Case #2: Managing a Patient with Chronic Hepatitis C and Pruritus

Eugenia Tsai, MD

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Texas Liver Institute

Case Presentation

- 45 year old female referred for further evaluation of “Elevated Liver Tests.”
- Referral paperwork: “HCV infection” and “echogenic liver”
- ROS: pruritus x 2 years
- Medical history: Dyslipidemia
- Social history: IVDU 20 years ago but quit 5 years ago, no alcohol use

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Physical Exam

- VSS; BMI 24
- General: Well-appearing, well-nourished, no distress
- Skin: +tattoos, +excoriations from scratching but no jaundice or telangiectasia
- HEENT: Normocephalic, atraumatic, conjunctiva normal
- Heart: RRR, S1/S2, no murmurs
- Lungs: CTAB and to percussion
- Abdomen: Nondistended, soft, normal bowel sounds
- Extremities: No LE edema, peripheral pulses intact
- MSK: normal gait
- Neuro: AAOx4, no asterixis

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Initial Labs

Lab	Value
WBC	5.7
Hb	12.9
Plt	320
INR	1.0

Lab	Value
AST	97
ALT	112
ALP	250
Albumin	4.2
Tb	0.7

What do you do next?

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Chronic Liver Disease Workup

Classification	Diagnosis	Screening Test	Confirmatory / Additional Tests
Viral	**HBV**	HBsAg	HBVDNA, HBeAg, anti-HBe
	HCV	Anti-HCV	HCVRNA
Toxin	**Alcohol**	History *Note: AST>ALT, ↑↑ GGT, ↑IgA*	Biopsy if uncertain
Metabolic	**MAFLD (NAFLD)**	None (Risk factors: obesity, DM, ↑ lipids) *Note: fasting glucose (HbA1c), lipids, rule out other diseases*	Biopsy if uncertain
Autoimmune	**AIH**	ANA, ASMA, ↑IgG (all non-specific)	Biopsy **required** for diagnosis
	PBC	AMA *Note: ↑IgM, ↑ lipids*	AMA is diagnostic
	PSC	None *Note: autoantibodies common*	MRCP if normal biopsy for small duct PSC
Genetic	**HH**	Fe/TIBC (TS) >45% *Note: ferritin >1000 is non-specific*	HFE gene testing (C282Y/C282Y or C282Y/H63D)
	A1AT deficiency	A1AT level (low)	A1AT phenotype (ZZ)
	WD	Ceruloplasmin (low)	24h urine copper, slit lamp (KF rings)

Lab	Value
HCV RNA	**>1,000,000**
ASMA	**1:40**
AMA	**21**
IgG	**1900**
IgM	**480**

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Diagnosing, Staging and Treating HCV

Eugenia Tsai, MD

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Comparison of Hepatitis A, B and C

	Transmission	Chronic Infection	Vaccine	Treatment
Hep A	• Fecal-oral	No	Yes	Not needed
Hep B	• Mother to child • Blood to blood • Sexual contact	Yes	Yes	Effective treatments to slow liver damage
Hep C	• Blood to blood	Yes	No	Cure available with 8-12 weeks of oral therapy

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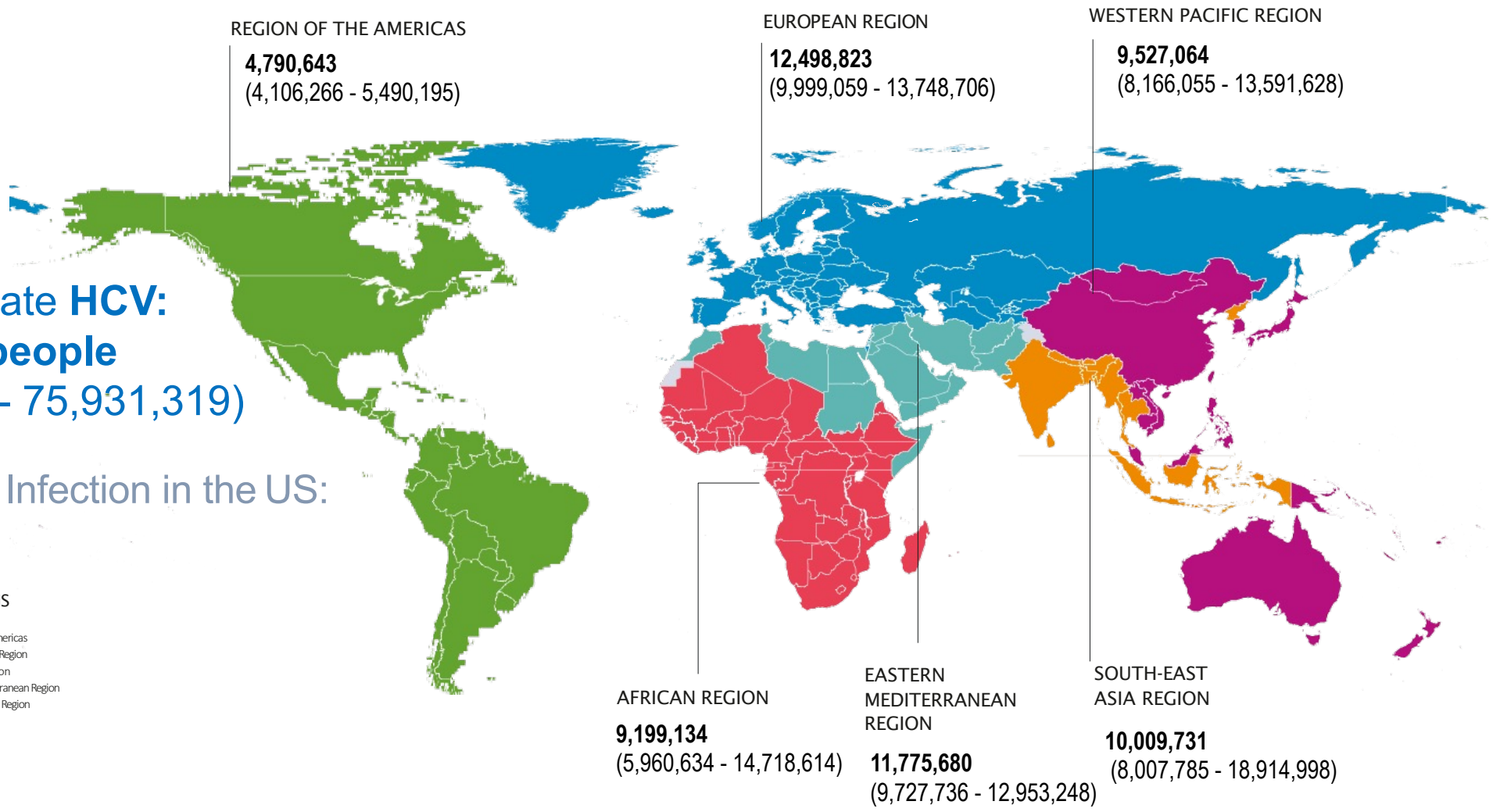
Prevalence of Hepatitis C Virus Infection by WHO Region, 2019



Global Estimate **HCV:**
57,801,076 people
(46,240,860 - 75,931,319)

Chronic HCV Infection in the US:
~2.4 Million

Source: WHO. 2021.

