Maximizing Diagnostic Value & Efficiency for Abnormal LFTs in the Primary Care Setting

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Disclosures

No conflicts of interest to disclose

Learning Objectives

At the completion of today's talk, physicians will:

1. Recognize high value practices in evaluating and referring patients with abnormal liver enzymes

2. Identify essential components of the diagnostic evaluation of abnormal liver enzymes

3. Apply high value principles to complex patients requiring co-management by liver specialists

https://www.ncbi.nlm.nih.gov/pubmed/27995906

ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries

Paul Y. Kwo, MD, FACG, FAASLD[1], Stanley M. Cohen, MD, FACG, FAASLD[2] and Joseph K. Lim, MD, FACG, FAASLD[3]

https://www.ncbi.nlm.nih.gov/pubmed/27995906

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AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Home > Publications > Practice Guidelines > Practice Guidelines

Practice Guidelines

Alcoholic liver disease
NAFLD/NASH
Autoimmune hepatitis
Hepatitis B virus
Hepatitis C virus
Hemochromatosis
Primary biliary cholangitis
Primary sclerosing cholangitis
Wilson's disease

https://www.aasld.org/publications/practice-guidelines

What is normal…?

ACG 2016 Guidelines

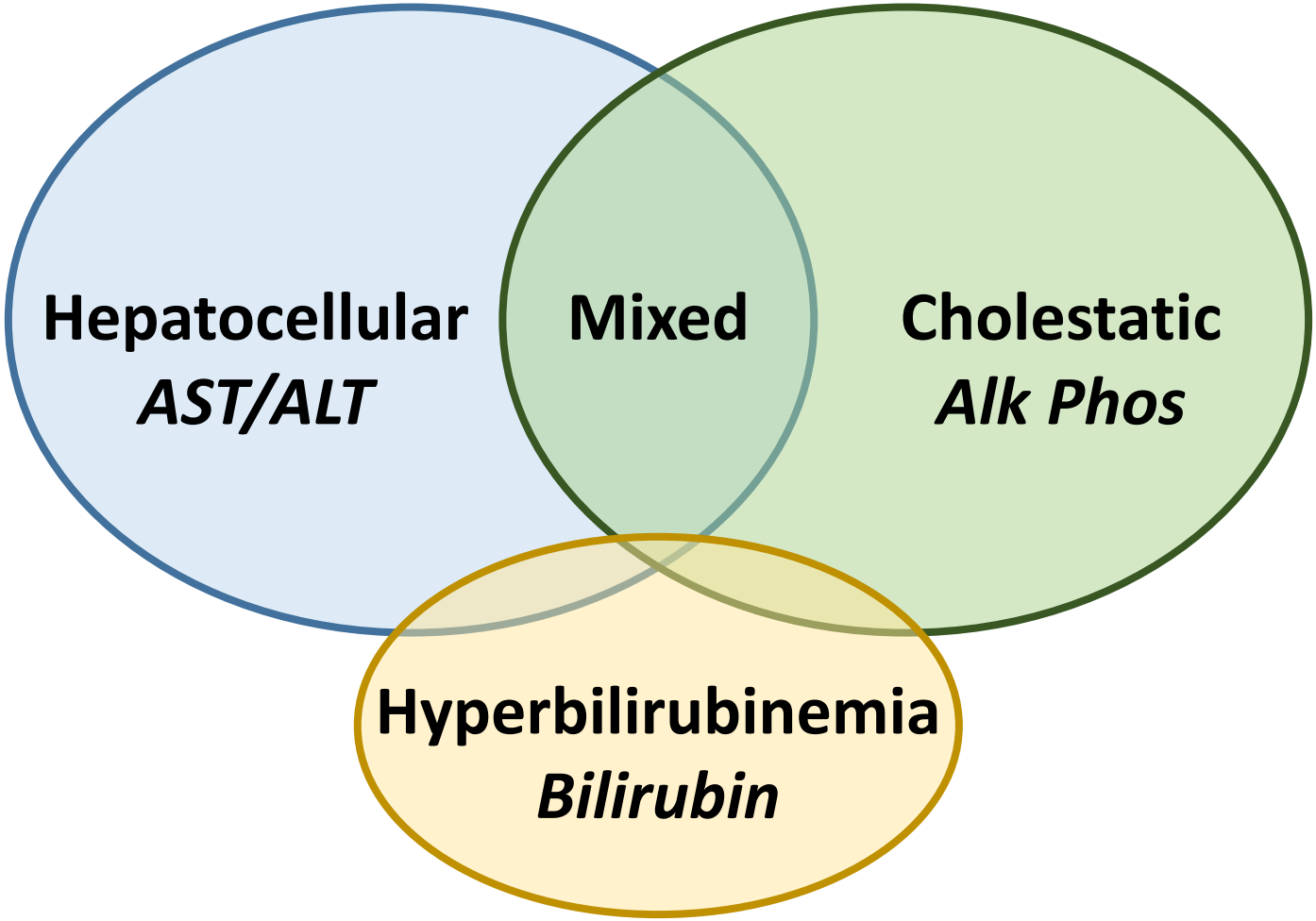
"A true healthy normal ALT level in prospectively studied populations without identifiable risk factors for liver disease ranges from 29 to 33 IU/l for males and 19 to 25 IU/l for females, and levels above this should be assessed by physicians"

"Clinicians may rely on local lab ULN ranges for alkaline phosphatase and bilirubin"

