Bootcamp for Elevated Liver Function Tests

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Objectives

- To define Non Alcoholic Fatty Liver Disease (NAFLD) and Non Alcoholic Steato Hepatitis (NASH)
- To recognize frequently encountered gallbladder and common duct dilemmas
- To identify the changing paradigm in Hemochromatosis evaluation
- To describe what a primary care provider should know about Hepatitis C

Disclosures:

I have no relevant relationships with ineligible companies to disclose within the past 24 months. (Note: Ineligible companies are defined as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)

Should all abnormal LFTs be evaluated?

YES!

- After repeat and/or clarifying tests for confirmation
- Minimally elevated abnormal LFTs do not preclude significant liver disease
- To detect liver diseases as early as possible

Kwo PY et al

ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries

Am J Gastroenterol 2017:112;18

Let’s Not Miss Opportunities

- Over 50% of patients presenting with end stage liver disease AND
- Without a specific diagnosis DESPITE
- Previous ABNORMAL LFTs

Donnan PT et al

Development of a Decision Support Tool for Primary Care Management of Patients With Abnormal Liver Function Tests Without Clinically Apparent Liver Disease: A Record-Linkage Population Cohort Study and Decision Analysis (ALFIE)

Health Technol Assess 2009:13;1

Artie

- Is a 5’8” 285 lb male with type II diabetes running glucoses 170 – 201 before meds.
- Currently on Metformin 850 mg bid
- HCTZ 50 mg daily
- Atenolol (Tenormin) 100mg daily
- No ETOH

Artie

Exam unremarkable except for obesity and BP 180/100

Glucose 120

Alk phos normal

Alt 120 (nl 12 – 78u/L)

Ast 100 (nl 15-37u/L)

Cholesterol 270

TG 200

CBC nl

How do you work up mildly elevated LFTs in a Primary Care setting?

What are the important items we need to learn when taking a history?

How do you work up mildly elevated LFTs in a Primary Care setting?

- Check ETOH hx
- Check meds for potential hepatotoxicity
- Check herbs (Black cohosh, kava kava, green tea, ginko, etc)
- Illicit drug use

How do you work up mildly elevated LFTs in a Primary Care setting?

What tests should we be ordering?

How do you work up mildly elevated LFTs in a Primary Care setting?

- CBC/platelets
- HB_sAg, HB_cAb, HB_sAb
- HCV Ab/ RNA confirmation
- Fe/TIBC, and Ferritin
- Ultrasound

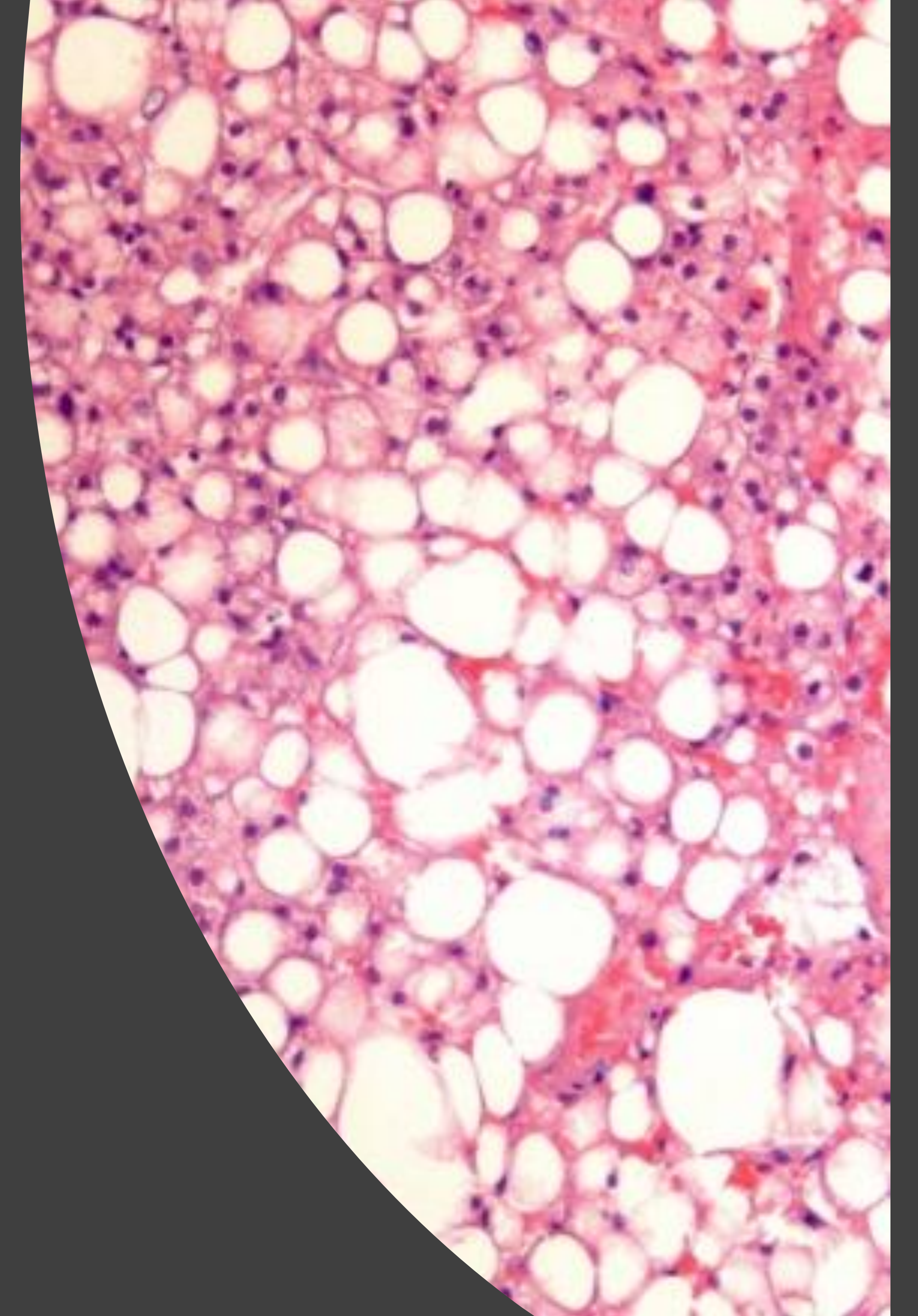
Common Things to Consider

- Hepatitis C*
- Hepatitis B – related to country of origin
- Alcohol
- Non Alcoholic Fatty Liver Disease*
- Drugs/Herbs
- Iron Overload*

