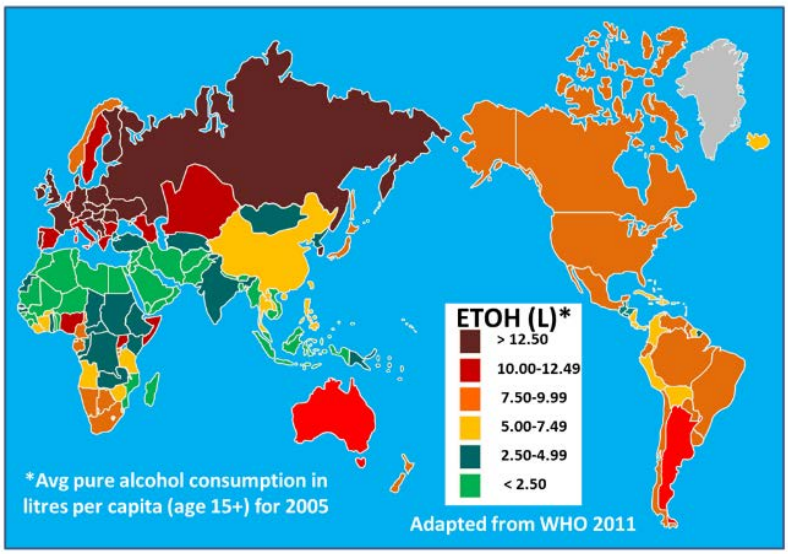
Chapter 7. Steatohepatitis

7.1 Alcoholic Liver Disease (ALD)

Epidemiology & Pathophysiology

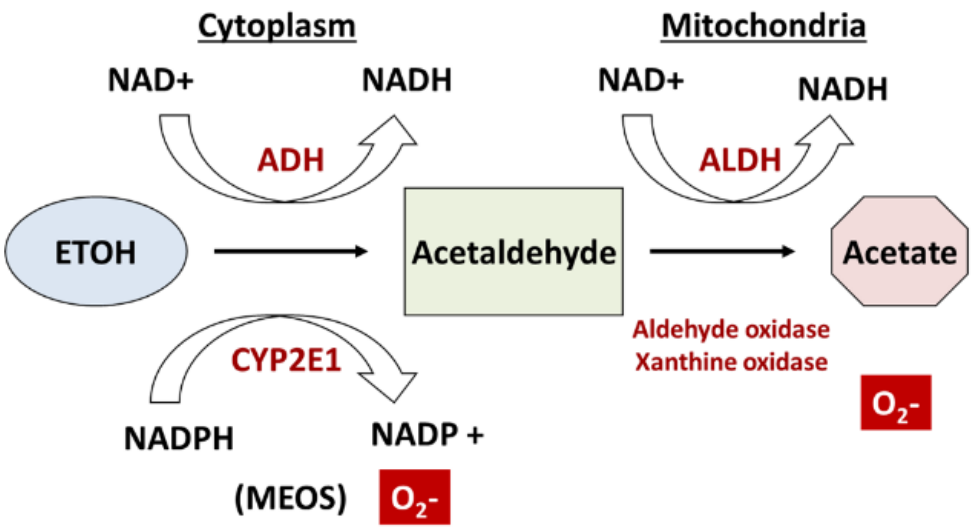
- 1 drink (12 oz. beer, 5 oz. wine, 1.5 oz. liquor) = 10 grams of ethanol (ETOH), but "standard drink" definition varies by country (Canada uses 13.6 grams = 1 drink)
- Approximately, 20-30% of those who drink >40g daily for 10 years will get cirrhosis
  - Influenced by body composition, sex and genetics
- **Alcohol consumption varies by country**
  - ~ 16 million people in USA (6% of adult population) have alcohol use disorder (AUD)
  - 2% have alcohol-related liver disease



- **Safe threshold for alcohol use in Canada**
  - **Men** = ≤ 3 drinks most days, ≤ 15/week and ≤ 4 on a single occasion
  - **Women** = ≤ 2 drinks most days, ≤ 10/week and ≤ 3 on a single occasion

- **Binge drinking =** 5 drinks in men or 4 in women over 2 hours and binge drinkers should be screened for AUD (previously called alcohol abuse and alcohol dependence)

