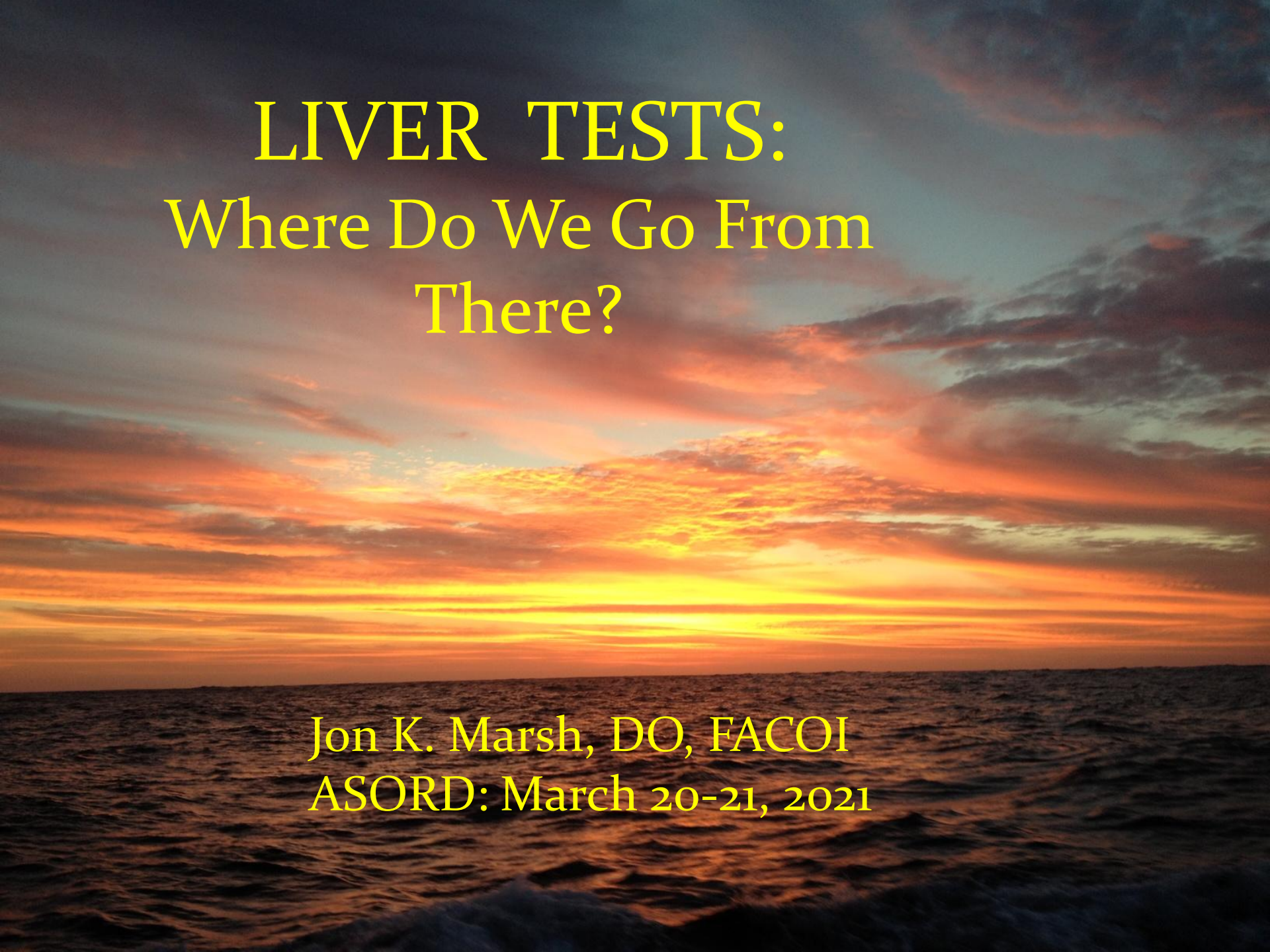


LIVER TESTS: Where Do We Go From There?

Jon K. Marsh, DO, FACOI

ASORD: March 20-21, 2021

Learning Objectives

To review the Clinically Relevant concepts and pathophysiology behind Standard laboratory LFT's.

To review the "workup" and ongoing evaluation of the common Liver diseases.

To Look at common *therapies and the rational behind their use, or in other words what we do about these abnormal tests.*

Disclosure

- Conflicts of Interest: None

Which of the following are considered to measure the "Function" of the Liver?

- A) AST
- B) ALT
- C) Alk Phos
- D) GGTP
- E) None of the above

What is the Best Test to Evaluate the Liver?

- A) ALT
- B) Ultrasound
- C) Dynamic IV contrast CT
- D) MRI
- E) None of the above – They all look at different things and are complimentary

What is the “Best Treatment” for Acute Alcoholic Hepatitis Besides Cessation?

- A) Steroids If Maddrey Discriminant Score >32
- B) Trental (Pentoxyphyline)
- C) Probiotics
- D) Immunomodulator Drugs
- E) Good Nutrition

What is the Most Efficacious Drug Class for Inducing Remission in Acute AutoImmune Hepatitis?

- A) Anti TNF"s
- B) Probiotic's (VSL#3)
- C) Steroids
- D) Thiopurines (Imuran)
- E) None of the above

Let's Talk About What's Important !

If Abnormal LFT's, First ask are they Hepatocellular or Cholestatic in Nature to help classify etiology

Lets Talk About What's Important!

Stages of Evaluation:

First Level/First visit back

Second Level Tests ordered after First Level Evaluation is done

“Liver Function Tests”

Liver Enzymes:

- ALT: the best true hepatocyte enzyme
- AST
- Alkaline Phosphatase
- GGTP (very sensitive for bile duct Disease)

Liver “Synthetic” Tests:

- Bilirubin, Albumin, and Protime/INR

First Level Testing

- Alcohol history: What do you buy it in and how often
- Medication review & Medication review
- OTC, Herbal, and Diet Supplements
- Iron Saturation and serum ferritin
- Hep C Ab's
- Hep B Surface and Hep B core Ab's
- Metabolic Eval.: BMI, FBS - Hg A1C, TSH, & Lipid panel
- Ultrasound

Physical Exam Findings

"Signs of Chronic Liver Disease Changes Everything"

- Spider angiomas, Dupuytren's contractures, Caput medusa, Nail clubbing, Gynecomastia and Testicular atrophy, Palmer erythema, Edema, Hepatomegally, Spleenomegally, Ascities, & Scleral icterus

These findings mean do not delay evaluation

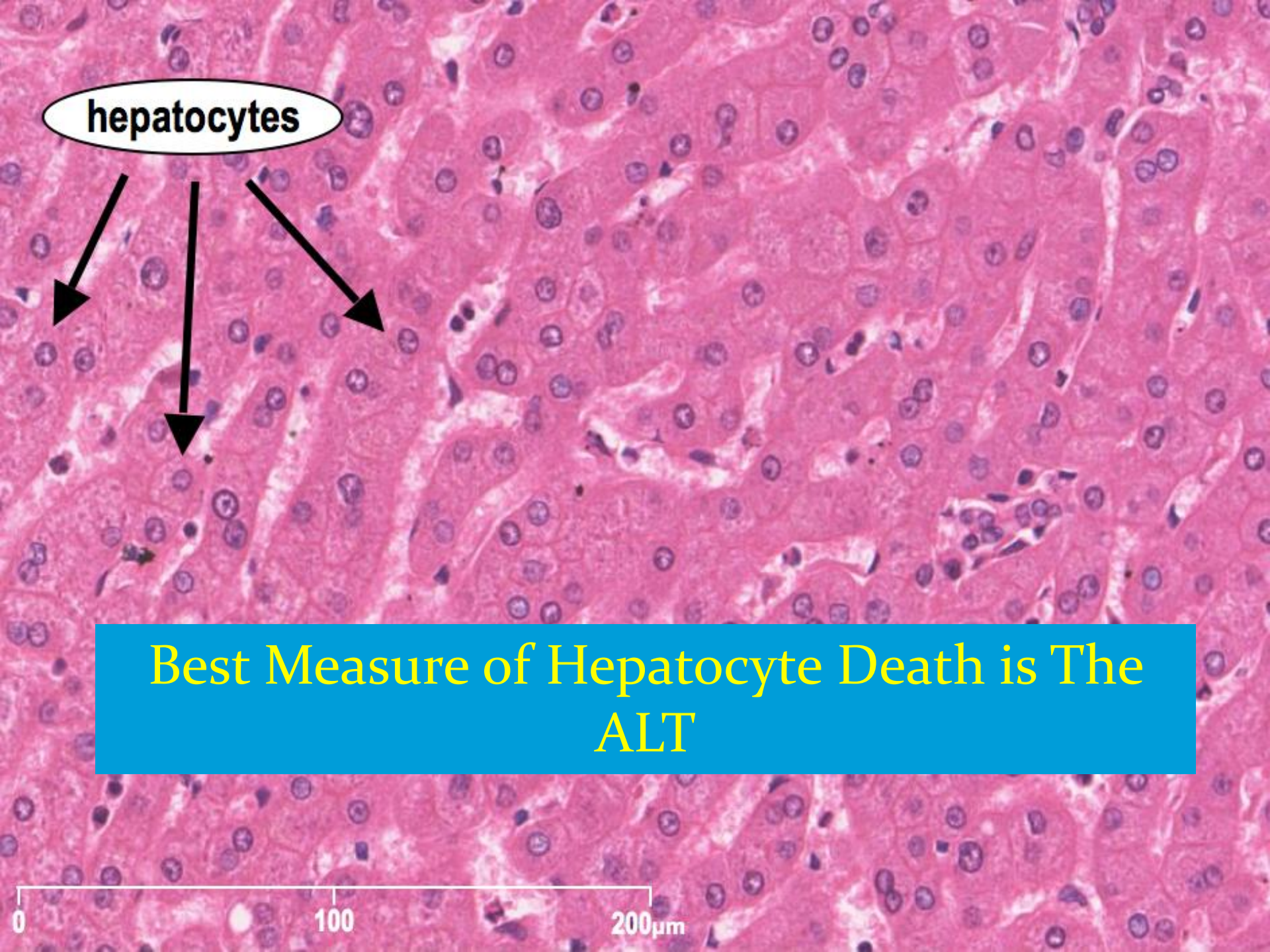
Second Level Testing: Hepatic

- Hepatic:
  - Viral Hepatitis: A, B,C, E (EBV & CMV)
  - Autoimmune (AIH): ANA , ASMA, ? Anti-Citrulline Ab's (Anti CCP Ab's), and for Pediatric AIH do ALKM Ab's/ anti- Soluble Liver AG Ab's.
  - Hemochromatosis Genetic Analysis
  - Wilson's disease (serum copper and ceruloplasmin)
  - Alpha 1 Antitrypsin deficiency
  - Liposomal Acid Lipase Level (mimics Fatty Liver Disease)