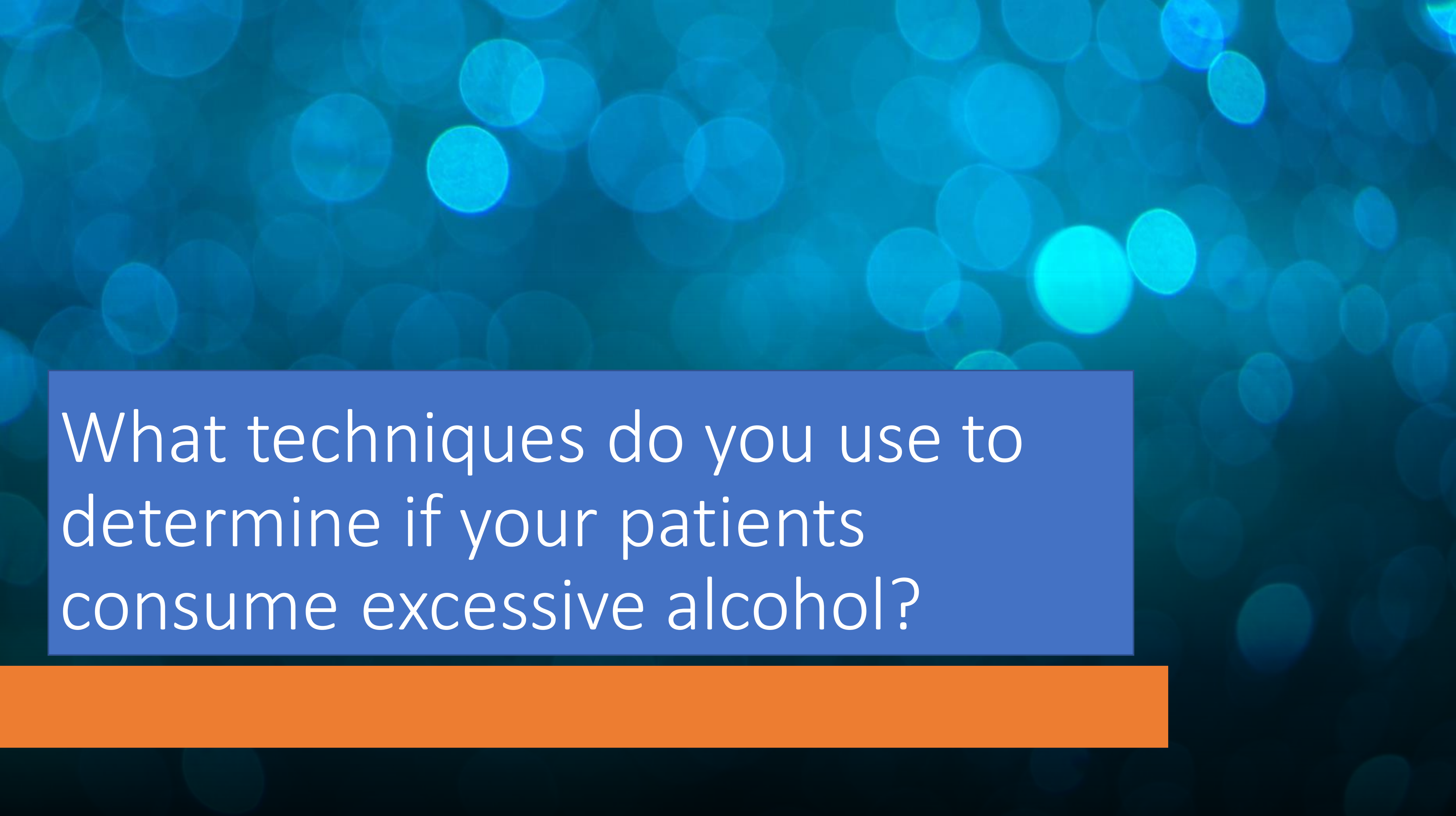
What is Non Alcoholic Fatty Liver Disease?

What is Non Alcoholic Fatty Liver Disease?

- The presence of hepatic steatosis when alcohol is NOT a cause of hepatic fat accumulation



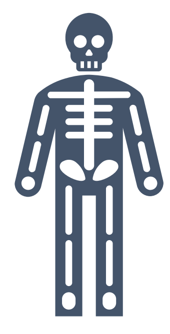
What is the difference between alcoholic and non alcoholic fatty liver disease?


What techniques do you use to determine if your patients consume excessive alcohol?

”CAGE” Questions

1. Have you ever felt you needed to Cut down on your drinking?
2. Have people Annoyed you by criticizing your drinking?
3. Have you ever felt Guilty for drinking?
4. Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover?

Subjects With NAFLD



Have 10% higher mortality than without NAFLD

Why?

Cardiovascular Disease

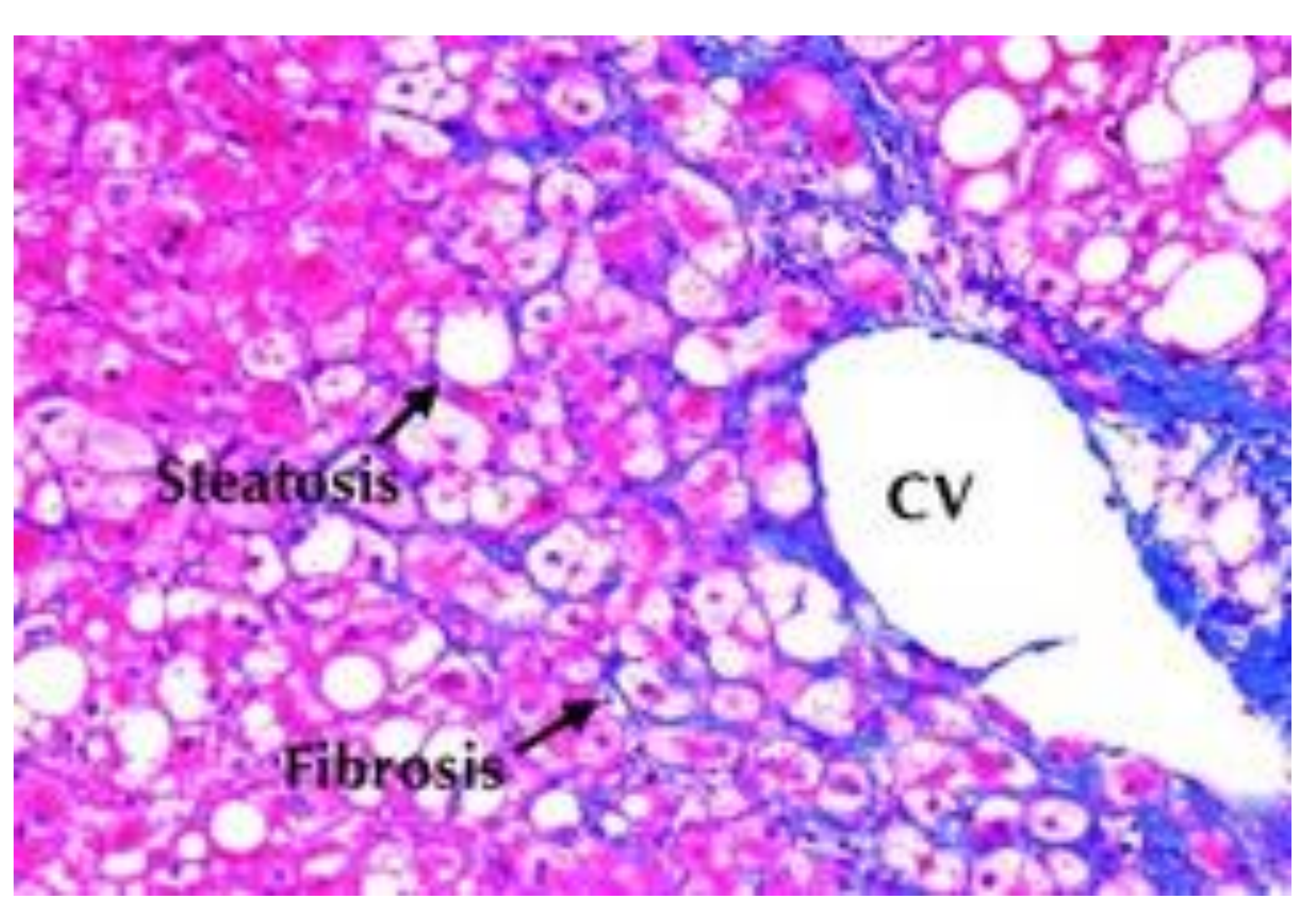
- And cirrhosis/hepatoma is not the main cause of early morbidity and mortality

