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.
- ~ 3% of the population has nonalcoholic steatohepatitis (NASH).
- 2nd most common reason for liver transplant.
- 3rd most common cause of HCC in Western countries.

Younossi ZM et al. Hepatology 2016

NAFLD

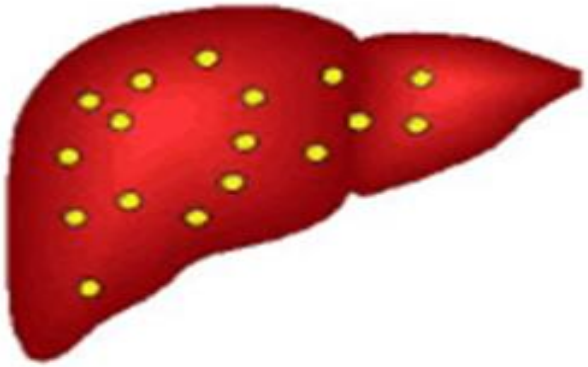
- The hepatic manifestation of metabolic syndrome.
- Incidence of new NAFLD is rising with increasing rates of obesity, diabetes and physical inactivity.
- NAFLD is also present in 7% of normal-weight (lean) individuals.

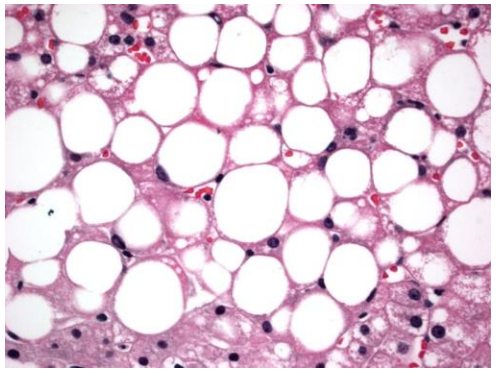
Metabolic Syndrome

- The Adult Treatment Panel III
- Any 3 of the following 5 features:
  1. WC ≥ 102 cm (40 in) in men or ≥ 88 cm (35 in) in women
  2. TG ≥ 150 mg/dL
  3. HDL < 40 mg/dL in men or < 50 mg/dL in women
  4. BP ≥ 130/85 mm Hg
  5. FPG ≥ 110 mg/dL