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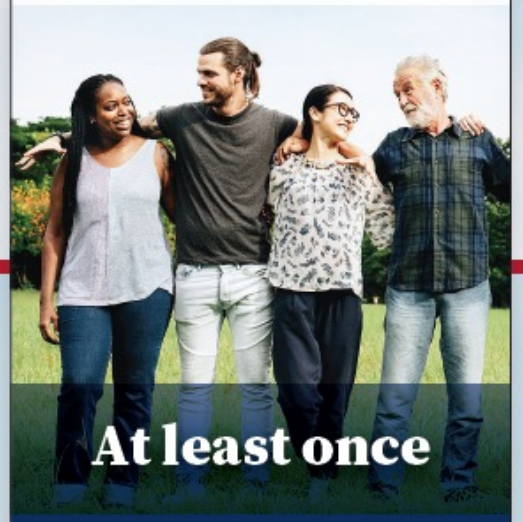
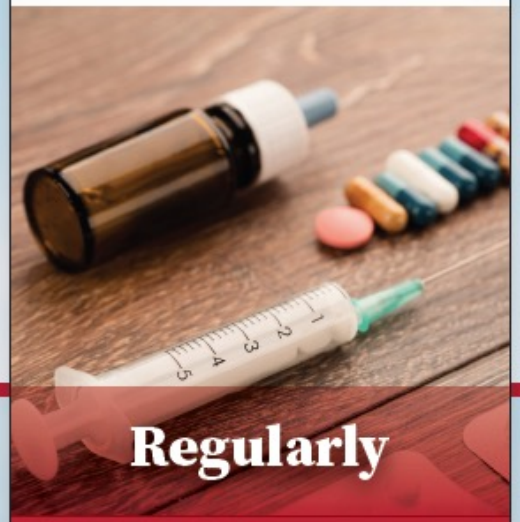
Who Should Get Tested for Hepatitis C?

EVERY ADULT



At least once

EVERYONE WITH RISK FACTORS



Regularly

- Persons who inject drugs and share needles, syringes, or other drug preparation equipment
- Persons receiving maintenance hemodialysis
- Persons with abnormal liver tests or liver disease (persistently abnormal ALT levels)
- Children born to mothers with HCV infection