Wong et al

The Association Between Nonalcoholic Fatty Liver Disease and Cardiovascular Disease Outcomes

Clin Liver Dis (Hoboken) 2018:12;39

What is Non Alcoholic Steato Hepatitis?

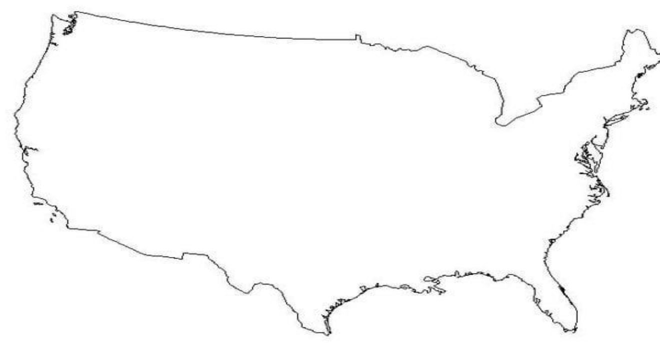


- Inflammation of the liver
- That leads to scarring

The Stats

- 100 million in US with potential for NAFLD

- 25 million with potential for NASH



Williams CD et al

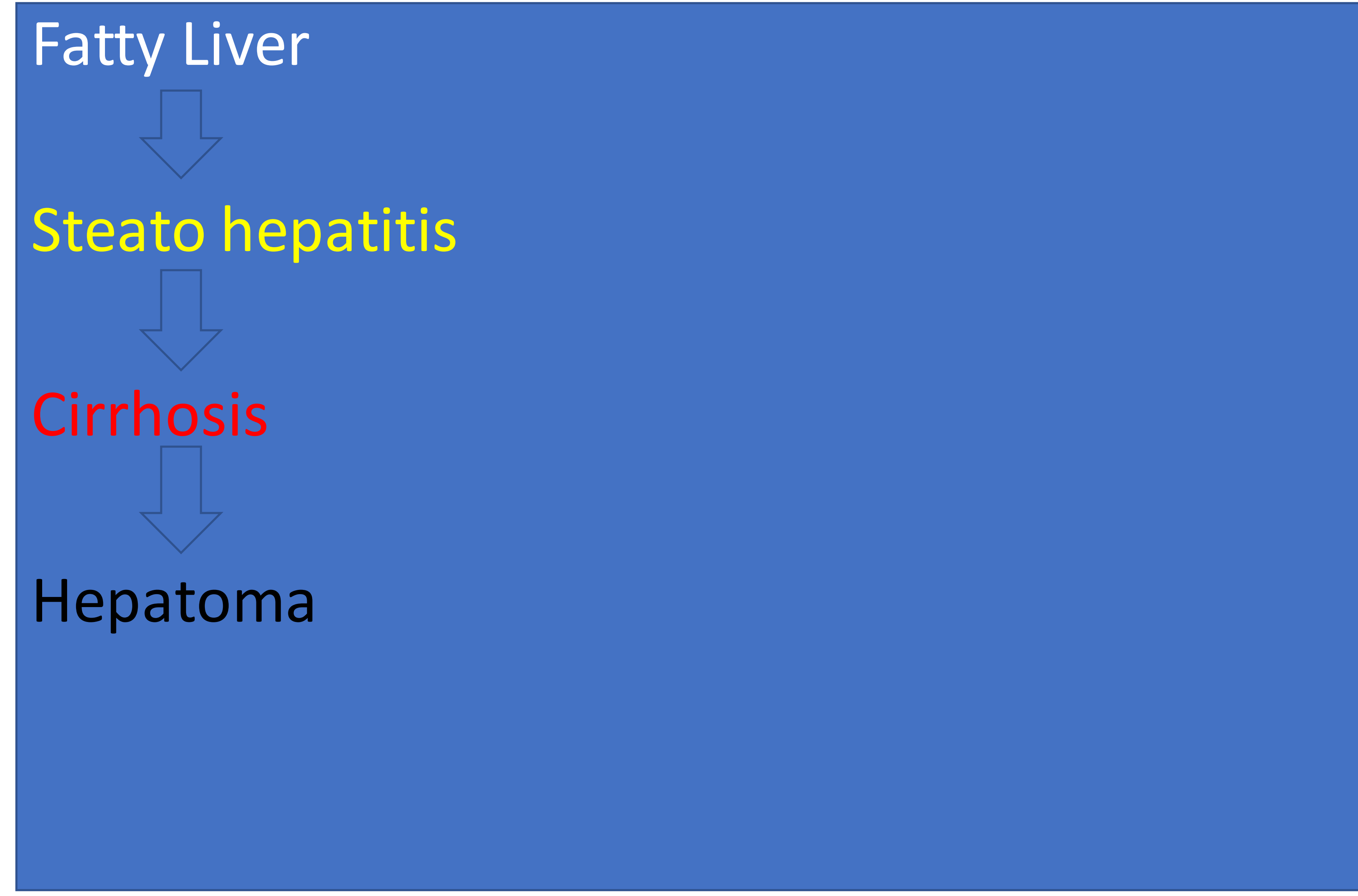
Prevalence of non alcoholic fatty liver and non alcoholic steatohepatitis among a largely middle aged population utilizing ultrasound and liver biopsy: a prospective study

Gastroenterology 2011:140;124

Risk Factors for Non Alcoholic Fatty Liver Disease &NASH

- Type 2 D.M
- BMI over 28
- High adipose tissue
- Dyslipidemia
- Metabolic syndrome

Progression of Disease



Why is NASH Important in Primary Care?