1.) Ann Rhem Dis 2007; 66:511-516 doi: 10.1136/ard.2006.058933

Second Level: Cholestatic

- Obstructive: Stones, Cancer, Parasites, & Medications
- PBC: Primary Biliary Cholangitis (Cirrhosis)
- PSC: Primary Sclerosing Cholangitis
- Granulomatous Disease such as Sarcoidosis
- Infiltrative Disease: Cancer, Amyloidosis, & Infections
- Medications: 6MP, Tylenol, Phenergan, Quinine, NSAID's, Clavulonic acid, Psychotropic's, Erythomycin, & Anabolic steroids.
- Gilbert Syndrome (glucuronyl transferase def.)



Best Measure of Hepatocyte Death is The ALT

ALT

- Cheap
- Noninvasive
- Quick
- Specific for Hepatocyte "death"

ALT > 3000 means Hepatocellular Necrosis

Sensitivity of the ALT

In NAFLD:

- Over 40% of patients undergoing bariatric procedure that had from Steatosis to Severe NASH had a normal ALT

This normal ALT may explain why we see so many patients with "Cryptogenic Cirrhosis"

2.) Garcia-Monzon C, et al. J Hepatol. 2000; 33(5): 716-724

Definition of Normal Values

- Statistical Definition: Meaning within 2 standard deviations of the mean on a bell shaped curve

- Clinical Definition: Meaning that below this number we tend to think risk of developing disease is low (we tend to ignore it or check it off our list)

Updated Normal "ALT" Level

- 9221 first time blood donors where 26% were excluded for: seizures, anemia, and/or other risk factors
- 57% looked at with "low risk factors for liver disease:

  BMI < 25, Negative viral studies, No Medications, and Normal FBS & lipid panel

Normal Top ALT: ACG 2016 guidelines-

Males: 29-33 U/L

Females: 19-25 U/L

3.) Prati. Ann Intern Med. 2000; 137: 1-10

BMI and ALT

1033 blood donors with negative viral serology

	BMI ≤ 23	BMI > 23
Male	31	44
Female	42	66

4.) Piton A, et al. Hepatology. 1998; 27: 27: 1213-1219

Problems With "NEW" Normal ALT"

- Anxiety
- Unnecessary Testing
- Rejection of Blood Donors
- Medical – Legal Issues

Though to ponder:

Note the level and apply to each patient individually keeping in mind that the higher the level the higher the Morbidity and Mortality of the patient

5.) Kim HC, et al. BJM. 2004; 328: 983-988

Too Many Liver Problems To Count, So We Are Going To Be Focusing On?

San Diego Offshore 50 miles, 2015
Fish Box “Full” of Mahi Mahi and Tuna

The Diseases You See A Lot of

- Drug induced
- Viral
- Non Alcohol Fatty Liver disease (NAFLD)
- Alcoholic Hepatitis
- Hemochromatosis (Metabolic Diseases)
- Auto Immune Hepatitis (AIH)
- Gilbert's Syndrome and/or Bile Duct obstruction
- Cancer and Stones

Drug Induced Liver Injury (DILI) "Hepatocellular"

#1 cause of drug induced liver failure in the USA: APAP

- 46% of "ALL" causes of Acute Liver Failure"
- Most use to be Intentional Suicidal Overdoses
- Now various studies showing "Unintentional" is taking over: mostly caused by addition of APAP to Narcotics.
- Greater than 3 Grams APAP per day can cause injury
- > 6 Vicodin ES per day is a worry. Now mix this with Alcohol, Dilantin, Valproic acid, …

DILI

- Remember any and all drugs can have an Idosyncratic Reaction regardless of no published data
- Stop if possible all drugs/OTC's/Supplements
- Change all others
- Retest lab within days to 2 weeks: Is it going down or up. Note the half life of the medicines they are on.
- Follow until they go back to normal
- IV Mucomyst protocol for severe cases

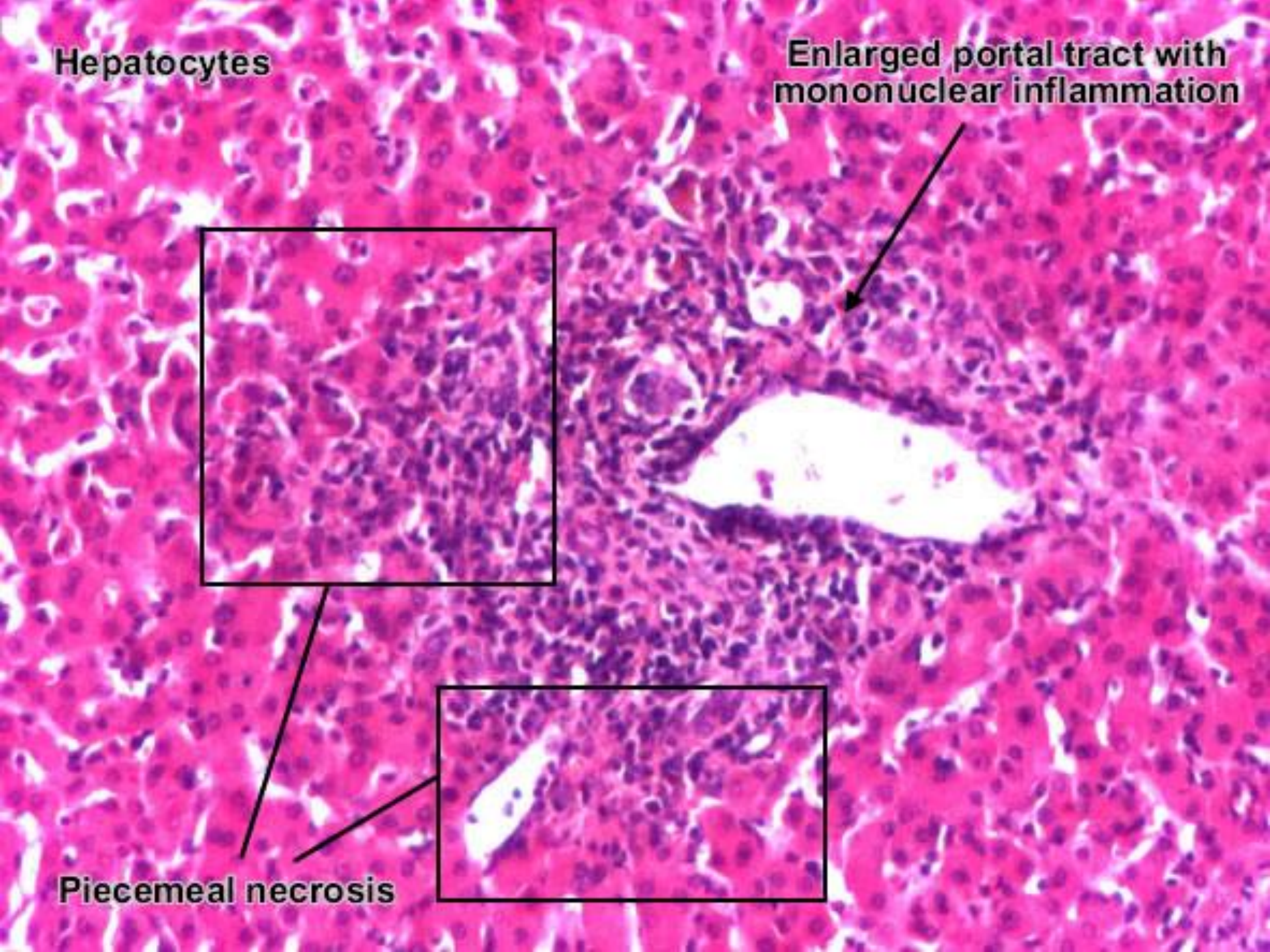
Hepatocellular: Viral

- Hepatitis A: Pos IgM and self limited. May have prolonged Cholestatic phase for months
- Acute Hepatitis B: Pos Hep B SAg and Hep B core IgM Pos
- Chronic Hepatitis B: Positive Hep B SAg and Hep B core IgG positive. HBe Ag Pos = more viral replication then Hep Be Ag Neg patients.
- Chronic Hepatitis C: Positive Hep C AB's with Positive Qualitative PCR assay or Pos Quant assay.

