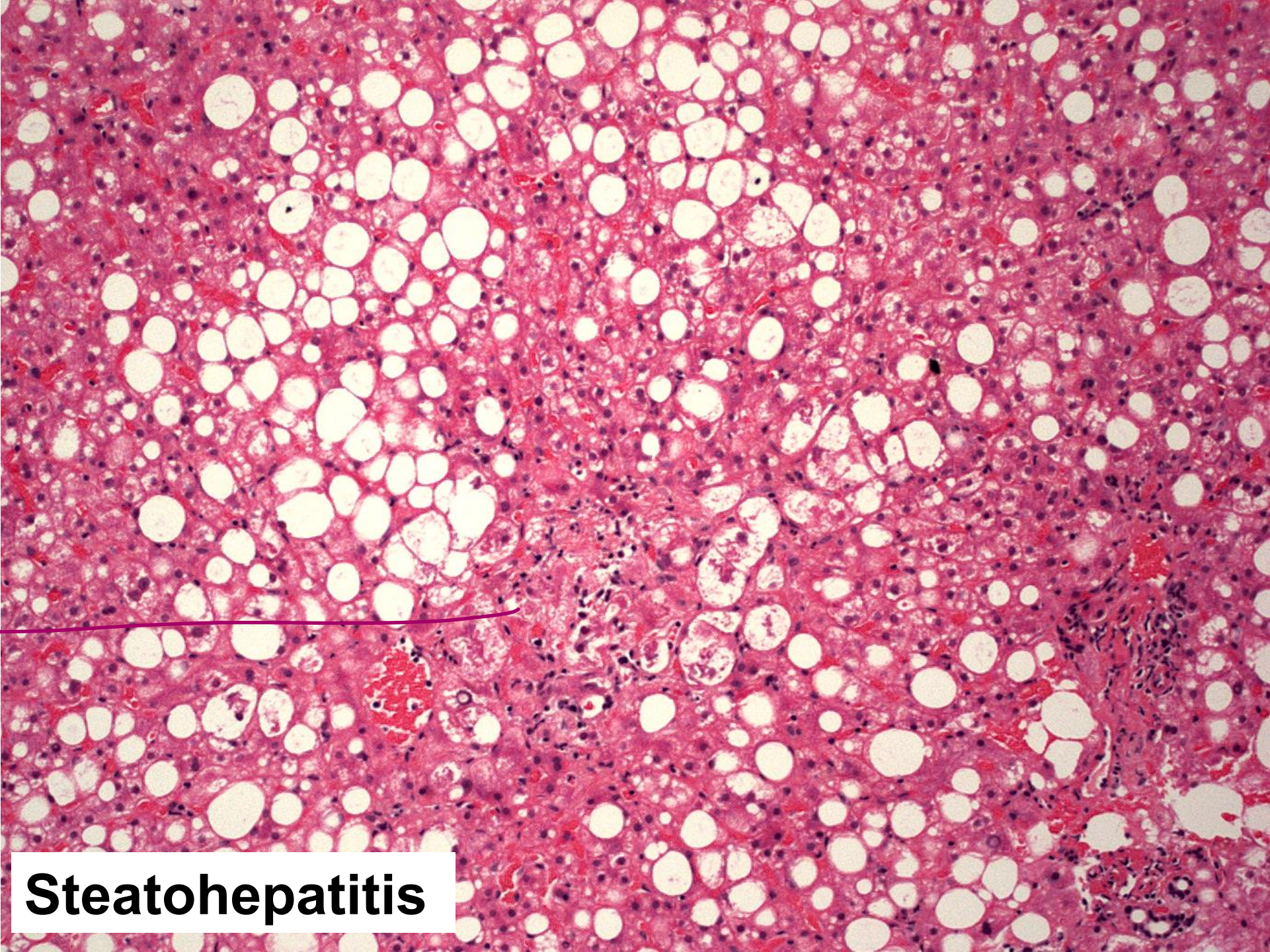
Simple steatosis

No
inflammation



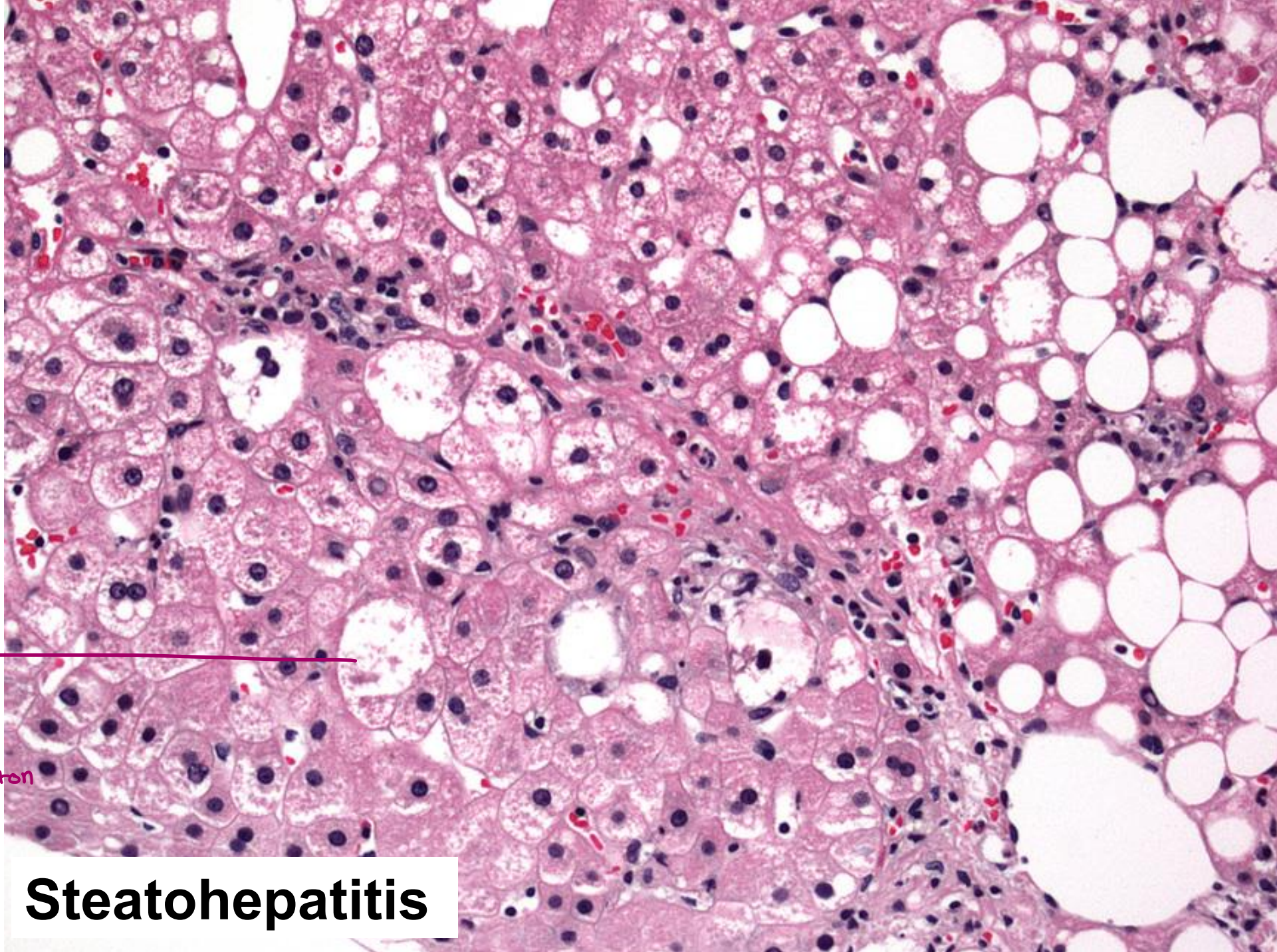
Simple steatosis

inflammation in
hepatic