- Risk of Cirrhosis

- NASH increases hepatocellular cancer risk 10 fold

Younossi Z et al

Non-Alcoholic Steatohepatitis is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates

Clin Gastro and Hepatol 2019:17;748

What is the Lifetime Risk of Cirrhosis in NASH?

1. 2%

2. 10% - 15%

Bertot LC and Adams LA

The natural course of nonalcoholic fatty liver disease

Int J Mol Sci 2016:17;773

What is the 10 Year Risk of Liver Cancer in NASH?

1. 1%
2. 10%
3. 20%

Ascha MS et al

The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis

Hepatology 2010:51;1972

What is the Best Way to Diagnose NAFLD?

1. CT scan
2. MRI
3. U/S
4. Liver biopsy

High Risk for Fibrosis

11% of these patients with incidentally discovered hepatic steatosis might be at high risk for advanced fibrosis

This may exist with/without elevated LFT's

Wright et al

Gaps in Recognition and Evaluation of Incidentally Identified Hepatic Steatosis

Dig Dis Sci 2015:60;333

What Are the Standard Ways of Treating NASH in 2022?

Exercise and wt loss

Hep A and B vaccinations

Avoid ETOH Aberg et al Risks of Light and Moderate Alcohol Use in Fatty Liver Disease: Follow Up of Population Cohorts Hepatology 2020:71;835

Which is the ”best” diet?

- Mediterranean is best studied
- Not enough literature yet on other diets
- Also avoid fructose**

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Younossi ZM et al

AGA Clinical Practice Update on Lifestyle Modification Using Diet and Exercise to achieve Weight Loss in the management of Nonalcoholic Fatty Liver Disease: Expert Review

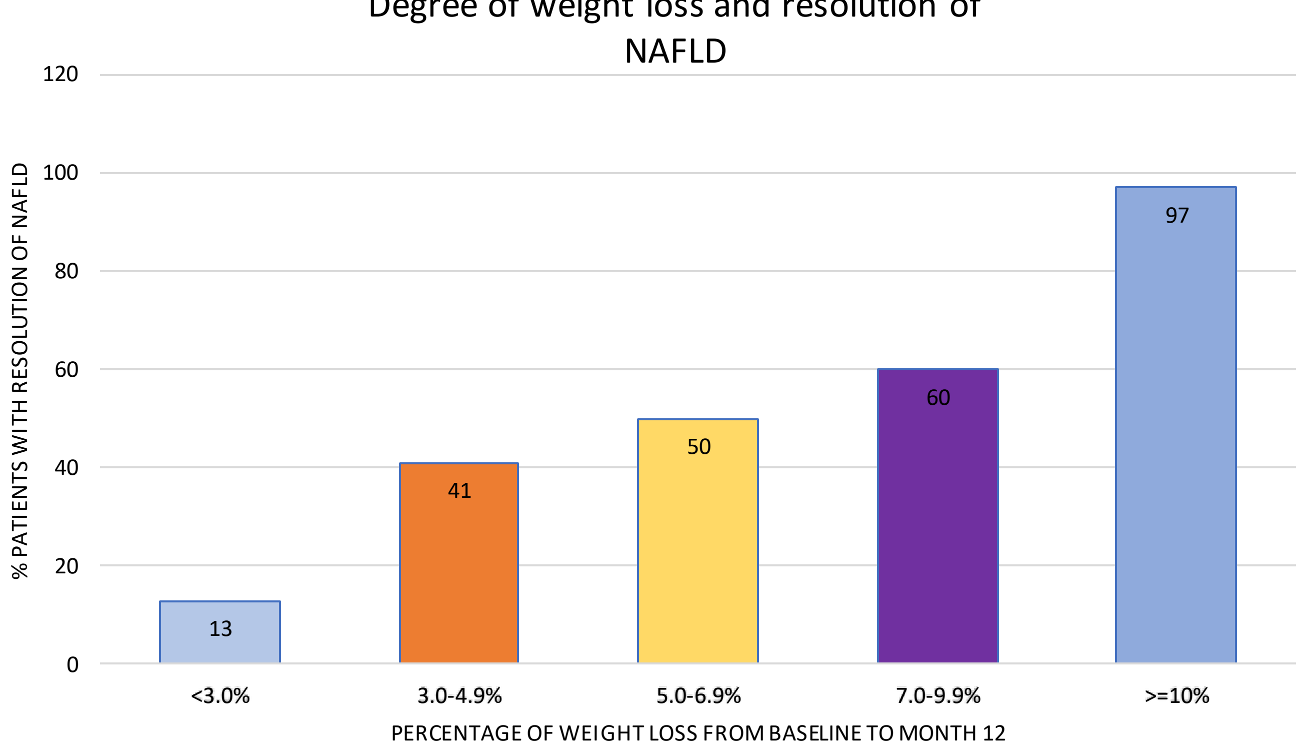
Gastroenterology 2021:160;912

**Nseir W et al

Soft drinks consumption and nonalcoholic fatty liver disease

World J Gastroenterol 2010:16;2579

Degree of Weight Loss and Resolution of NAFLD (similar improvement in NASH)



Adapted from Wong VW J Hepatol 2013

How Should We Treat the Non Obese for NAFLD?

- Hypocaloric diet
- Weight loss target of 3 – 5%
- Will have similar benefit to the obese with NAFLD

Younossi ZM et al

AGA Clinical Practice Update on Lifestyle Modification Using Diet and Exercise to Achieve Weight Loss in the Management of Nonalcoholic Fatty Liver Disease: Expert Review

Gastroenterology 2021:160;912

Controversies Over Medicines to Treat NASH

Vitamin E (alpha tocopherol)

- Patients with **NASH**, no DM
- 80 subjects
- 800IU/day for 4 years

- 43% of pts had improvement in histology

- Do I recommend vitamin E?

Sanyal AJ et al et al

Pioglitazone, Vit E or Placebo for NASH

NEJM 2010; 362: 1675 – 1685

What risks exist with vitamin E ingestion?

Abner EL et al

Vitamin E and all cause mortality: a meta analysis

Curr Aging Science 2011::4;158

Klein EA

Vitamin E and the risk of prostate cancer: updated results of the selenium and vitamin E cancer prevention trial (SELECT)

JAMA 2011:306;1549

What about these meds to treat **fatty** liver disease?