Hepatocellular: Viral

- Hep A: Prophylaxis with Immunoglobulin/Vaccine
- Hep B: Acute Hep B has < 5% go to chronic. If Chronic then DNA virus inserts into genome and over years increased risk of Hepatoma: can treat with Tenofovir(Viread), Entecavir(Baraclude), Adefovir(Hepsera), Telbivudine, Interferon, Lamivudine

Hep B: Decreasing Viral Load decreases risk of Hepatoma


Hepatocytes
Enlarged portal tract with mononuclear inflammation
Piecemeal necrosis

Hepatitis C

- Direct Acting Antiviral Agents (DAA's): Harvoni, Epclusa, Solvaldi, Mavyret, Zepatier, & others.
- Rapidly moving for Primary Care to initiate treatment in "naïve treatment" patients and patients that have no evidence of cirrhosis or decompensation
- But why would Primary Care want to?

  Pain: hassle- time- expense of getting auth.

  Performing surveillance for Hepatoma in cirrhotics is a medical-legal risk

Hepatitis B: Surveillance

- Asian/African/North American blacks: men > 40 & women over age 50
- Family history of Hepatoma
- Caucasians with Active inflammation for years in noncirrhotics: Men over 40 & Women > 50
- All cirrhotics

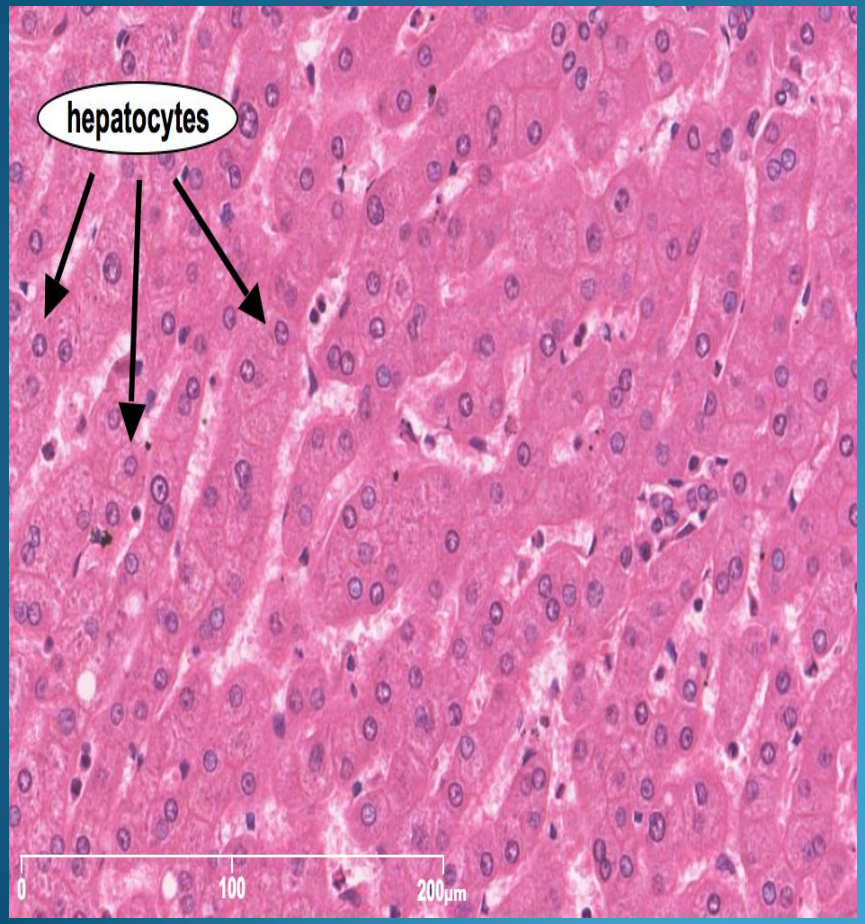
6.) AASLD guidelines 2011

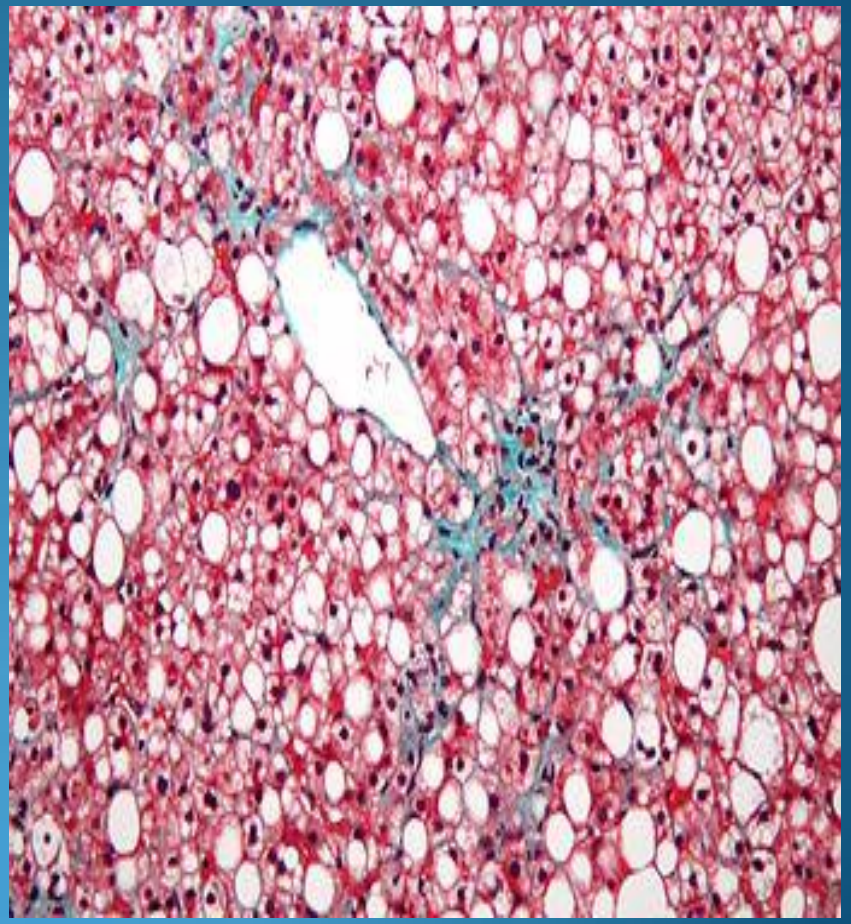
Few Words on Hepatoma for Cirrhotics and Chronic Hep B

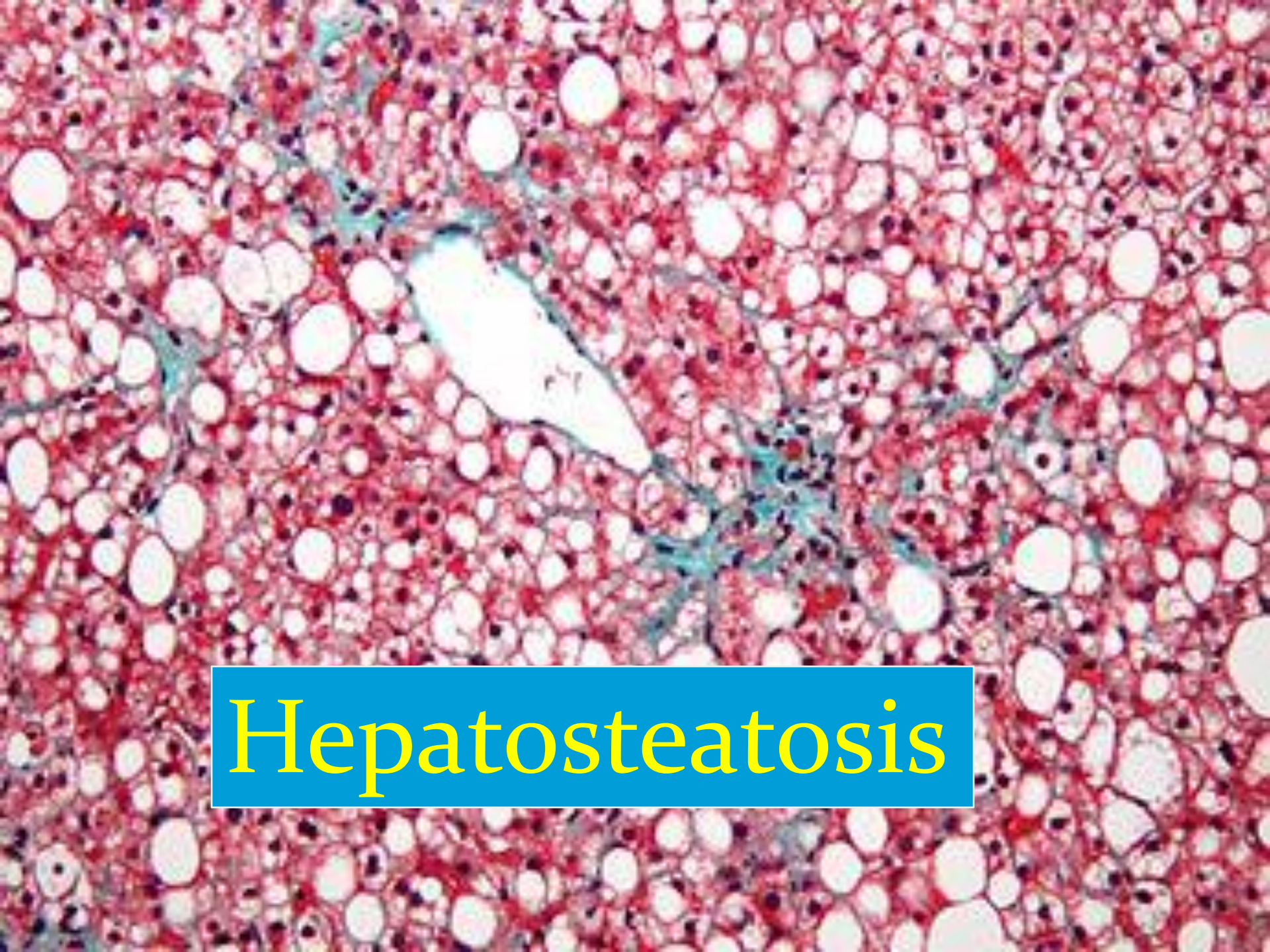
- Every 6 months AFP and Ultrasounds
- Most agree to alternate US with MRI. CT with 3-4 phase ("Dynamic Flow") IV contrast is good but with RT and Dye
- IF AFP elevated RECHECK in 6-8 weeks (AFP-L3)
- If imaging study abnormal, do referral and Do Not Biopsy as a percutaneous biopsy will track and changes staging and survivability
- Document in chart "Standard Surveillance Discussion"