parenchyma



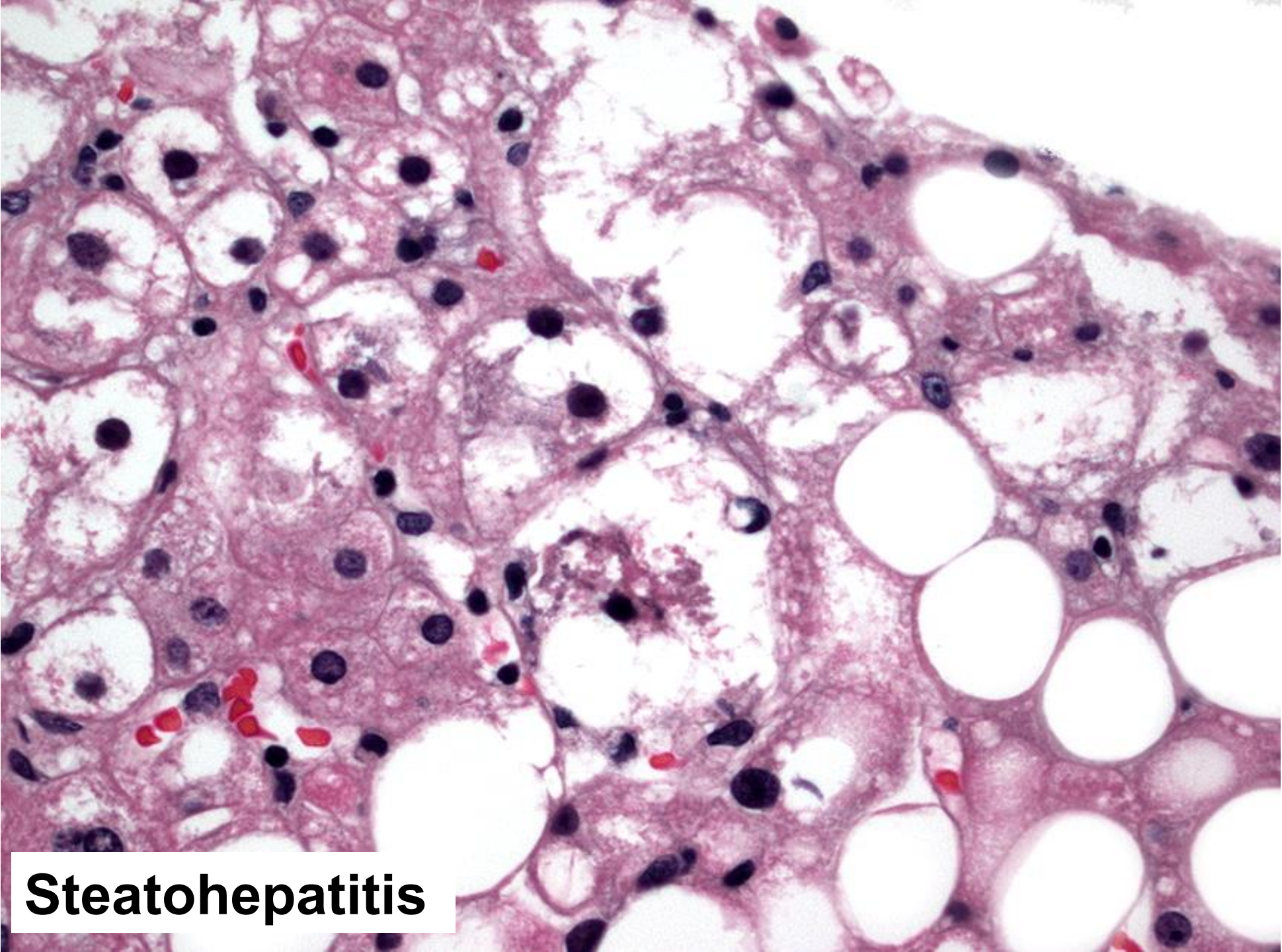
Steatohepatitis

ballon's ←
hepatocytes
due to cytoskeleton
destruction



Steatohepatitis

Liver injury
"Apoptosis"