- Vitamin E No

- Metformin No

- Lovastatin/Pravastatin etc To treat hyperlipidemia; not effective in fatty liver without hyperlipidemia

Chalasani N et al

The diagnosis and management of non alcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases

Hepatology 2018:67;328

Non Invasive Tests for Fibrosis

- Elastography (Fibroscan)
- Fibrotest (Fibrosure)

How to track the progression of fatty liver disease

NFS (NAFLD fibrosis score) http:nafldscore.com

Elastography (Fibroscan)

The annual or semiannual use of Fibrosure has not yet been validated

Younossi ZM et al Role of noninvasive Tests in Clinical Gastroenterology Practices to Identify Patients With Nonalcoholic Steatohepatitis at High Risk of Adverse Outcomes: Expert Panel Recommendations

Am J Gastroenterol 2021:116;254

Suzie

- A 60 y.o. female, otherwise healthy, with severe RUQ for the past 2 weeks
- Also nausea/vomiting
- Cholecystectomy 5 years ago
- On no meds
- Exam : normal except for moderate RUQ pain
- CBC and LFTs normal, Lipase normal
- U/S; s/p cholecystectomy, normal CBD

What do you suggest?   And why?

1. Repeat ultrasound
2. MRCP
3. ERCP
4. Endoscopy

What should we now consider if no ulcer found?

1. Antispasmodics
2. Treat muscle pain
3. Evaluate stress factors
4. Any of the above are possible

Myra

- Is a 42 y.o. female, otherwise healthy, with severe RUQ pain for 1 week
- With N/V
- Cholecystectomy 5 years ago
- On no meds
- PE t 101.6, scleral icterus, moderate RUQ tenderness

Labs: normal (including lipase) except for:

- WBC 17,200 with shift to L
- Alk phos 272 nl 50 – 136 U/L
- AST 200 nl 12 – 78 U/L
- ALT 150 nl 15 – 37 U/L
- Total Bilirubin **4.0** mg/dL

- U/S shows s/p cholecystectomy, 1 cm CBD (dilated)

What should we do next?

1. MRCP
2. ERCP
3. CT
4. Endoscopy

Buxbaum JL et al

ASGE guideline on the management of cholangitis

Gastrointestinal Endoscopy 2021:94;207

Would We Approach Myra Differently If She Had a Normal Common Bile Duct?

All of the following are risk factors for gallstone disease except

1. Obesity
2. Pregnancy
3. Rapid wt loss
4. Atorvastatin use

Lisa

- Is a 62 y.o who had a laparoscopic cholecystectomy 2 days ago for multiple gallstones
- She now has diffuse abdominal pain and a fever to 103
- Tried to reach her surgeon who is out of town
- After telling her to go to the ER, you review the case in your mind

What tests should be done in the ER?

Statins and the Liver

Statins and the Liver

- Statins cause benign elevation of ALT in 3% of patients
- Statins are not contraindicated in patients with pre existing liver disease
- ALT/AST elevations greater than 3X normal AND evidence of bilirubin 2X normal after statins are started require a discontinuation of statins and a workup

- Bays H et al
- An assessment by the Statin-Liver Safety Task Force:2014 update
- J Clin Lipidol 2014:8;s47

What’s New in Hemochromatosis

- **John** is a 70 yr old referred for mildly elevated liver function tests
- He has been feeling tired for months and thinks it’s due to the fact that he works two jobs
- He also has joint pains and diabetes
- PE: unremarkable
- Labs: Fe 2000 mcg/dL

  TIBC 300 mcg/dL

  Ferritin 220 mgm/ml

Which test should we consider first to make the diagnosis?

1. Liver biopsy

2. Genetics

3. Hepatic MRI

- C282Y homozygosity
- C282Y/H63D heterozygosity
- Confirm hemochromatosis in the appropriate clinical setting

Kowdley KV et al

ACG Clinical Guideline: Hereditary Hemochromatosis

Am J Gastroenterol 2019:114;1202

Jack

- Is a 26 y o who used heroin once while in college
- On a routine exam 3 months ago the physical was normal but:

AST 80 nl 12 -78 u/L

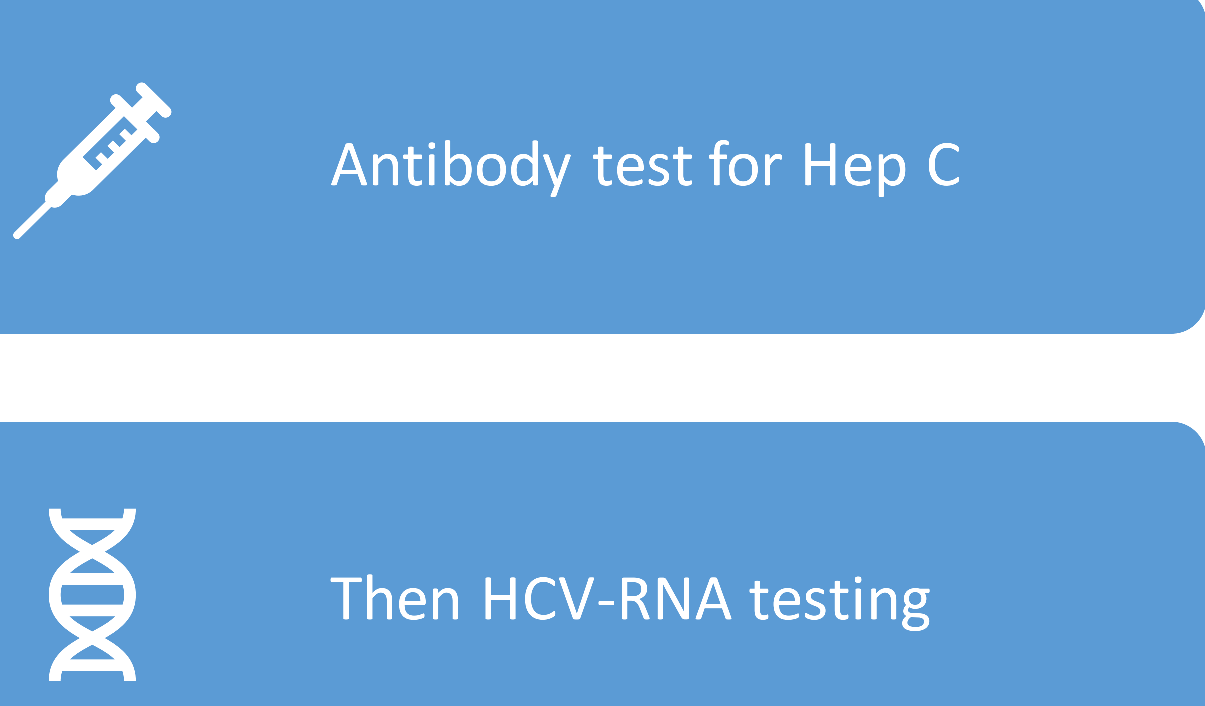
ALT 100 nl 15 – 37 U/L

Follow Up

- 3 months later, normal LFTs
- 1 month later, again elevated

- What tests should be done?