Kwo PY et al. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. AJG 2017

Critical to characterize pattern…

Abnormal LFT 101

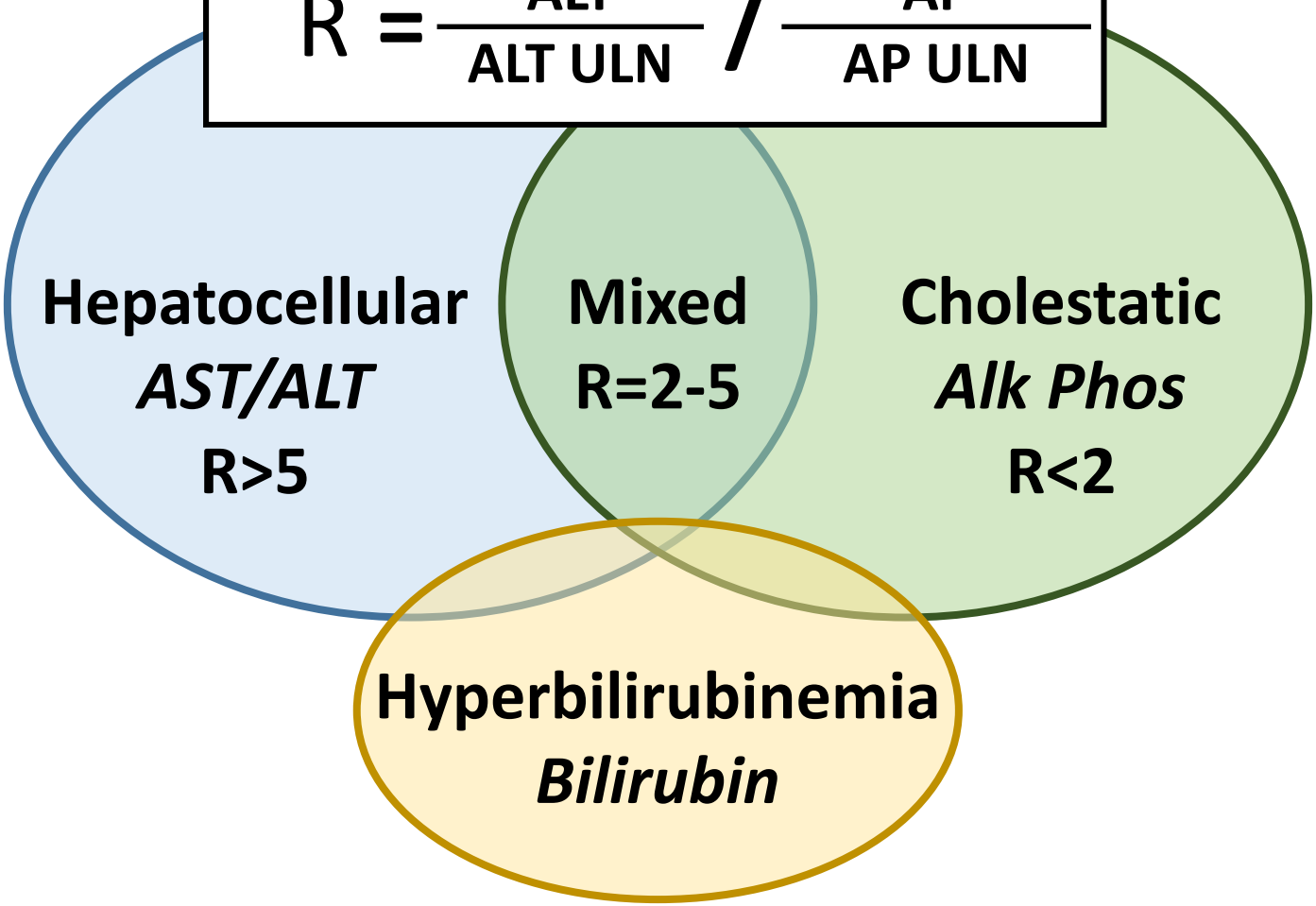


Kwo PY et al. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. AJG 2017

Critical to characterize pattern…

Abnormal LFT 101

$$R = \frac{\text{ALT}}{\text{ALT ULN}} / \frac{\text{AP}}{\text{AP ULN}}$$

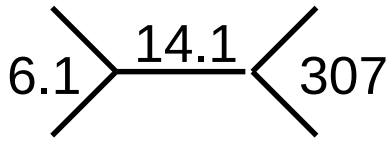


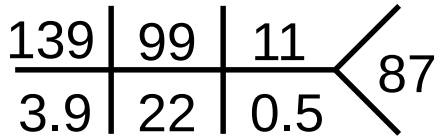
Kwo PY et al. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. AJG 2017

HEPATOCELLULAR INJURY PATTERN

Case #1

A 45-year old woman presents to your clinic for her annual exam. Her PMH is notable for hypothyroidism and obesity (BMI 31). Her only medication is levothyroxine. Routine labs reveal the following:





Ca 8.6

AST	79
ALT	67
TB	0.5
AP	116
Alb	4.2
TP	7.9

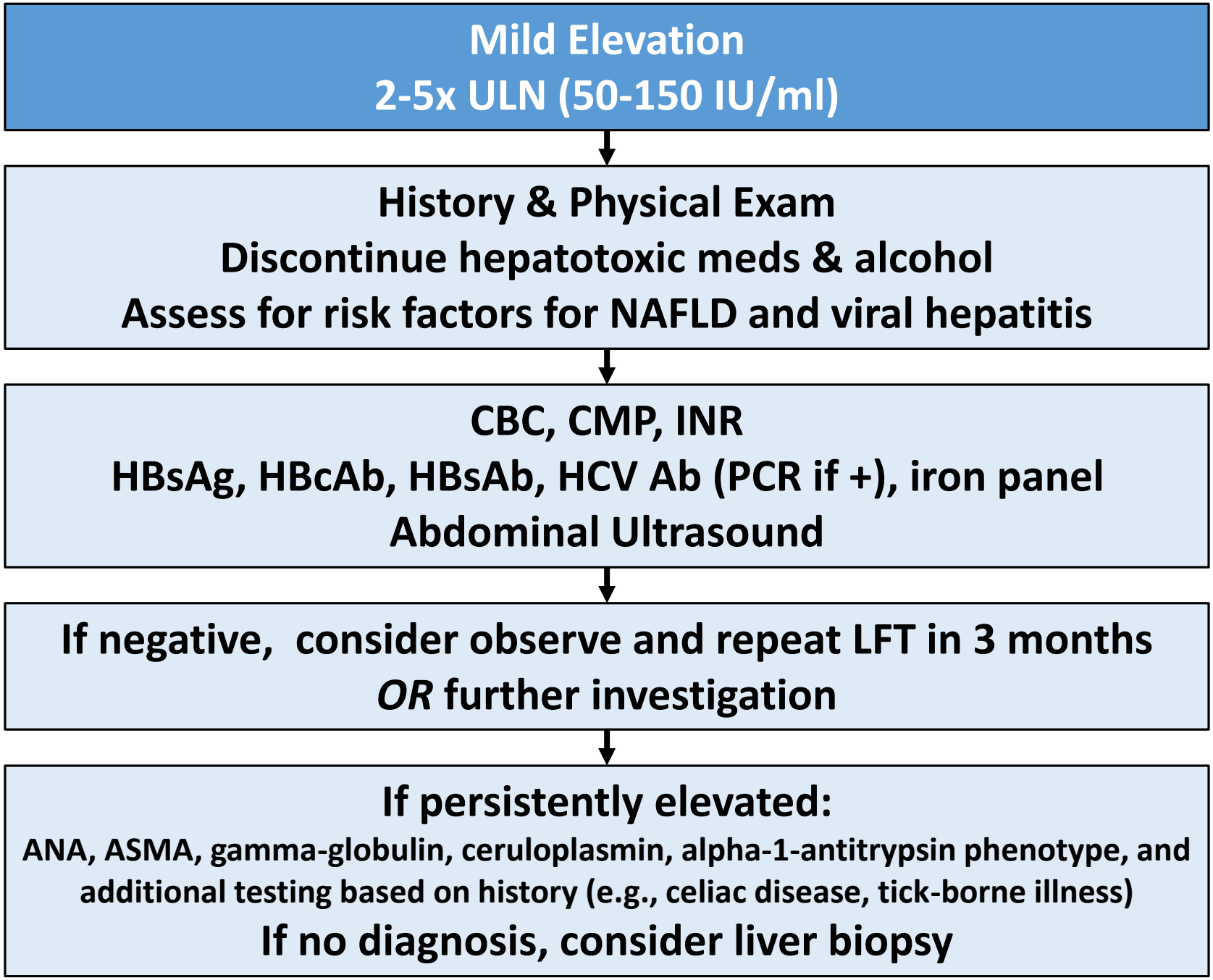
HgA1c 5.1
TSH 1.98

Total cholesterol 215
LDL 141, HD 59, TG 132

Case #1

What do you hypothesize is the most likely cause of this patient's abnormal liver enzymes?