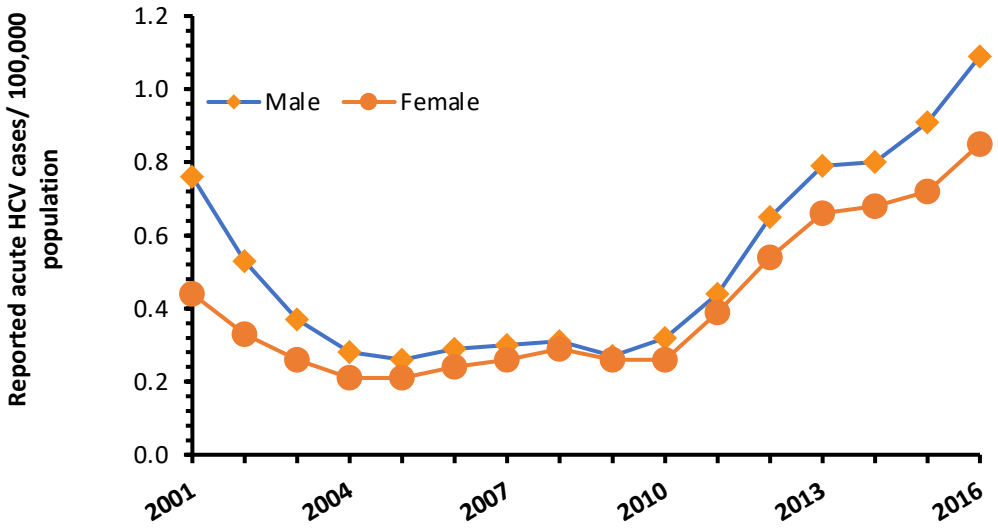
EVERY PREGNANT WOMAN

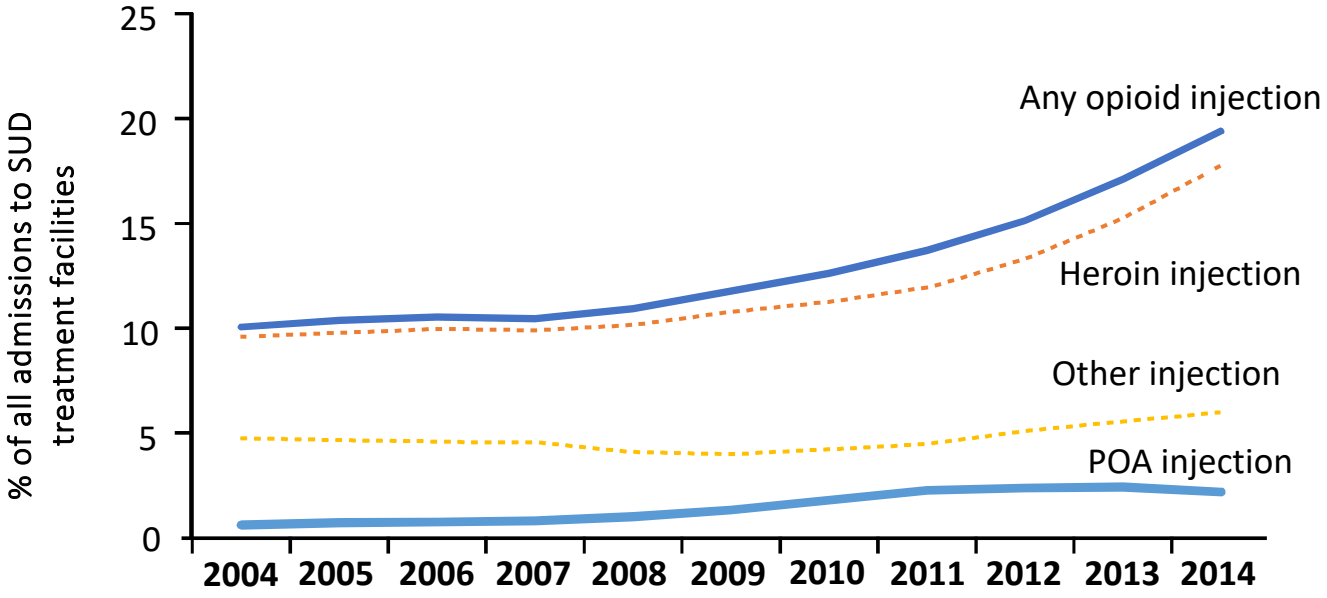
Every pregnancy

SOURCE: CDC Recommendations for Hepatitis C Screening, MMWR, April 2020

Acute HCV Infections Related to Opioid Epidemic

Incidence of acute HCV by sex in US, 2001-2016





Increases in acute HCV infections attributed to rising rates opioid injection drug use[1,2]

POA, prescription opioid analgesic; SUD, substance use disorder.

1. Centers for Disease Control and Prevention Surveillance for Viral Hepatitis – United States, 2016. https://www.cdc.gov/hepatitis/statistics/2016surveillance/pdfs/2016HepSurveillanceRpt.pdf; 2. Zibbell JE, et al. *Am J Public Health*. 2018;108:175-181.

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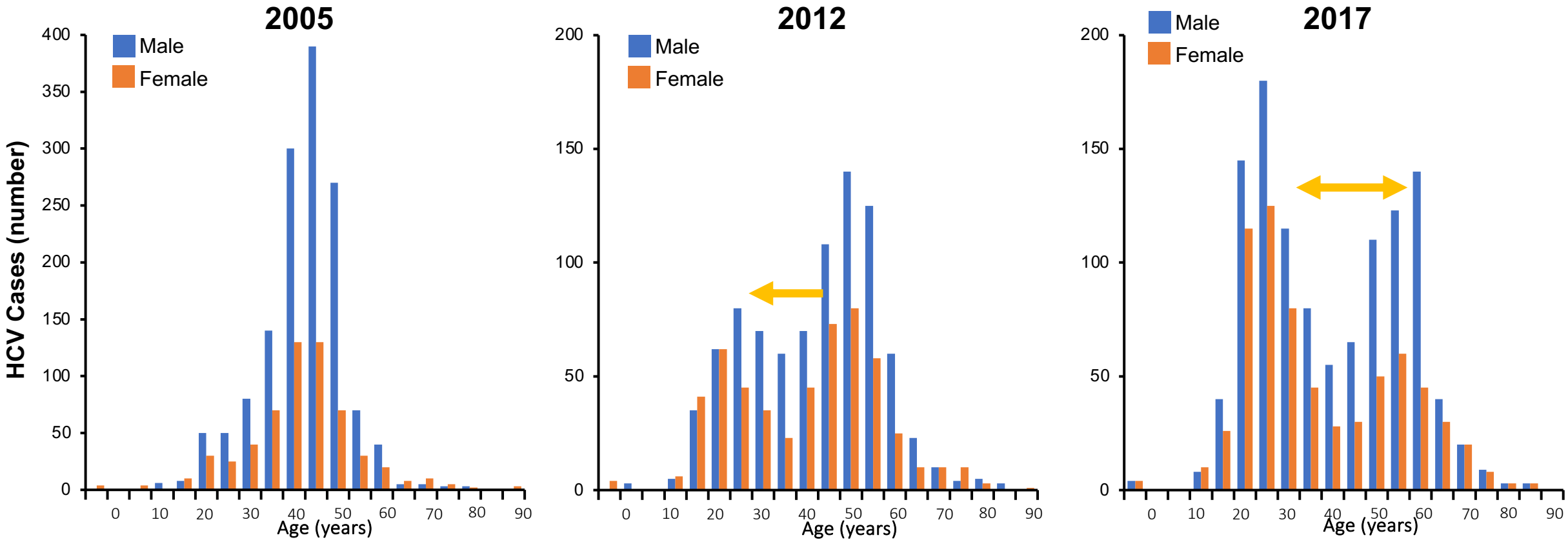
Changing Epidemiology: HCV Is Now BI-Modal



Recent HCV Infection Increase Among Women of Reproductive Age in United States

Data for New York State (excluding NYC). https://www.health.ny.gov/statistics/diseases/communicable/index.htm.

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HCV Can Be Cured

- Unlike HIV and HBV infection, HCV infection is a curable disease
  - HCV does not archive its genome in the nucleus and does not integrate in the host DNA
- What does cure mean?
  - Undetectable HCV RNA 12 weeks after completion of antiviral therapy for chronic HCV infection
  - SVR12 is almost invariably durable

Ghany MG, et al. *Hepatology*. 2009;49(4):1335-1374.

