# Nonalcoholic Steatohepatitis & Cirrhosis

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# Objectives

- Present a patient case and recognize complications of nonalcoholic steatohepatitis (NASH)/cirrhosis
- Review etiology of nonalcoholic fatty liver disease
- Review common causes of NASH
- Review pathophysiology of NASH
- Review presenting clinical features and lab values associated with NASH
- Review treatment options for NASH and common complications
- Review complications and management of cirrhosis

# Patient Case

- CC
  - SOB
- HPI
  - 84 y/o female admitted 11/20 to the ED with a history of cirrhosis secondary to nonalcoholic steatohepatitis presenting with worsening shortness of breath and an approximate 8 lb. weight gain over the previous 7 days. She has had a recent TIPS procedure and has had pleural effusions in the past.

# Patient Case

- Past medical History
  - Diastolic CHF
  - T1DM
  - HTN
  - CKD – stage 3
  - Hypothyroidism
  - COPD
  - Glaucoma
  - Moderate pulmonary HTN
  - h/o hepatic encephalopathy
  - h/o esophageal varices
  - h/o GI bleed
- Surgical History
  - TIPS procedure 3/13
- Medications
  - Spironolactone 50mg daily
  - Furosemide 20mg bid
  - Amlodipine 5mg daily
  - Lactulose 20g/30ml – 50ml qid
  - Levothyroxine 125mcg daily
  - Amitriptyline 25mg daily
  - Pantoprazole 40mg daily
  - Rifaximin 550mg bid
  - Insulin lispro slide scale
  - Magnesium oxide 400mg daily
  - Albuterol neb tid prn SOB