The Spectrum of NAFLD

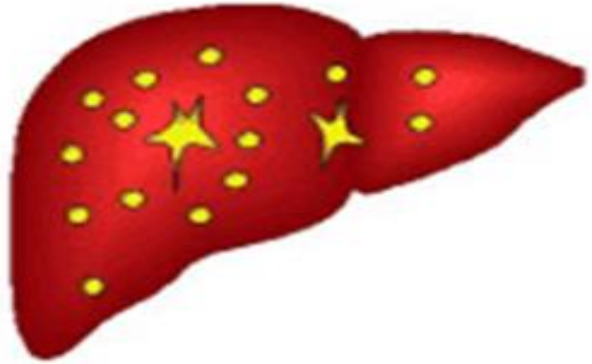
Fatty Liver

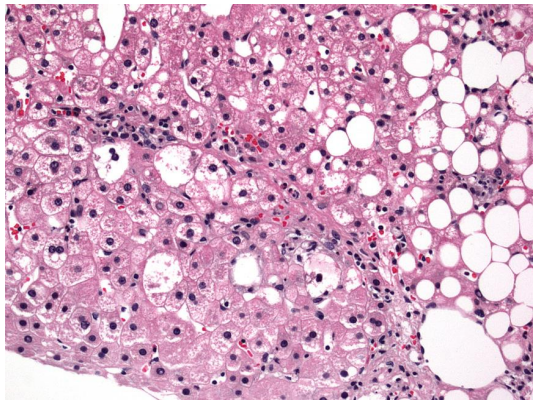




Steatosis

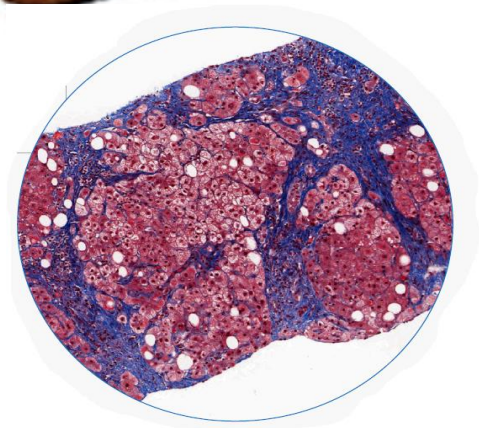
NASH





Steatosis + inflammation + liver injury (ballooning) +/- fibrosis

Cirrhosis

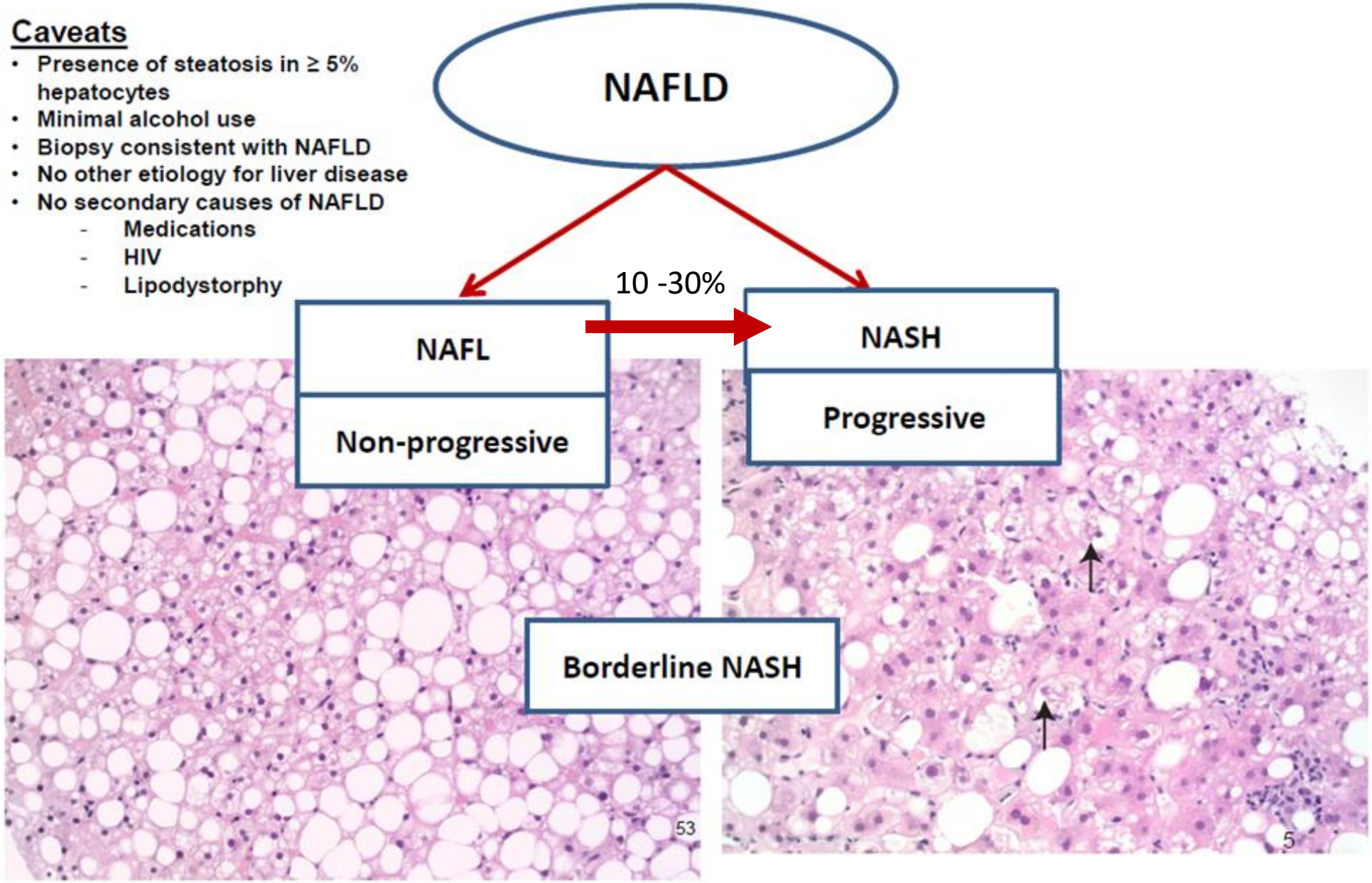


Fibrosis and nodular regeneration

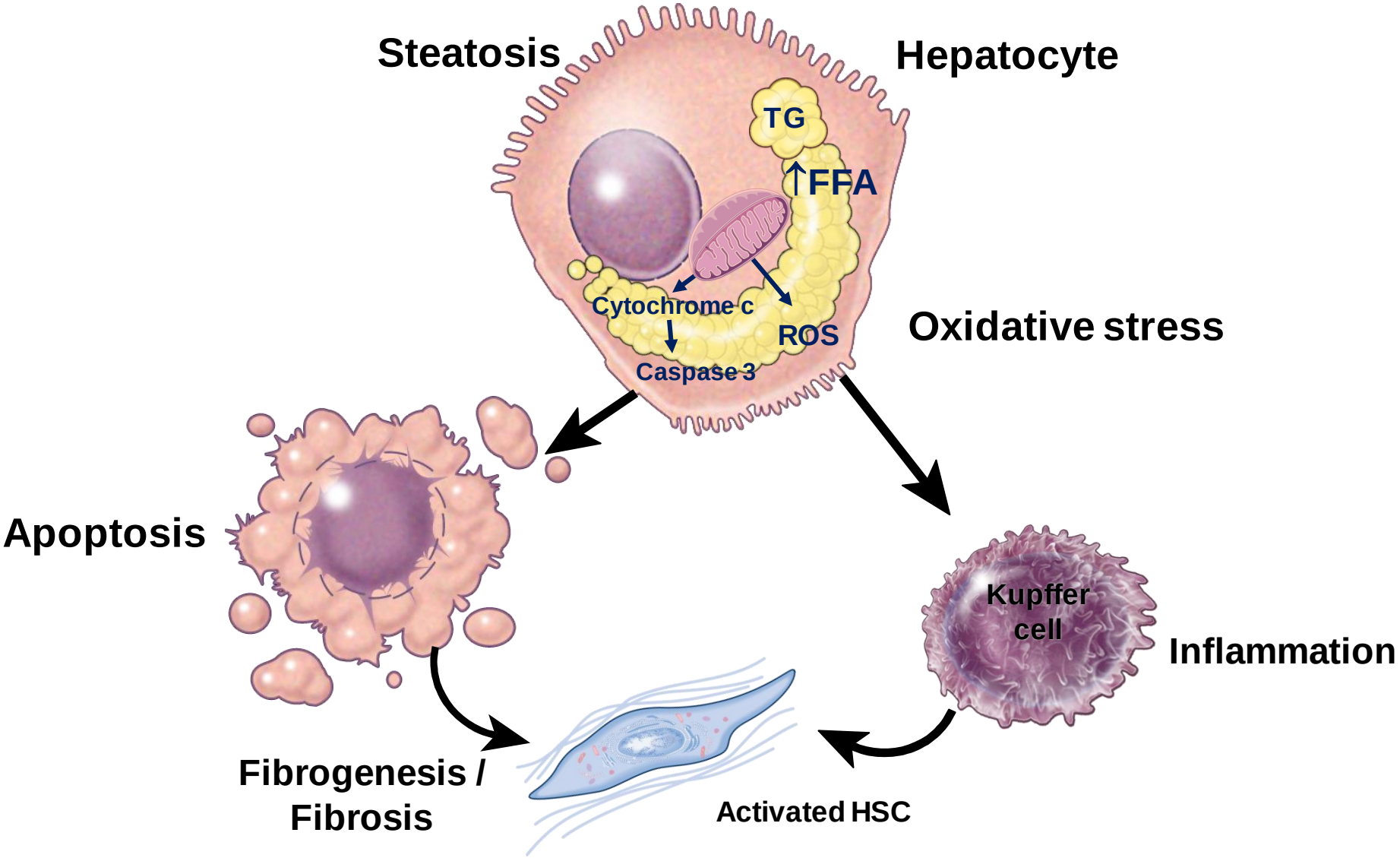
Subtypes of NAFLD

Caveats

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



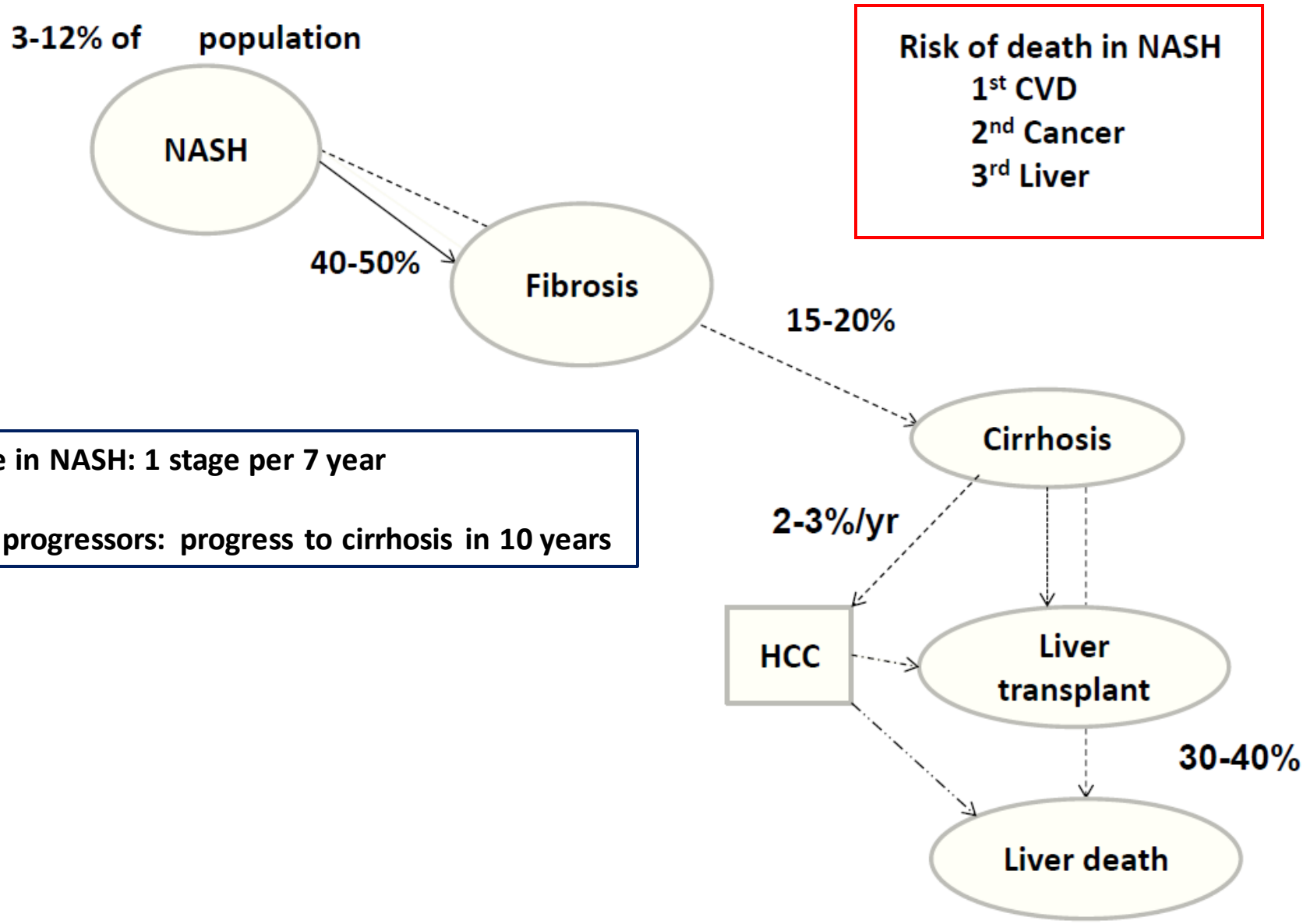
Pathogenesis



Wieckowska et al. Hepatology 2007; 46:582-589

(Courtesy of Ariel Feldstein, MD)

Natural History of NASH



Risk of death in NASH
1st CVD
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

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
AST/ALT ratio	< 1 (in 65 – 90% of pts)
Alkaline phosphatase	↑ 2 – 3 fold (< 50% pts)
Albumin, Bilirubin , INR	Normal (unless cirrhosis has developed)
Serum Ferritin	↑ed ~ 50 % of pts

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

McCullough AJ. Clin Liver Dis 2004;8:521-33

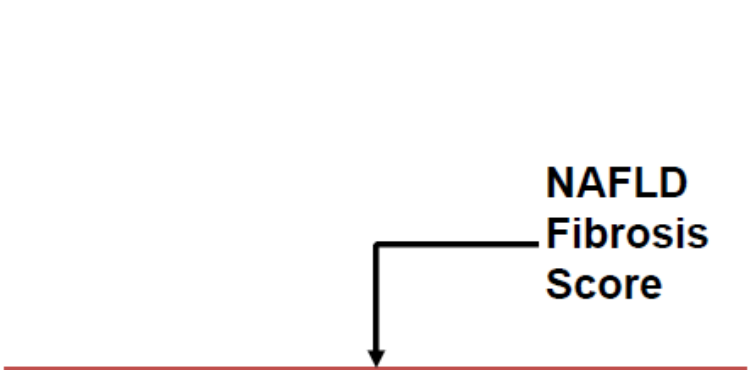
Fibrosis Assessment for Patients With NAFLD

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

NAFLD Fibrosis Score

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

FIB-4 Score

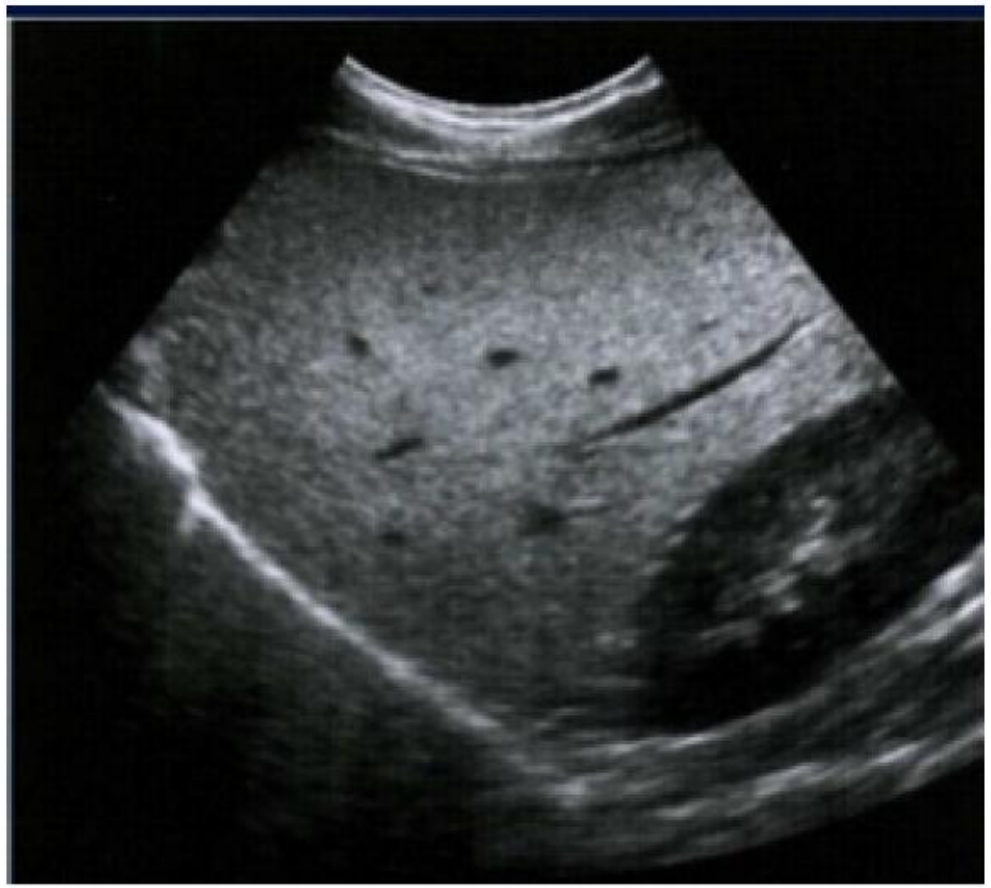
FIB-4 Score[2,3]	Effect	NPV or PPV, %
< 1.3	Rules out fibrosis	95
> 3.25	Predicts fibrosis	75

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.