7.) AFP-L3 @ questdiagnostics.com

Normal vs. Hepatosteatosis






Hepatosteatosis

Non-Alcohol Induced Fatty Liver

- Easy to diagnose with US/CT/MRI
  - These cannot distinguish between Steatohepatitis and hepatosteatosis. This requires a Liver Biopsy.
  - Remember this is a Hepatocellular disease so don't get fooled and look for other diseases.
  - Check : Alcohol history, Medication history, TSH, FBS/HgA1-C, Lipid panel, Hepatitis C, Crohn's, and possibly a Liposomal Acid Lipase level
    - Drugs: Amiodarone, Valproate, Temoxifen, & Methotrexate

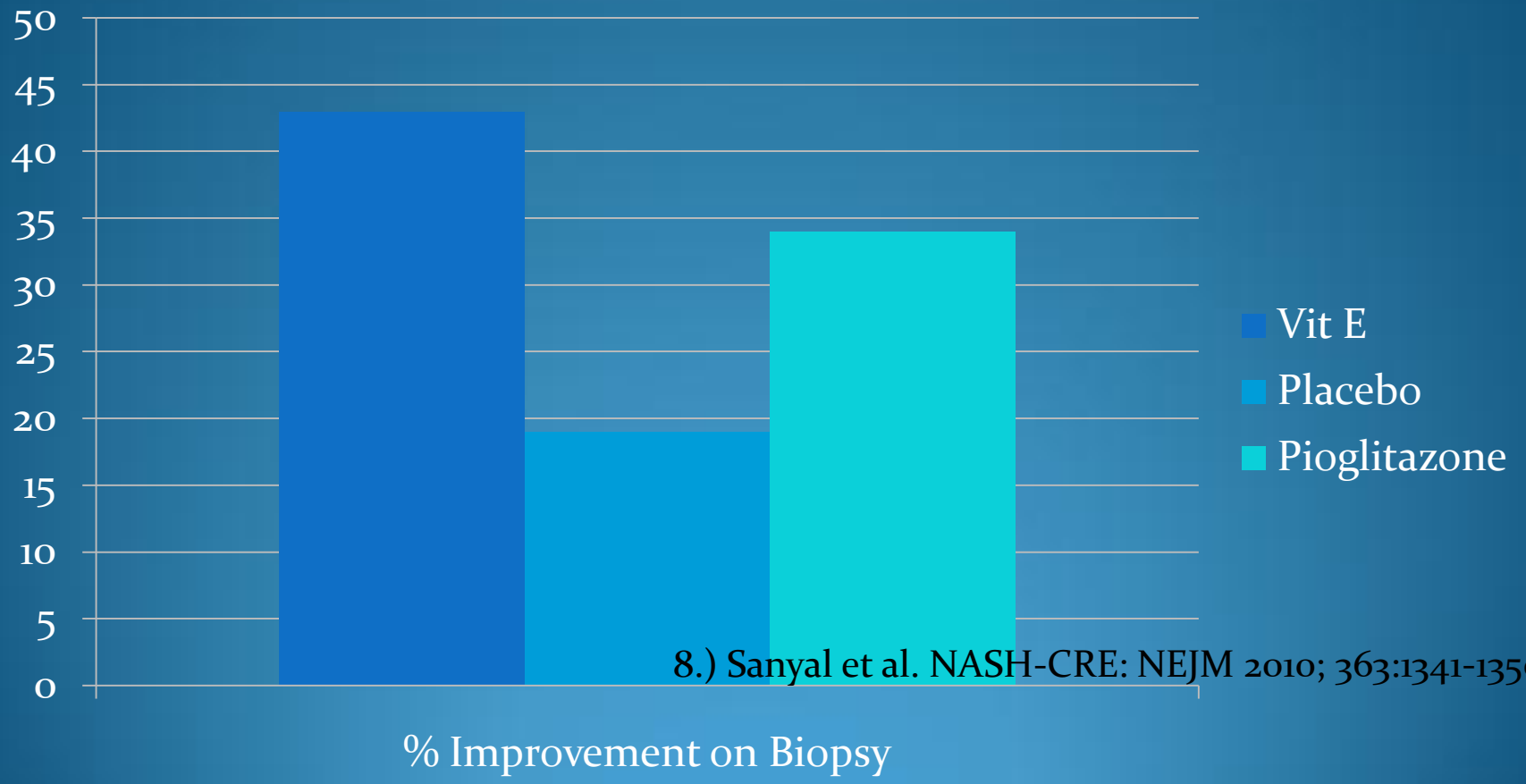
Fatty Liver and Hepatosteatosis What to do

- Remove offending cause
- Treat the Underlying Problem of “insulin resistance”
- Diet and Exercise!!!
  - 20-30 minutes 3-4 times per week
  - Sleep and circadian rhythms (night shift is bad)
  - Modified Low Carbohydrate Diet: I restrict grains (including pasta), sugars (including “frappes” & sodas), alcohol, potatoes, fast food, Fruits (and juices), but not most fats (olive oil) and I don’t count carbs in vegtables like broccoli & I tell them not to count Protein

Therapy for Non-Alcohol Fatty Liver

- Treat the "Insulin Resistance"
- For diet and exercise failures: < 25% in my practice.
- Other therapies in addition to Diet and Exercise:
  - Vit E 800 units/day
  - Thioglitazones (Metformin & Actos)
  - Statins
  - VSL #3
  - New drugs: ? Pentoxyfylline, ? Losartan, Elafibranor, Myo-Inositol, and Obeticholic acid

PIVENS Study Outcome



8.) Sanyal et al. NASH-CRE: NEJM 2010; 363:1341-1350

Unpublished Data: Dr. Martin Blaser at New York University

Mice engineered to be prediabetic ingested Ralstonia developed insulin resistance and hyperglycemia.

When the same mice were given AB's to Ralstonia they lost weight and their glycemic profile normalized.

The idea that the Microbiome plays a significant role in the pathogenesis of Steatosis/NASH

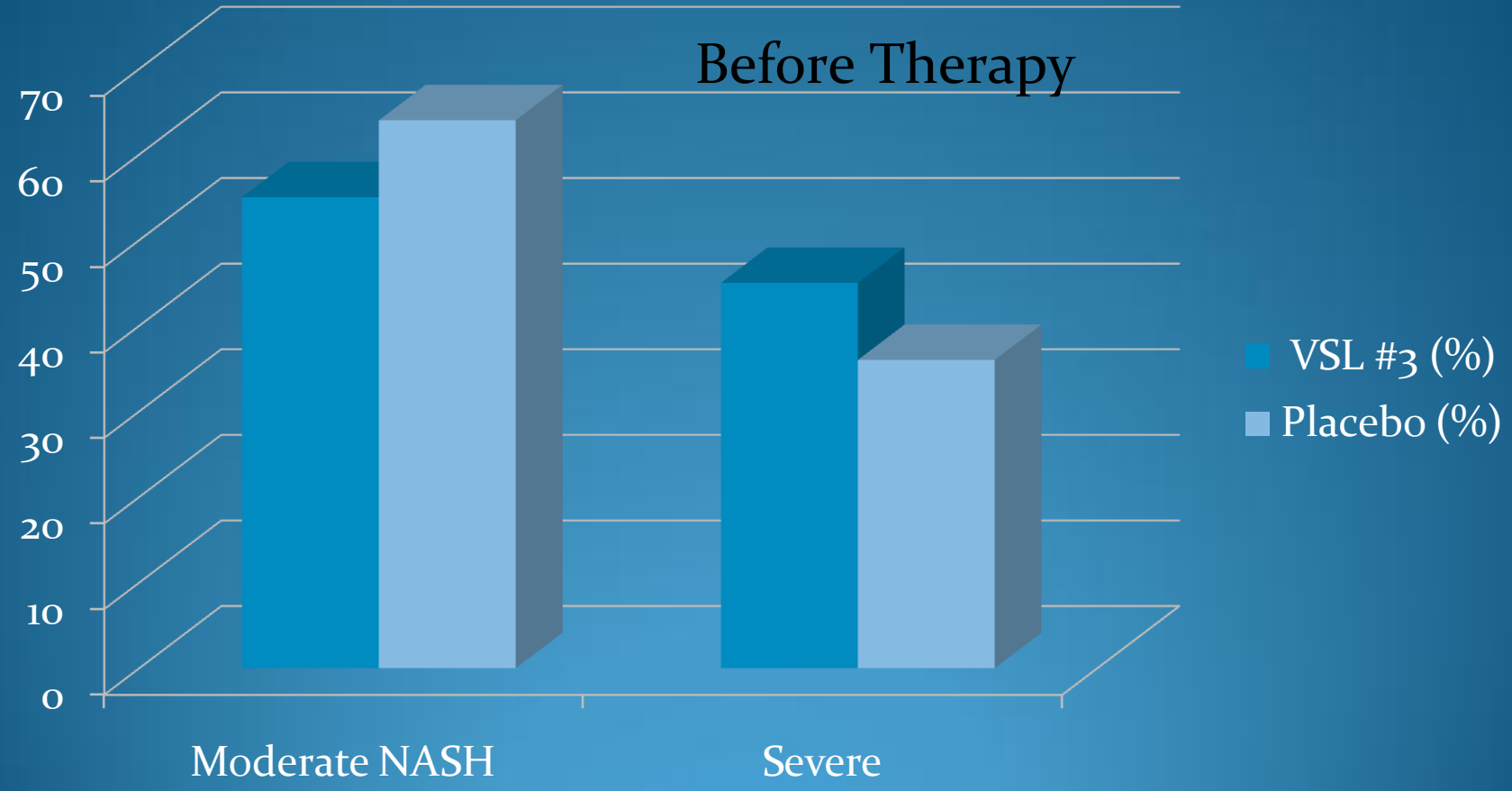
9.) GI & Hepatology News; vol. 9, No 5. May, 2015: 1 & 30