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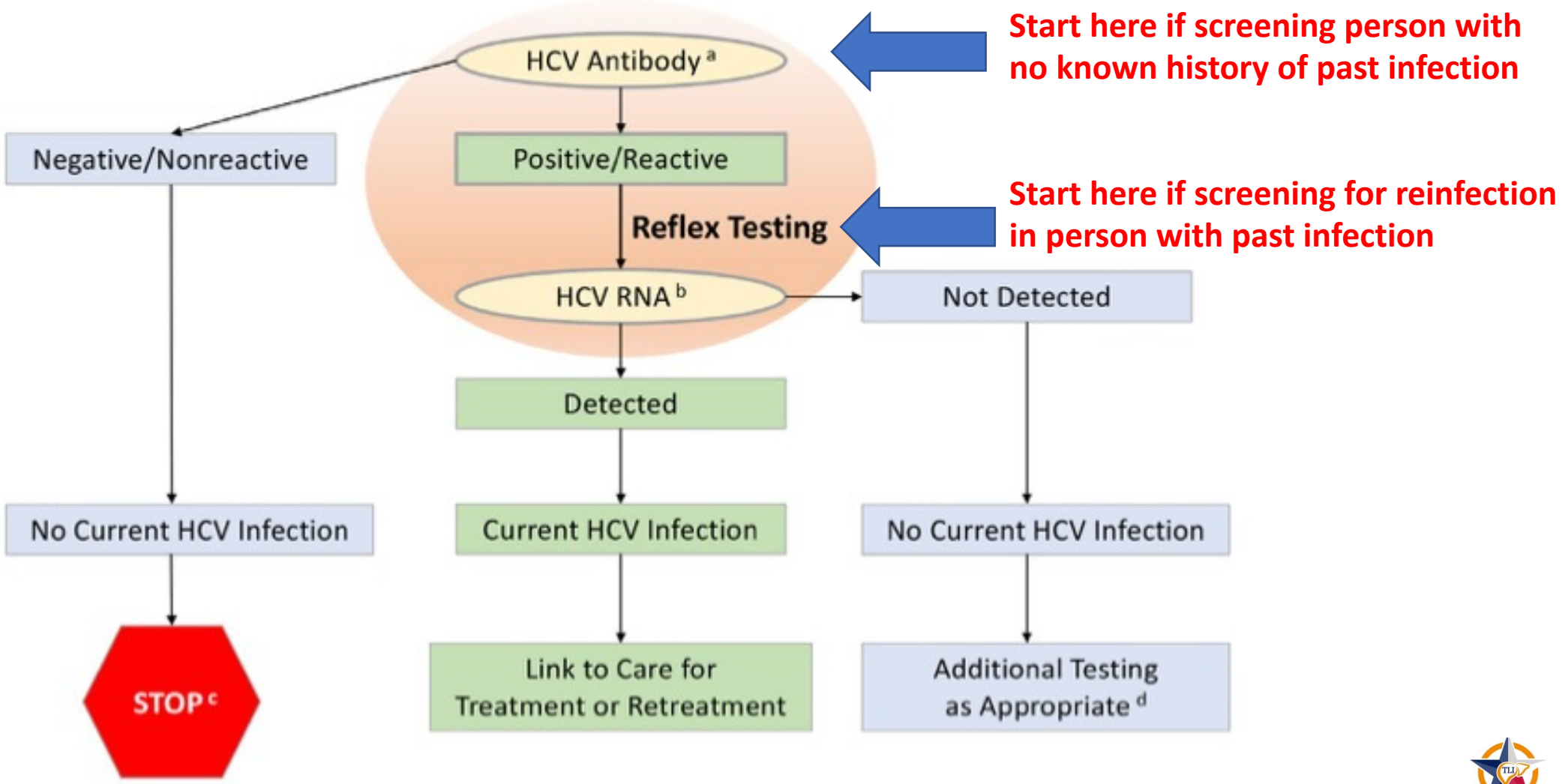
Recommended Testing Sequence for Identifying Current HCV Infection or Reinfection



AASLD-IDSA Hep C Guidance Panel, *Hepatology*, 71 (2), 2020

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Does a Reactive HCV Antibody Test Mean My Patient Has Chronic HCV Infection?

- No! It's a SCREENING test
- Individuals who were successfully treated and cured will remain antibody positive but will be HCV RNA negative
- Approximately 15%-25% of individuals clear the virus without treatment and do not develop chronic infection
- HCV RNA (viral load) is required to confirm chronic infection

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Staging Hepatic Fibrosis is Important for Long-term Management

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Laboratory Tests For Liver Fibrosis

- Simple
  - Fibrosis-4 (FIB-4)
  - NAFLD fibrosis score (NFS)
  - AST/platelet ratio index (APRI)
- Proprietary
  - Enhanced Liver Fibrosis Test (ELF)
  - ADAPT/Pro-C3
  - FibroSure
  - Hepascore

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Imaging For Liver Fibrosis

- Measure liver stiffness, which is an indirect measure of hepatic fibrosis
- Types
  - Vibration controlled transient elastography (VCTE) (e.g., FibroScan)
    - Most reliable in ruling out advanced hepatic fibrosis (great NPV)
    - Can be point of care
  - 2D shear wave elastography
    - May require radiology referral
    - Can be point of care with minimal training
  - Magnetic resonance elastography (MRE) or corrected T1 (cT1) (Liver MultiScan)
    - Requires radiology referral