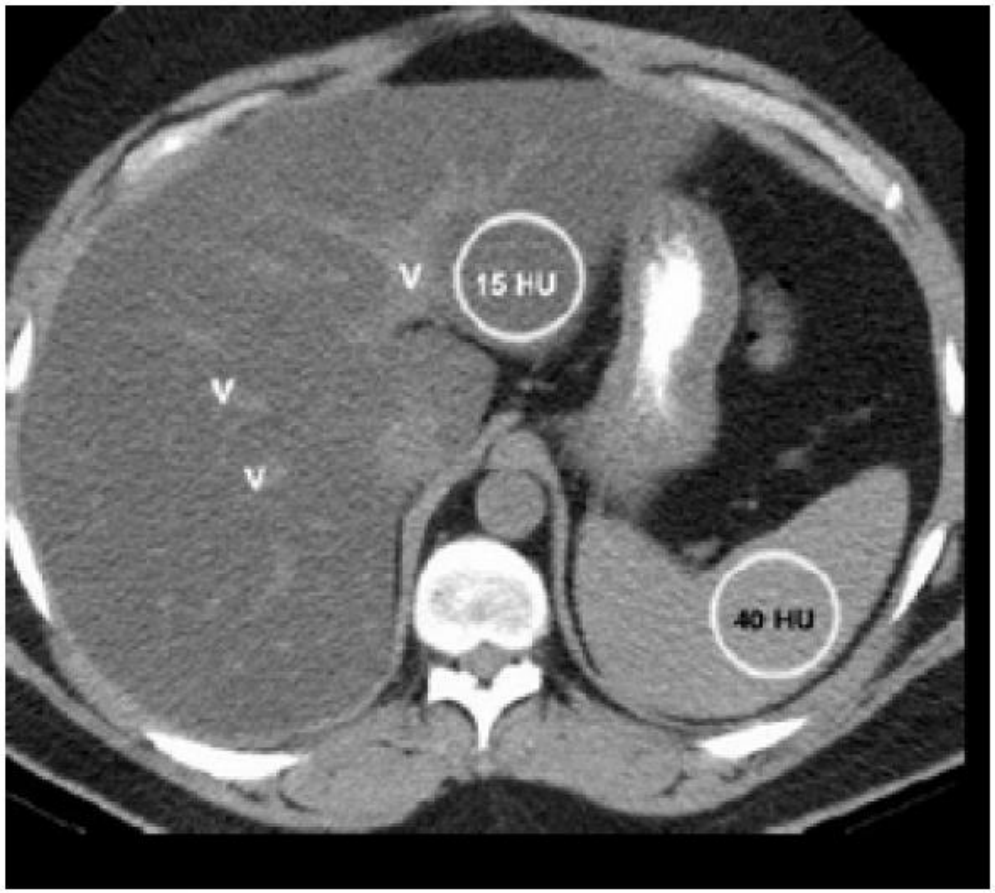
Imaging Modalities in NAFLD

- Ultrasound
- CT scan
- Transient elastography
- MR technologies

Imaging Findings



- Increased echogenicity
- Hepatomegaly

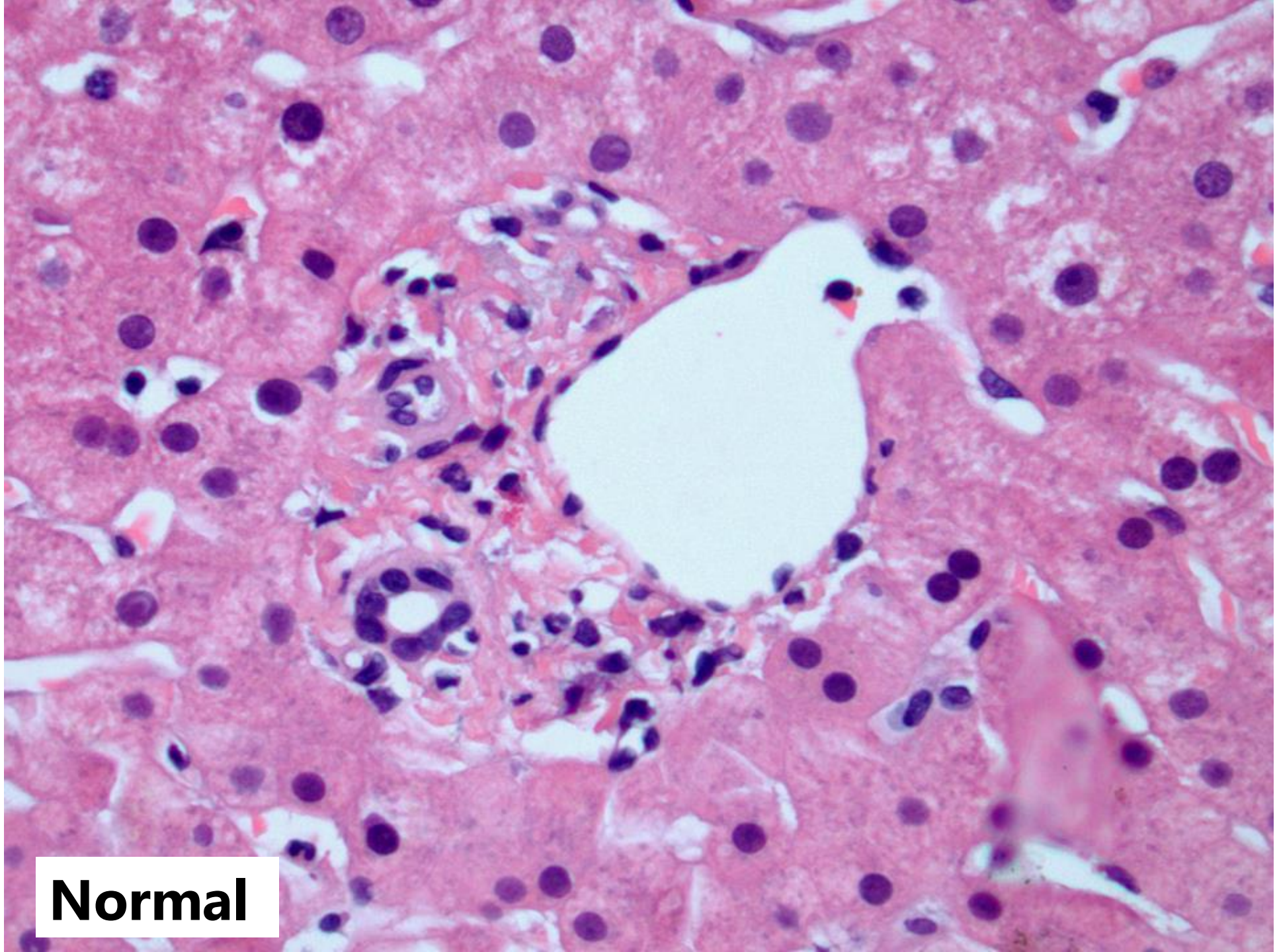


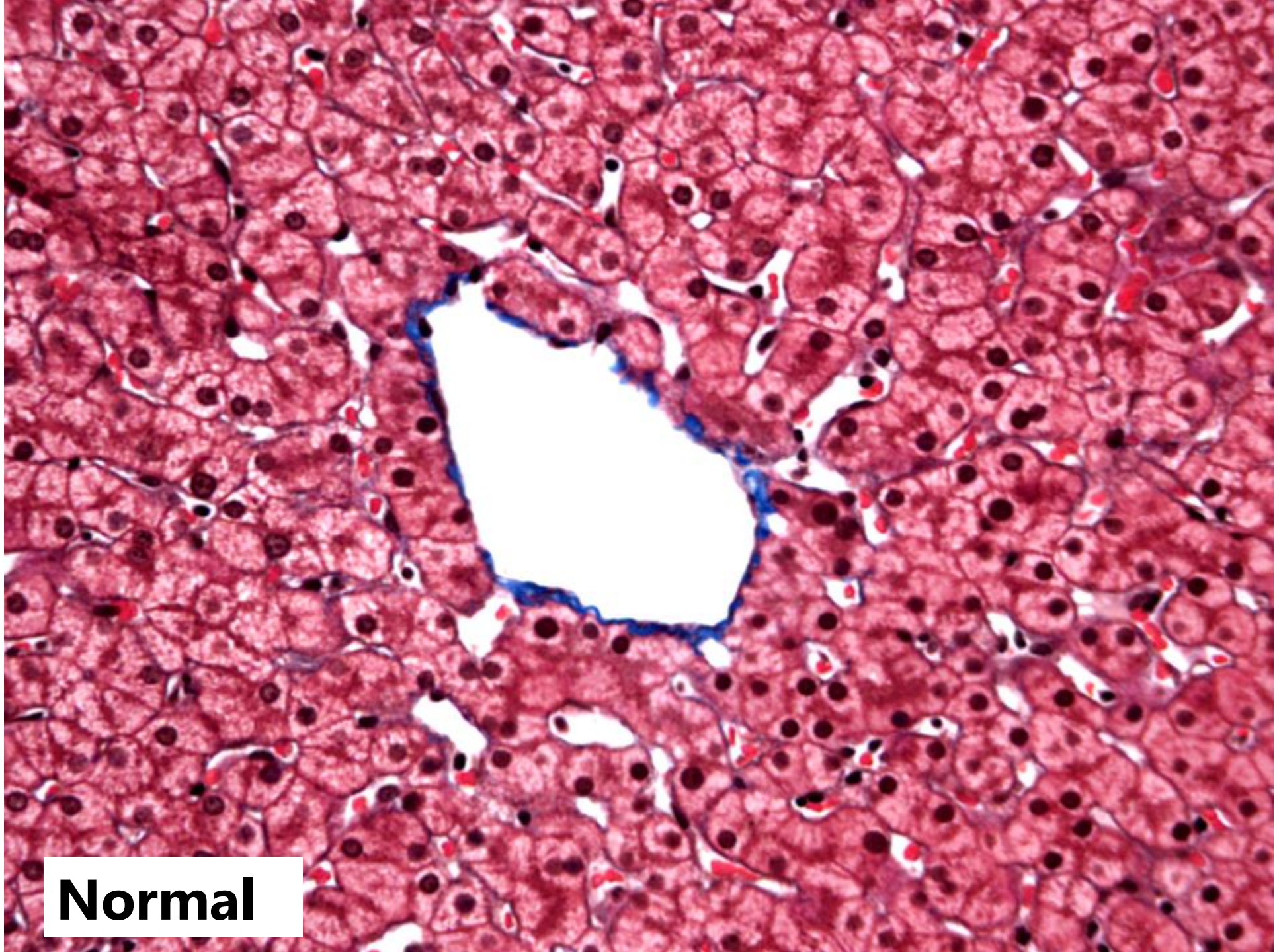
- Low attenuation compared with the spleen

Liver Biopsy

- The gold standard for diagnosis
  - To assess severity of hepatic steatosis
  - To differentiate simple steatosis from NASH
  - To stage fibrosis

- Histological criteria for NASH :
  - Steatosis (≥ 5% of hepatic parenchyma) AND
  - Mixed lobular inflammation AND
  - Hepatocellular ballooning