RCT: The Benefit of VSL #3 in Obese Children w NASH

- 44 children w biopsy proven NASH DB -RCT to VSL #3 or Placebo.
- Study duration of 4 months then assessed for US changes for Fatty Liver.
- Also assessed changes in Trigly, Insulin Resistance, ALT, BMI, GLI-1, and Activated GLP-1.

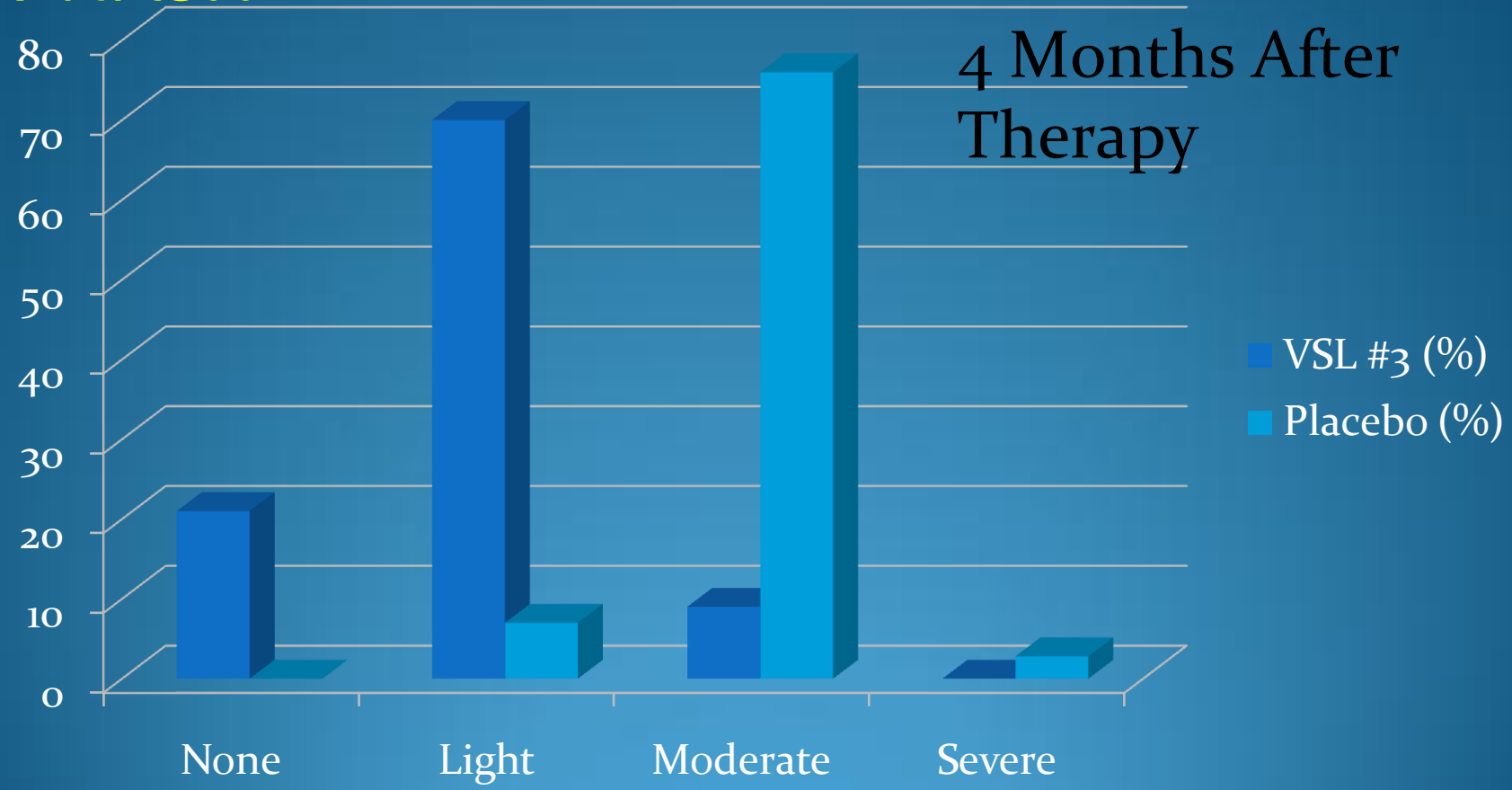
A. Alisi, et.al., Aliment Phar Therapy: June; 39(11) 1276-1285.doi 10.1111/apt.12758

RCT: The Benefit of VSL #3 in Obese Children w NASH



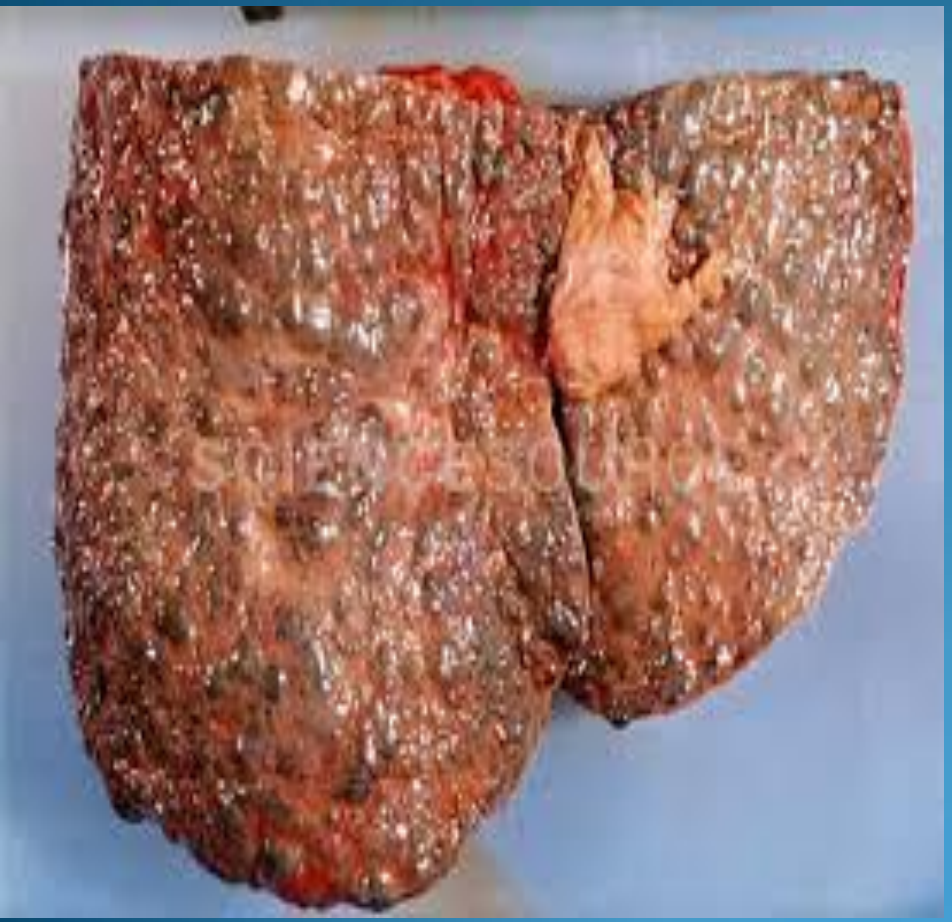
A. Alisi, et.al., Aliment Phar Therapy: June; 39(11) 1276-1285.doi 10.1111/apt.12758