A. Alcohol-related liver disease
B. Non-alcoholic steatohepatitis
C. Chronic hepatitis C infection
D. Autoimmune hepatitis



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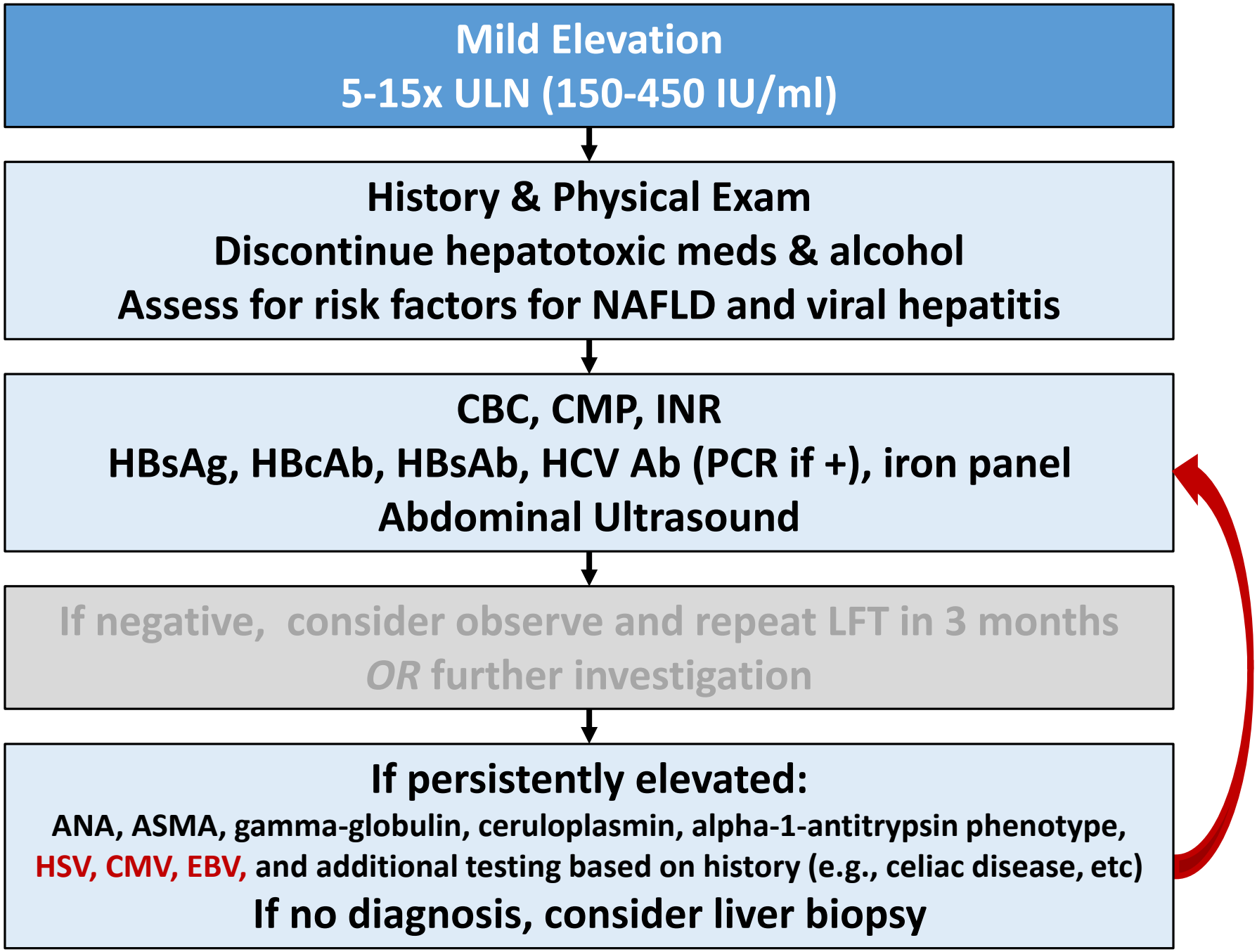

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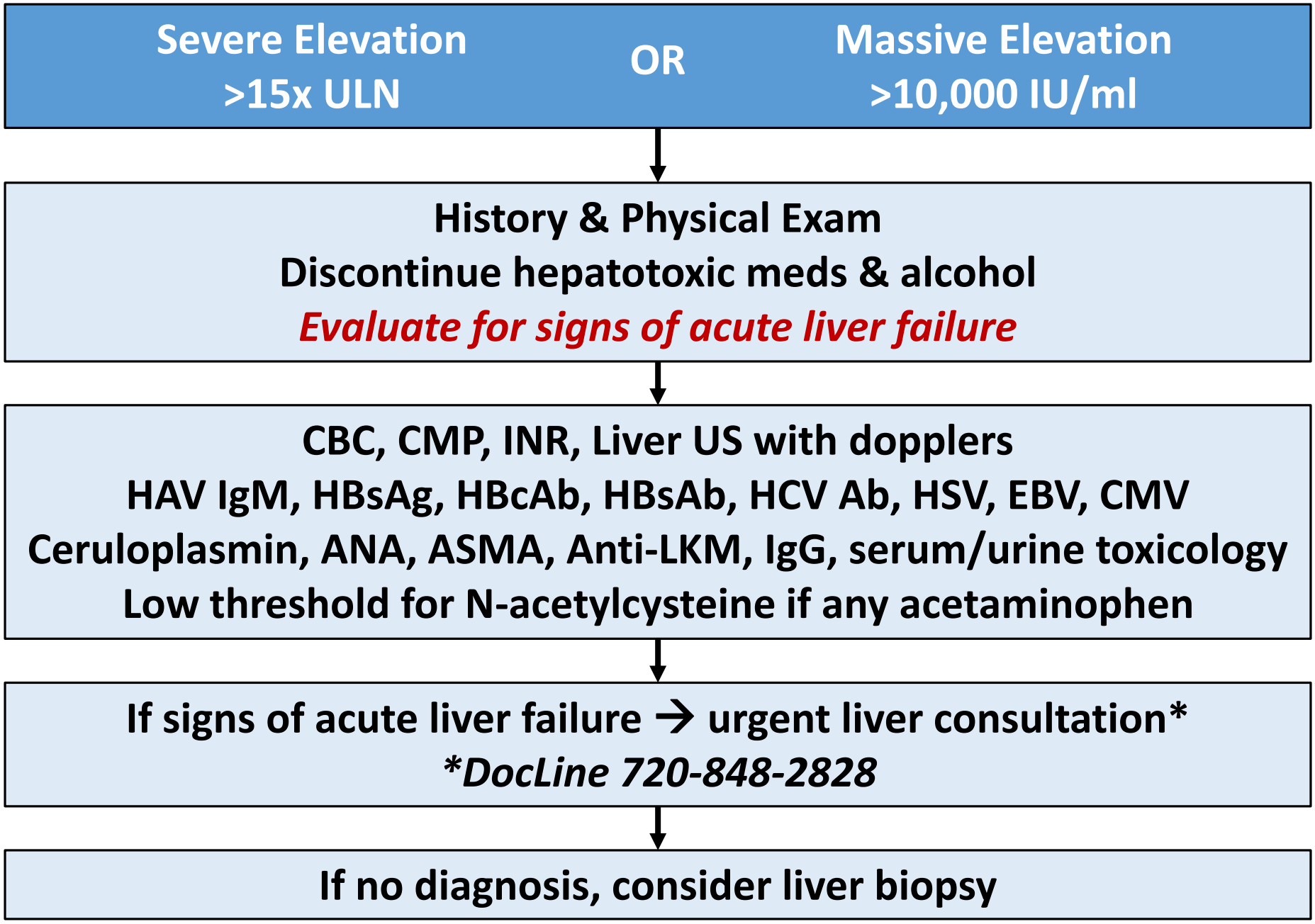


Kwo PY et al. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. AJG 2017

Performance metric of diagnostic tests

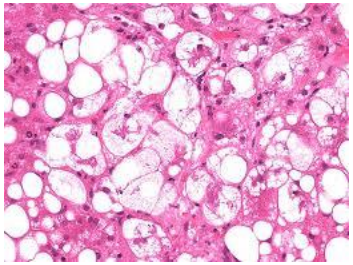
Non-alcoholic steatohepatitis (NASH) vs Alcohol-related SH (ASH)

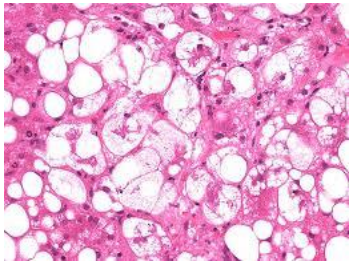
NASH

- Prevalence = 1.5-6.5%
- ALT>AST (<10X ULN, 300 IU/ml)
- Metabolic risk factors
- No serologic testing

ASH

- Prevalence = 1.4%
- AST:ALT 2:1 (<10X ULN, 300 IU/ml)
- >40g alcohol/day (drink = 12g)
- **Phosphatidylethanol (PETH)**
  - **Moderate-heavy use past 30d**





Histologically indistinguishable!