Normal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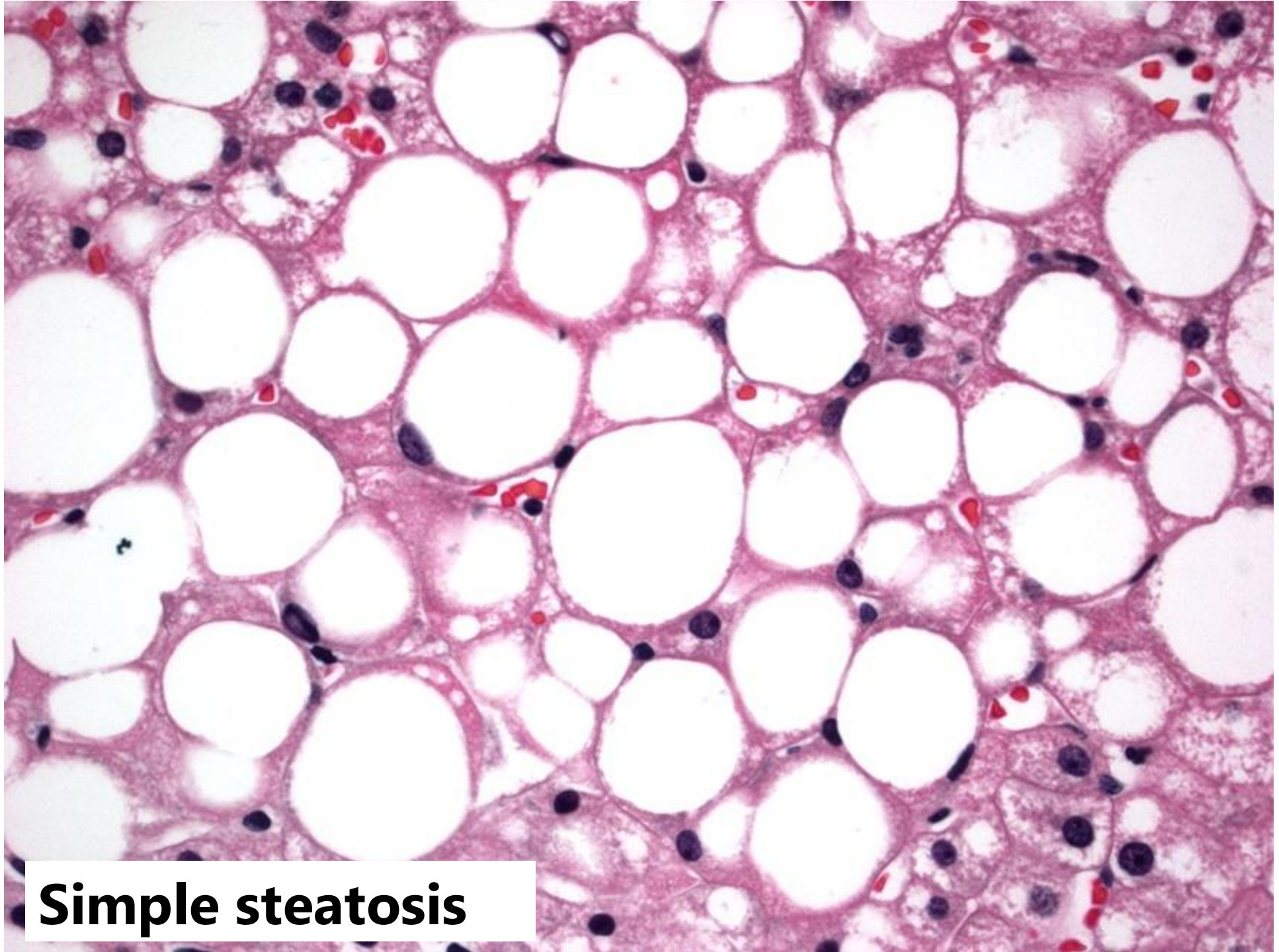
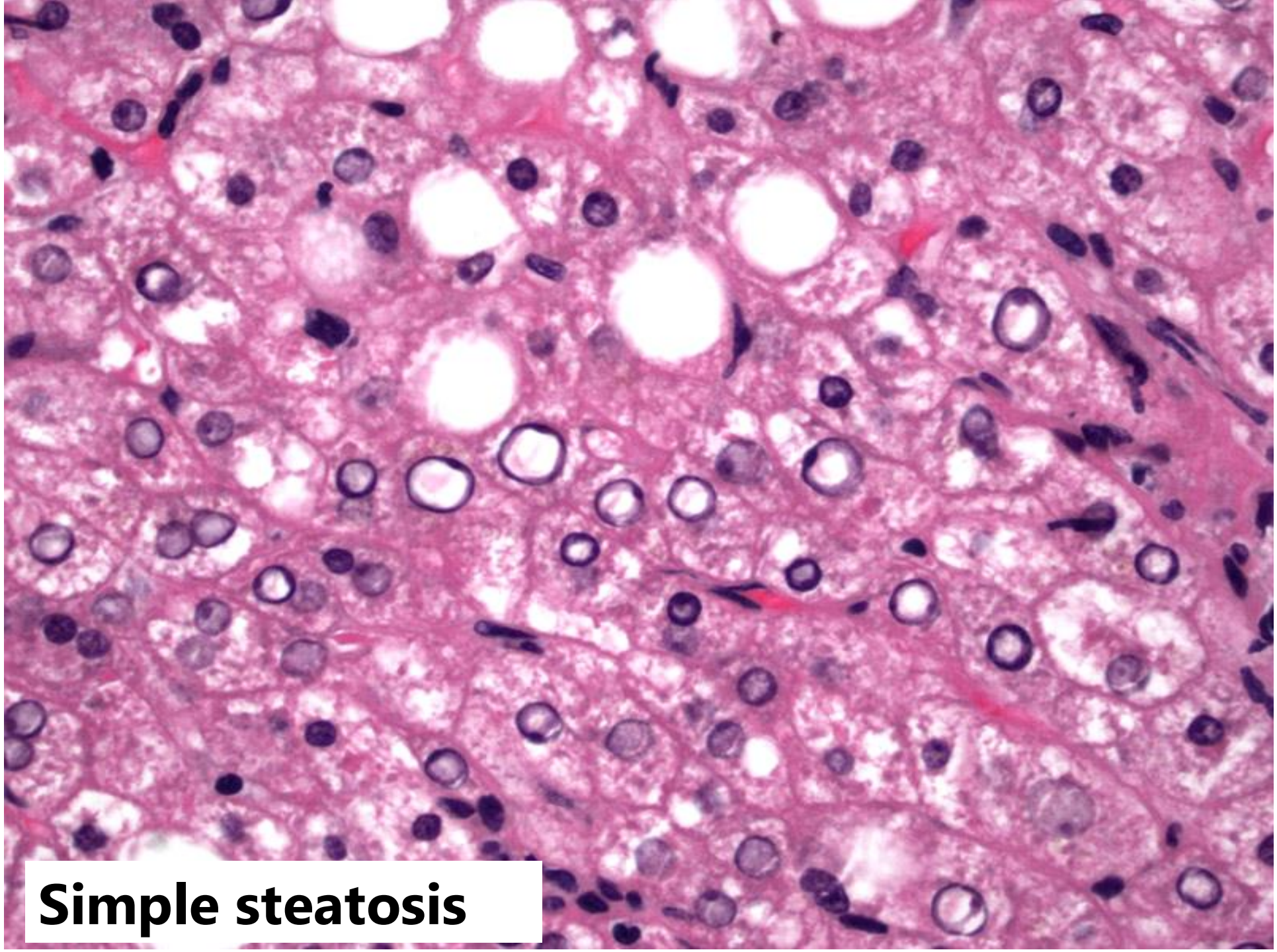
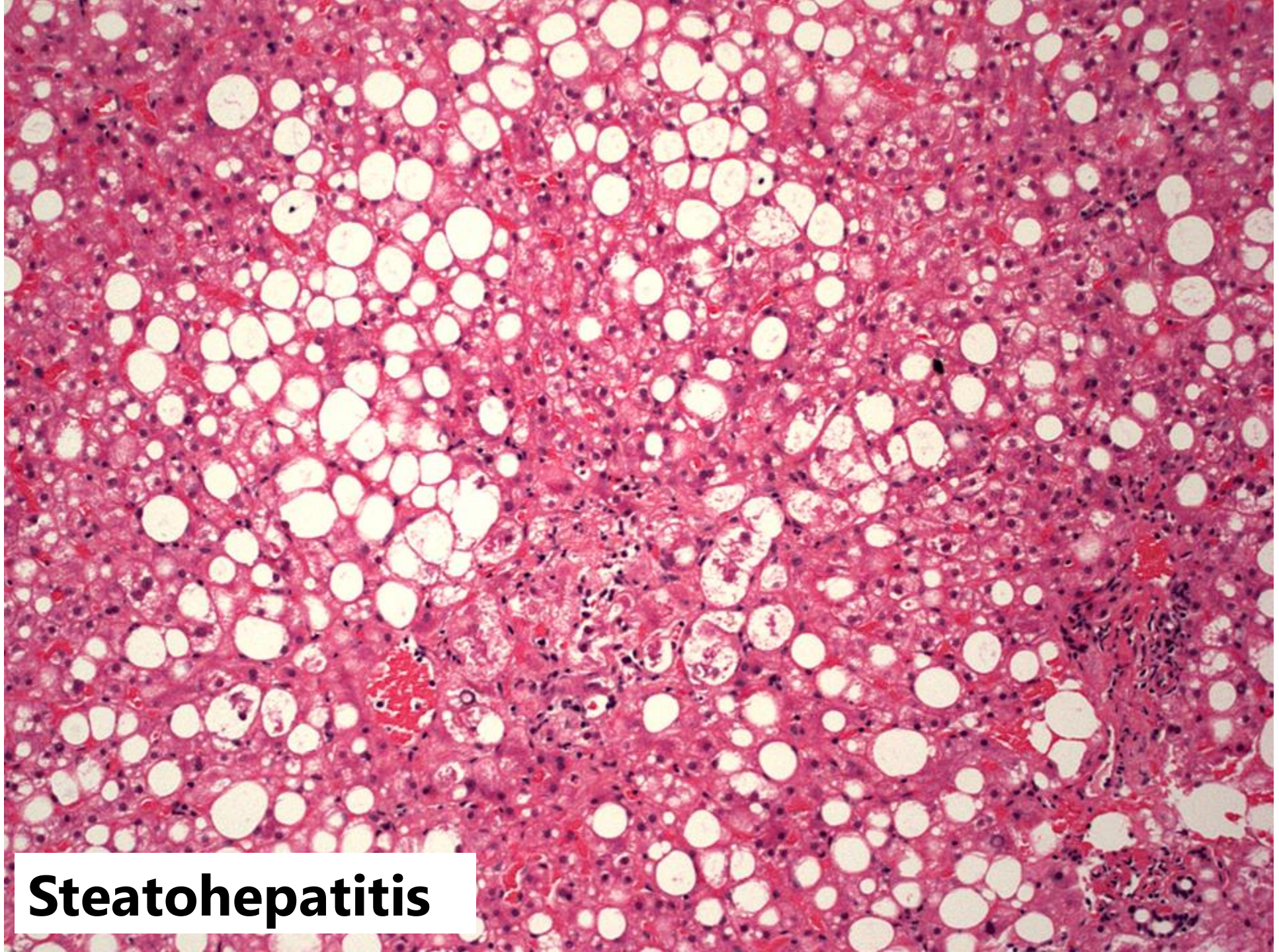
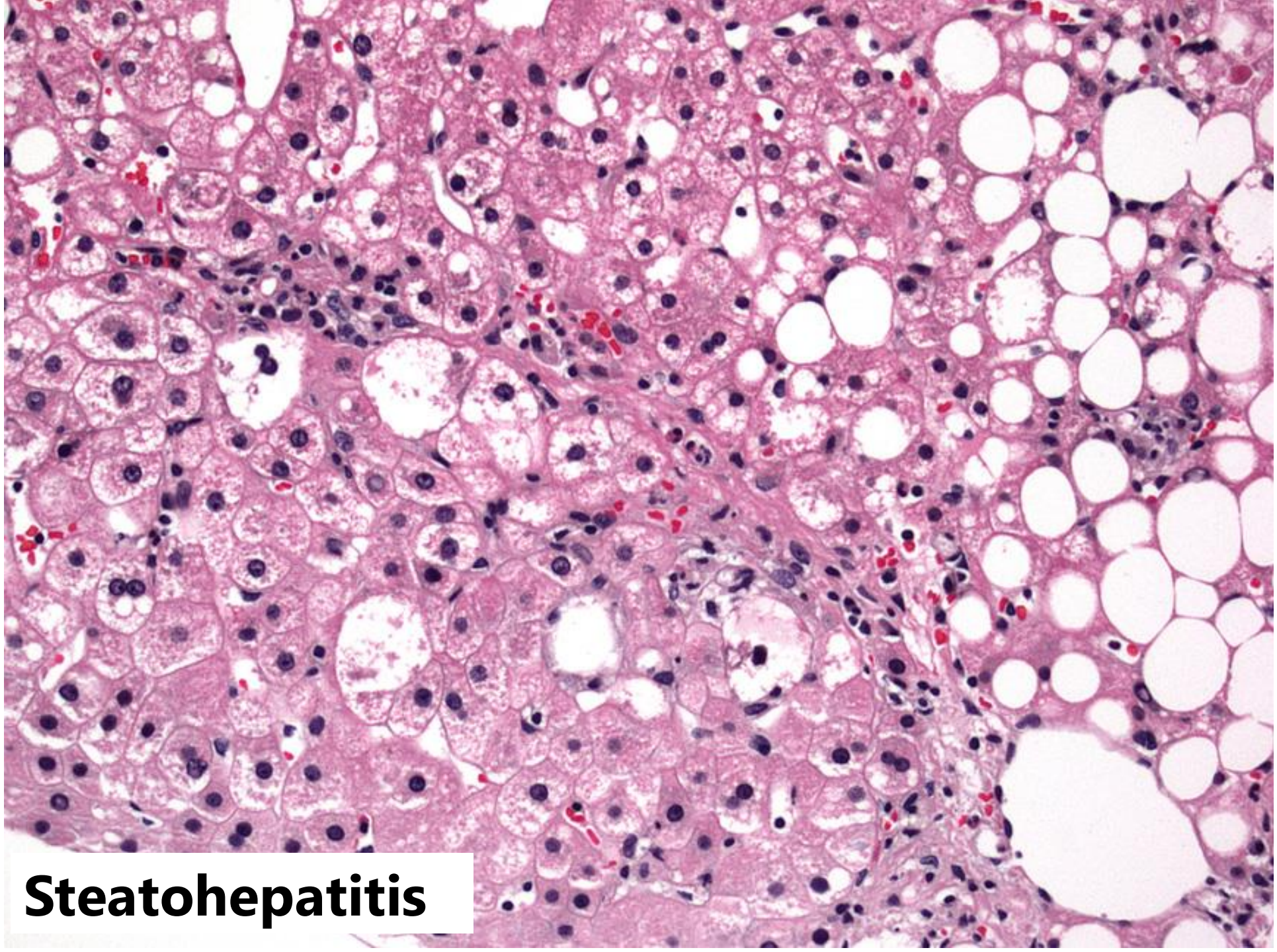