Steatohepatitis

Fibrous tissue
لونه أزرق
بيته بالصبغة

centri-lobular
Fibrosis
↳ fibrosis around
the central vein &
progressing to the
paranchyma
(in NAFLD)

Centrilobular fibrosis

activation of
HSCs → leads
to fibrosis

Trichrome stain
is used to iden-
tify fibrosis

Indications for Liver Biopsy in Pts With NAFLD

Perform liver biopsy

- More features of metabolic syndrome
 - Obesity, hypertension, increased TG, low HDL, impaired glucose tolerance
- Diabetes
 - Family history of diabetes
- Older age
- High AST/ALT
- Low platelets/albumin

**or at least doing fibroscan (transient elastography)*

Consider liver biopsy

- Cholecystectomy
- Bariatric surgery
- Clinical trials

Evaluation of Suspected NAFLD

- Exclude significant alcohol consumption
 - no more than 1- 2 drinks per day
- Exclude secondary causes of fatty liver:
 - Drugs: steroids, amiodarone, MTX, CCB, tamoxifen
 - Altered nutritional states: intestinal bypass surgery, rapid weight loss, TPN, **Total parenteral** cachexia (starvation)
 - Metabolic/genetic: Wilson's disease, lipodystrophy
 - Miscellaneous: HIV, IBD, bacterial overgrowth

Evaluation of Suspected NAFLD

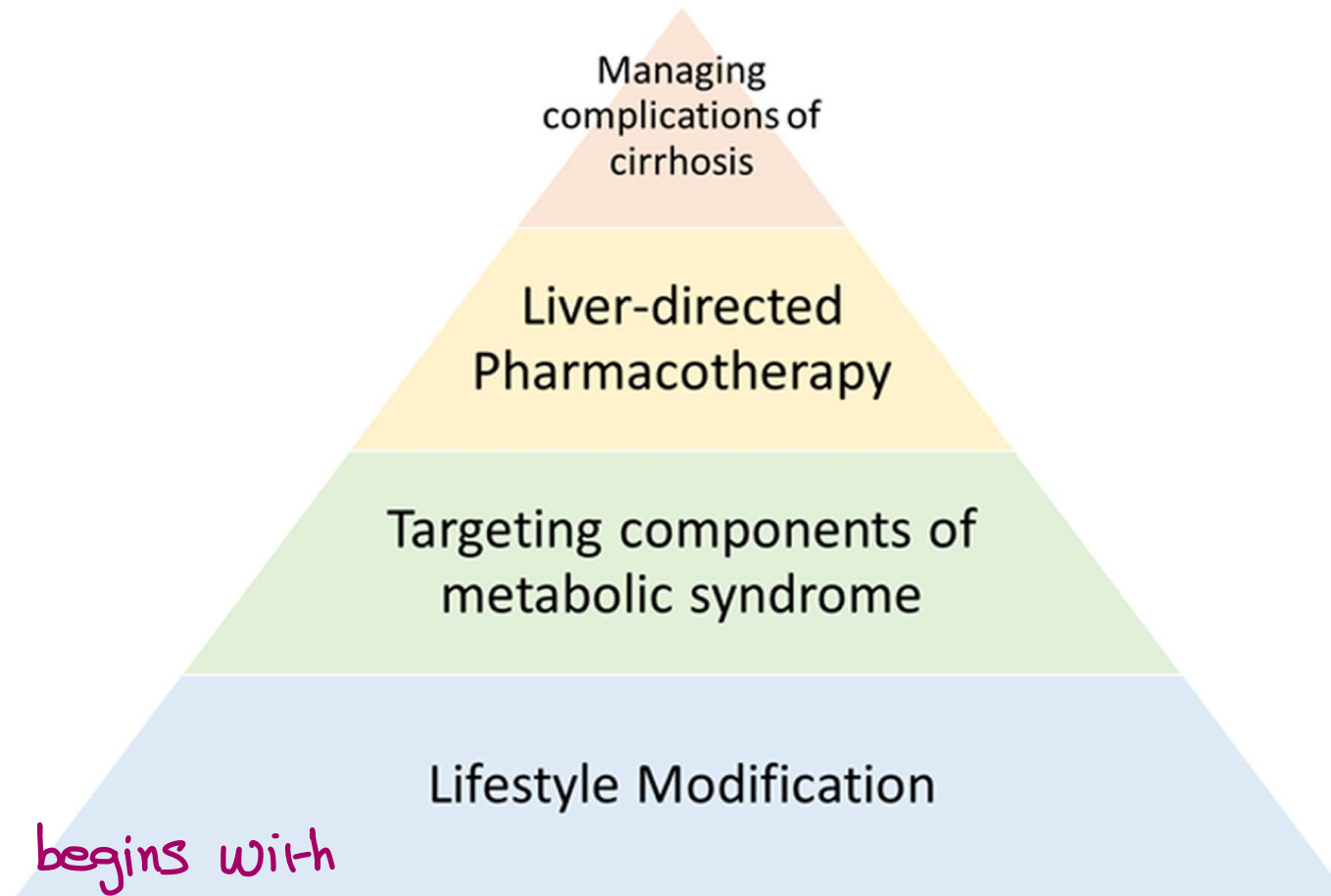
- Exclude other liver diseases such as:
 - HBV, HCV (genotype 3)
 - Alpha-1 antitrypsin deficiency
 - Hemochromatosis (iron studies)
 - Autoimmune hepatitis (ANA, ASMA)
 - Wilson disease (ceruloplasmin)
- Imaging studies to look for hepatic steatosis:
 - Ultrasonography with increased echogenicity
 - CT with low attenuation
- Liver biopsy when risk for NASH or advanced fibrosis is high
 - Fatty liver: fat accumulation in at least 5% of hepatocytes
 - NASH: steatosis, hepatocyte ballooning, and lobular inflammation