- **ETOH is metabolized by two pathways**
  - Alcohol dehydrogenase (ADH) metabolizes alcohol to acetaldehyde and then metabolized to acetate
  - MEOS (microsomal ethanol oxidizing system) = cytochrome P450 enzymes (CYP2E1)
  - Both generate free radicals leading to oxidative stress
  - Polymorphisms in these enzymes are associated with risk of AUD and alcohol-related liver disease



Diagnosis & Natural History

- Alcohol History *[see Chapter 2.3]*
  - Scoring 2 or more on the **CAGE questionnaire (cut down, annoyed, guilty, eye opener)** suggests a problem with alcohol

- 10 question Alcohol Use Disorders Identification Test (AUDIT) is a recommended screening tool, and first three questions on consumption (AUDIT-C) are better than the CAGE at identifying alcohol misuse

  https://auditscreen.org/~auditscreen/cmsb/uploads/audit-english-version-new_001.pdf

- Important to get collateral history as patients will under-report their alcohol intake

- **Alcohol Use Disorder[1]**

  - The presence of at least two of these symptoms indicates an Alcohol Use Disorder (AUD).

    In the past year, have you:

    1. Taken alcohol in larger amounts or over a longer period than intended.
    2. Had a persistent desire or unsuccessful efforts to cut down or control alcohol use.
    3. Spent a great deal of time in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
    4. Had craving or a strong desire or urge to use alcohol.
    5. Had recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
    6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
    7. Given up or reduced important social, occupational, or recreational activities because of alcohol use.
    8. Recurrently used alcohol in situations in which it is physically hazardous.

9. Continued alcohol use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance, defined as either of the following:
    a. Need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
    b. Markedly diminished effect with continued use of the same amount of alcohol.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic alcohol withdrawal syndrome.
    b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

- Based on responses to the above, AUD is classified as:
  - **Mild**: 2-3 symptoms
  - **Moderate:** 4-5 symptoms
  - **Severe:** ≥ 6 symptoms

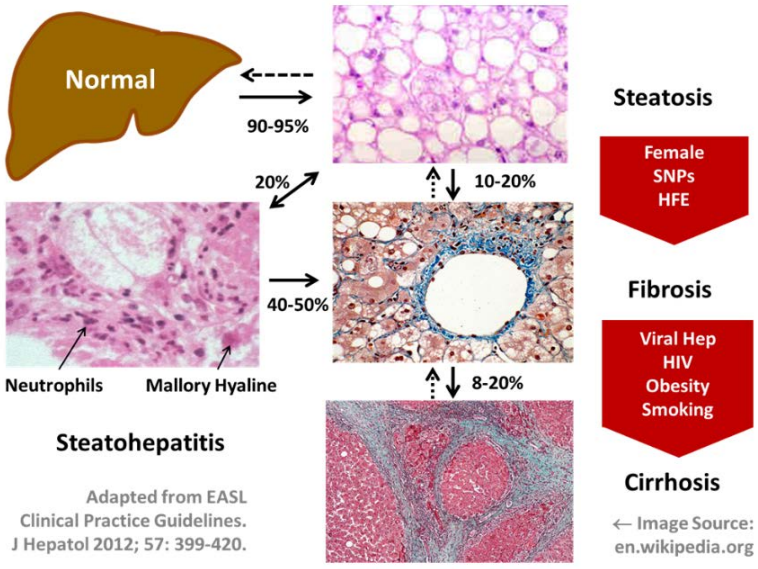
- Clinical presentations
  - **Steatosis** (fatty liver) and/or **steatohepatitis** (fat and inflammation)
    - Fatty infiltration on ultrasound
    - AST > ALT (usually more than 2:1) but ALT should not be >300 from alcohol alone
    - GGT is often very high (induced by ETOH)
    - May have large red blood cells (macrocytosis)
    - IgA is often elevated [**REMEMBER** A = alcohol]
  - **Alcoholic Hepatitis**
    - Typically follows prolonged binging