Simple steatosis


Simple steatosis



Steatohepatitis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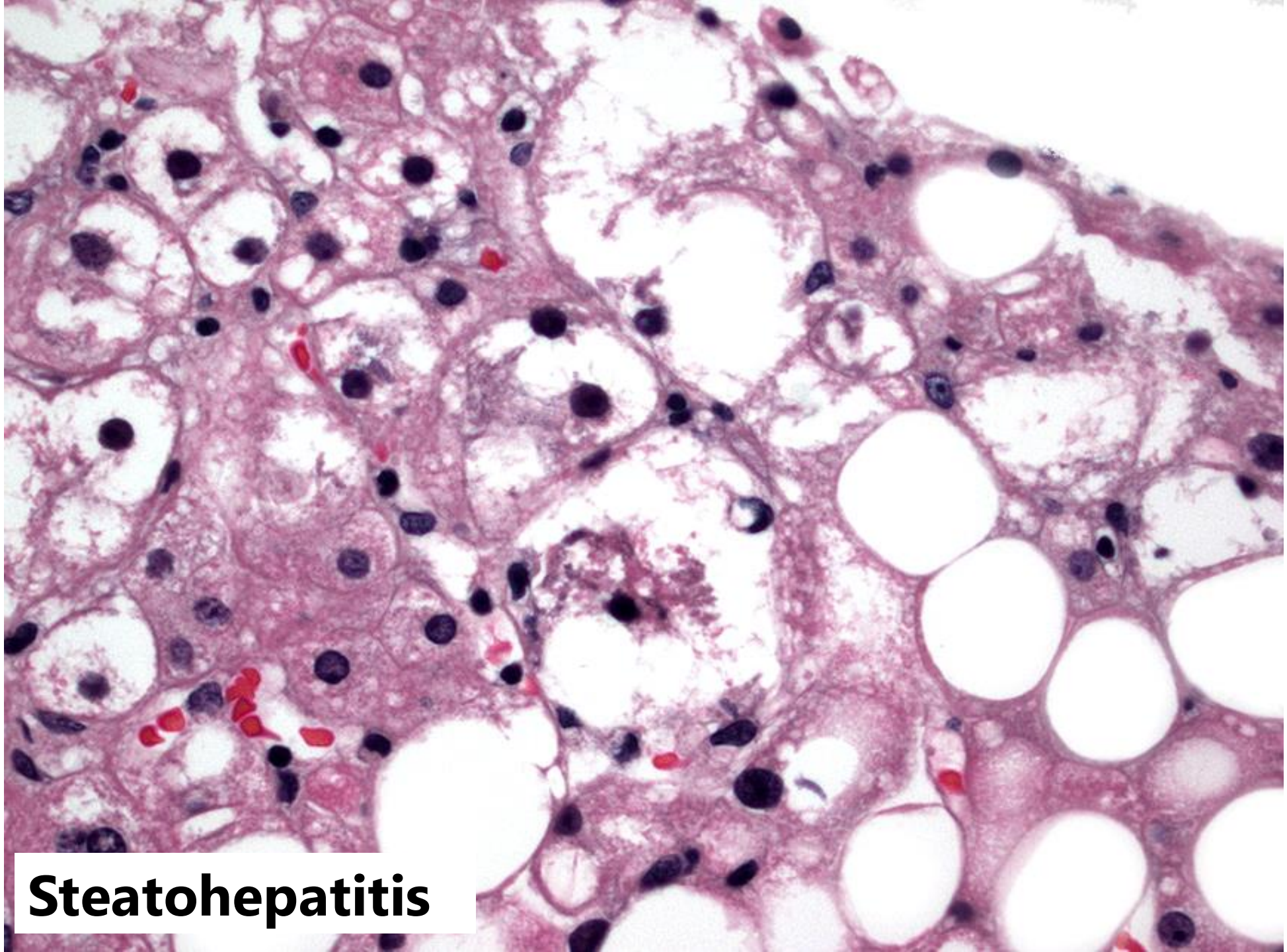
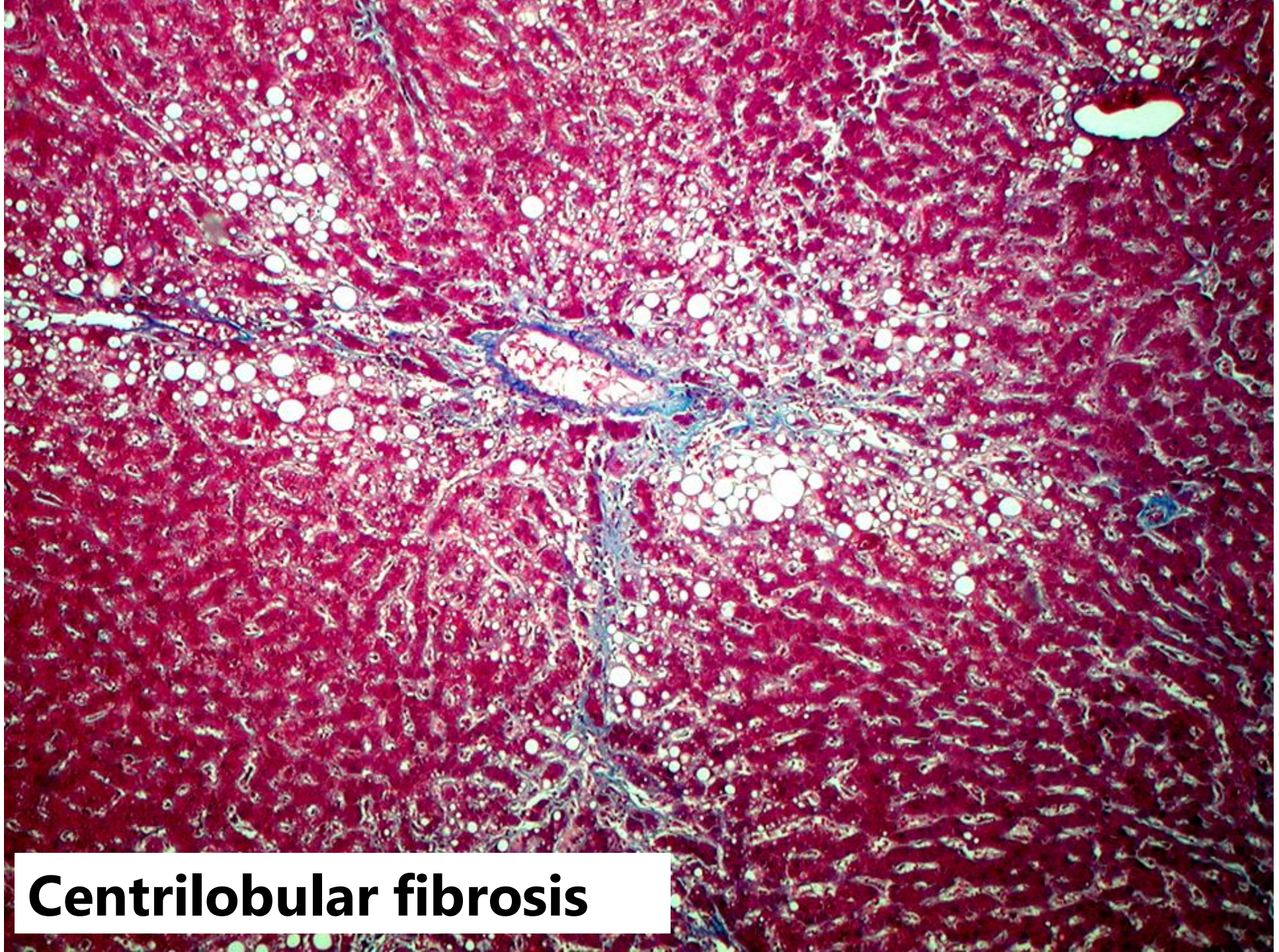

Steatohepatitis



Centrilobular 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

Consider liver biopsy

- Cholecystectomy
- Bariatric surgery
- Clinical trials

Chalasani N, et al. Hepatology. 2012;55:2005-2023. Noureddin M, et al. Clin Liver Dis. 2012;1:104-107.

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, cachexia (starvation)
  - Metabolic/genetic: Wilson's disease, lipodystrophy
  - Miscellaneous: HIV, IBD, bacterial overgrowth

Kim CH and Younossi ZM. Cleve Clin J Med. 2008;75:721-8

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

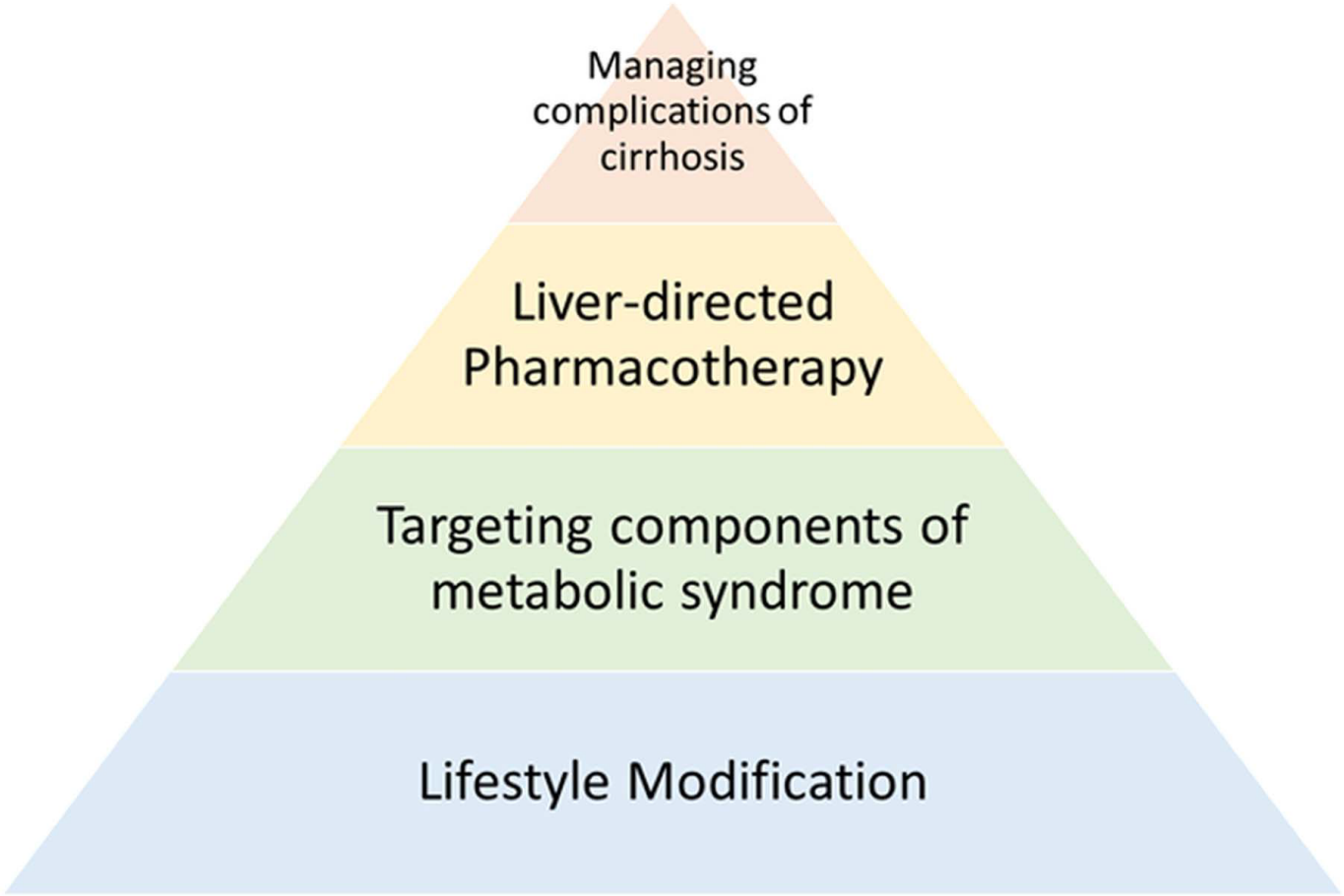
Kim CH and Younossi ZM. Cleve Clin J Med. 2008;75:721-8

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



Dyson JK et al. Frontline Gastroenterol 2014;5:277–286

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
- Exercise

E Villar-Gomez et al. Gastroenterology 2015; 149:367-378.