Management of NAFLD

This should be categorized into:

- Aggressive management of CV risk factors (all NAFLD pts)
- Treatment of liver disease (NASH)

Management of NAFLD



NAFLD : TREATMENT

- Weight loss
 - Weight loss
 - Weight loss
 - Weight loss
 - Weight loss
 - Weight loss
- Diet
 - Severely restrict carbohydrates
 - Adkins or Mediterranean diet
 - Avoid fructose
 - Coffee 2-4 cups/d *good for them*
 - Exercise *improves metabolism*

Lifestyle Modification: Weight Loss

- Loss of at least 5% of body weight appears necessary to improve steatosis
- Greater weight loss (7- 10%) is needed to improve necroinflammation
- Aim to lose 0.5 – 1.0 kg/week
- Achieve target weight within 6 – 12 months
- Maintain loss

Lifestyle Modification: Diet

- Atkins or Mediterranean diet
 - ↳ no carbohydrates
 - ↳ rich in vegetables
- Calorie restriction: 600 calories less than daily requirement
- Low in sodium and simple carbohydrates
- ↓^{ed} saturated and trans-fat intake
- ↑^{ed} mono and polyunsaturated fatty acids
- Increase consumption of fruits and vegetables

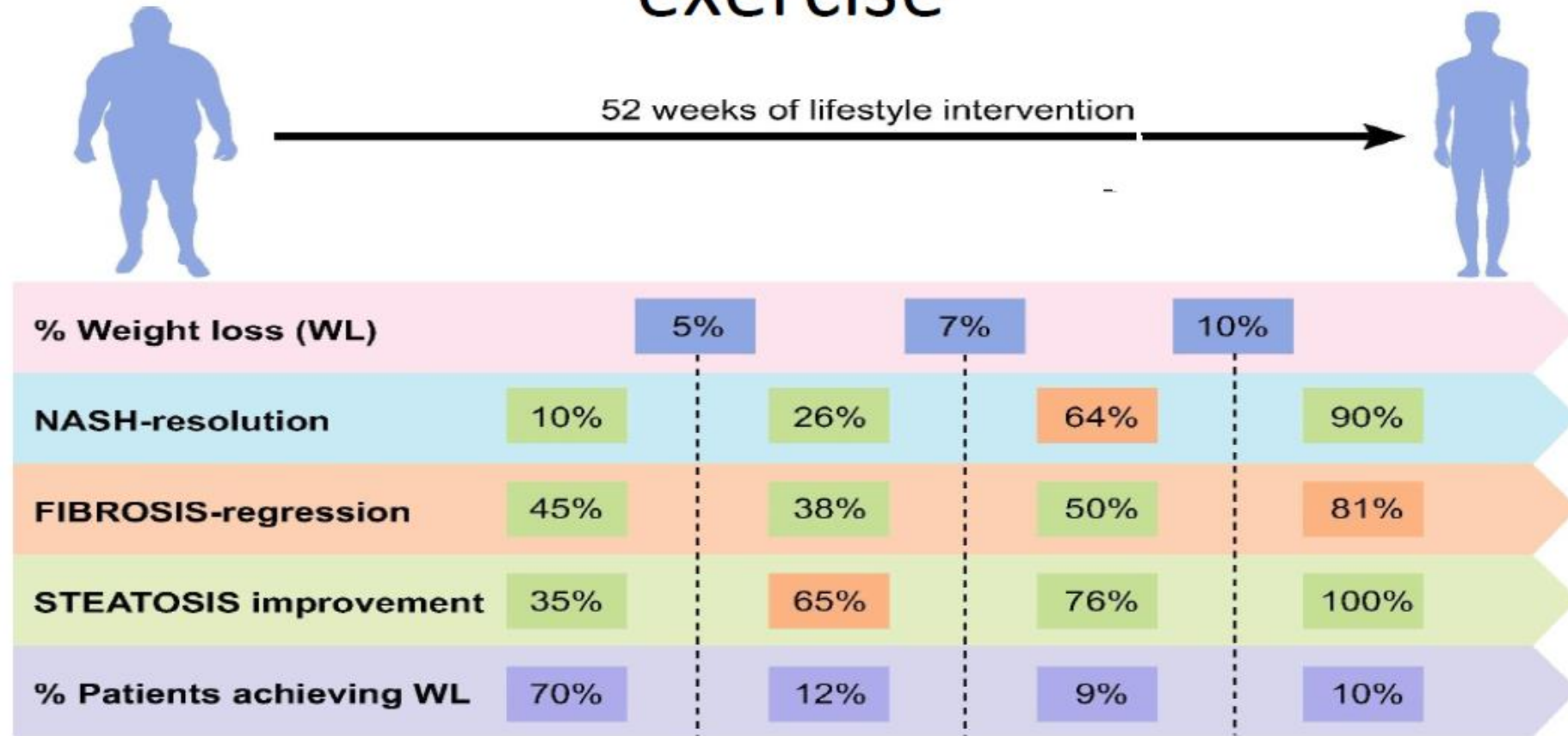
Lifestyle Modification: Diet

- Coffee consumption has been associated with a lower risk of metabolic syndrome and a reduced diabetes risk in a dose dependent manner
- A study in NAFLD patients indicated an inverse association between coffee consumption and liver fibrosis
- Large prospective cohort study demonstrated that those who drank 2-3 cups of coffee per day had a 38% risk reduction for HCC compared with non-coffee drinker.