- May have jaundice, hepatomegaly, RUQ pain, ascites, confusion due to hepatic encephalopathy (HE) and fever
- AST and ALT are often normal or minimally elevated, and GGT may be high
- ALP is elevated (cholestasis)
- Liver dysfunction with ↑bilirubin, ↑INR, ↓albumin, renal dysfunction (↑creatinine)
- WBC is often very high (even in absence of infection)
- **Prognosis** is poor and can be predicted by Maddrey Discriminant Function (MDF) or Model for End-Stage Liver Disease (MELD) or other scoring systems
- Biopsy should be done if the diagnosis is in question

o **Cirrhosis**

- Complications include ascites, varices, HE or HCC *[see Chapter 14]*

- **Natural History** (and **Pathology**)[2]
  - o 90-95% who drink alcohol above the safe thresholds will have steatosis (fat) in liver
  - o 20% with steatosis will have steatohepatitis (fat and inflammation)
    - Biopsy shows neutrophil infiltration and Mallory Hyaline
  - o Fibrosis (which often will line the sinusoids) will develop in 10-20% of those with steatosis versus 40-50% of those with steatohepatitis
    - This can be influenced by female sex and genetics with presence of specific single nucleotide polymorphisms (SNPs) or the HFE gene mutations *[see Chapter 8.1]*
  - o Up to 20% with fibrosis will progress to cirrhosis
    - This can be influenced by coexisting viral hepatitis, HIV, obesity or smoking



Treatment

- **Mainstay of therapy is abstinence** from further alcohol
  - Some liver transplant programs require 6 months of abstinence with or without formal rehabilitation program to qualify for transplantation, although some will now consider selected patients with severe alcoholic hepatitis for transplantation
- Specific therapies have been studied for **Alcoholic Hepatitis**
  - Nutritional support and intervention with alcohol cessation is important for all patients
  - If MDF ≥ 32 or MELD ≥ 21 two treatments were previously recommended
  - **Prednisone** 40mg daily for one month (then taper over next month)
    - Meta-analysis of RCTs have shown mortality benefit if MDF ≥ 32 or hepatic encephalopathy (HE)
    - If the bilirubin not falling by day 7 (and Lille score remains ≥ 0.45) then prednisone should be stopped as it is unlikely to work and can increase risk of infection

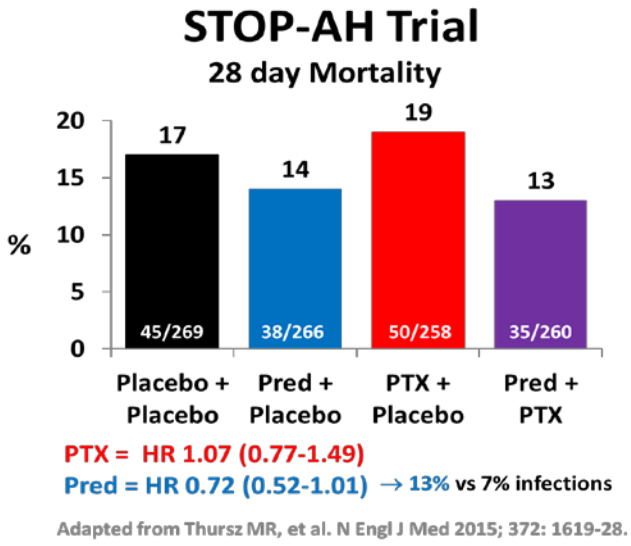
- A placebo-controlled RCT showed that **N-acetylcysteine** (given as in acetaminophen overdoses) improved 1 month, but not 6-month (primary end-point of trial), when added to prednisone

o **Pentoxifylline (PTX)** 400mg TID for one month

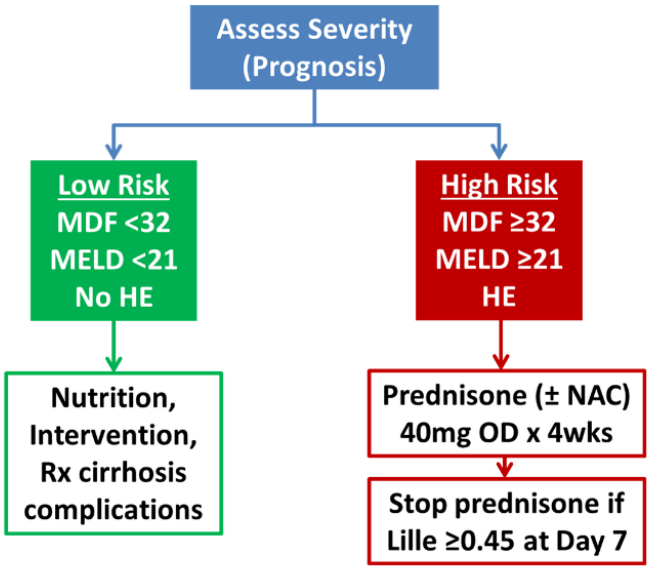
- RCT from Mexico found PTX to be superior to placebo
- Small RCT from India found PTX to be superior to prednisone

o **STOP-AH trial**[4] compared combination of prednisone, PTX or placebos in 1053 patients