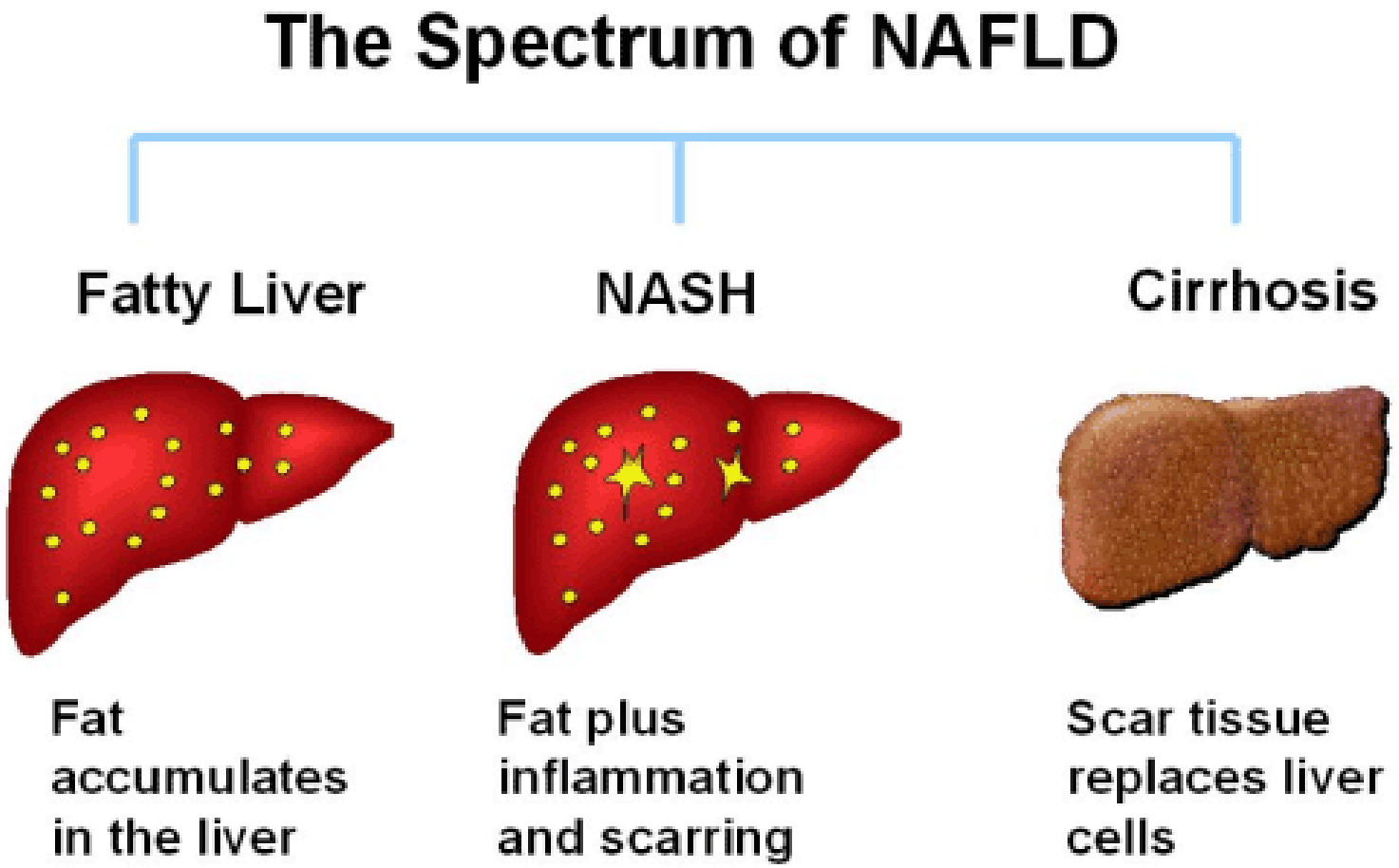
# Patient Case

- Laboratory data
  - AST – 32
  - ALT – 26
  - Alk Phos – 224
  - Albumin – 2.8
  - T. Bili – 0.9
  - Ferritin – 95
  - Ammonia – 46
  - TSH – 0.058
  - Free T4 – 1.63
  - A1C – 4.9
  - Hgb – 8.1
  - Hct – 23.9
  - Plt – 130
- CXR
  - Large right pleural effusion with increasing left effusion. Perihilar edema.

# Nonalcoholic Fatty Liver Disease (NAFLD)

- Most common liver disorder
- Frequent cause of chronic liver disease
- Two types
  - Nonalcoholic fatty liver (NAFL) and Nonalcoholic steatohepatitis (NASH)
- NAFL
  - Benign fatty infiltration – liver functions normal
  - Normal to slightly elevated AST/ALT
  - Without inflammation
- NASH
  - Inflammation with hepatocyte injury and accumulation of fat and fibrous tissue in the liver

# Nonalcoholic Fatty Liver Disease



# NASH Epidemiology

- Ludwig 1980
- Prevalence in the U.S. is unclear because it causes no symptoms
- Prevalence has mirrored the rising obesity and diabetes mellitus epidemic
- Diagnosed in approximately 7-9% of people who have a liver biopsy
- Most common between the ages of 40 and 60 years
  - Can also occur in children over the age of 10
- More common in women

# NASH Causes

- Exact cause is unknown but is most frequently seen with:
  - Metabolic syndrome
    - Obesity, diabetes, hyperlipidemia, insulin resistance
  - Drugs and toxins
    - Amiodarone, tamoxifen, diltiazem, steroids, synthetic estrogens
  - Severe weight loss
    - Jejunoileal bypass, gastric bypass, starvation
  - Total parental nutrition
  - Refeeding syndrome
  - Disorders of lipid metabolism