Lifestyle Modification: Exercise

- Increase physical activity
- Reduce total sedentary time
- 5 - 7 sessions/week of moderate to vigorous exercise
- Each session lasting for 30 - 45 minutes
- Aerobic or resistance exercise
- Aim > 10,000 steps/ day (pedometer)

Treatment of NAFLD with diet, physical activity and exercise



Pharmacotherapy for NASH

- Pioglitazone, a thiazolidinedione, improves liver histology in patients with and without T2DM with biopsy-proven NASH. Discuss benefits and risks (weight gain, ? bladder cancer, bone loss in women).

can cause →

- Non-DM adults with biopsy-proven NASH (noncirrhotic): Vitamin E 800 IU/day. Discuss risks and benefits.

high dose

↳ in diabetics can increase the risk of cardiomyopathy

↳ increases bleeding tendency

Vitamin E: Risks

- Increases risk of bleeding in a dose-dependent manner
 - Especially ≥ 400 units daily^[1]
- Increases risk of prostate cancer in older men^[2]
- Increases risk of hemorrhagic stroke^[3]
 - May be preventive in reducing the risk of ischemic stroke^[3]

Bariatric Surgery

- Not a primary treatment for NASH
- Treatment for obesity:
 - BMI > 40
 - BMI 35 – 40 with other significant disease
- Improves insulin sensitivity and lipid profile
- Reduces steatosis, necroinflammation and fibrosis
- Contraindicated in pts with *portal HTN and *gastroesophageal varices

NAFLD Summary

- The prevalence of NAFLD is high and is on the rise
- Is most commonly found in patients with metabolic syndrome
- NASH is not a benign disease
- Cirrhosis develops in ~ 20% of NASH patients
- Established cardiovascular disease, liver related mortality and HCC
- Weight loss remains the primary treatment for NAFLD including NASH



“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”

Alcohol-Related Liver Disease

Current Terminology

Previous term	Current term	Abbreviation
Alcoholic	Alcohol use disorder	AUD
Alcoholic liver disease	Alcohol-related liver disease	ALD
Alcoholic cirrhosis	Cirrhosis due to alcohol-related liver disease	ALD cirrhosis
Alcoholic steatohepatitis (histologically-defined lesion)	Steatohepatitis due to ALD	ASH
Alcoholic fibrosis	Fibrosis due to ALD	ALD fibrosis
Alcoholic hepatitis	Alcoholic hepatitis*	AH

Term “alcoholic” is stigmatizing and undermines patient dignity and self-esteem.

How much is “just one drink” (12-14 g)?

**12 fl oz of
regular beer**

=

**8–9 fl oz of
malt liquor**
(shown in a
12 oz glass)

=

**5 fl oz of
table wine**

=

**1.5 fl oz shot of
80-proof spirits**
 (“hard liquor”—
whiskey, gin, rum,
vodka, tequila, etc.)



about 5%
alcohol



about 7%
alcohol



about 12%
alcohol



about 40%
alcohol

The percent of “pure” alcohol, expressed here as alcohol by volume (alc/vol), varies by beverage.

Drinkers underestimate alcohol consumption by ~ 40%

Low Risk Drinking: NIAAA Definitions

National Institute of Alcohol Abuse and Alcoholism Definition of Drinking at Low Risk for Developing Alcohol Use Disorder (AUD):

- For women, low-risk drinking is defined as no more than 3 drinks on any single day and no more than 7 drinks per week.
- For men, no more than 4 drinks on any single day and no more than 14 drinks per week.
- NIAAA research shows that only about 2 in 100 people who drink within these limits have AUD.

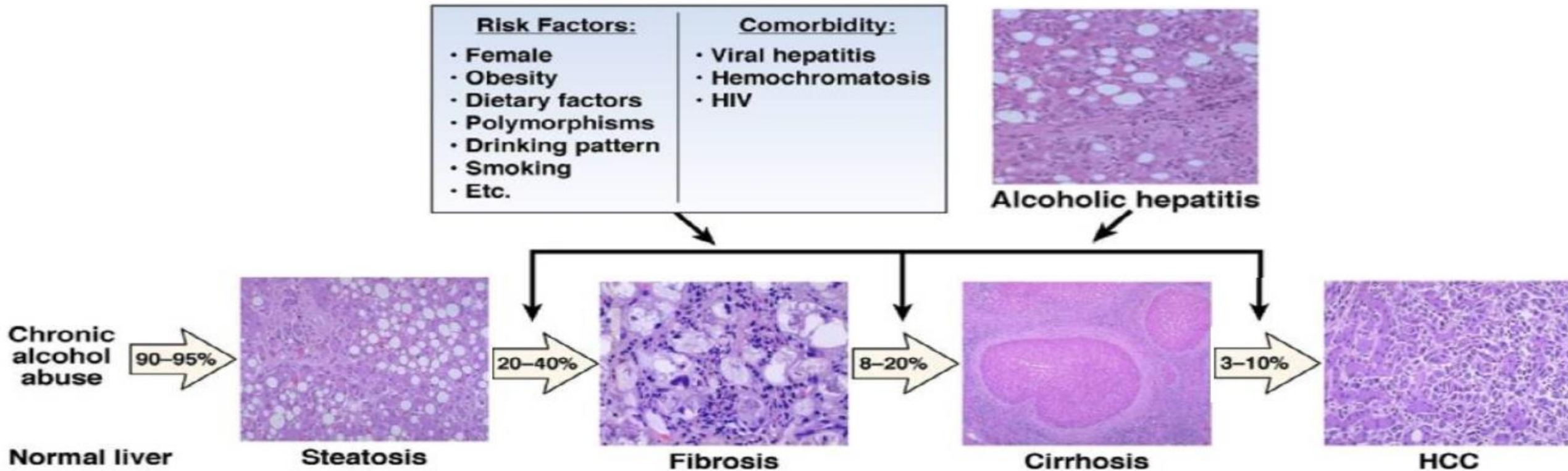
Women: 3 OR 7 Rule (Caution: Breast cancer and other risk increases with 1 drink per day)