- **PTX was of no benefit** and is therefore no longer recommended
- Prednisone showed a only a trend to improved 28 day mortality (but not at 3 or 12 months) and more developed infections on prednisone
- Therefore, controversy remains about the role of steroids



- **Updated Approach to Treatment of Alcoholic Hepatitis**



Adapted from EASL Clinical Practice Guidelines. J Hepatol 2012; 57: 399-420.
O'Shea R, et al. AASLD & ACG Practice Guidelines. Hepatology 2010; 51(1): 307-28.
Crabb DW, et al. AASLD Practice Guidance; Hepatology 2019; in press.

7.2 Non-Alcoholic Fatty Liver Disease (NAFLD)

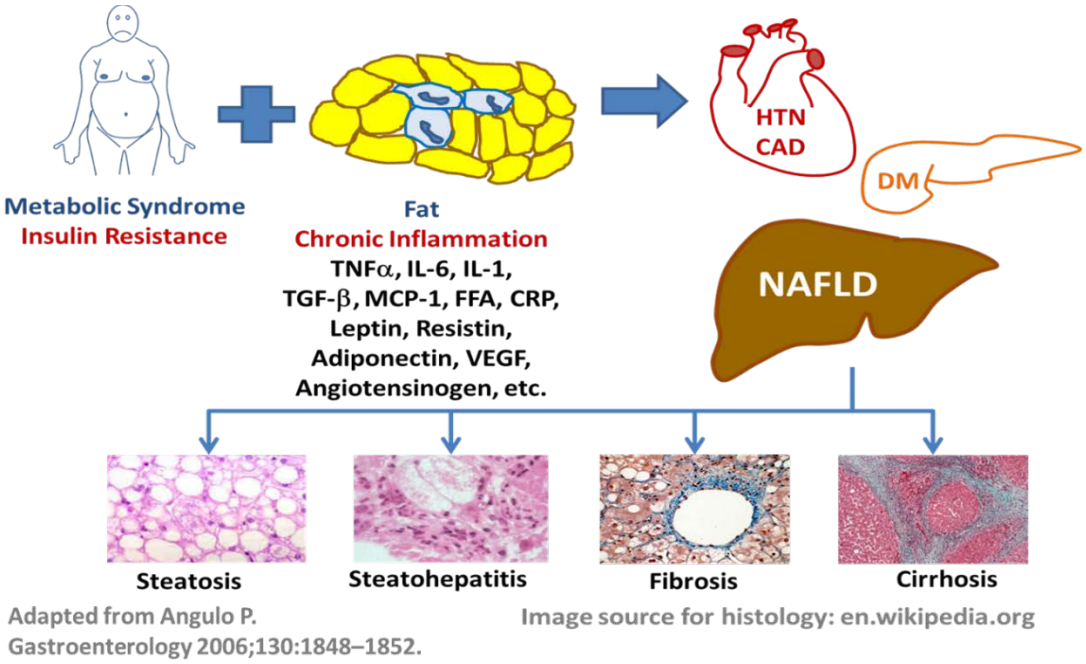
Epidemiology & Pathophysiology

- **Causes of Steatosis**
  - **Non-alcoholic fatty liver disease (NAFLD)**
    - **Risks** include obesity (central), type 2 diabetes mellitus (DM), dyslipidemia
    - Obesity is defined by body mass index (BMI) = height (metres)^2 / weight (kg)
    - BMI > 30 is obese
    - Frequently seen with the **metabolic syndrome** (≥3 of following)
      - Waist circumference >102 cm in men or >88 cm in women
      - Triglycerides (TG) ≥ 1.7 mmol/L
      - High density lipoprotein (HDL) <1.0 mmol/L in men or <1.3 mmol/L in women