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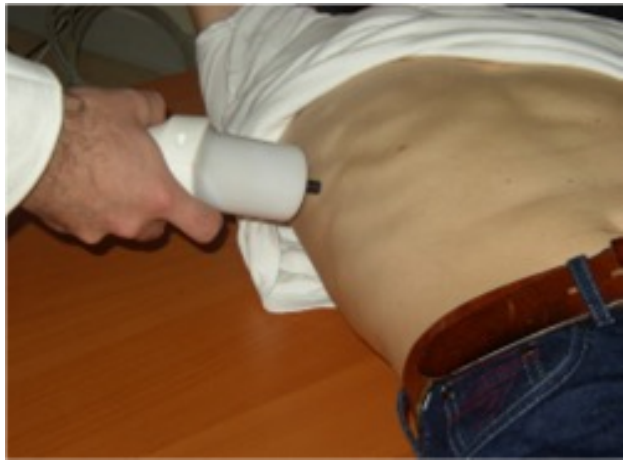
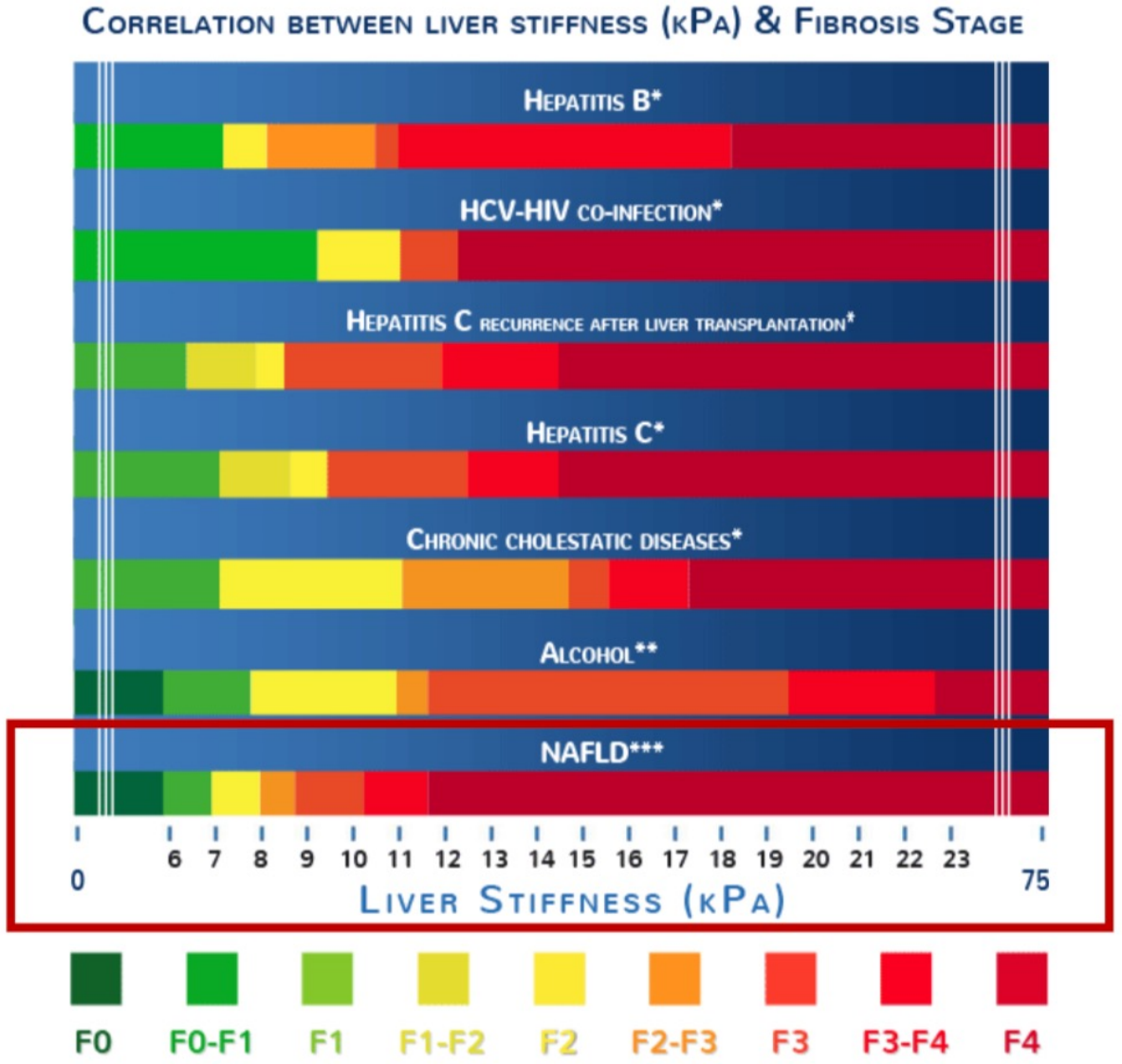
FibroScan





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Back to Our Case

- HCV RNA >1,000,000
- Genotype 1a
- FibroScan: CAP 230, kPa 14

Should you treat this patient's chronic Hep C?

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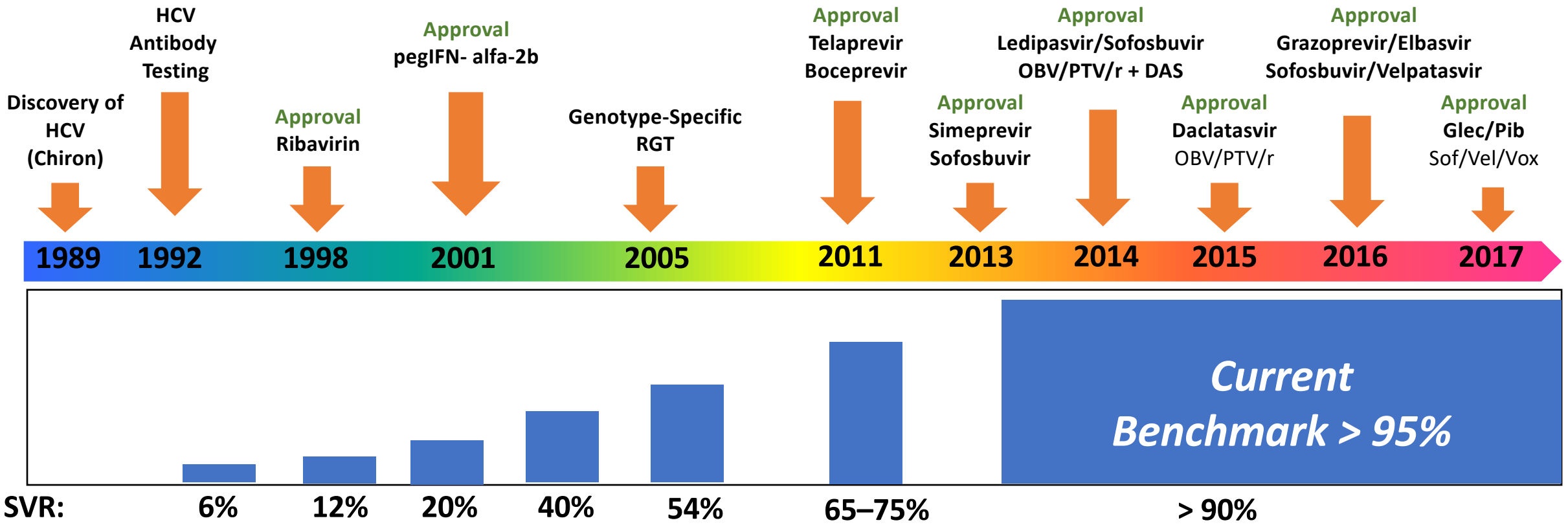
Timeline of HCV Therapy



pegIFN-alfa 2b = peg-interferon alfa-2b; RGT = response-guided therapy; OBV/PTV/r + DAS = ombitasvir/paritaprevir and ritonavir + dasabuvir (or 3D).Houghton M. *Liver Int*. 2009;29(Suppl 1):82-88; Carithers RL, et al. *Hepatology*. 1997;26(3 Suppl 1):S83-S88; Zeuzem S, et al. *N Engl J Med*. 2000;343(23):1666-1672; Poynard T, et al. *Lancet*. 1998;352(9138):1426-1432; McHutchison JG, et al. *N Engl J Med*. 1998;339(21):1485-1492; Lindsay KL, et al.*Hepatology*. 2001;34(2):395-403; Fried MW, et al. *N Engl J Med*. 2002;347(13):975-982; Manns MP, et al. *Lancet*. 2001;58(9286):958-965; Poordad F, et al.*N Engl J Med*. 2011;364(13):1195-1206; Jacobson IM, et al. *N Engl J Med*. 2011;364(25):2405-2416; Lawitz E, et al. *N Engl J Med*. 2013; 368(20):1878-1887;Jacobson IM, et al. *Lancet*. 2014;384(9941):403-413; Afdhal N, et al. *N Engl J Med*. 2014;370(20):1889-1898; Nelson DR, et al. *Hepatology*. 2015;61(4):1127-1135; Zeuzem S, et al. *Ann Intern Med*. 2015;163(1):1-13.