Men: 4 OR 14 Rule

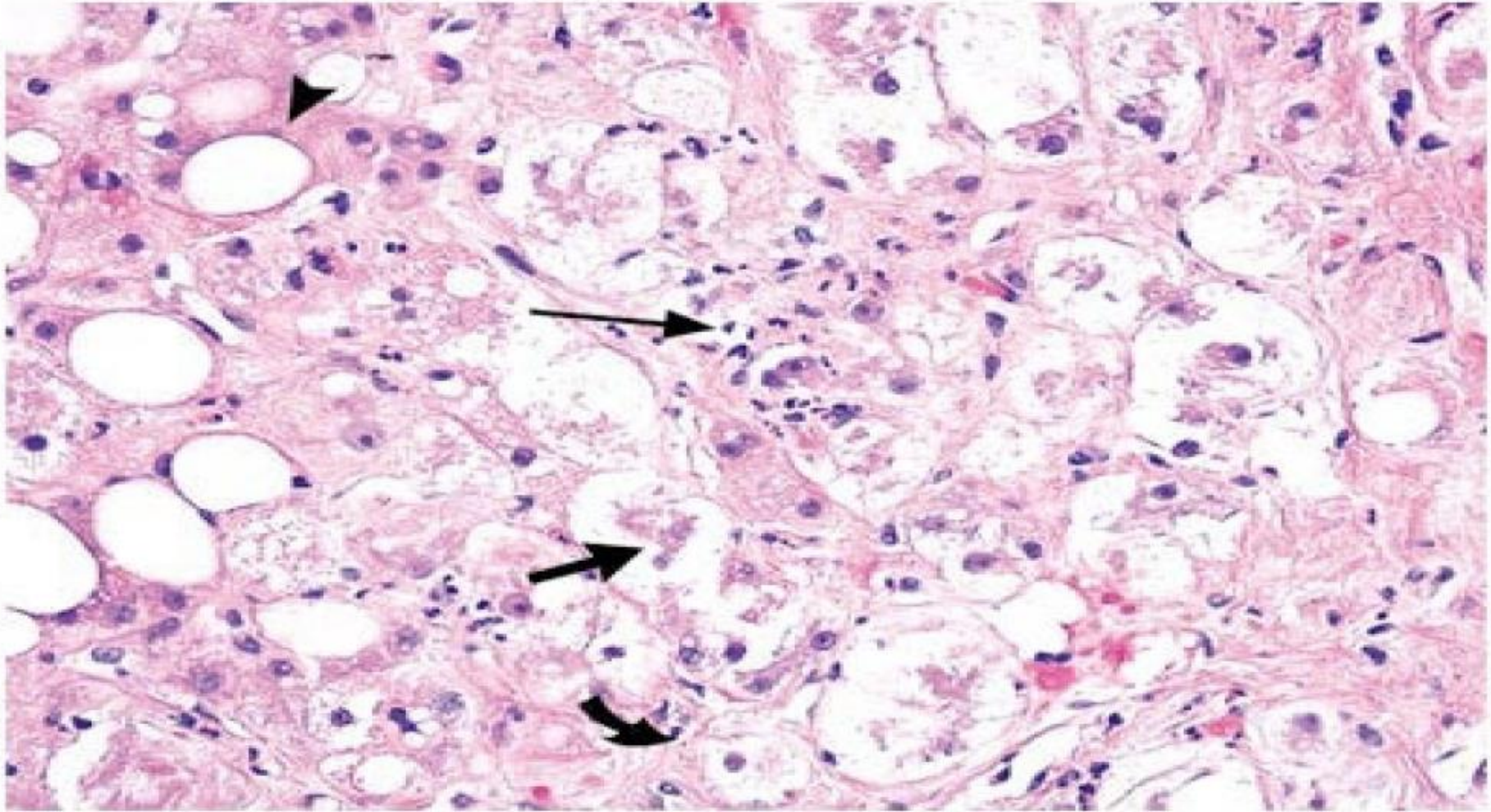
How Much Should you Drink to Get Alcohol Related Disease

- Heavy alcohol :3 drinks per day for women (≥ 40 grams of alcohol), and four drinks per day for men (≥ 50 -60 grams of alcohol).
- Strong correlation between severity and duration of alcohol misuse and the presence of cirrhosis.
- 3% of patients with alcoholic hepatitis progress to cirrhosis annually
- Rate of cirrhosis higher in patients consuming ≥ 30 g / d than abstinent controls or consuming < 30 g / day (2.2% vs 0.08%)
- Alcohol consumption > 120 g /day highest risk of cirrhosis (13.5%)

Histopathological progression of ALD: Risk factors and Co-morbidities



Histopathological Features of Alcoholic Hepatitis.



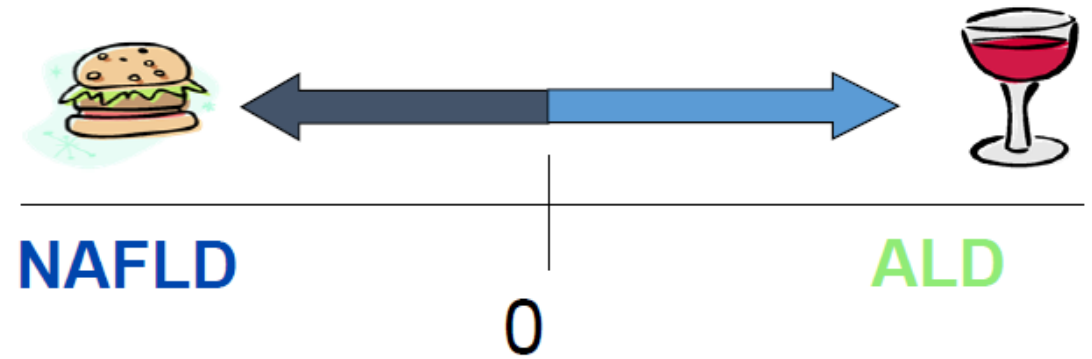
Mallory - Denk bodies

Outpatient management of alcohol related liver disease

- Differentiating between alcohol related steatohepatitis and non-alcohol related steatohepatitis
- Diagnosing alcohol use disorder
- Management