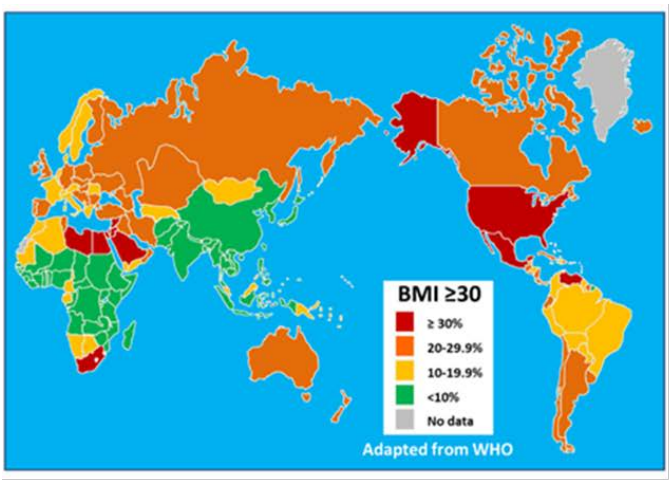
- Fasting glucose ≥ 6.1 mmol/L
- Systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg

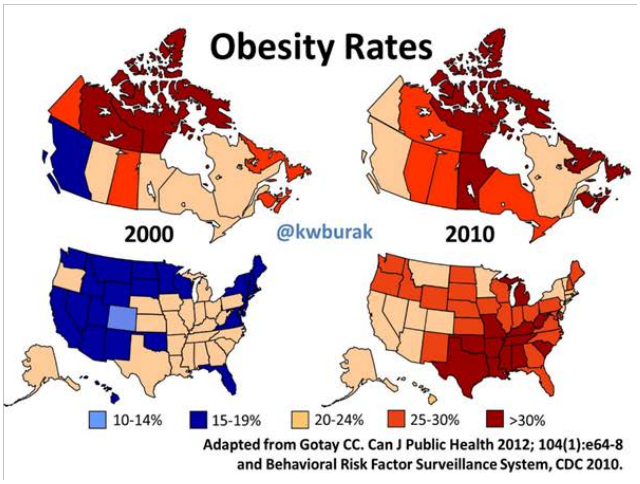
- **Other causes** (should be considered and ruled out before diagnosing NAFLD)
  - Alcohol
  - HCV (genotype 3)
  - Wilson's disease
  - Starvation
  - Total Parenteral Nutrition (TPN)
  - Metabolic = lipodystrophy, abetalipoproteinemia (rare conditions)
  - Pregnancy including acute fatty liver disease of pregnancy (AFLP)
  - Medications including amiodarone, methotrexate, tamoxifen, steroids, valproate, and highly active anti-viral therapy (HAART) for HIV

- **Pathophysiology** and **Pathology**
  - Genetics may play a role (e.g. PNPLA3 gene)
  - The metabolic syndrome leads to insulin resistance
  - The adipose tissue in those with central obesity is metabolically active and releases many inflammatory cytokines and other hormones which lead to the complications including hypertension, coronary heart disease, diabetes and NAFLD
  - **Pathology** is very similar to alcoholic liver disease with a spectrum from simple steatosis (**non-alcoholic fatty liver** or **NAFL**) to **non-alcoholic steatohepatitis (NASH),** to fibrosis and finally **NASH-related cirrhosis**



- **NAFLD is most common cause of liver disease in North America**
  - Obesity (BMI>30) is very prevalent and there have been dramatic increases in obesity seen recently in North America
  - >20% of Americans have fatty liver on ultrasound
  - 10% of Americans have abnormal liver tests (3/4 likely due to NAFLD) after excluding alcohol and viral hepatitis (NHANES study)[4]





- **Coffee and the Liver**
  - Population based studies have shown that coffee drinkers have lower ALTs, less diabetes and lower rates of hepatocellular carcinoma
  - This association is seen for coffee, but not tea, and the association is strengthened by a dose response (the more coffee the better)
  - More recent data suggests that coffee drinkers have lower mortality