What tests



All of the Following are Risk Factors for Hepatitis C EXCEPT

1. High risk sexual behavior
2. Breast feeding
3. HIV infected person
4. Anyone age 18 – 79

US Preventive Services Task Force Recommendations Statement

Screening for Hepatitis C Virus Infection in Adolescents and Adults

March 2 2020

JAMA published online doi:10.1001/jama.2020.1123

Questions

What does a positive Hep C antibody test mean when the Hep C RNA is negligible?

Does normalization of liver function tests in a Hepatitis C patient without treatment mean that the infection has disappeared?

Sources of Infection for Persons With Hepatitis C

Injection drug abuse	70-90%
Accidental needlesticks	1.8% chance of getting infected
Birth to HCV + mom	under 6%
Receiving blood transfusion prior to 1992	under 1%

CDC Hepatitis C Information

Question?

- What is the risk of Hepatitis C transmission by sexual activity in a longstanding monogamous heterosexual couple?

1. .07%
2. 2%
3. 15%

Terrault NA et al

Sexual Transmission of Hepatitis C Virus Among Monogamous Heterosexual Couples: The HCV Partners Study

Hepatology 2013:57;881

- Do you use Acetaminophen in patients with chronic liver disease?

- Should cirrhotic patients “cured” of hepatitis C still be evaluated periodically for hepatoma?

Tang An et al

Introduction to the liver imaging reporting and data system for hepatocellular carcinoma

Clinical gastroenterology and Hepatology 2019:17;1228

What percentage of Hepatitis C patients develop cirrhosis in 20 years?

1. 15%
2. 50%
3. 100%

Thein HH et al

Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta analysis and meta regression

Hepatology 2008:48;418

Therapies for Hepatitis C 2022

Generic	Brand
Sofosbuvir + Ledipasvir	Harvoni
Simeprivir	Olysio
Daclatasvir	Daklinza
Grazoprevir+Elbasivir	Zepatir
Sofosbuvir+Velpatasvir	Epclusa
Sofosbuvir+Velpatasvir+Voxilaprevir	Vosevi
Glecaprevir + Pibrentasvir	Mavyret

AND These Medicines are Working

- Annual decrease of Hepatocellular Ca of -3.5% from 2014 -2018
- Direct acting antiviral agents became available 2013
- In contrast Hepatocellular Ca from Nonalcoholic Fatty Liver Disease is increasing

Kim D et al

Decline in annual mortality of Hepatitis C virus-related hepatocellular carcinoma in the United States, from 2009 to 2018

Gastroenterology 2020:159;1558

All of the following are complications of hepatitis C **EXCEPT:**

1. Renal disease
2. Cardiomyopathy
3. Diabetes
4. Thyroiditis

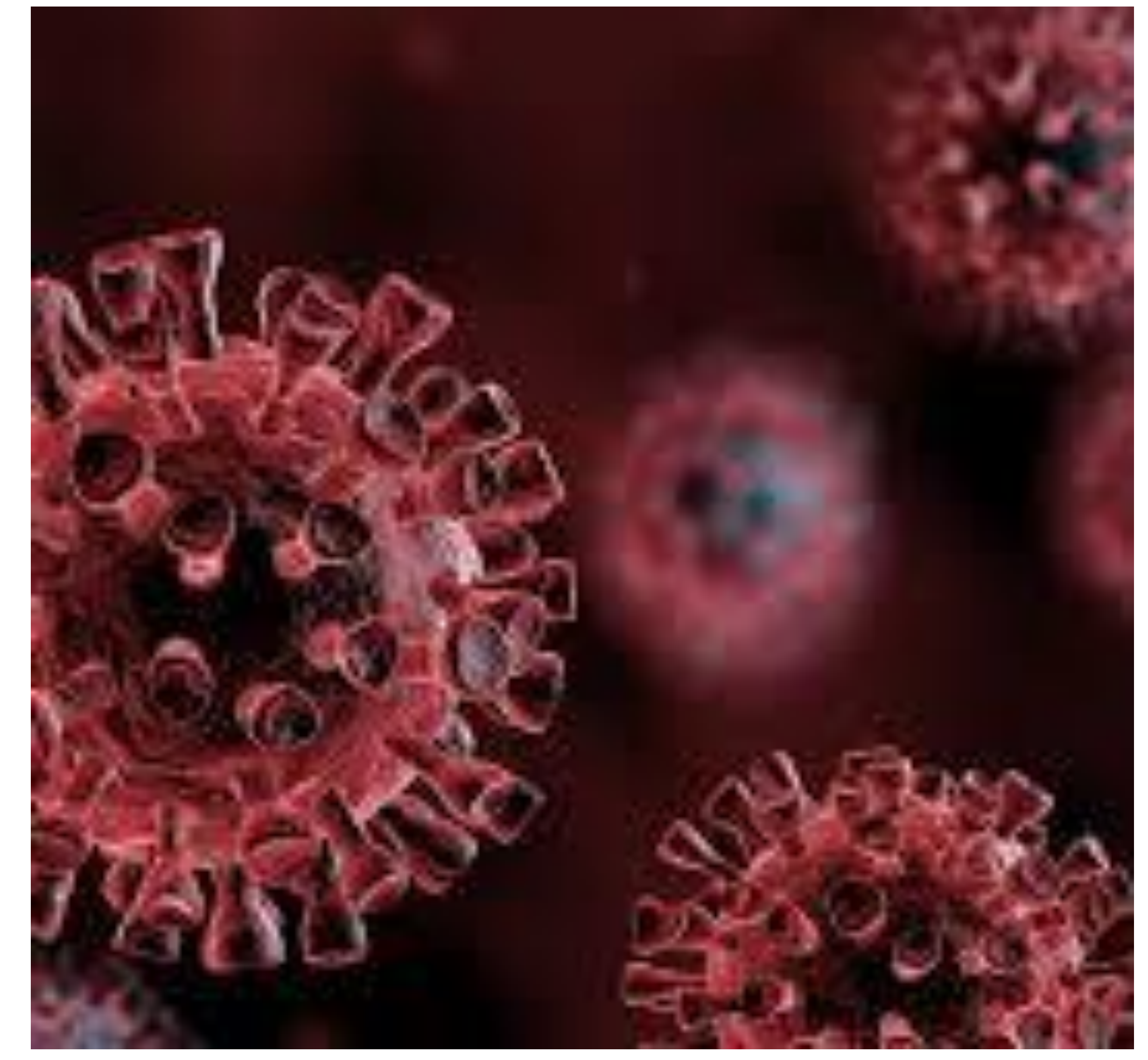
The Liver and COVID; Things to Consider

- 28% of patients with COVID 19 presented with elevated liver function tests
- 6.8% had chronic liver disease
- 4.5% had a history of alcohol abuse