# Pathophysiology

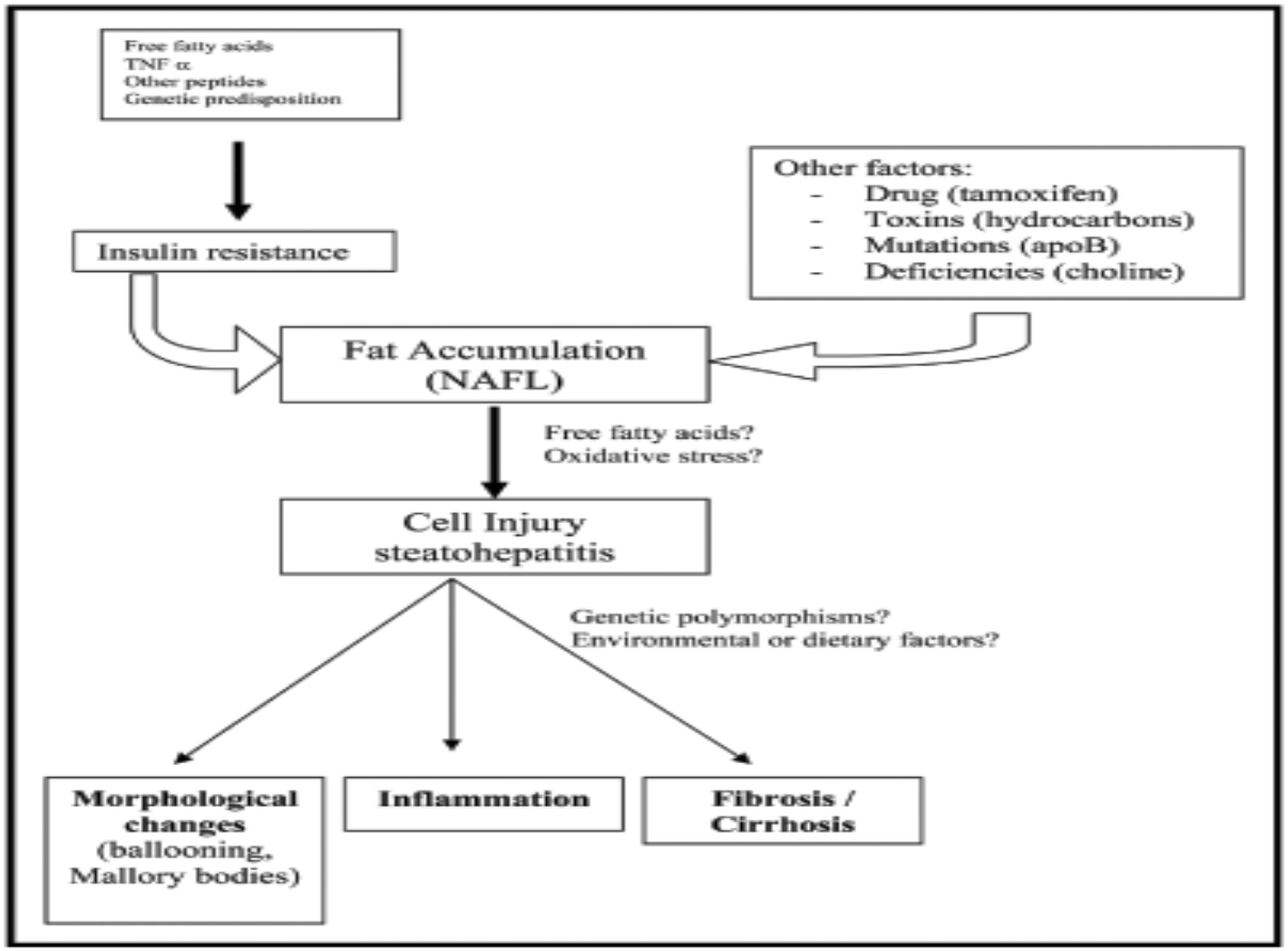
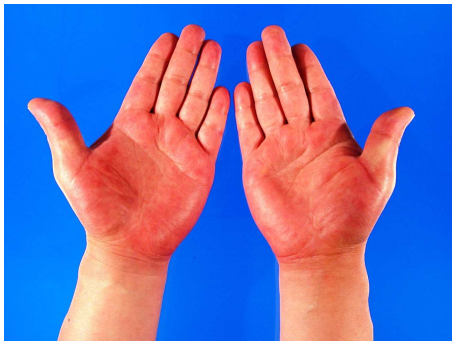



**FIGURE 1** - Pathophysiology of the nonalcoholic fatty liver disease

Salgado W, et al. Acta Cir. *Bras*. 2006;21.