    TAKE HOME MESSAGE: Drink more coffee…not more alcohol

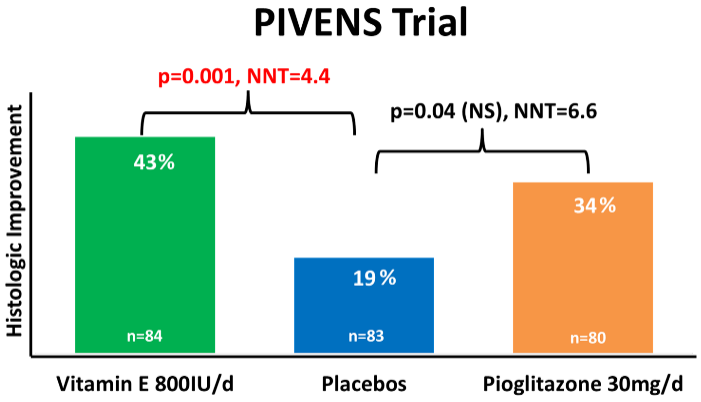
Diagnosis & Natural History

- Fatty liver may be seen on ultrasound
  - Screen these patients for the metabolic syndrome and check their liver tests
- Most commonly they will present with mild elevation of ALT or AST
  - If the AST > ALT (and you have excluded alcohol by history) there could be cirrhosis
  - GGT is often high
  - Ferritin is frequently elevated
- Patients may present with cirrhosis or its complications *[see Chapter 14]*
  - NASH related cirrhosis may have a lower risk of HCC than with viral hepatitis
- Must exclude alcohol by history and rule out other liver disease by ordering screening tests for chronic liver disease *[see Chapter 3.5]*
- Natural History
  - NAFLD patients have increased overall mortality compared to controls with cardiovascular disease being the leading cause of death
  - NASH (but not NAFL) is associated with increased liver related mortality

- **How can we predict fibrosis and who to biopsy?**
  - Metabolic syndrome predicts NASH
  - **NAFLD Fibrosis Score (NFS)** [based on age, BMI, glucose, platelets, albumin, AST/ALT ratio] and the Fibrosis-4 **(FIB-4)** [based on age, AST/ALT ratio, platelets] predicts fibrosis, although in primary care they perform less well than **transient elastography** (FibroScan™) or **acoustic radiation force impulse (ARFI)** *[Chapter 3.8]*

Treatment[5,6]

- **Weight loss** through **diet and exercise** is the mainstay of therapy
- Management of other risk factors includes management of diabetes (**metformin** may assist with weight loss, **pioglitazone** improves NAS score but causes weight gain) and hyperlipidemia (with statins or fibrates)
- **Vitamin E** (800 U/day) improved NAS score in non-cirrhotic, non-diabetic patients with NASH (PIVENS trial)[7], but vitamin E has been associated with increased cardiovascular events and prostate cancer (therefore, some recommend 400/day instead of 800/d)



Adapted from Sanyal AJ, et al. N Engl J Med 2010; 363(18): 1675-85.

- Ursodeoxycholic acid (UDCA) showed no benefit in a large RCT
- Omega-3 fatty acids may have some benefit

- **Bariatric surgery** is the best treatment for morbidly obese (BMI>35) but can be associated with increased complications in cirrhotic patients
- Limited alcohol use may have some benefits, but heavy alcohol use must be discouraged

Abbreviations

ADH – alcohol dehydrogenase

AFLP – acute fatty liver disease of pregnancy

ALD – alcoholic liver disease

ADH – alcohol dehydrogenase

ALDH – acetaldehyde dehydrogenase

CAD – coronary artery disease

HAART – highly active anti-viral therapy

HFE – hemochromatosis gene

HIV – human immunodeficiency virus

HTN – hypertension

MDF – Maddrey Discriminant Function

MELD – Model for End-Stage Liver Disease

MEOS – microsomal ethanol oxidizing system

NAD+/NADH – nicotinamide adenine dinucleotide

NAFL – non-alcoholic fatty liver

NASH – non-alcoholic steatohepatitis

PTX – pentoxifylline

RCT – randomized clinical trial

SNP – single nucleotide polymorphisms

TG – triglycerides

TID – three times a day

TPN – total parenteral nutrition

Figure Citations

Global Alcohol Consumption. Adapted from http://cdn.static-economist.com/sites/default/files/20110219_WOM582.gif

Alcohol Prognostic Scores. Adapted from Mathurin, P, Lucey, MR. Management of alcoholic hepatitis. *J Hepatol* 2012; 56: S39-S45.

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Global Obesity Map. Adapted from https://americandiabetesassn.files.wordpress.com/2014/06/global-obesity-map.png

North American Obesity Rates (2000→2010). Adapted from Gotay CC, Katzmarzyk PT, Janssen I, et al. Updating the Canadian obesity maps: an epidemic in progress. *Can J Pub Health* 2012; 104(1):e64-8 AND Behavioural Risk Factor Surveillance System, CDC https://www.cdc.gov/obesity/data/prevalence-maps.html

NAFLD PIVENS Trial. Adapted from Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. *New Engl J Med* 2010; 362(18): 1675-1685.

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