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
- 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

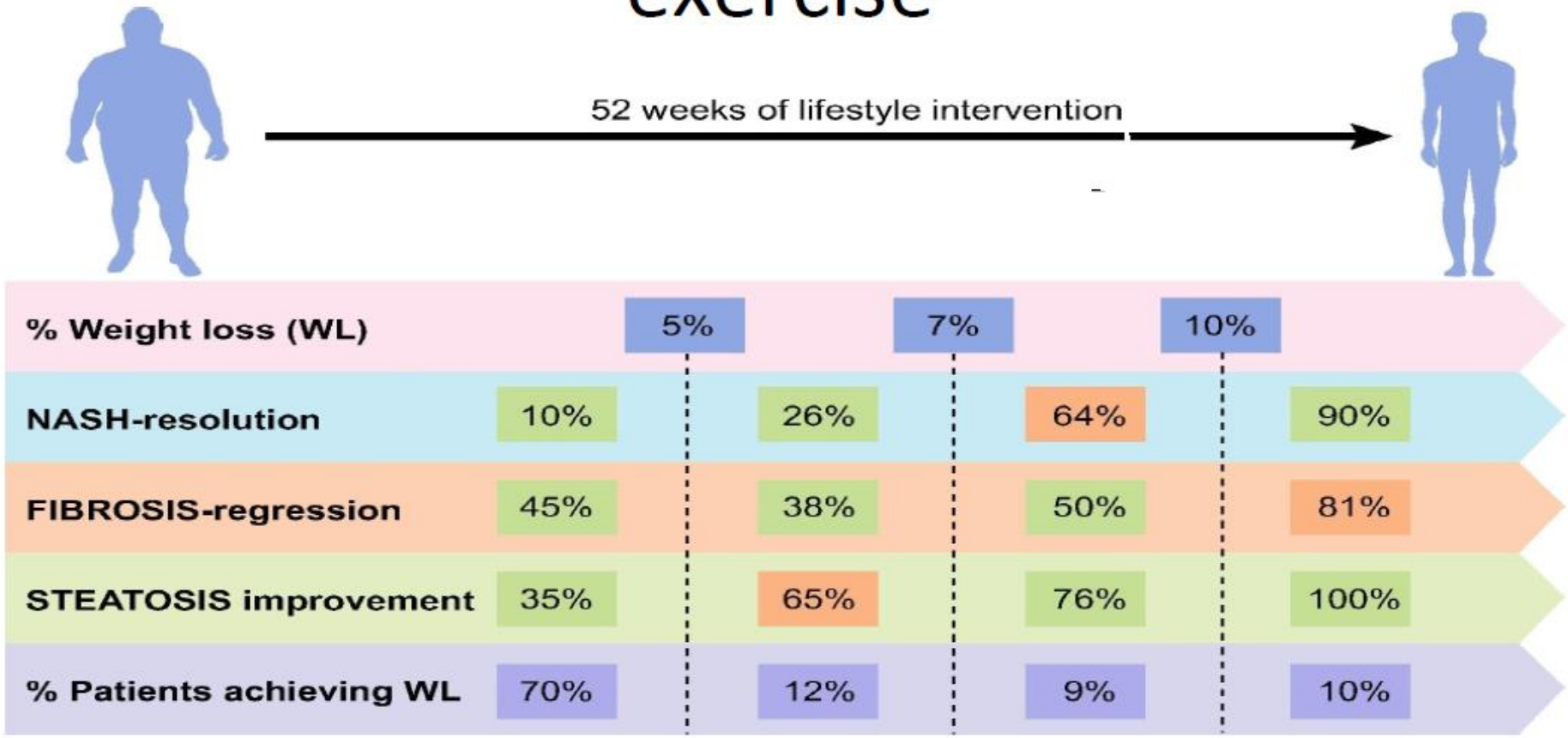
- Coffee consumption has been associated with a lower risk of metabolic syndrome and a reduced diabetes risk in a dose dependent manner
- A study in NAFLD patients indicated an inverse association between coffee consumption and liver fibrosis
- Large prospective cohort study demonstrated that those who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

J Hepatol. 2017 May 23. pii: S0168-8278(17)32052-4

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



Romero-Gomez et al. Journal of Hepatology 2017 67, 829-846DOI: (10.1016/j.jhep.2017.05.016)

Pharmacotherapy for NASH

- Pioglitazone, a thiazolidinedione, improves NASH and can be considered for patients with NASH and T2DM. Discuss benefits and risks (weight gain, ? bladder cancer, bone loss in women).

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

AASLD Guidelines 2023

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]

1. Miller ER III, et al. Ann Intern Med. 2005;142:37-46. 2. Klein EA, et al. JAMA. 2011;306:1549-1556. 3. Schürks M, et al. BMJ. 2010;341:c5702.

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):

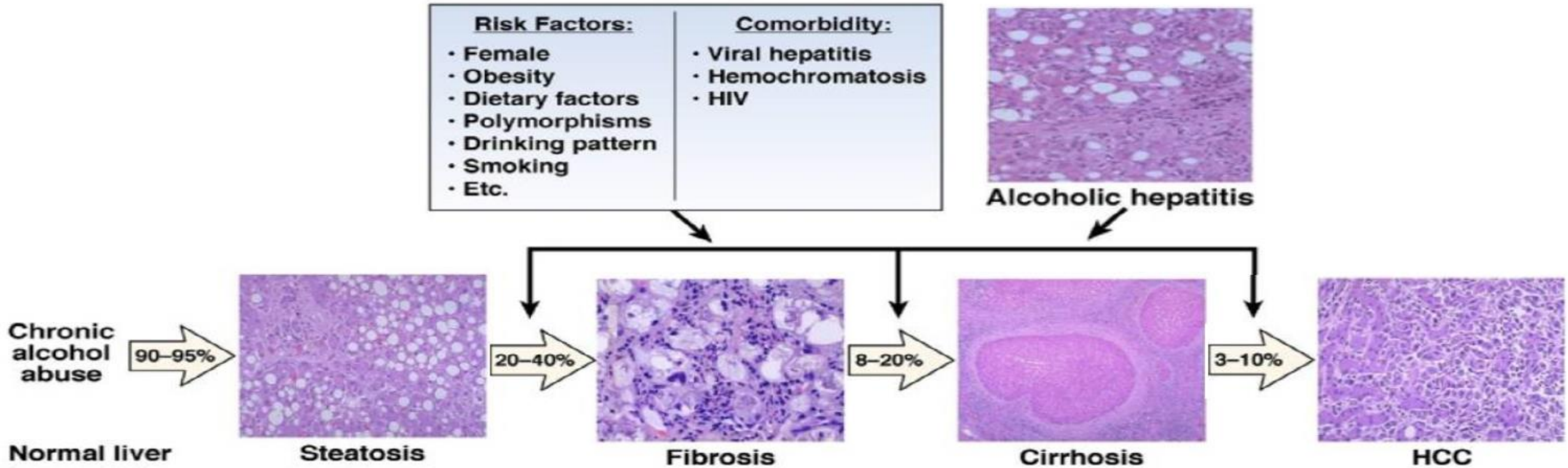
- For women, low-risk drinking is defined as no more than 3 drinks on any single day and no more than 7 drinks per week.
- For men, no more than 4 drinks on any single day and no more than 14 drinks per week.
- NIAAA research shows that only about 2 in 100 people who drink within these limits have AUD.

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

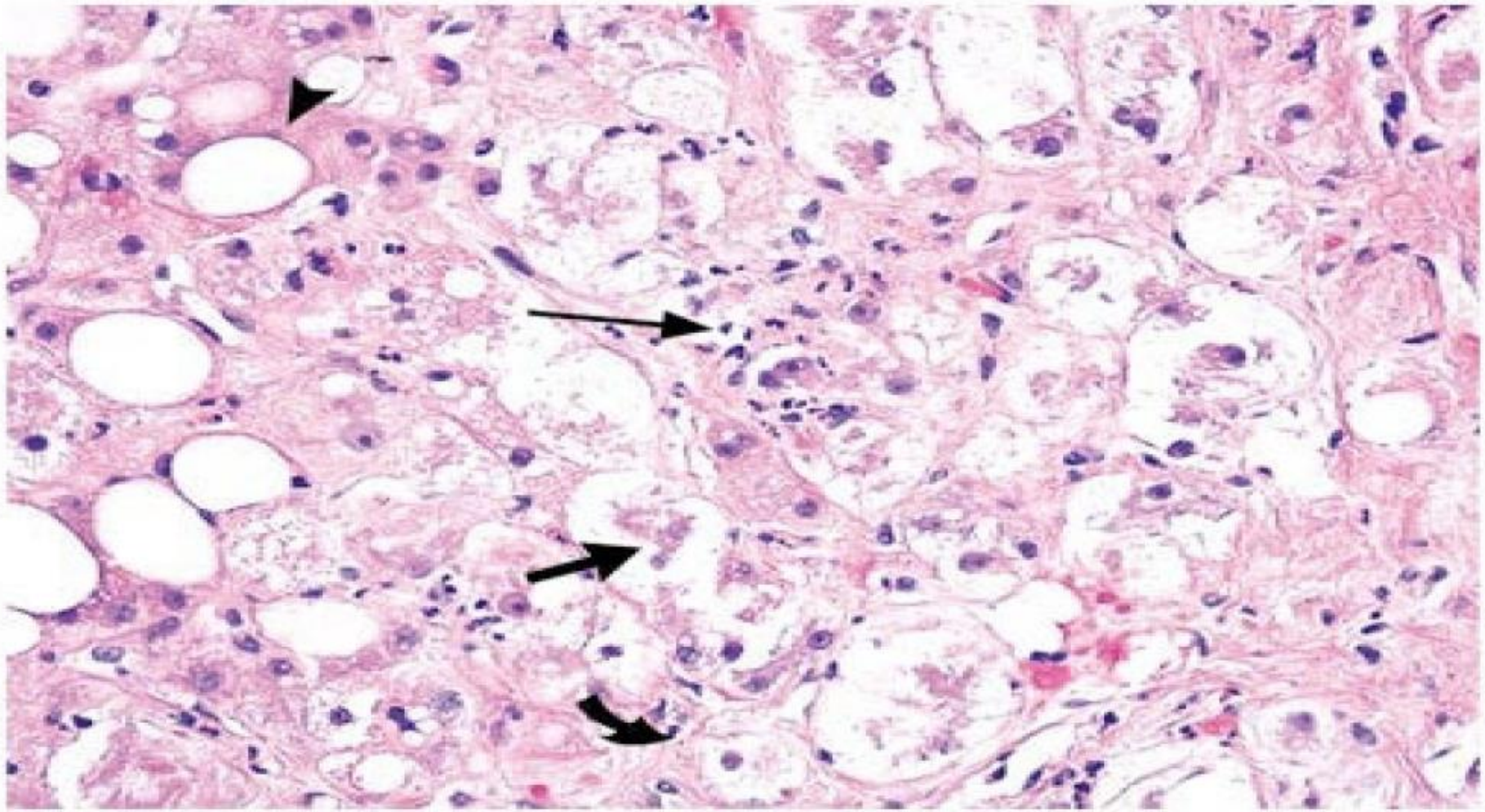
- Heavy alcohol :3 drinks per day for women (≥40 grams of alcohol), and four drinks per day for men (≥50-60 grams of alcohol).
- Strong correlation between severity and duration of alcohol misuse and the presence of cirrhosis.
- 3% of patients with alcoholic hepatitis progress to cirrhosis annually
- 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



Gao et al *Gastroenterology* 2011

Histopathological Features of Alcoholic Hepatitis.