Hao SR et al

Liver Enzyme Elevation in Coronavirus Disease 2019: A Multicenter, Retrospective, Cross-Sectional Study

Am J Gastroenterol 2020:115;1075



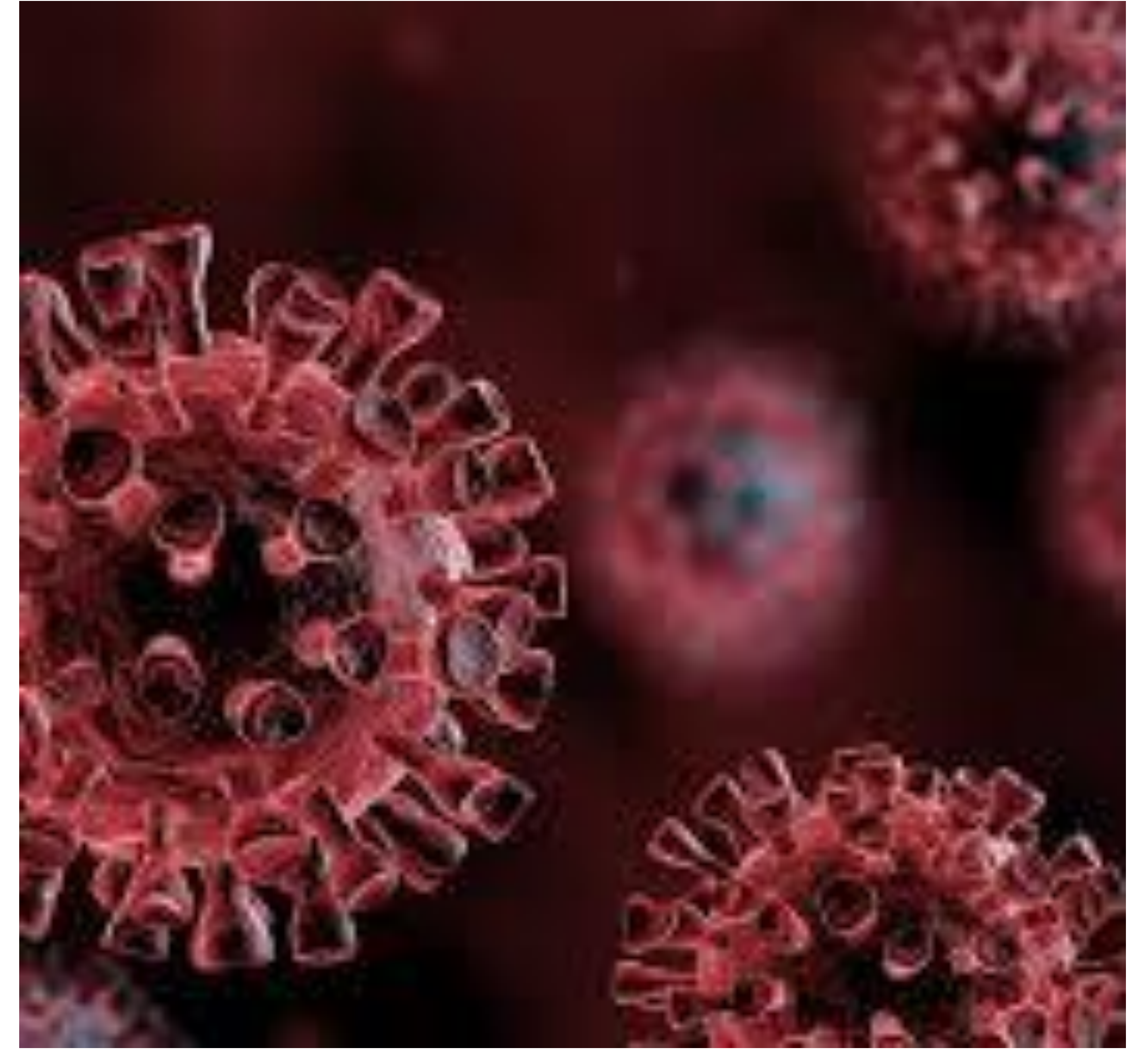
The Liver and COVID; Things to Consider II

- Obesity tends to be a risk factor
- Most enzyme elevations were mild
- No liver failures

Hao SR et al

Liver Enzyme Elevation in Coronavirus Disease 2019: A Multicenter, Retrospective, Cross-Sectional Study