Chalasani N et al. AASLD NAFLD Guidelines. Hepatology 2018
O'Shea R et al. AASLD ALD Guidelines. Hepatology 2010

Performance metric of diagnostic tests

Hepatitis B virus

- Prevalence (based on endemnicity):
  - Low = <2%
  - Intermediate = 2-7%
  - High = >8%
- Progress to chronic infection
  - Vertical = >90%
  - Childhood = 5-25%
  - Adult = <5%

Terrault N et al. AASLD HBV Guidelines. Hepatology 2018

Performance metric of diagnostic tests

Hepatitis B virus

- Serologic testing:
  - HBsAg = acute or chronic infection
  - HBcAb = IgM window period, IgG prior exposure*
  - HBsAb = immune
  - HBeAg = replicating virus
  - HBV DNA = viremic

Not all patients with detectable ***HBV DNA*** need antiviral therapy

Some patients with ***HBcAb+ and negative DNA*** need antiviral therapy

Terrault N et al. AASLD HBV Guidelines. Hepatology 2018

Performance metric of diagnostic tests

Hepatitis C virus

- US Prevalence (1.2% or 3.5 million w chronic HCV):
  - Birth cohort = 5%
  - Hemodialysis = 8%
  - PWID = >60%
- HCV antibody test:
  - 5-32% false-positive rate, associated with LVAD
  - 20% of patients will spontaneous clear virus
  - Takes up to 6 months to seroconvert

Always check HCV RNA PCR if antibody screen positive or concern for acute infection with negative antibody screen

Patel PR et al. Am J Kidney Dis 2010
Moorman AC et al. J Clin Vir 2017
Armstrong GL et al. Ann Intern Med. 2006
Midgard H et al. J Hep 2016

Performance metric of diagnostic tests

Epstein-Barr virus (EBV) and Cytomegalovirus (CMV)

- Prevalence:
  - EBV seroprevalence = 90-95%
  - CMV seroprevalence = 50.4%
- Serologic tests:
  - EBV – EBV DNA, EBV IgM
  - CMV – CMV DNA, CMV IgM, 4-fold increase in IgG

Always check CMV and EBV <u>DNA</u> if evaluating for acute viral hepatitis

Performance metric of diagnostic tests

Hereditary hemochromatosis

Ferritin is secreted by activated hepatic macrophages
Non-specific for hemochromatosis in the setting of liver inflammation

Performance metric of diagnostic tests

Hereditary hemochromatosis

- Prevalence: RARE – 0.2-0.5%
- Subtypes:
  - **Type 1 – HFE gene mutation**
  - Type 2 – HJV gene mutation
  - Type 3 – TFR2 gene mutation
  - Type 4 – SLC40A1 gene mutation
- Penetrance:
  - Only 10% of C282Y homozygotes develop iron overload

VanWagner L, Green R. Elevated Serum Ferritin. JAMA 2014
Bacon BR et al. AASLD Hemochromatosis Guidelines. Hepatology 2011
Crownover BK et al. Am Fam Physician 2013

Performance metric of diagnostic tests

Hereditary hemochromatosis

- Screening:
  - Transferrin Saturation >45% or Ferritin >ULN
    - NPV of TS <45%, Ferritin <200 = 97% (20% PPV)
    - Ferritin >1000 associated with advanced disease if HH
- Diagnostic test:
  - HFE gene mutation
    - C282Y/C282Y – Tissue iron overload
    - C282Y/H63D or C282Y/S65C – *RARELY* tissue iron overload
    - C282Y/WT or H63D/WT or S65C/WT – *NO* Tissue iron overload
    - H63D/H63D or S65C/WT – *NO* tissue iron overload
  - Hepatic iron quantification (MR or Liver biopsy)

VanWagner L, Green R. Elevated Serum Ferritin. JAMA 2014
Bacon BR et al. AASLD Hemochromatosis Guidelines. Hepatology 2011

Performance metric of diagnostic tests

Wilson's Disease

- Prevalence: RARE – 0.003% (age <55)
- Screening:
  - Ceruloplasmin <20 mg/dL
  - AP:TB <4 (94% Sens, 96% Spec in acute WD)
- Diagnostic test:
  - Hepatic copper content
  - Serum free and 24h urine copper
  - Keyser-Fleischer rings
  - ATP7B mutation testing

Roberts EA et al. AASLD Wilson's Disease Guidelines. Hepatology 2008
Korman JD. Screening for WD in ALF. Hepatology 2008

Performance metric of diagnostic tests

Alpha-1-Antitrypsin Deficiency

- Prevalence: RARE – <0.003%
- Screening:
  - A1AT level
    - If low, proceed with gene testing
    - If undetectable (null mutation), NO liver disease
- Diagnostic test:
  - SERPINA1 mutation testing
    - PI*ZZ or PI*SZ = clinical liver disease
    - PI*MZ or PI*MM = NO clinical liver disease
  - Liver biopsy – PAS-D granules

Roberts EA et al. AASLD Wilson's Disease Guidelines. Hepatology 2008
Korman JD. Screening for WD in ALF. Hepatology 2008

Performance metric of diagnostic tests

Celiac Disease

- Prevalence = **9%** of patients with abnormal LFT
  - 15-55% of patients with Celiac have abnormal LFT
- Diagnostic test:
  - Anti-Tissue Transglutaminase antibody
    - IgA (if IgA is normal)
    - IgG (if IgA is low)
  - Sensitivity 81-100%, Specificity 97-99%
- LFT should normalize on gluten-free diet

Armstrong D et al. Can J Gastro. 2011
Volta U. Clin Rev Aller Immun. 2009

Performance metric of diagnostic tests

Structural or thrombotic etiologies

- Cross-sectional imaging has a low diagnostic yield for evaluating hepatocellular injury
  - 18% yield in mild elevations
  - 31% yield in moderate-severe elevations
- If Budd-Chiari is suspected, US should be performed by experienced provider or CT/MRI

Rothschild JM et al. J Eval Clin Prac 2002
DeLeve LD et al. Vascular Disorders of the Liver. Hepatology 2008

Case #1

A 45-year old woman with hypothyroidism, obesity (BMI 31), and AST/ALT 2-5X ULN.

Initial work-up:

Liver US with dopplers – mild hepatic steatosis, otherwise normal

HAV IgM	NR	Iron	45	AST	123
HBsAg	NR	% Saturation	32	ALT	101
HBcAb	NR	Ferritin	55	TB	0.8
HBsAb	27.1			AP	102
HCV Ab	NR			Alb	4.1
				TP	8.3

Case #1

A 45-year old woman with hypothyroidism, obesity (BMI 31), and AST/ALT 2-5X ULN.