Alcohol related Steatohepatitis Versus NASH

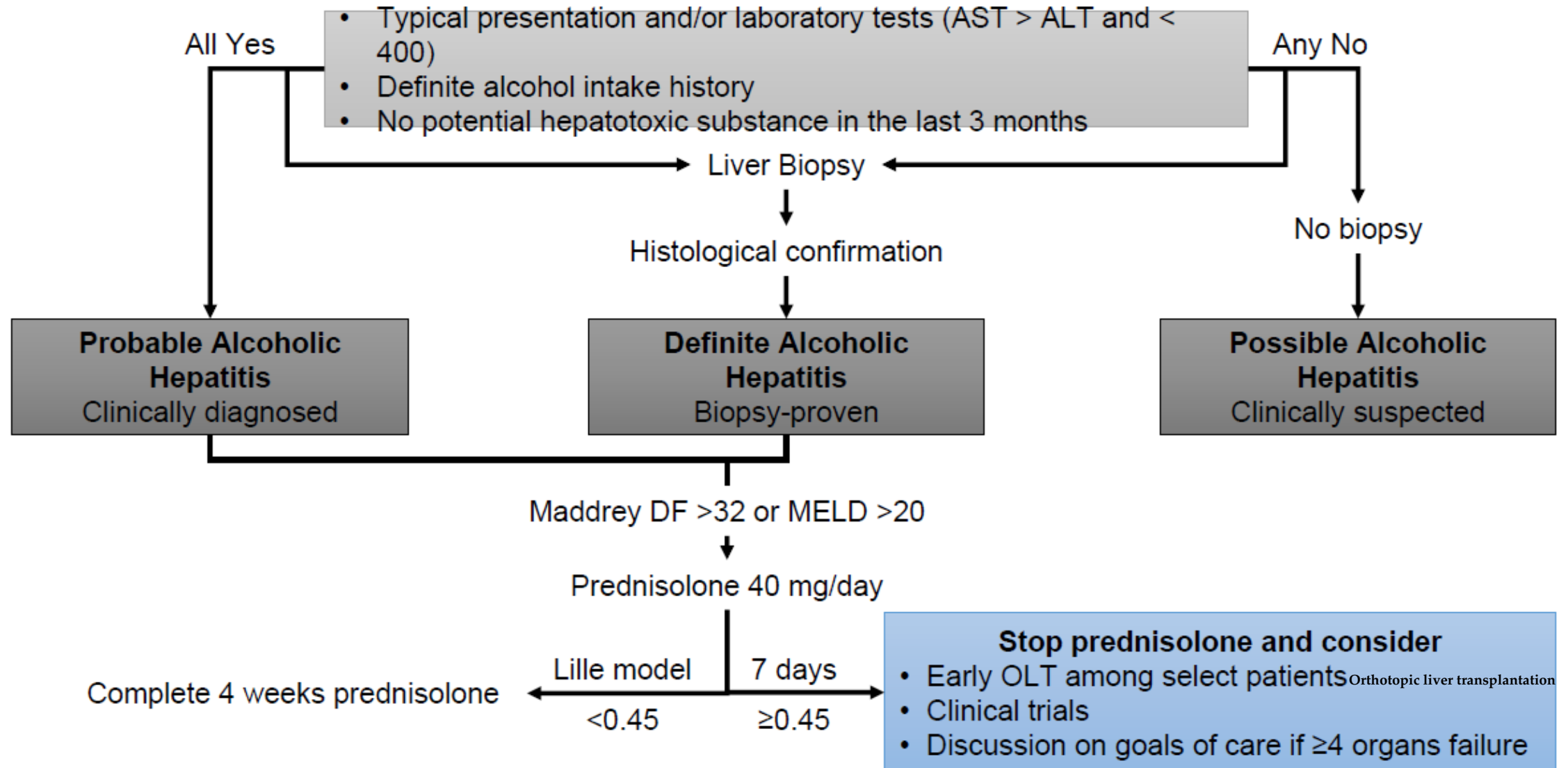
- Difficult to obtain accurate alcohol consumption history: AUDIT questions and history from multiple sources
- High MCV, male sex, low BMI, and $AST > ALT$ favor Alcohol as factor
- Normal MCV, female sex, obesity, $ALT > AST$ favor NASH diagnosis



Diagnosing Alcohol Use Disorder

- AUDIT (Alcohol Use Disorders Inventory Test): 10 questions that explore consumption (1–3), dependence (4–6), and alcohol-related problems (7–10)
- C-off points: 8–15 “risky drinking”; ≥ 16 “harmful drinking”
- AUDIT-C includes just the first three questions of AUDIT: reliable for the screening of ‘risky drinking’.
- NIAAA (National Institute of Alcohol Abuse and Alcoholism) recommends third question of the AUDIT (*How often do you have six or more drinks on one occasion?*) as single screening question, followed by the whole AUDIT if answer is rated positive.

Alcoholic Hepatitis: Management



DF and MELD predict AH mortality

DF Discriminant Function

- Extensively validated
- DF >32 predicts 50% mortality
- $4.6 (\text{PT} - \text{Control}) + \uparrow \text{Bilirubin} \uparrow \text{INR}$
- Especially useful for steroid treatment