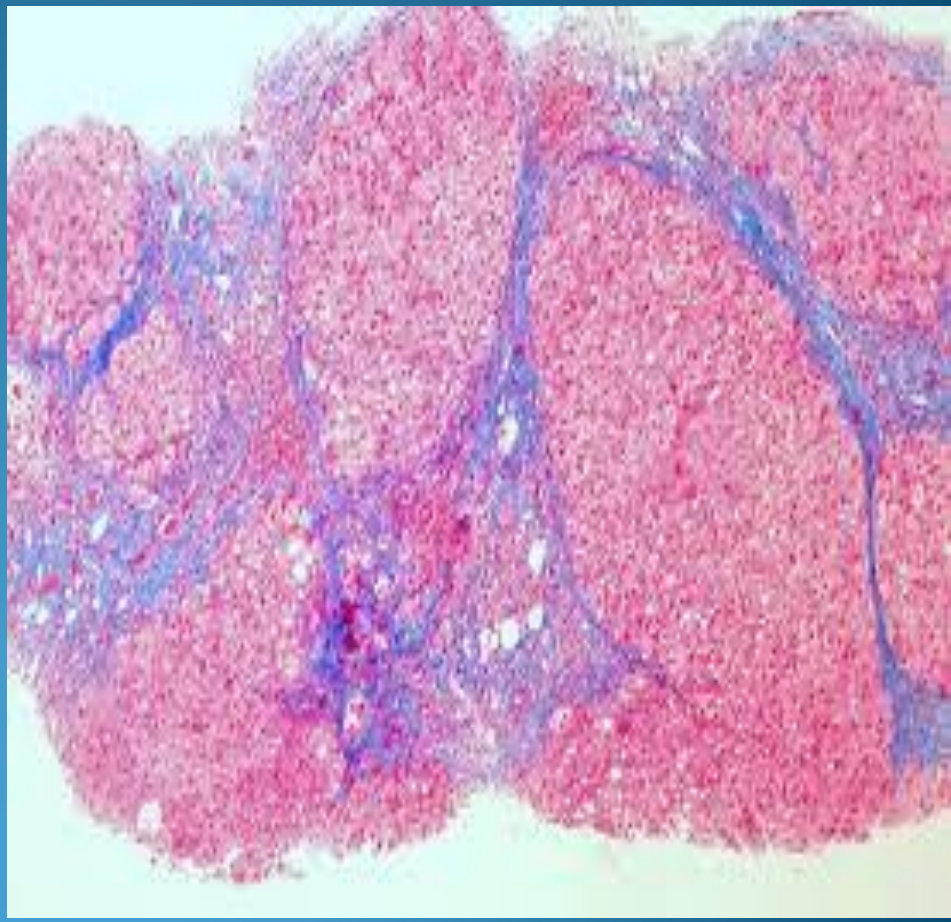
RCT: The Benefit of VSL #3 in Obese Children w NASH



10.) A. Alisi, et.al., Aliment Phar Therapy: June; 39(11) 1276-1285.doi 10.1111/apt.12758

Progression of NASH to Cirrhosis and How do we Score Fibrosis?





Scoring Techniques

- Gold Standard considered Biopsy but this has a 15-20% sampling error
- FIBROSpect II: a Blood Test which claims “up to” 90% accuracy and 95% sensitivity (Scored: 0-4) from Prometheus Labs
- FibroScan® also called transient elastography is a painless/easy/bedside scoring of Fibrosis.
  - Works by measuring shear wave velocity. In this technique, a 50-MHz wave is passed into the liver from a small transducer on the end of an ultrasound probe

Scoring Techniques

- Magnetic Resonance Elastography -**MRE**: noninvasive functional MR imaging method for detecting and staging liver fibrosis.

Increased shear stiffness measured on MRE is associated with increased severity of the fibrotic process. In addition, MRE has a relatively high sensitivity and specificity for predicting the stage of hepatic fibrosis

Fibrosis Scoring Summary

- MRI and MRE are better than liver biopsy for quantifying Fat and fibrosis
  - Noninvasive, Quantitative, Accurate, and Precise for Fibrosis Assessment.
- FibroScan® can be done in the office, easy to use, and should be able to make access more easily available if reimbursements come into line. It is limited by: Ascites, Obesity, and Acute Inflammation, and Cirrhosis.

What To Do When All Your Efforts To Treat NASH Fails

- ***"When all else fails, complicate matters".***

Quote from Aaron Alston

What To Do When All the Above Fails

- **Bariatric Surgery**

- Some patients can't or won't lose weight
  - 10% weight loss leads to resolution of NASH
  - 5-7 % weight loss leads to improvement in NASH

Moving Fast With Hepatocellular Disease

Alcoholic Hepatitis

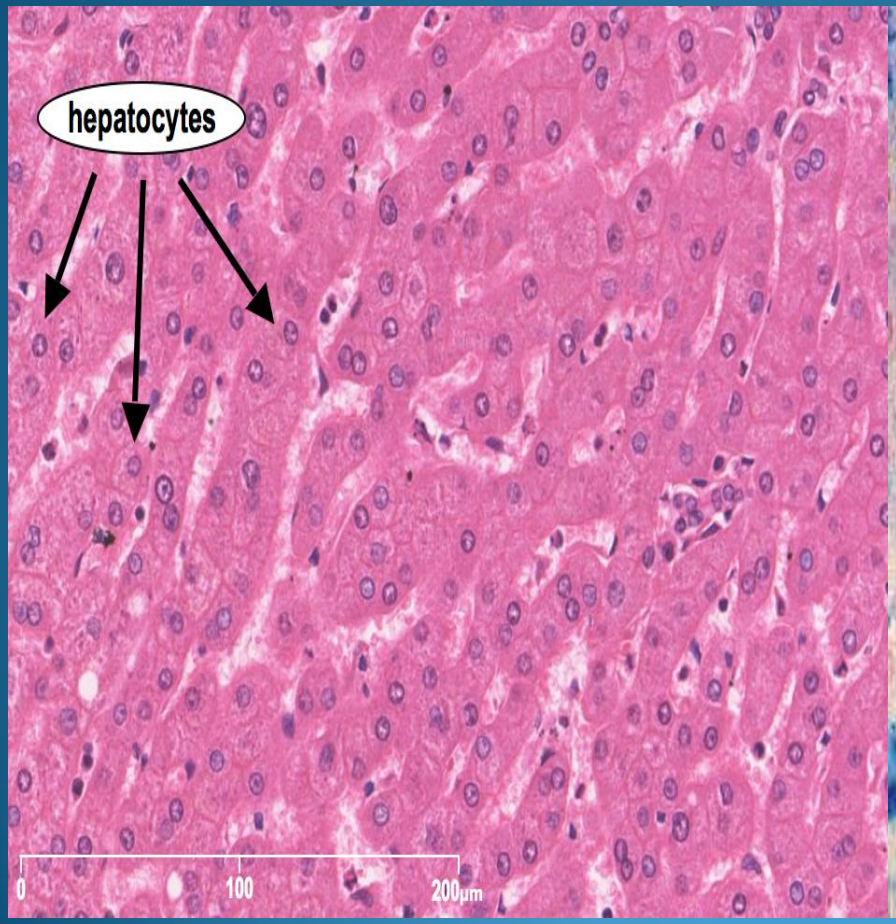
- Primarily Hepatocellular changes with AST > ALT (if ratio > 2:1 then highly suggestive)
- Late phase when they quit drinking and are jaundiced is Cholestatic and can last months
- Treatment is cessation of Alcohol and Nutritional
- If they satisfy "Maddrey Criteria" (4.6 x (PT test - control))+ S.Bilirubin in mg/dl), If score > 32 then 1 month mortality 35-45%
- Candidate for Pentoxifylline if score >32 (no steroids)

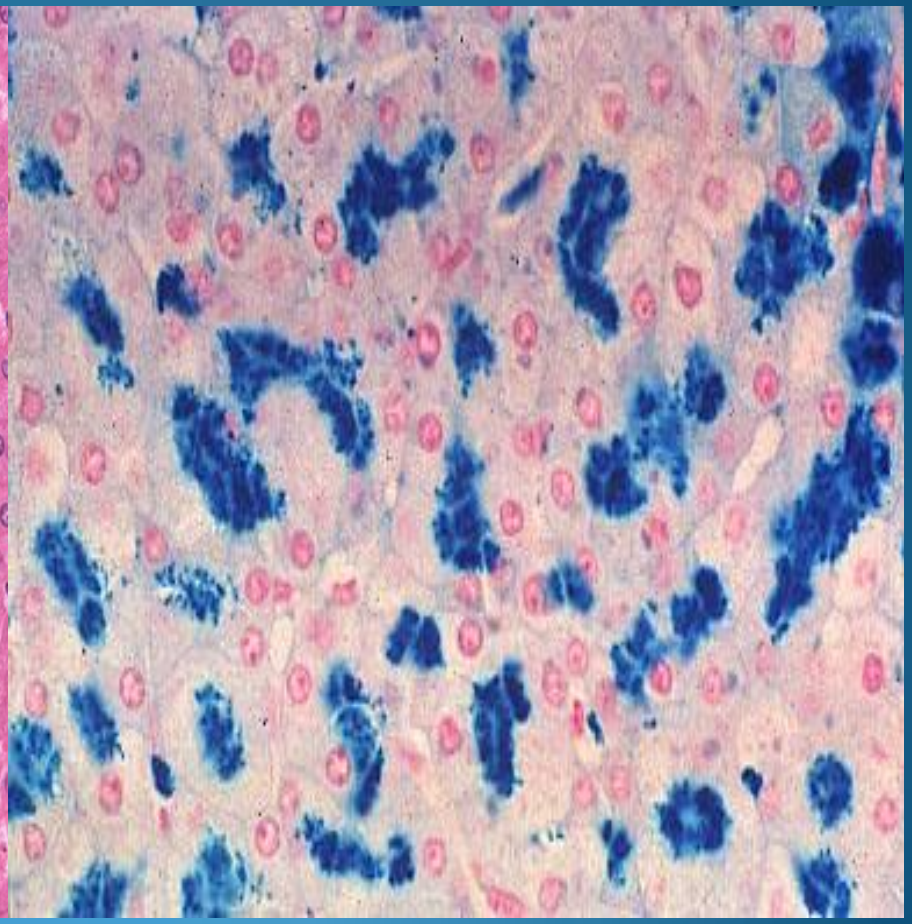
13.) NEJM 2015; 372: 1619-1628, April 2015