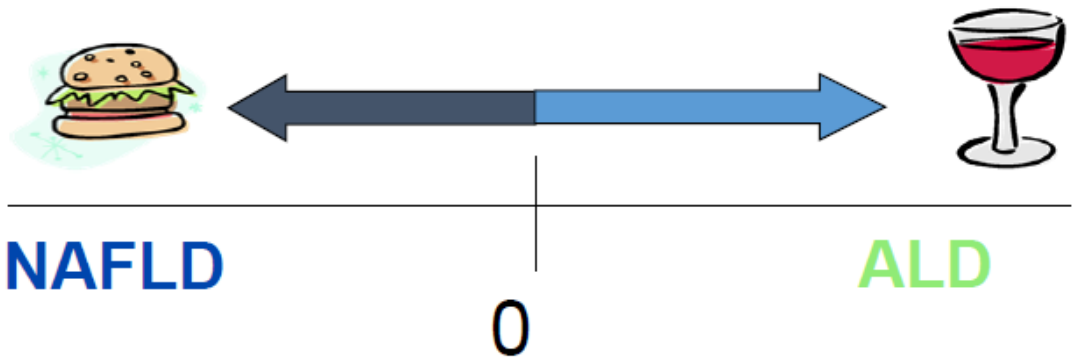
Lucey MR et al. N Engl J Med 2009;360:2758-2769.

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

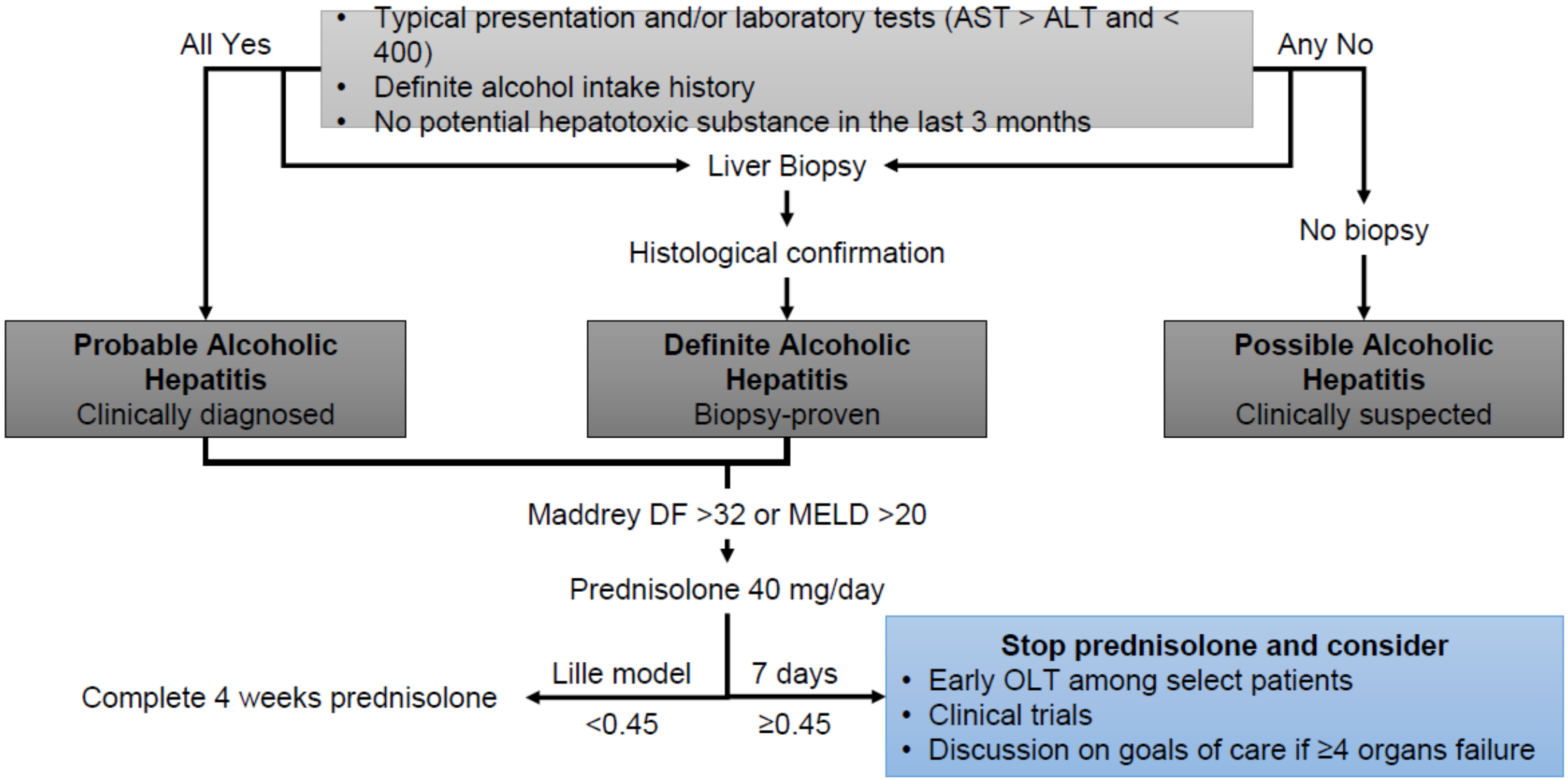


Dunn W et al Gastroenterology. 2006 Oct;131(4):1057-63 http://www.mayoclinic.org/gi-rst/mayomodel10.html

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

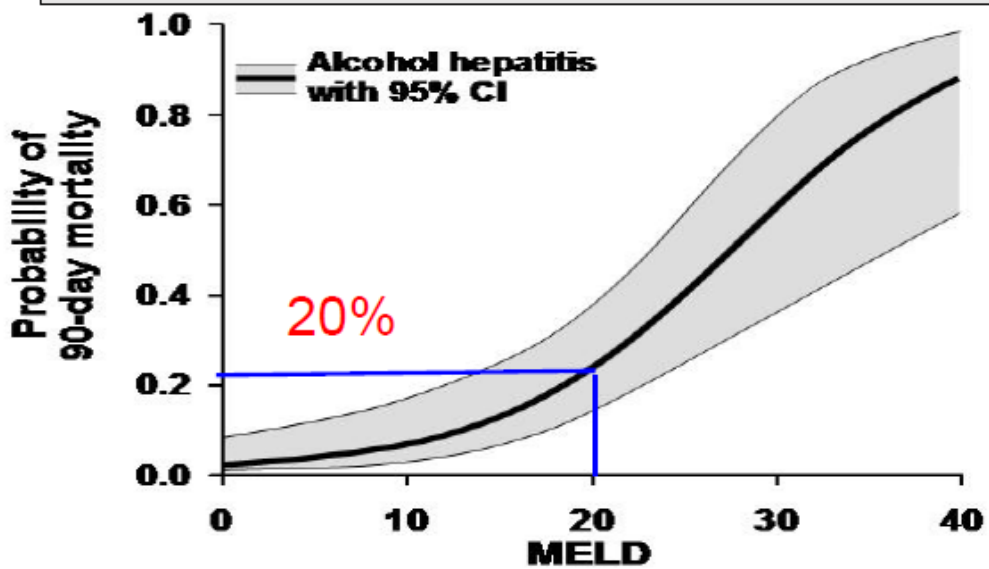
DF

- Extensively validated
- DF >32 predicts 50% mortality
- 4.6 (PT – Control) + Bilirubin
- Especially useful for steroid treatment