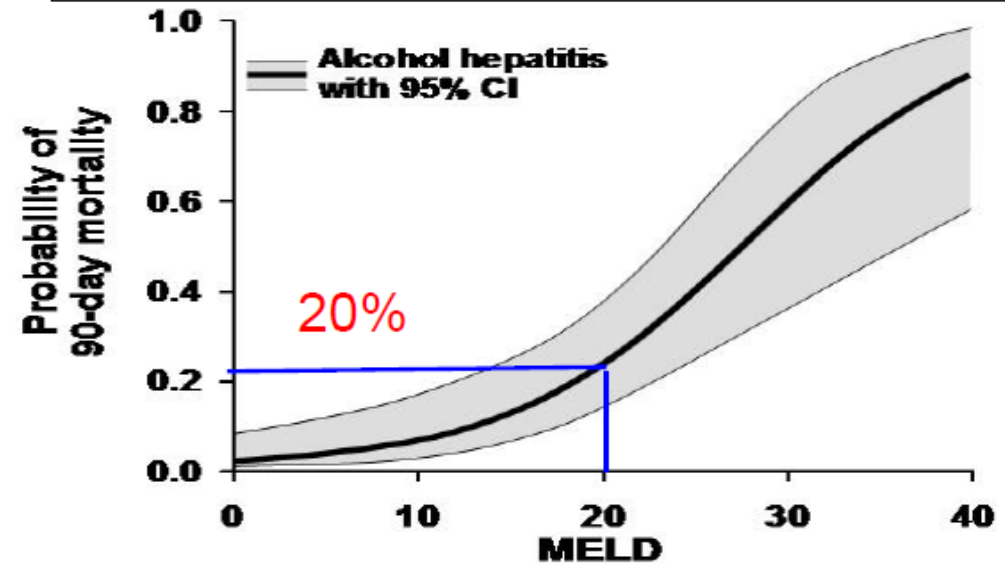
↳ if the score is >32 → severe alcoholic hepatitis
50% risk of death within the next three months

MELD Model for end-stage liver disease

- INR is more generalizable than PT
- Easily available calculators
- Cut point can be based on side-effects of proposed treatment

↳ if the score is >20 → 20% mortality within the next three months

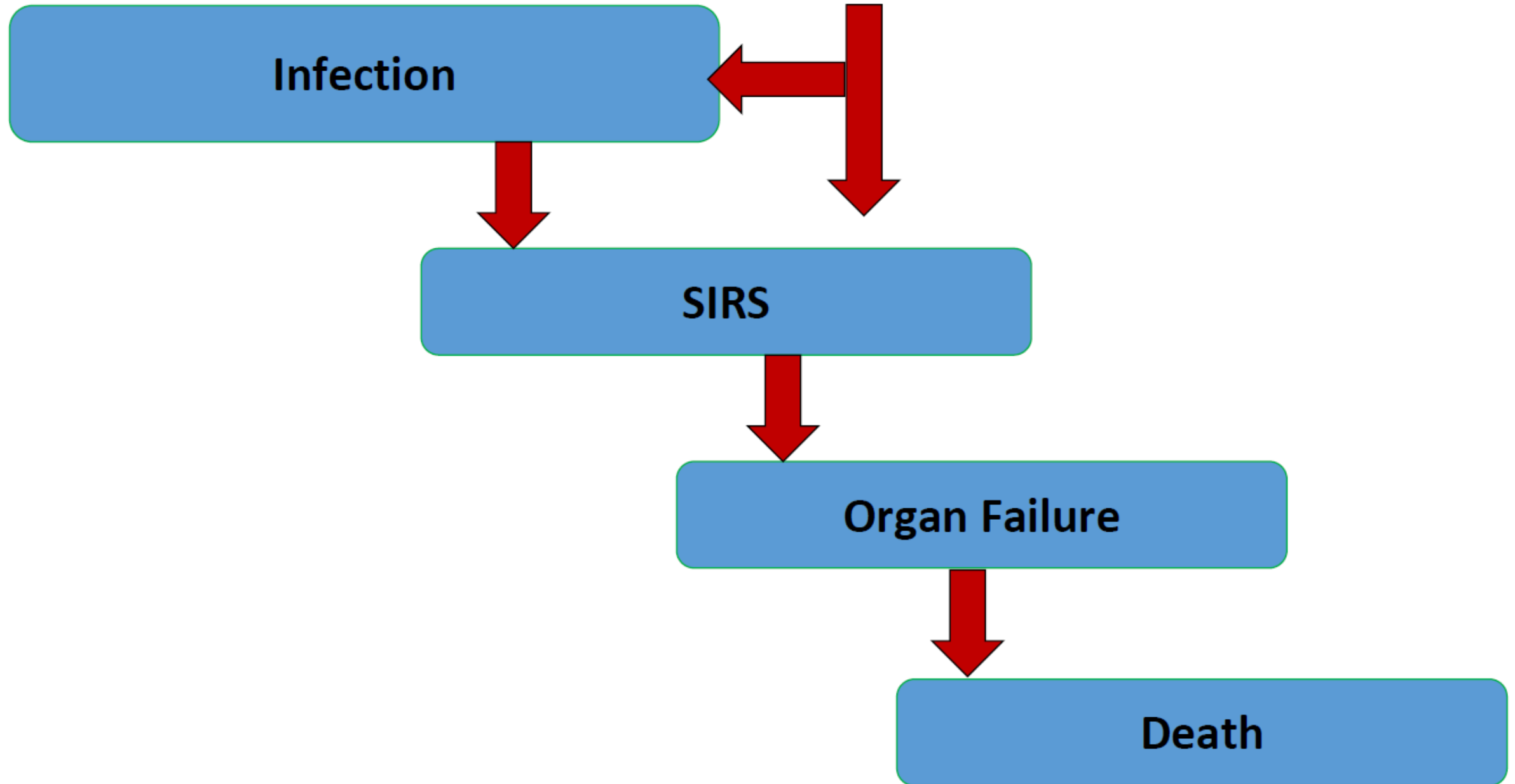
**Lower but still
important
risk of death in
patients
with DF<32...**



Clinical Manifestations of Alcoholic Hepatitis

- Consequences of liver failure: Jaundice
 - Ascites
 - Encephalopathy
- Systemic Inflammation and sepsis: SIRS
 - Multiple organ failure
- Impaired hepatocyte regeneration: Propagation of liver failure
- Features of alcohol withdrawal syndrome

SEVERE ALCOHOLIC HEPATITIS: COURSE



Alcohol Related Liver Disease

Alcoholic Hepatitis Initial Evaluation