Follow-up Testing:

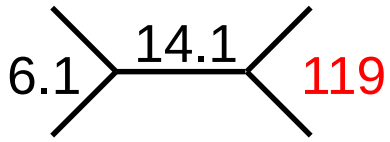
ANA	1:160	IgA	187	Ceruloplasmin	32
ASMA	1:80	TTG-IgA	<4	A1AT level	141
AMA	<1:40			A1AT Pheno	MM
IgG	2321 (H)				
IgM	132				

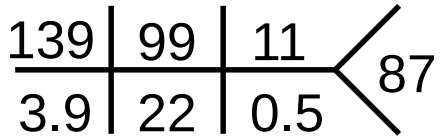
Referred to hepatologist, biopsy confirms AIH, started on azathioprine

CHOLESTATIC INJURY PATTERN

Case #2

A 67-year old woman presents to your clinic for evaluation of fatigue. The only other symptom she notes is itching, but attributes this to allergies. She is on vitamin D and calcium for osteopenia but has no other PMH. Her initial labs reveal:





Ca 8.6

AST	39
ALT	47
TB	0.9
AP	436
Alb	3.4
TP	6.6

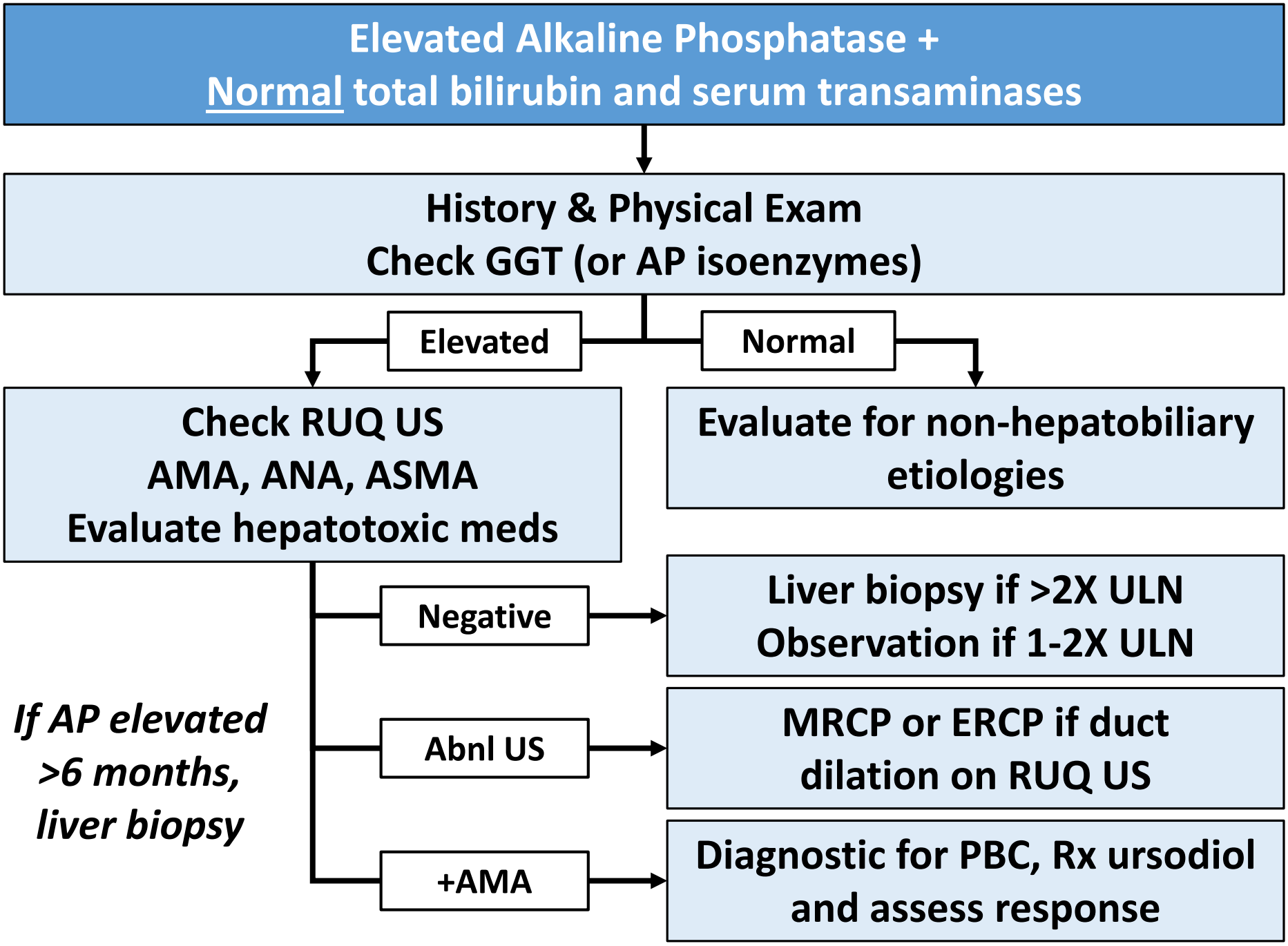
HgA1c 5.7
TSH 3.24

Total cholesterol 166
LDL 102, HD 53, TG 107

Case #2

What would be the next best diagnostic test to confirm the suspected diagnosis?

A. Anti-nuclear antibody
B. Anti-mitochondrial antibody
C. MRCP
D. Liver biopsy



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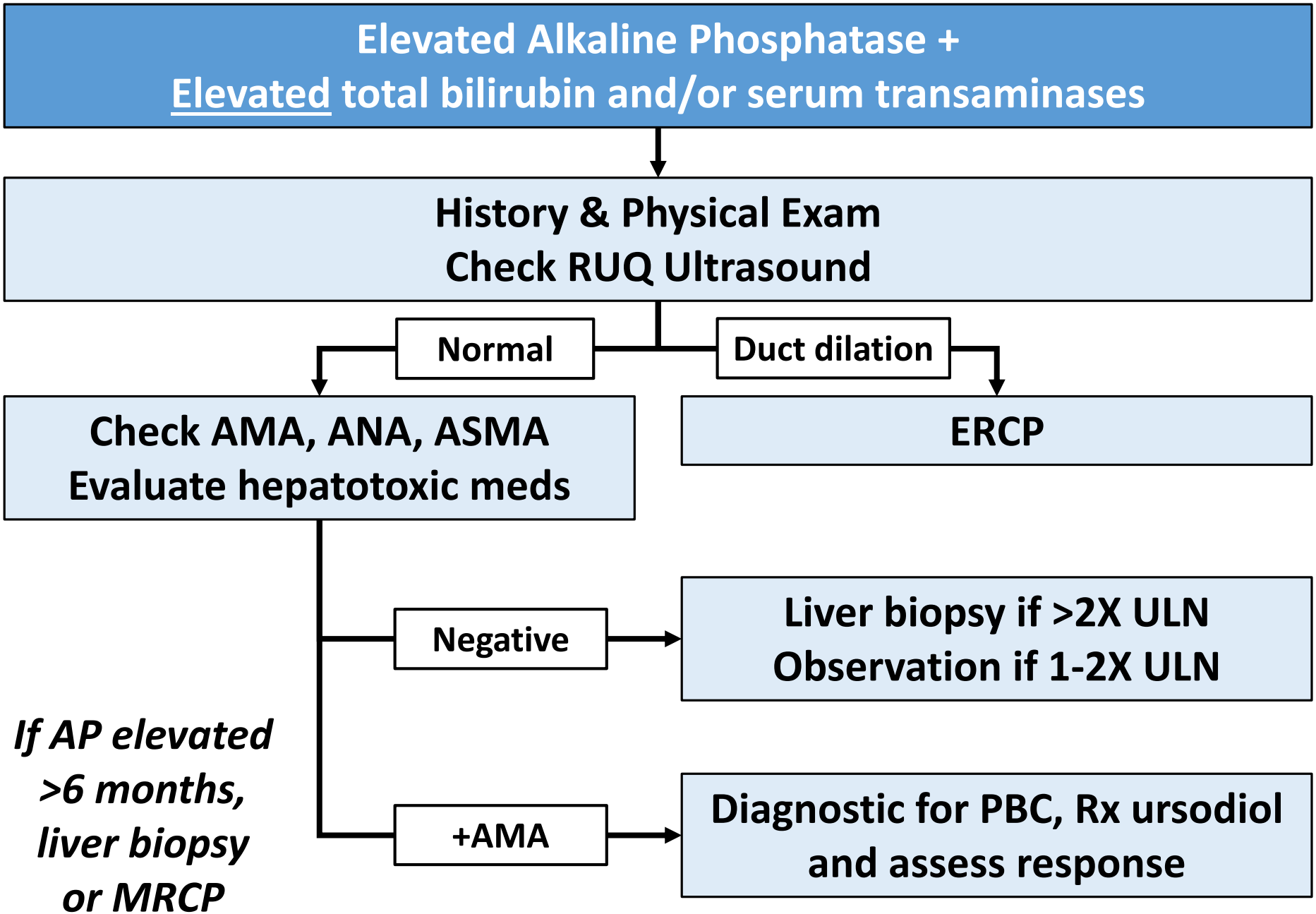