MELD

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

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



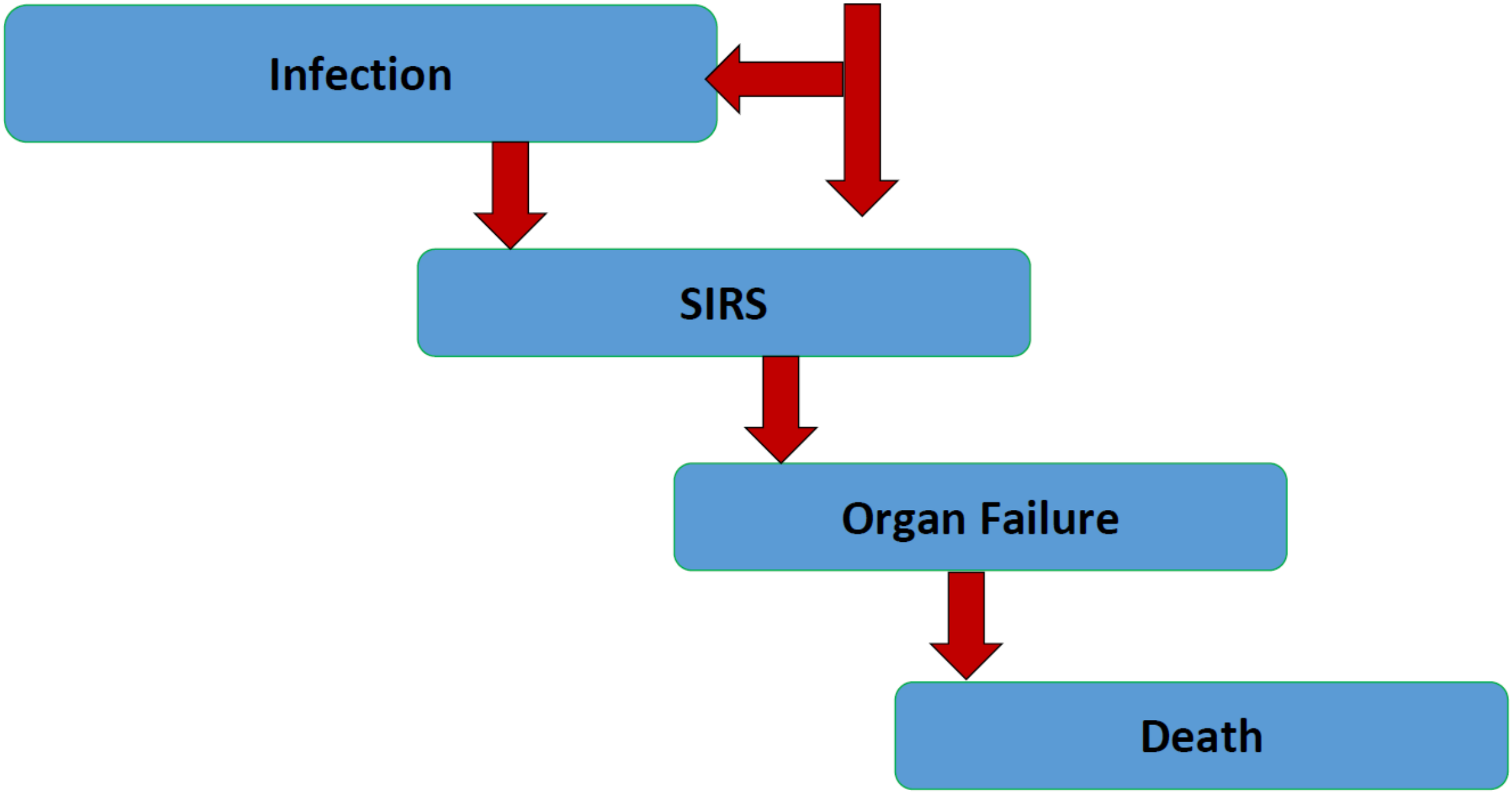
MAYO CLINIC

Dunn et al; Hepatology 2005;41:353-58 www.mayoclinic.org/gi-rst/mayomodel7.html

Clinical Manifestations of Alcoholic Hepatitis

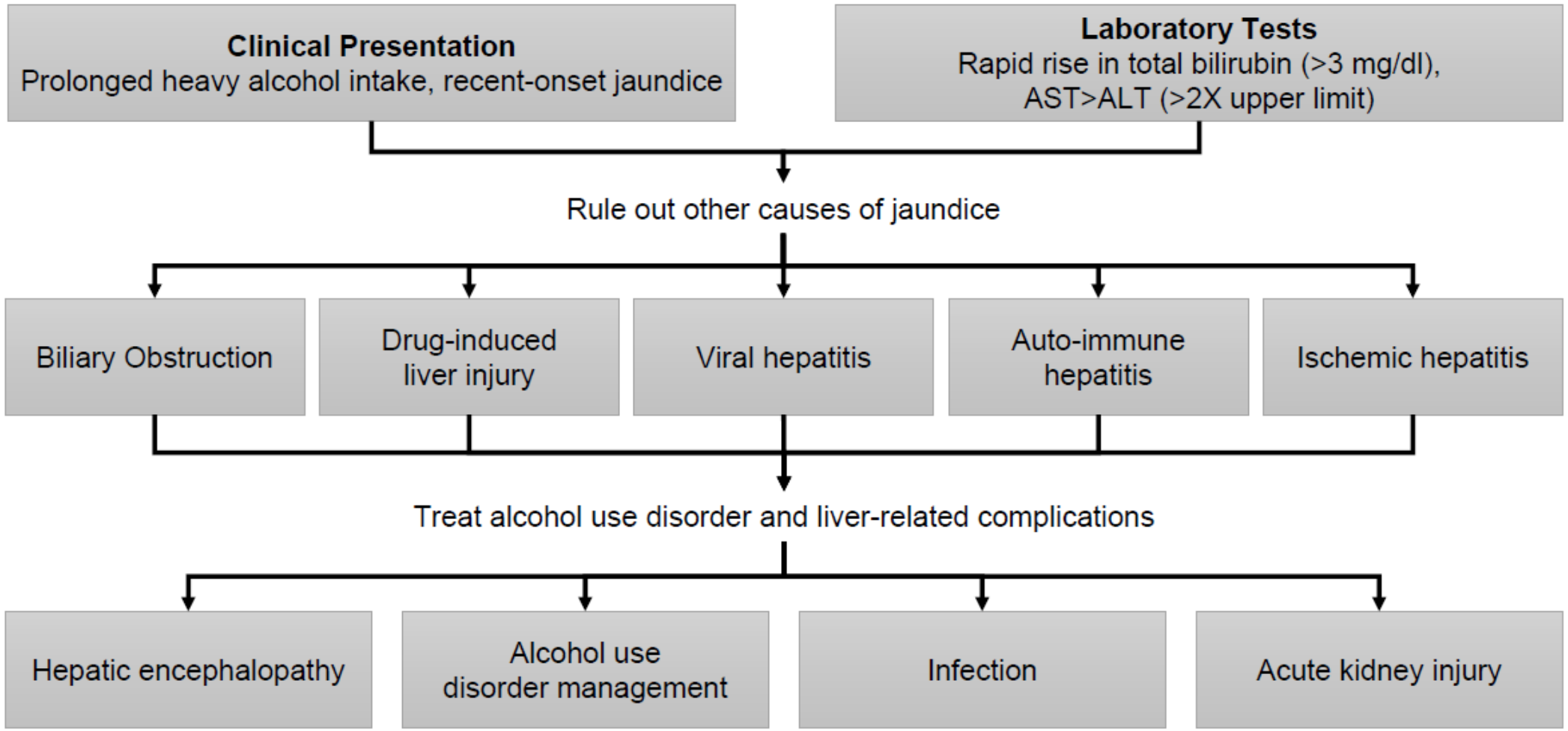
- Consequences of liver failure: Jaundice
- Ascites
- Encephalopathy
- Systemic Inflammation and sepsis: SIRS
- Multiple organ failure
- Impaired hepatocyte regeneration: Propagation of liver failure
- Features of alcohol withdrawal syndrome

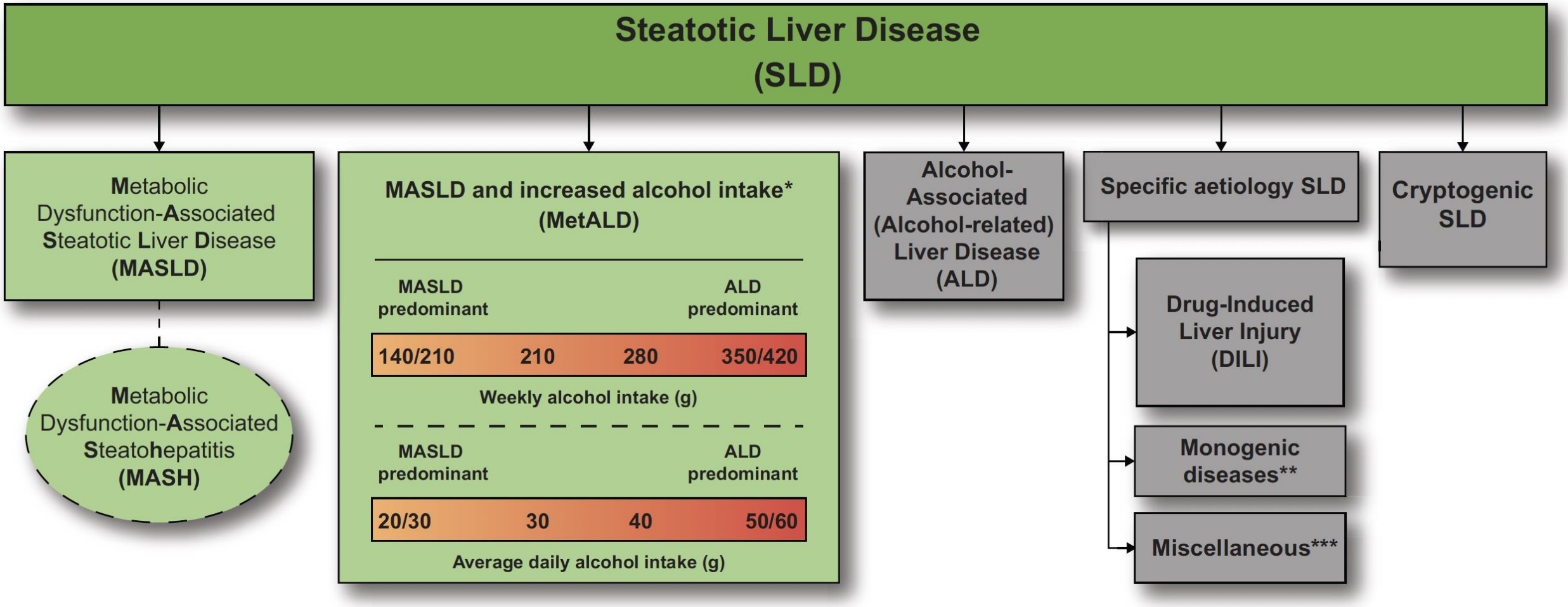
SEVERE ALCOHOLIC HEPATITIS: COURSE



Alcohol Related Liver Disease

Alcoholic Hepatitis Initial Evaluation





*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease, human immunodeficiency virus (HIV)

*Cardiometabolic criteria

Adult Criteria

At least 1 out of 5:

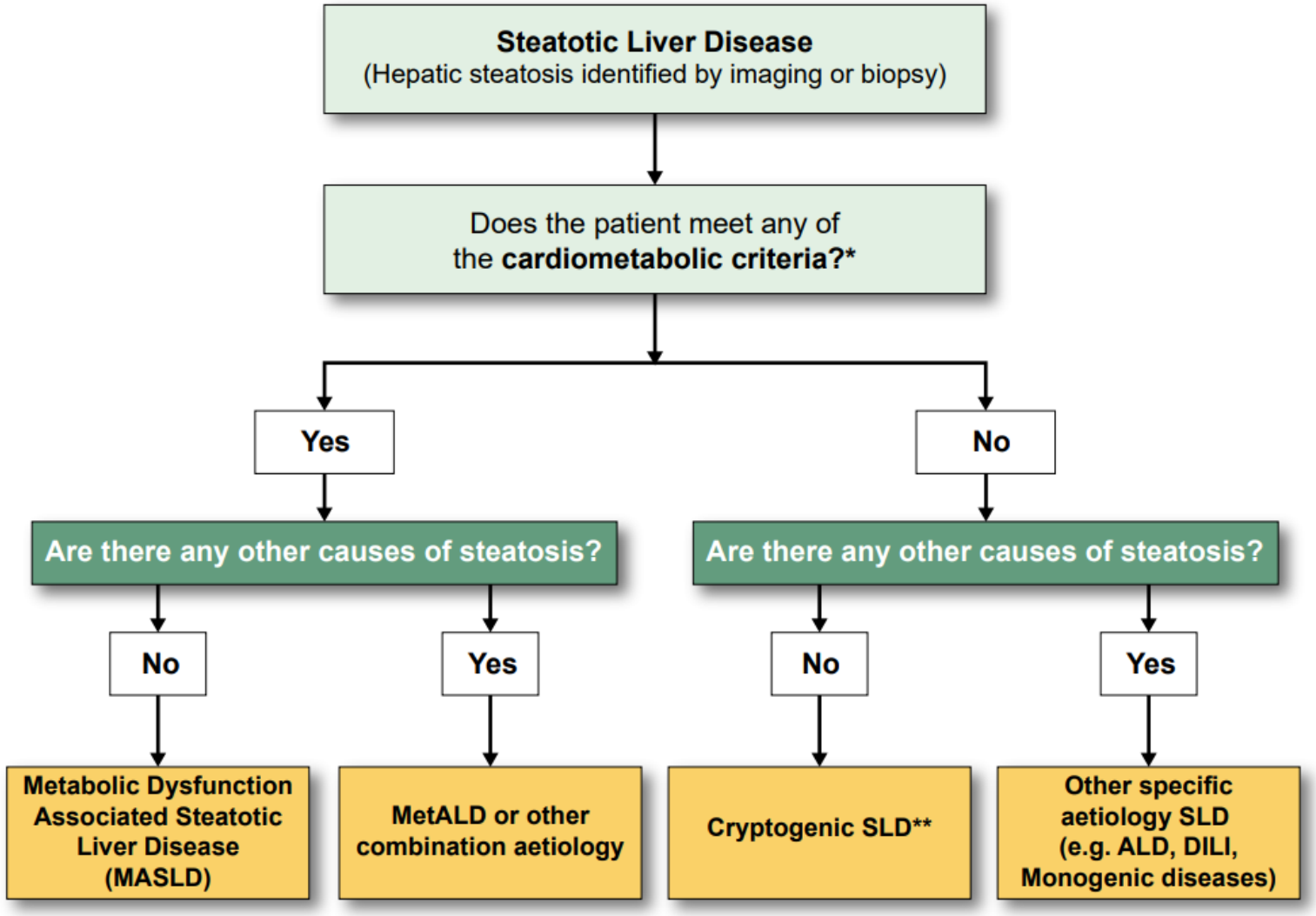
- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

Pediatric Criteria

At least 1 out of 5:

- ☐ BMI ≥ 85th percentile for age/sex [BMI z score ≥ +1] **OR** WC > 95th percentile **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] **OR** serum glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol [140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** already diagnosed/treated type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure age < 13y, BP ≥ 95th percentile **OR** ≥ 130/80 mmHg (whichever is lower); age ≥ 13y, 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides < 10y, ≥ 1.15 mmol/L [≥ 100 mg/dL]; age ≥ 10y, ≥ 1.70 mmol/L [≥ 150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [≤ 40 mg/dL] **OR** lipid lowering treatment

Decision Support Tool



Questions?