AutoImmune Hepatitis
AIH

- Presents as Acute Hepatitis, Chronic, or Fulminant
- Elevated Aminotransferases (primarily Hepatocellular)
- Elevated IgG, ANA, ASMA, Anti-LKM, or anti-Soluble liver antigen
- Liver Biopsy is mandatory looking for typical Plasma Cell infiltration
- If signs of decompensation then transfer to Transplant Center
- Typically treated with lifelong Prednisone & Imuran

Hemochromatosis



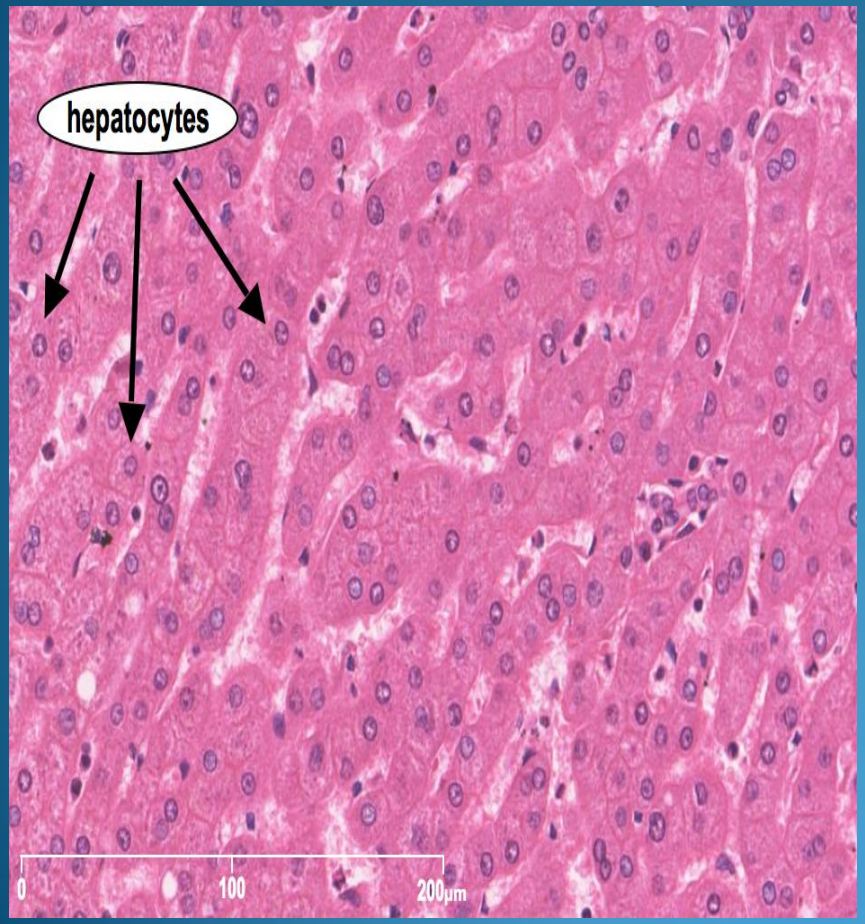


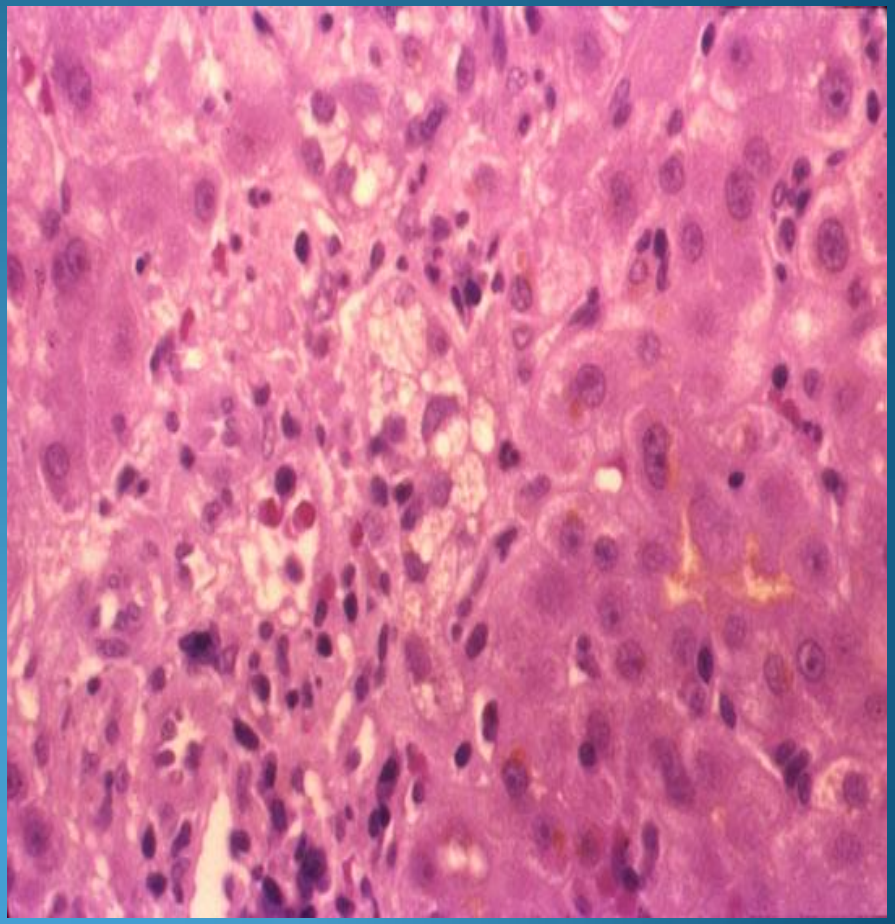
Hemochromatosis

- Most common genetic disorder with 1:9 carriers
- Iron Sat > 45% or Ferritin >200 ng/ml in men and >150 ng/ml in females
- Genetic analysis: C282Y, H63D, S65C
- Heterozygote's Don't get Disease 90% of the time
- Genetic analysis is very helpful in screening children
- Phlebotomy prevents end organ damage
- If aminotransferases normal then no liver Biopsy

AASLD guidelines 2011

Normal vs. Cholestasis





GilBert's Syndrome

- Glucuronyl Transferase Deficiency
- Problem with conjugating the Bilirubin which leads to a problem with transporting it out of the hepatocyte into the bile canaliculi
- Rise in Indirect/Unconjugated Bilirubin <3.5 mg/dl
- Not associated with disease – benign condition
- Precipitated by: fasting, stress, pneumonia,…
- You must rule out hemolysis

Cholestatic Diseases

- Primarily Elevation of Bilirubin and Alk Phos associated with pruritus
- Drugs: BCP's, Anabolic Steroids, captopril, dicloxacillin, nafcillin, amoxicillin-clavulanate, erythromycin, chlorpromazine, naproxen, and terbinafine, 6 MP, APAP, Psychotropic's, etc…
- Stones with Obstructed Bile Ducts
- Cancers
- Rare: Primary Biliary Cirrhosis or Primary Sclerosing Cholanagitis

Cholestatic Liver Disease Evalulation

- After Med's eliminated you have to rule out stones and or cancer.
- Ultrasound and CT are complimentary. What ones sees the other may not. Don't be mislead that if first screen test is read normal and patient's tests worsens you need to do the other.
- If these are eliminated then they need referral to exclude granulomatous disease, PBC, PSC, infiltrative diseases or cancer

Bile Duct Obstruction

- Biliary Dilatation: Intra and/or Extrahepatic
  - Precholecystectomy: CBD < 6-7 mm.
  - Postcholecystectomy: CBD up to 10 mm.
  - Focal dilatation

24 yr Old Female in ED With Mostly Midline Pain Radiation to Back. Mild RUQ Pain for 5 Days. BMI 23.

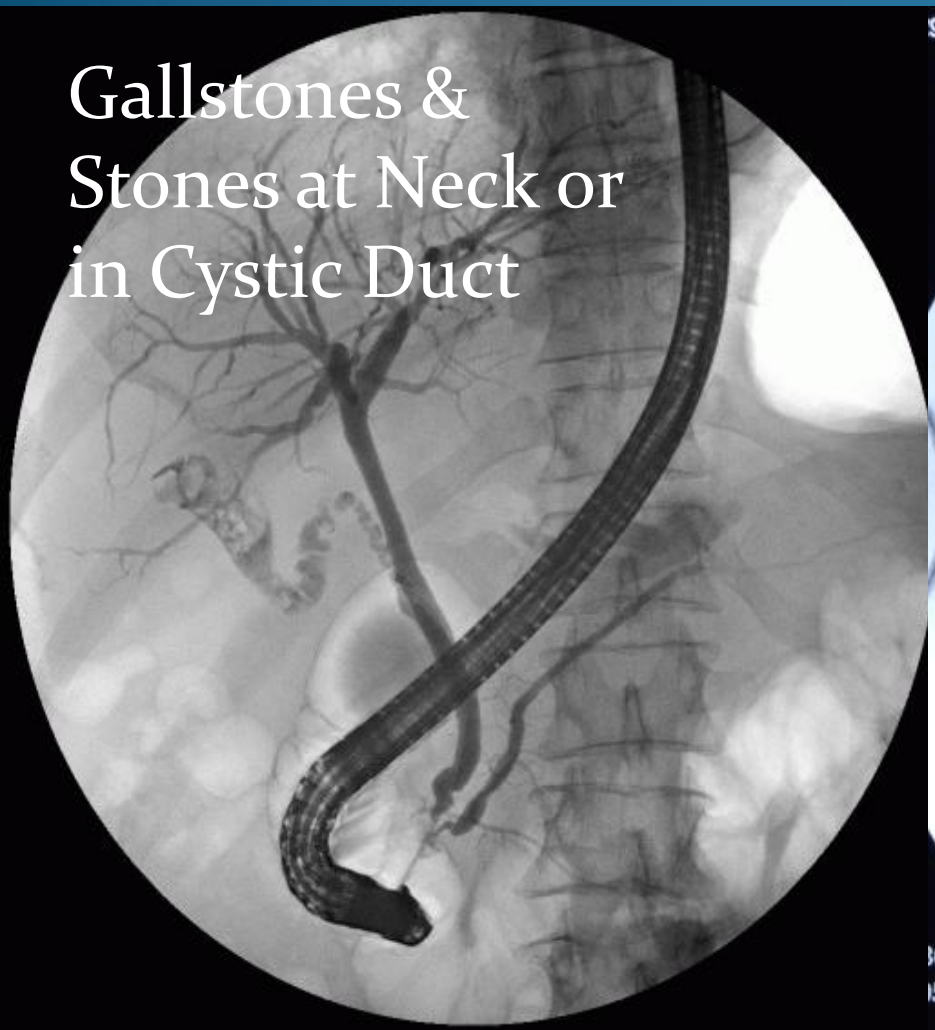
- AST=74, ALT=190, T-bili=1.7 (0.7 Direct) ALK-P=150 (<130). Normal CBC.
- US: cholelithiasis w ? Stone in Neck of Gallbladder. CBD normal and no evidence of Intrahepatic BIL DIL. No GB wall thickening of pericholecystic fluid.
- Sonographer reports "No Murphy's Sign".