Adapted from Kwo PY et al. ACG Practice Guideline: Evaluation of Abnormal Liver Chemistries. AJG 2017

Performance metric of diagnostic tests

Primary Biliary CHOLANGITIS (PBC)

- Prevalence = RARE – 0.03%
- Screening:
  - Elevated alkaline phosphatase on LFT +/- AST/ALT
  - ANA
  - IgM
- Diagnostic test:
  - Anti-mitochondrial antibody (AMA) – Sens 87.3%, Spec 98.7%
  - Liver biopsy
    - Only in AMA Neg, AST/ALT >5X ULN, or ursodiol refractory

Lindor KD et al. AASLD PBC Guidelines. Hepatology 2009
Leung PS et al. Hepatology 1992

Performance metric of diagnostic tests

Primary Sclerosing Cholangitis (PSC)

- Prevalence: RARE – 0.006% (5% of IBD patients)
- Screening test:
  - Liver ultrasound
- Diagnostic test:
  - MRCP
    - Sensitivity 86%, Specificity 94%
  - ERCP (Only for assessment of dominant stricture or intervention)
  - Liver biopsy (Only if small duct PSC suspected)

Chapman R et al. AASLD PSC Guidelines. Hepatology 2010
Dave M et al. Radiology 2010

Case #2

A 67-year old woman with fatigue and pruritus, labs notable for cholestatic predominant pattern of liver injury and thrombocytopenia.

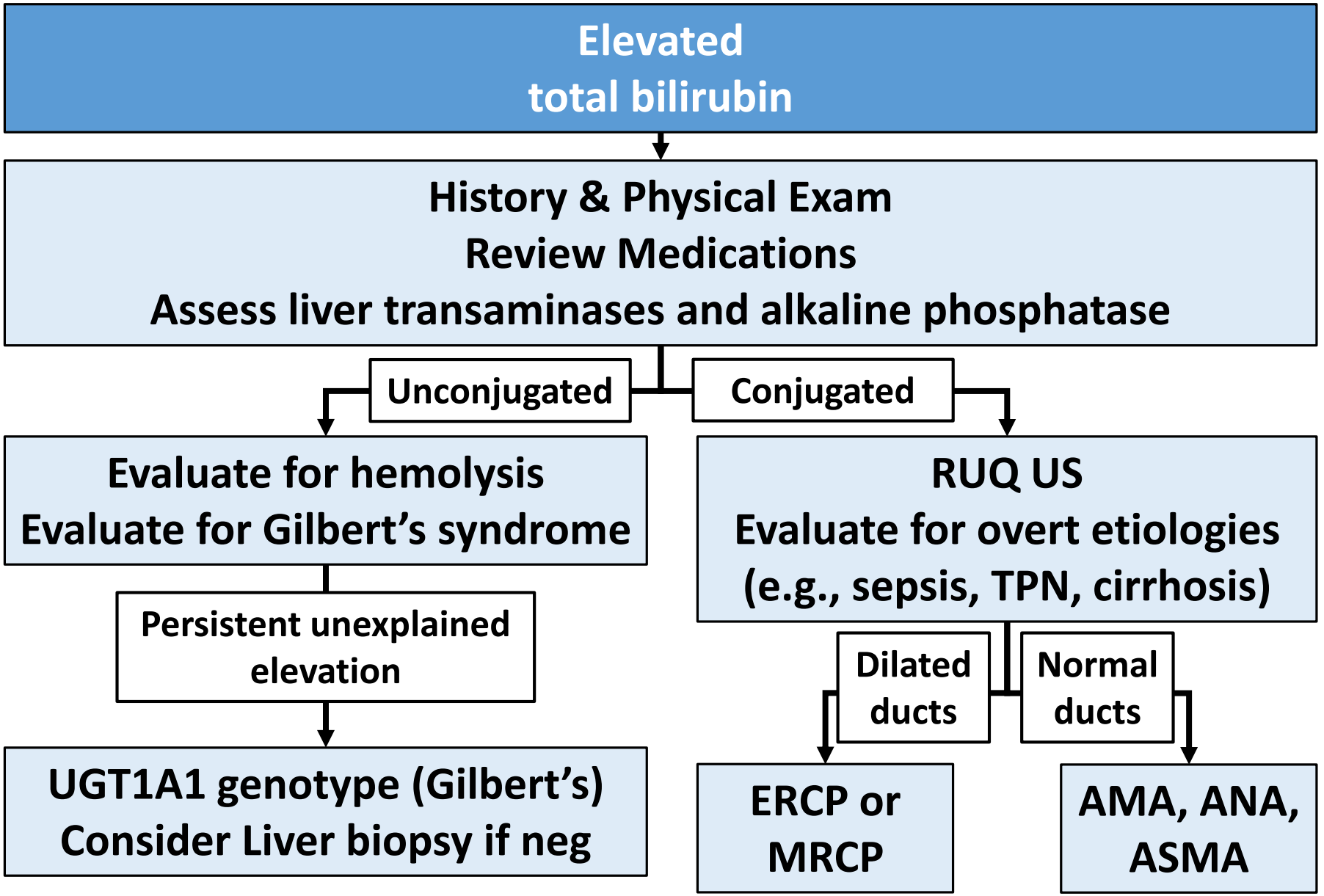
Initial work-up:

Liver US with dopplers w normal bile ducts, nodular liver, splenomegaly

HAV Total Ab	Reactive	ANA	<1:40	AST	32
HBsAg	NR	ASMA	<1:40	ALT	51
HBcAb	NR	AMA	1:320	TB	0.8
HBsAb	<3.1	IgG	1221	AP	298
HCV Ab	NR	IgM	342 (H)	Alb	3.5
				TP	6.6

Diagnosed with PBC, started on ursodiol, transient elastography confirms cirrhosis

HYPERBILIRUBINEMIA PATTERN

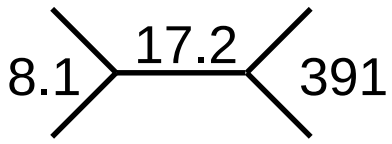


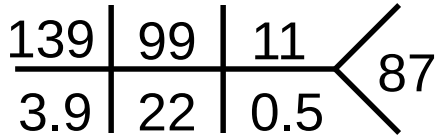
If TB remains elevated and unexplained, has upward trend, or is associated with elevated transaminases, consider liver biopsy

Adapted from Kwo PY et al. AJG 2017

Case #3

A 37-year old man presents to your clinic for evaluation of jaundice for 2 weeks. He has no PMH and received a 7 day course of amoxicillin/clavulanic acid 6 weeks ago after being diagnosed with a sinus infection at an urgent care clinic. His initial labs reveal:





Ca 8.6

INR 1.0

AST	67
ALT	51
TB	23.9
DB	13.2
AP	167
Alb	3.2
TP	6.6

Case #3

What is the next best step in managing this patient?