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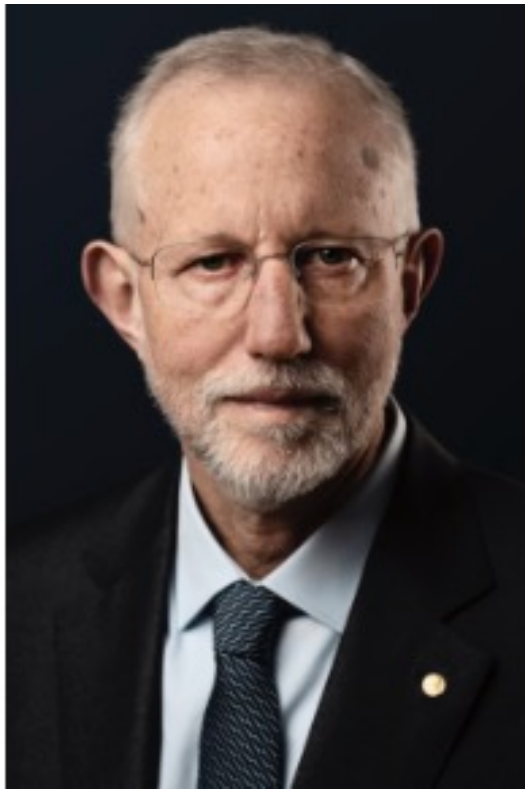
The 2020 Nobel Prize for Discovery of Hepatitis C Virus

Harvey Alter, MD

Michael Houghton, PhD

Charlie Rice, PhD



"For the first time in history, the disease can now be cured, raising hopes of eradicating Hepatitis C virus from the world population."

-The Nobel Committee

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Patient Follow Up

- Treated with DAA x 12 weeks
- Follow up 3 months after completion of treatment

Lab	Follow up Value	Initial Value
AST	41	97
ALT	44	112
ALP	258	250
Albumin	4.0	4.2
Tb	0.9	0.7
HCV RNA	Undetectable	>1,000,000

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Why is the ALP still elevated?

Lab	Value
HCV RNA	Undetectable
ASMA	1:40
AMA	21
IgG	1900
IgM	480

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Managing PBC

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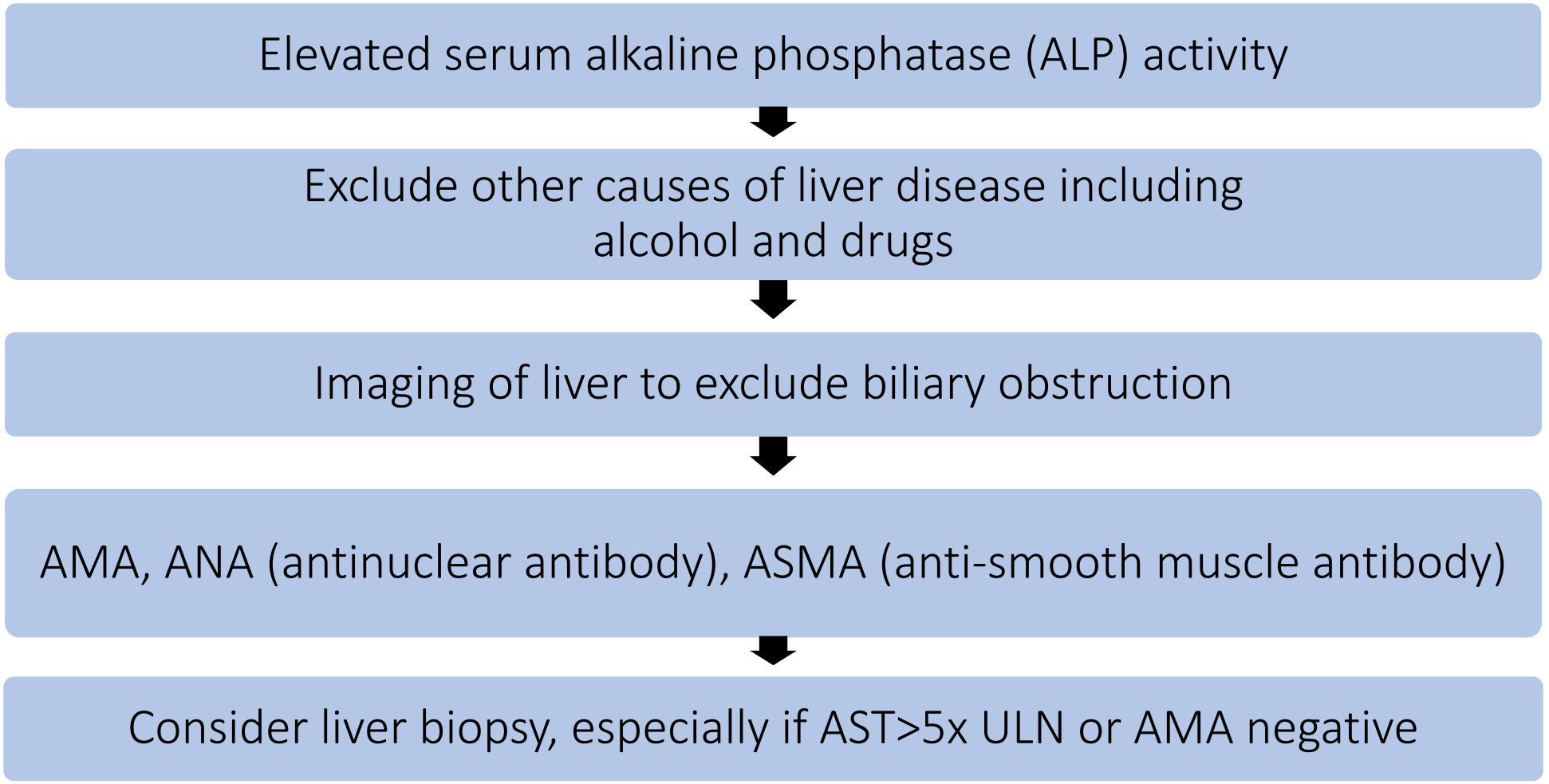
AASLD Suggested Diagnostic Algorithm for Patients with Suspected PBC