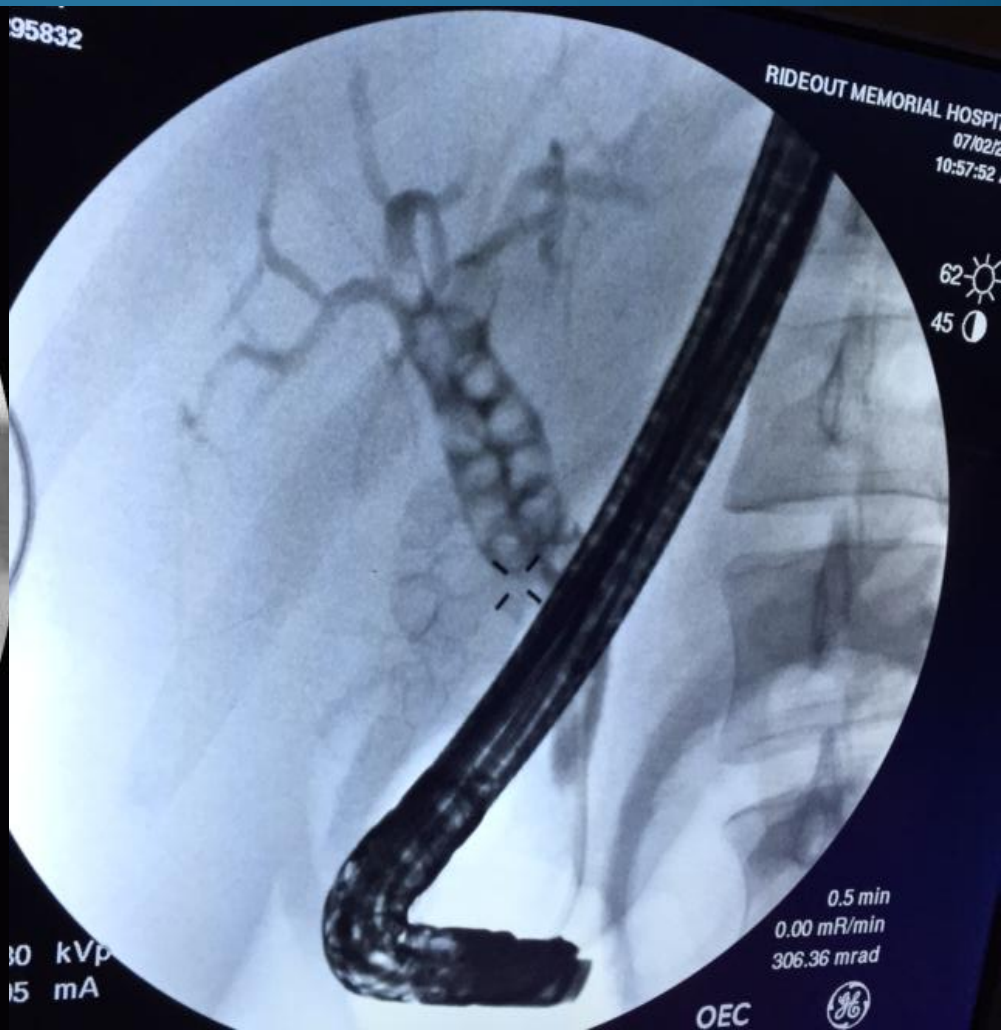
What is your next test/move and why?

AASLD guidelines 2011

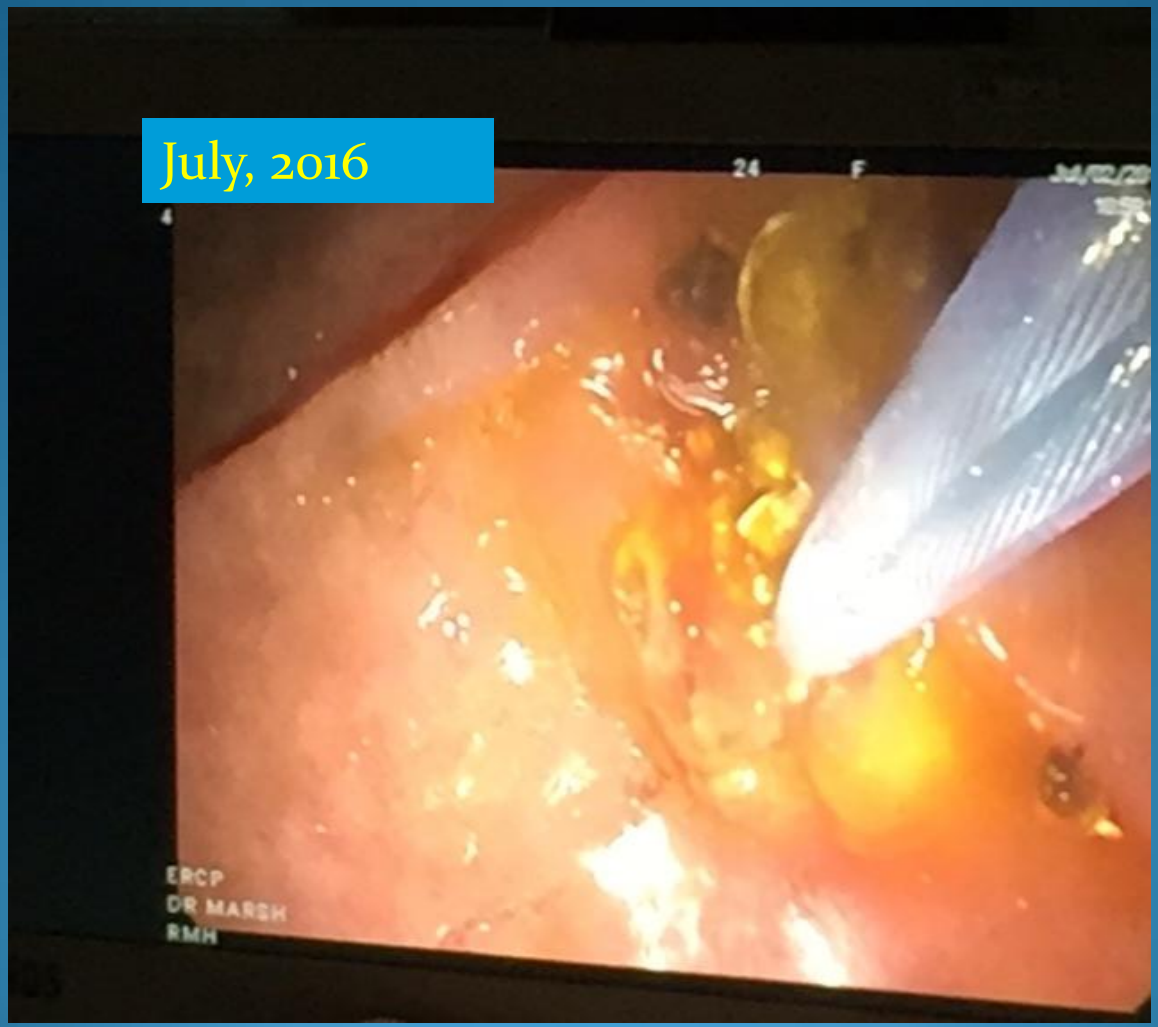
ERCP Images of Bile Duct Dilatation

Gallstones &
Stones at Neck or
in Cystic Duct





ERCP Image of Stone Removal



Summary

- Think, is this Hepatocellular or Cholestatic?
- Keep in Mind ALT <30 for men and < 20 When normal BMI
- See back sooner: If new abnormal don't recheck in again in one month
- Fatty Liver is a version of Metabolic Syndrome. Modified Low Carb Diet, mild – mod exercise, VSL#3, with more drugs to come. (Think Liposomal Acid Lipase Level: deficiency mimics Fatty Liver Disease)
- Be very careful with Cholestatic changes
- Be very careful with Surveillance for HCC