A. AMA
B. ERCP
C. Liver biopsy
D. Observation

https://livertox.nih.gov/

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Clinical and Research Information on Drug-Induced Liver Injury

Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-.

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Drug-induced Liver Injury (DILI) incidence = 0.001-0.0001%

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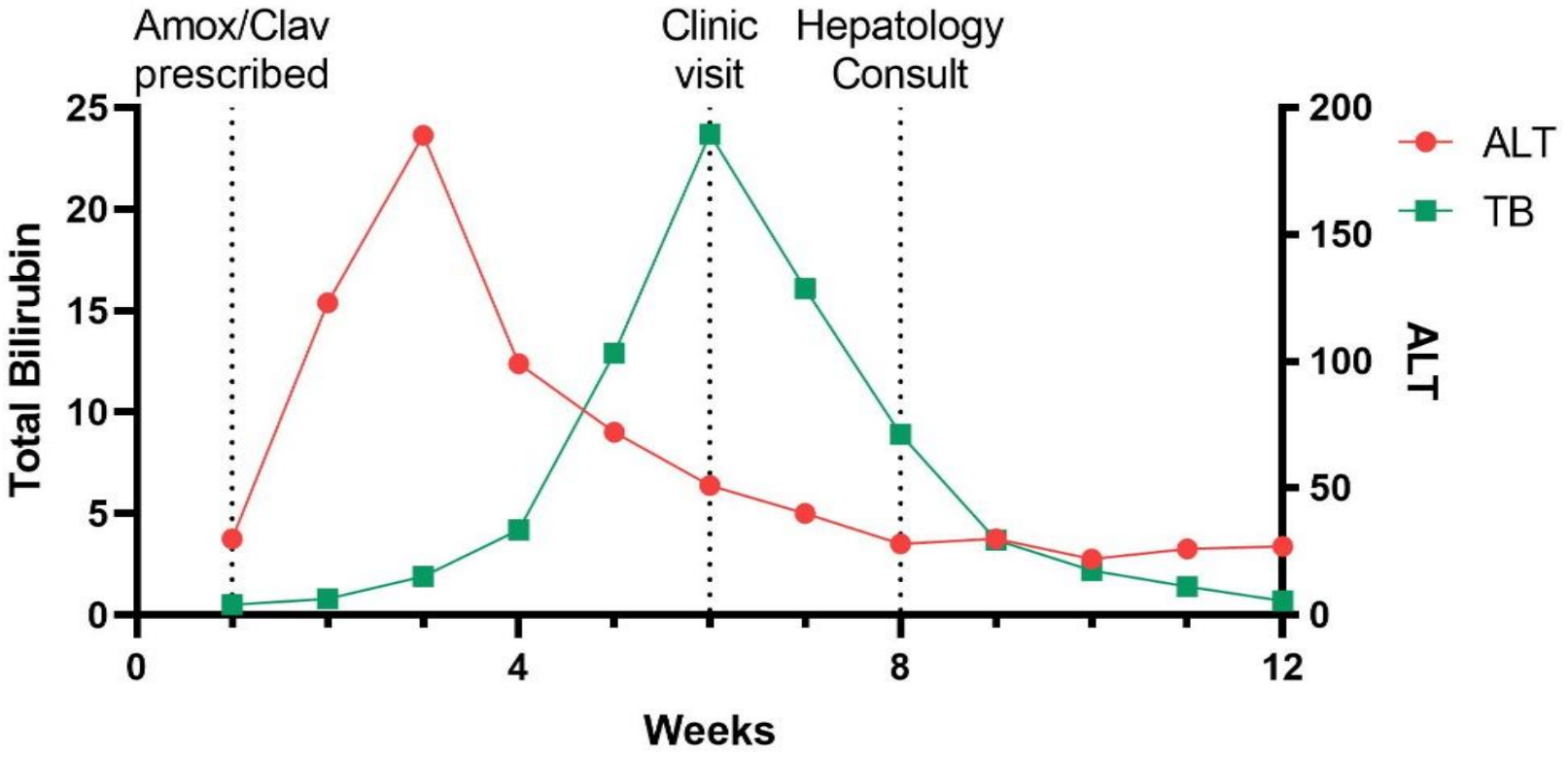
Case #3

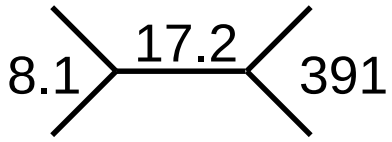


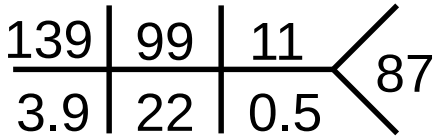
Labs normalize over 2 months without need for biopsy

ROLE OF LIVER BIOPSY

Case #4

A 55-year old man with PMH notable for hyperlipidemia, hypertension, and OSA presents to your clinic for follow-up of abnormal liver enzymes. He has had mild elevation in transaminases (2-3x ULN) for the past 2 years. Serologic work-up has been negative. Labs this visit reveal:





INR 1.0

Ca 8.6

AST	56
ALT	49
TB	0.4
AP	78
Alb	3.9
TP	6.6

Case #4

Which of the following tests is diagnostic of NASH?

A. Elevated transaminases
B. Hepatic steatosis on cross-section imaging
C. Transient elastography
D. Liver biopsy

Value of liver biopsy is diminishing…

- Diagnosis
  - Multiple diseases
  - Unknown etiology
  - Suspected NASH
- Prognosis
  - Fibrosis staging
  - Percent necrosis
- Management
  - Ongoing inflammation

Rockey D et al. AASLD Liver Biopsy Guidelines. Hepatology 2009

Value of liver biopsy is diminishing…

- **Diagnosis**
  - **Multiple diseases**
  - Unknown etiology
  - Suspected NASH
- Prognosis
  - Fibrosis staging
  - Percent necrosis
- Management
  - Ongoing inflammation

Effective therapy for concurrent diseases that may preclude need for biopsy

EXAMPLE: HCV + suspected NASH; treat HCV and biopsy only if LFT fail to normalize

Rockey D et al. AASLD Liver Biopsy Guidelines. Hepatology 2009

Value of liver biopsy is diminishing…

- **Diagnosis**
  - Multiple diseases
  - Unknown etiology
  - **Suspected NASH**
- Prognosis
  - Fibrosis staging
  - Percent necrosis
- Management
  - Ongoing inflammation