# Clinical Features

- Common
  - Symptoms
    - None
  - Signs
    - Hepatomegaly

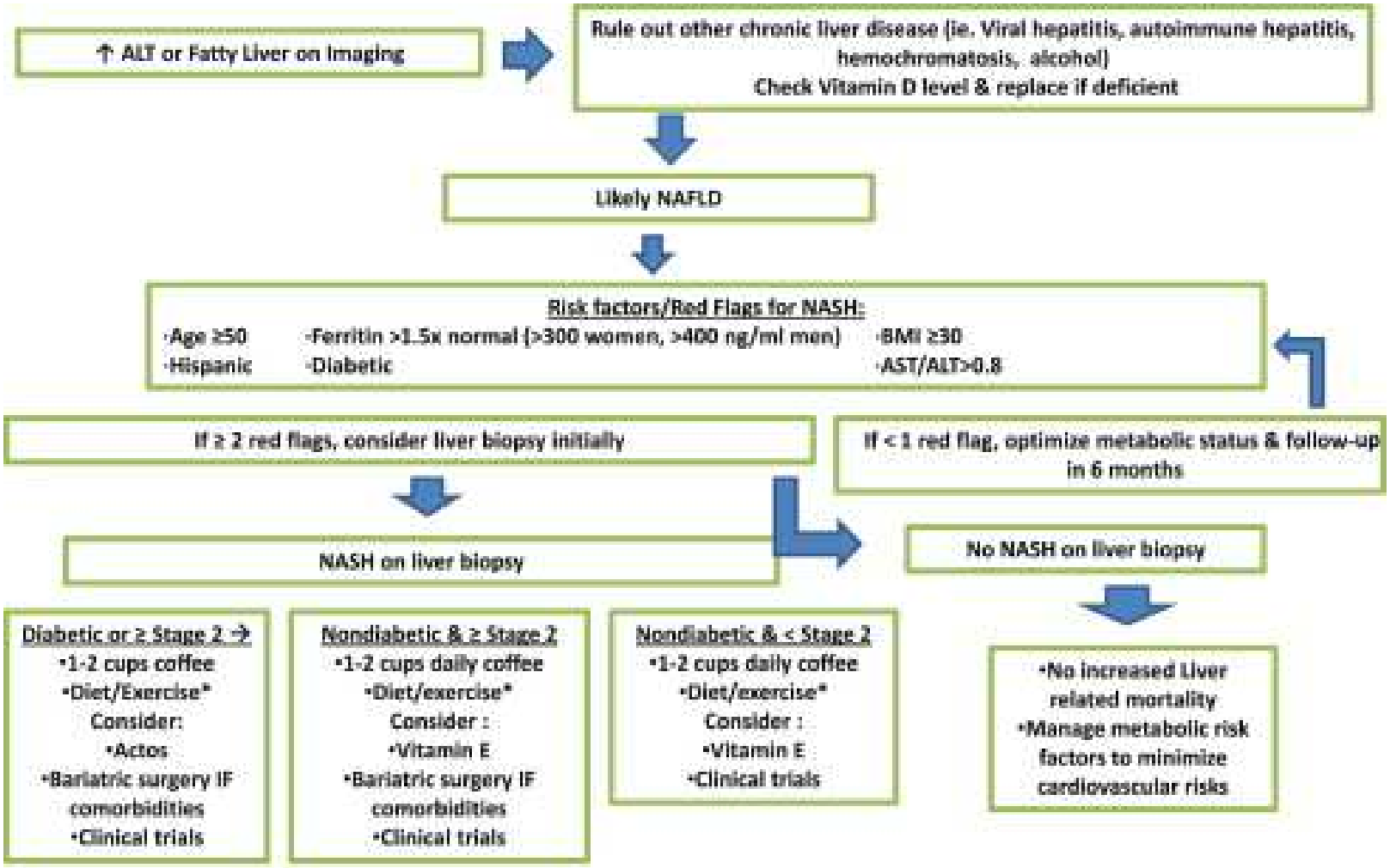


- Uncommon
  - Symptoms
    - RUQ vague pain
    - Fatigue
    - Malaise
  - Signs
    - Splenomegaly
    - Spider angiomata
    - Palmarerythema&ascites

# Laboratory Features

- AST and ALT elevations
- Serum alkaline phosphatase elevated in approximately 1/3 of patients
- GGT elevations
- Normal serum bilirubin and albumin
- Mild serum iron and ferritin elevations

# Diagnostic Approach




*See figure 2 for possible lifestyle modification approaches

Corrado, Richele L., MD,Torres, Dawn M., MD,Harrison, Stephen A., MD - Medical Clinics of North America