Am J Gastroenterol 2020:115;1075

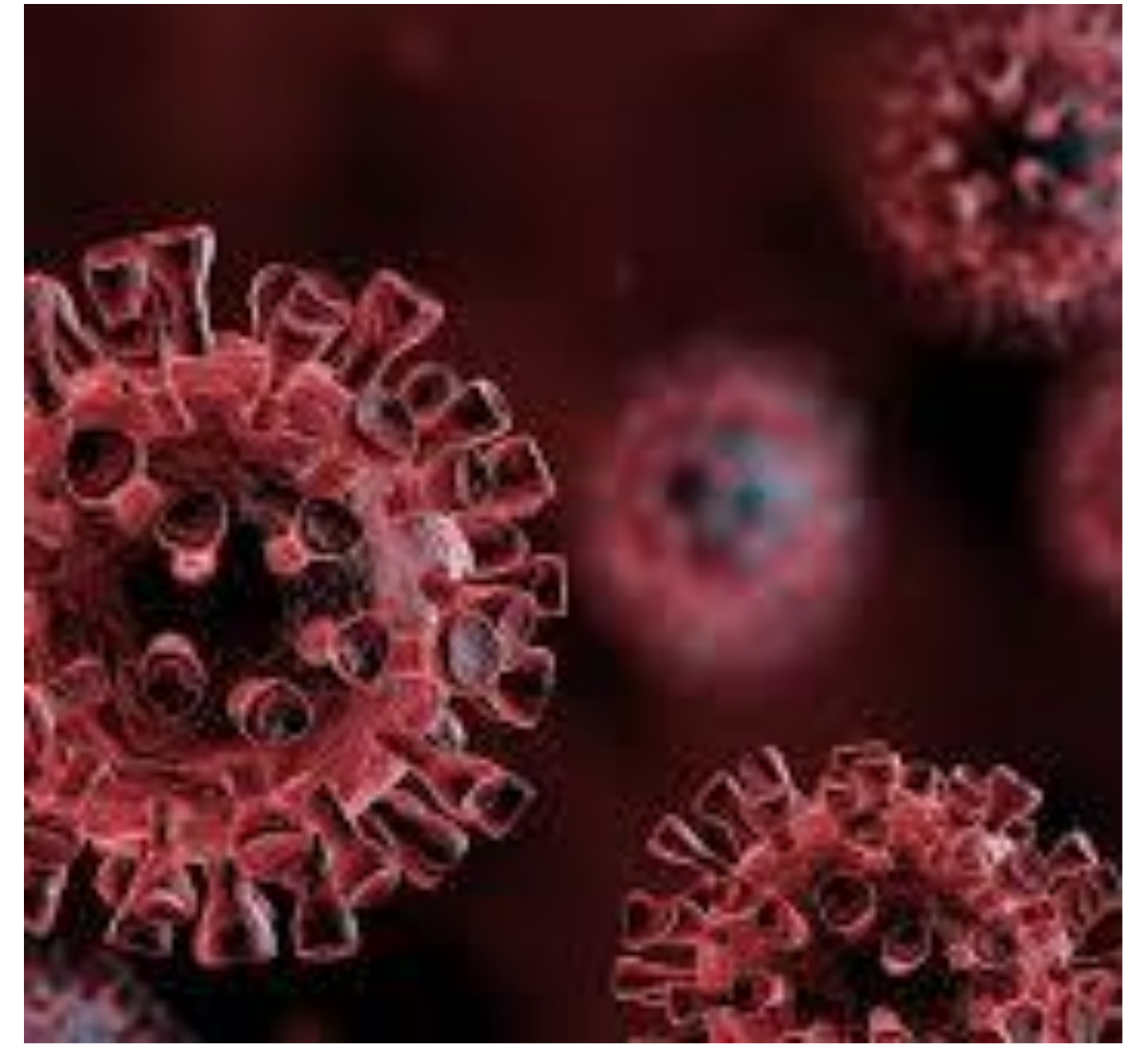


The Liver and COVID; Things to Consider III

Drug Toxicities: : Remdesivir
Dexamethasone
Acetaminophen

Myositis

Cytokine Release Syndrome



Summary

- Fatty liver disease is overtaking Hepatitis C as a major source of cirrhosis
- Hepatitis C + antibody test with negligible Hepatitis C RNA means the patient has recovered from their infection
- Our Hepatitis C patients will generally only have ONE course of antiviral therapy – make sure they are compliant

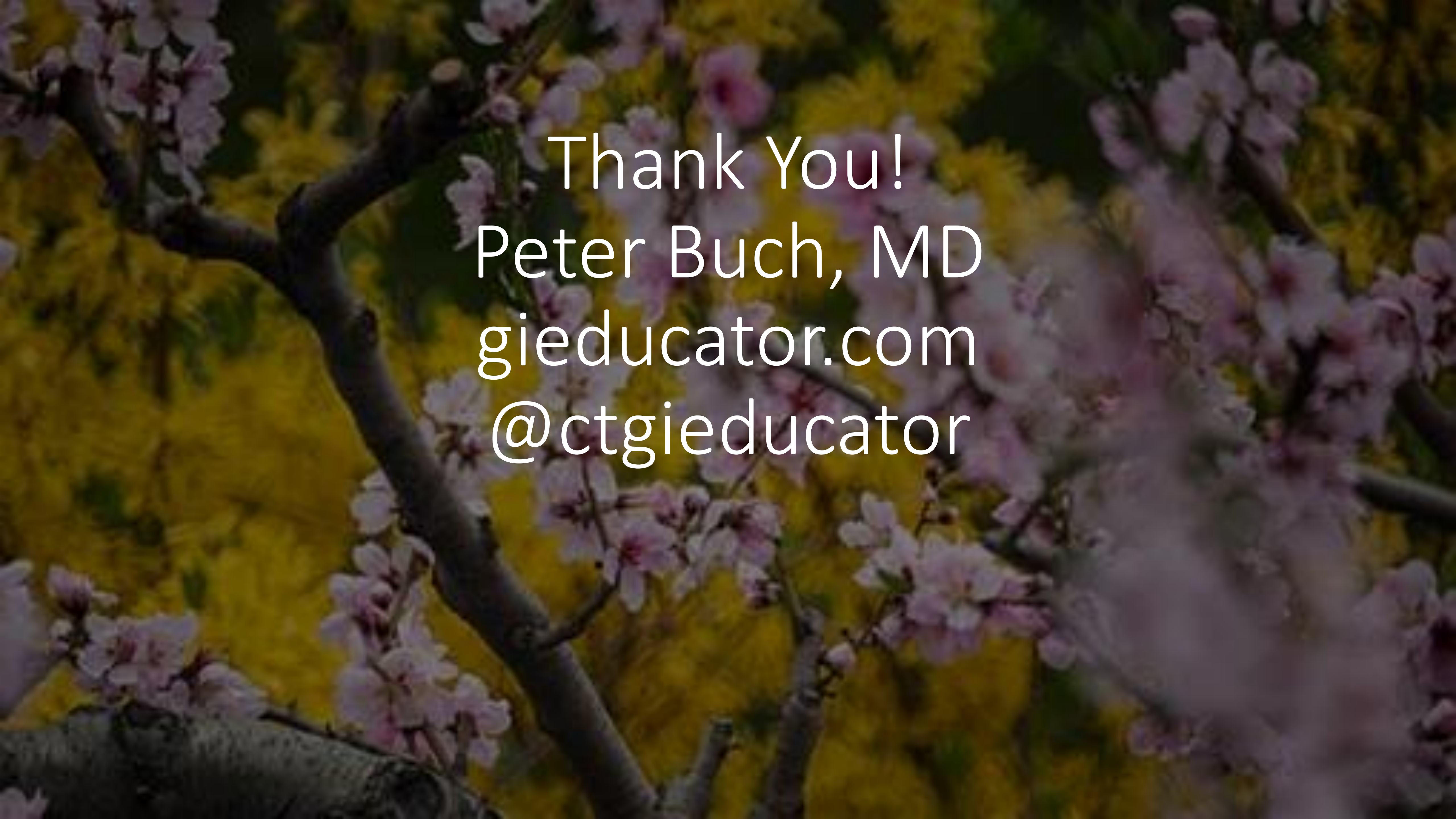
Additional Resources

HCVGuidelines.org

Kwo PY et al
ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries
Am J Gastroenterol 2017:112;18

AASLD
Clinical Insights for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic
Released April 7, 2020

Kanwal et al
Clinical Care Pathway for Risk Stratification and Management of Patients With Nonalcoholic Fatty Liver Disease
Gastroenterology 2021:161;1657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