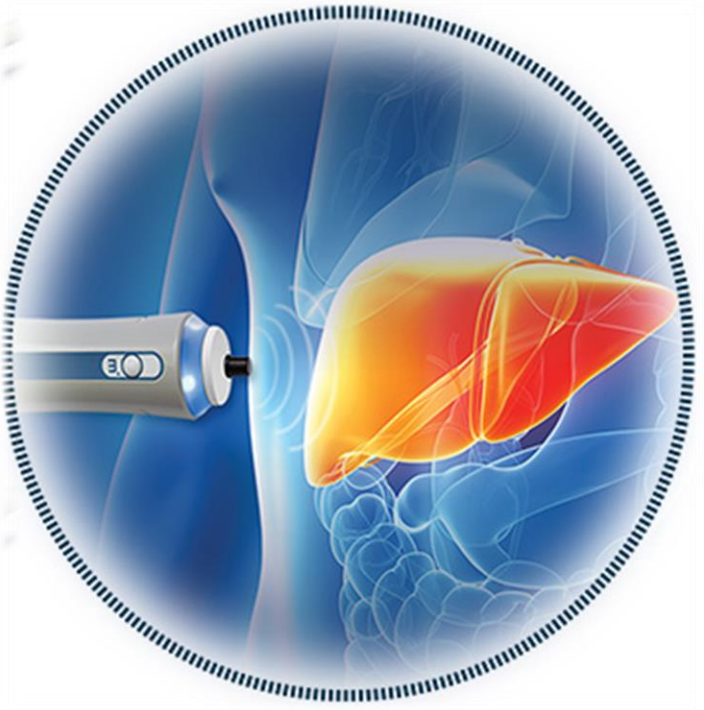
No NASH-specific therapies and have ability to stage fibrosis non-invasively

Only utility of biopsy is enrollment in clinical trials

Rockey D et al. AASLD Liver Biopsy Guidelines. Hepatology 2009

Value of liver biopsy is diminishing…

- Diagnosis
  - Multiple diseases
  - Unknown etiology
  - Suspected NASH
- **Prognosis**
  - **Fibrosis staging**
  - Percent necrosis
- Management
  - Ongoing inflammation



Transient Elastography
or
Well Validated Biomarkers

Rockey D et al. AASLD Liver Biopsy Guidelines. Hepatology 2009

Value of liver biopsy is diminishing…

- **Diagnosis**
  - Multiple diseases
  - **Unknown etiology**
  - Suspected NASH
- **Prognosis**
  - **Fibrosis staging**
  - Percent necrosis
- Management
  - Ongoing inflammation

If no/minimal fibrosis and low likelihood of treatable etiology, utility of biopsy may be limited unless progressive fibrosis

Rockey D et al. AASLD Liver Biopsy Guidelines. Hepatology 2009

Serum Biomarker Performance

* = to detect significant fibrosis, ≥F2 (or F4)

Test	AUROC*	Sens (%)	Spec (%)
Fibrotest®	0.87	75	85
FibrospectII®	0.83	77	73
Enhanced Liver Fibrosis score®	0.78 (0.89)	87	51
Hepascore®	0.82 (0.89)	63	89
Fibrometer®	0.89	80	84
APRI (AST-to-Plt Ratio)	0.80 (0.89)	41-91	47-95
Fibrosis Probability Index (FPI)	0.77	42-85	48-98
HALT-C model	0.81	47-88	45-92
ViraHep-C	0.83	51-90	54-90
FIB-4	0.85	38-74	81-98
NAFLD Fibrosis Score (NFS)	0.82	43-77	97

Adapted from EASL-ALEH Clinical Practice Guidelines. J Hep 2015

Serum Biomarker Performance

Equivalent performance to Transient Elastography

* = to detect significant fibrosis, ≥F2 (or F4)

	Disease/Study	AUROC*	Sens (%)	Spec (%)
Transient Elastography	HCV	0.82 (0.93)	97 (77)	35 (90)
	HBV	0.87 (0.93)	74 (75)	88 (90)
	PBC	0.91 (0.99)	67 (93)	100 (99)
	Alcohol-related	0.91 (0.92)	80 (86)	91 (84)
	NAFLD	0.80 (0.94)	76 (78)	80 (96)
Bio mark				

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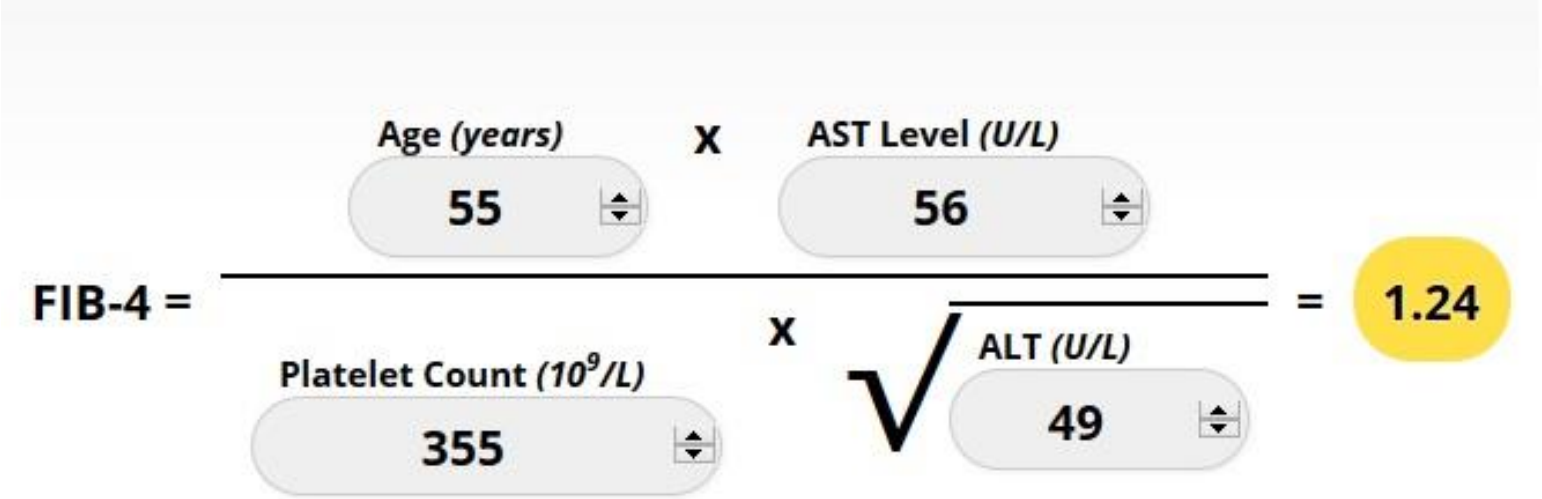
FIB-4 Score

https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4



<1.45 has 90% NPV to exclude advanced fibrosis (≥F3)
>3.25 is 97% specific for advanced fibrosis

NAFLD Fibrosis Score

http://gihep.com/calculators/hepatology/nafld-fibrosis-score/

-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×109/l) – 0.66 × albumin (g/dl)

<-1.455 = F0-F2

>0.675 = advanced fibrosis

Case #4

A 55-year old man with PMH notable for hyperlipidemia, hypertension, and OSA, with suspected NASH. A FIB-4 score and NAFLD Fibrosis Score are calculated:

FIB-4 = 1.24 (F0-F2)

NFS = -2.88 (F0-F2)

Monitor labs q6 months, repeat biomarker scores in 2 years, biopsy if labs rise or fibrosis progression

Conclusions

- Pattern recognition of LFT abnormalities allows you to focus work-up to highest yield testing
- Guidelines support a step-wise approach for mild elevation in transaminases focusing on highest prevalence diseases (ASH, NASH, viral hepatitis)
- Knowledge of prevalence and screening vs diagnostic tests is critical for high value diagnosis of less common causes of abnormal LFT
- Value of liver biopsy is diminishing with advent of non-invasive tools for fibrosis staging
- Biomarker scores are useful to stage fibrosis and can be helpful tools to triage patients to the appropriate level of care

Thank You!

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