# Treatment

- No cure for NASH
- Clinical efforts focus on treating comorbidities such as obesity, insulin resistance, T2DM, and dyslipidemia
- Lifestyle modifications – mainstay of treatment
  - Weight loss, diet and exercise
- Pharmacotherapeutic agents are being actively examined
  - Target insulin resistance, dyslipidemia, oxidative stress, proinflammatory cytokines, apoptosis, bacterial overgrowth, then angiotensin pathway and other pathways thought to contribute to hepatic fibrosis
- Vitamin E and moderate coffee consumption

# Treatment cont.

- Targeting insulin resistance
  - Metformin
    - Meta-analysis of 3 RCTs comparing metformin vs. placebo found no difference with regard to histologic response (steatosis, ballooning, inflammation or fibrosis), changes in LFTs or BMI
  - TZDs
    - Meta-analysis of 4 RCTs comparing TZDs vs. placebo found TZDs more likely to improve histologic parameters
- Orlistat, ursodeoxycholic acid, pentoxifylline and omega-3 fatty acids

# Complications

- Most serious complication of NASH is cirrhosis
- Difficult to predict the course of NAFLD
- Study of 187 patients with paired biopsies
  - 17% of patients with no inflammation developed advanced fibrosis compared to 49% with inflammation
  - Median time to develop advanced fibrosis with inflammation was 4.2 years vs. 13.4 years for those without inflammation

# Cirrhosis

- Represents a late stage of progressive hepatic fibrosis
- Characterized by distortion of hepatic architecture and formation of regenerative nodules
- Generally considered irreversible in its advanced stages
  - At which point, only option may be liver transplantation
- In earlier stages, specific treatments at the underlying cause may improve or even reverse cirrhosis

# Cirrhosis Complications

- Markedly reduced life expectancy
- Accounted for approximately 49,500 deaths & was the 8th leading cause of death in the U.S in 2010
- MELD score
- Complications
  - Variceal hemorrhage
  - Hepatic Encephalopathy
  - Portal hypertension
  - Hepatatic hydrothorax
  - Hepatopulmonary syndrome
  - Spontaneous bacterial peritonitis
  - Thrombocytopenia
  - Elevated INR
  - Hepatocellular carcinoma
  - Hepatorenal syndrome
  - Ascites

# Cirrhosis Management

- Slowing or reversing the progression of liver disease
- Preventing superimposed insults to the liver
- Avoid hepatic toxic medications
- Managing symptoms and lab abnormalities
- Preventing, identifying, and treating complications
- Determining the appropriateness and optimal timing for liver transplantation

# Patient Case

- On admission, increased aldactone and lasix for treatment of chronic hydrothorax and end stage liver disease
- 11/21
  - Right sided thoracentesis – removed 1.7 liters of fluid
- 11/23
  - Found to be in respiratory failure – placed on BiPAP
  - CXR
    - Severe diffuse bilateral infiltrates
    - Vancomycin, cefepime, and levofloxacin

# Patient Case

- 11/23 cont.
  - Acute on chronic kidney disease
    - Scr 0.93 → 1.23 → 1.92 → 2.38 →2.96 → 4.03
    - Stopped aldactone, started albumin & increased bumex drip
    - Kayexalate x 2
  - Progressed into sepsis
  - Discussed goals of care with family
- 11/25
  - Discontinued BiPAP
  - Patient deteriorated and pronounced shortly after

# Patient Case

- This patient had decompensated, end-stage liver disease
- Given history of esophageal varices and related GI bleed, patient was a strong candidate for a non-selective beta blocker for secondary prophylaxis
- All other available treatment options had been performed, including the TIPS procedure, which is considered to be last line
- Next option for this patient would have been catheter placement for recurrent pleural effusions
  - The utility of recurrent throracentesis is limited
  - Palliative care

# References


- Corrado, RL, Torres, DM, and Harrison, SA. Diagnosis and management of chronic liver diseases: review of treatment options for nonalcoholic fatty liver disease. *Medical Clinics of North America*. 2014;vol 98,issue 1,55-72.
- UpToDate: Natural history and management of nonalcoholic fatty liver disease in adults
- UpToDate: Patient information: Nonalcoholic steatohepatitis (NASH) (Beyond the Basics)
- UpToDate: Cirrhosis in adults: Overview of complications, general management, and prognosis.