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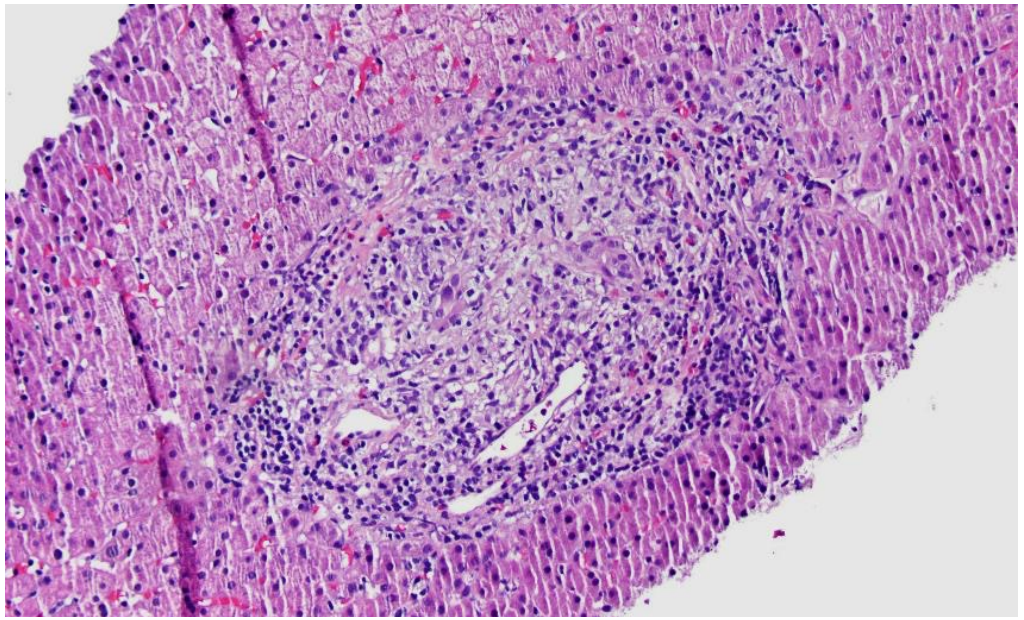
PBC Diagnostic Criteria

PBC Diagnosis

- Unexplained elevation of ALP ≥ 1.5x ULN
- Positive anti-mitochondrial antibody (AMA)
- Non-suppurative destructive cholangitis on histology



Two out of these 3 criteria are required for the diagnosis of PBC

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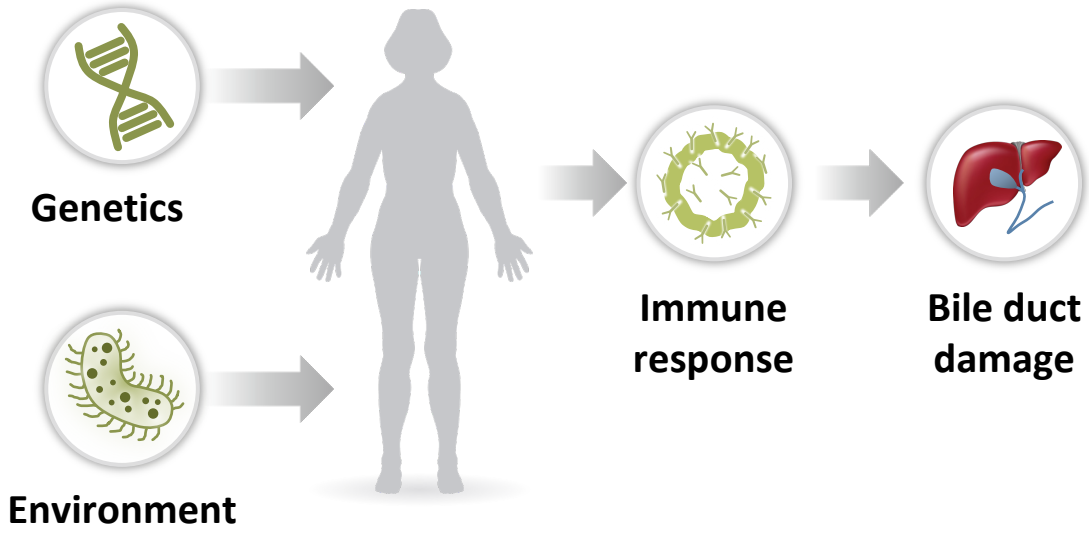
PBC is a Chronic, Progressive Autoimmune Disease

- Factors possibly associated with onset and perpetuation of bile-duct injury in PBC



PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis

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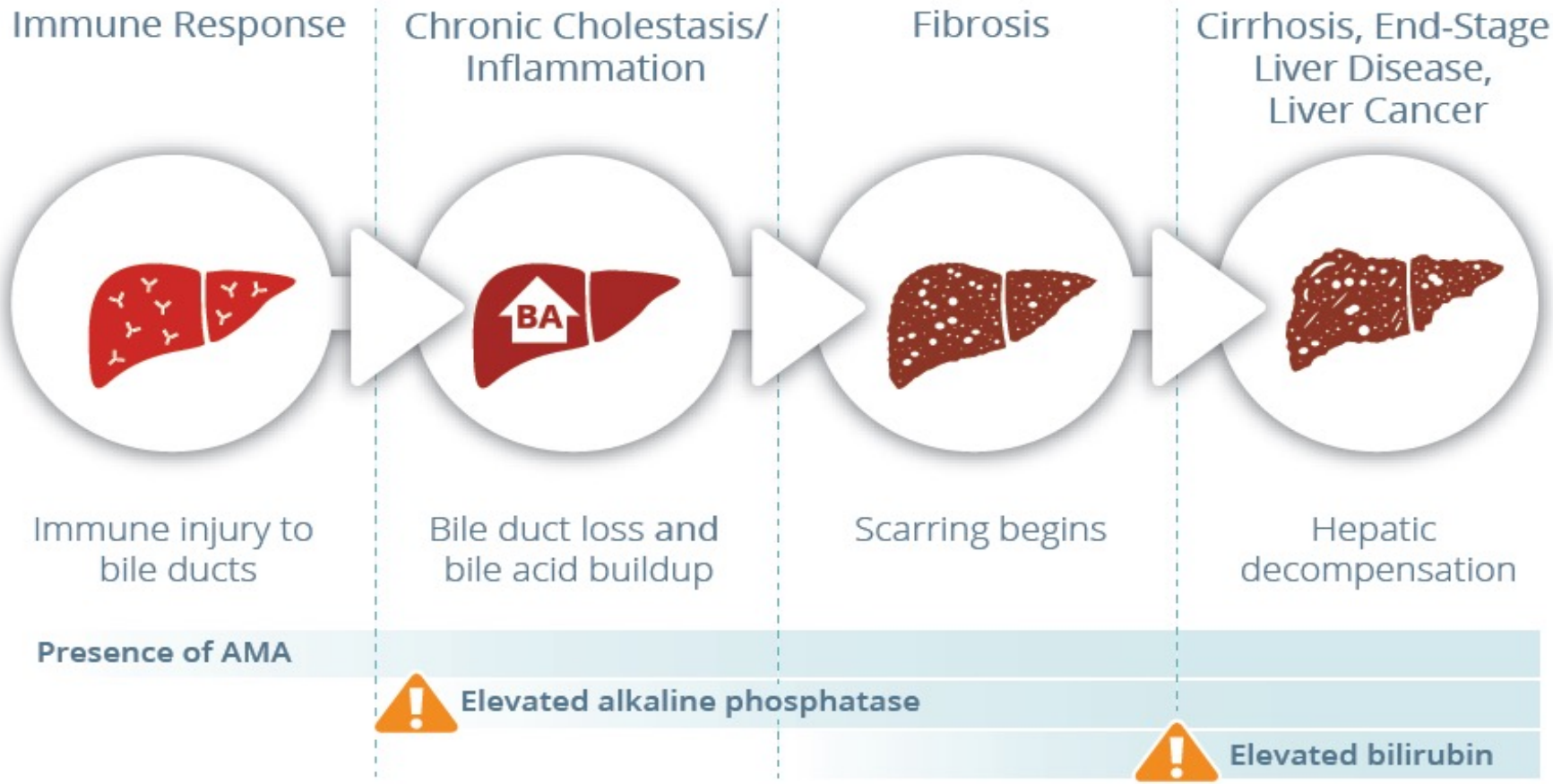
Poupon R. *J Hepatol*. 2010;52(5):745-758; Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609; Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575.

If Left Inadequately Treated, PBC May Result in Liver Failure, Transplant, or Death

Persistent, toxic exposure to bile acid buildup ultimately leads to end-stage disease



Poupon R. *J Hepatol.* 2010;52(5):745-758. Dyson JK, et al. *Nat Rev Gastroenterol Hepatol.* 2015;12(3):147-158. Lammers WJ, et al. *Gastroenterology*. 2014;147(6):1338-1349. Selmi C, et al. *Lancet.* 2011;377(9777):1600-1609.

Managing Fatigue and Pruritus

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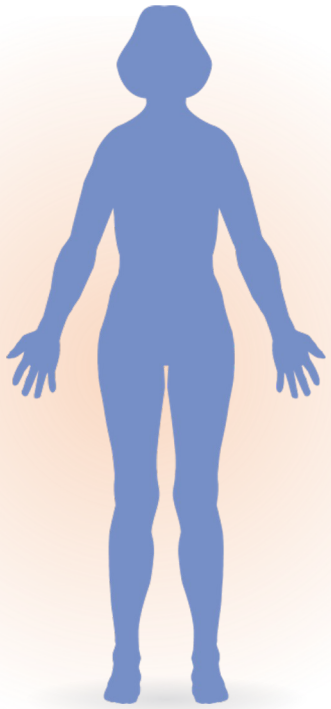
Clinical Features Vary Greatly Between Patients…[1-3]

…but there are disease-associated symptoms, clinical manifestations, and co-existing autoimmune diseases that are recognized[1-3]



- Fatigue[1,2]
- Pruritus[1,2]

Most common symptoms of PBC[2]

- Xanthoma and xanthelasma[2,3]
- Hyperlipidemia[1,2]
- Osteoporosis[1,2]
- Co-existing autoimmune diseases[1,2]

The absence of symptoms at diagnosis may not predict prognosis
(as many as ~60% of patients may be asymptomatic at diagnosis)[4]*

*Based on an examination of the natural history of a 770-patient cohort in Northeast England (incident cases, 1987-1994).[4]

1. Selmi C et al. *Lancet*. 2011;377(9777):1600-1609; 2. Carey EJ et al. *Lancet*. 2015;386(10003):1565-1575; 3. Lindor KD et al. *Hepatology*. 2018. doi:10.1002/hep.30145; 4. Prince MI et al. *Gut.* 2004;53(6):865-870.

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Fatigue Is the Most Common Symptom in PBC

- Present in up to 85% of patients with PBC[3]
  - >40% report moderate to severe[1]
- Mechanism not well understood[1,2]
- Unrelated to disease activity or stage
  - Tends to wax and wane throughout the course of illness[2]
- Typically characterized as daytime somnolence
  - Can impair QoL[1]

Despite sparse correlation between fatigue and severity of liver disease, fatigue can be associated with decreased overall survival[1]

1. Selmi C et al. *Lancet*. 2011;377(9777):1600-1609; 2. Carey EJ et al. *Lancet*. 2015;386(10003):1565-1575; 3. Huet PM et al. *Am J Gastroenterol*. 2000;95(3):760-767.

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Assessing and Managing Fatigue

- Though fatigue caused by PBC may not be reversible, associated causes of fatigue should be actively excluded—or identified and managed[1,2]

Rule Out:
Associated causes of fatigue (disease or medication): • Anemia[2] • Depression[2] • Sleep disorder[2] • Hypothyroidism[1-3] • Medications that can cause or contribute to fatigue (eg, excessive antihypertensive medication)[1]

Consider Fatigue Management Strategies:
Fatigue may be improved by: • Maintaining regular physical activity[4,5] • Modafinil (100-200 mg)[6,7] • Methotrexate for patients with severe fatigue[8]

1. European Association for the Study of the Liver. *J Hepatol*. 2009;51(2):237-267; 2. Lindor KD et al. *Hepatology*. 2009;50(1):291-308; 3. Elta GH et al. *Dig Dis Sci*. 1983;28(11):971-975; 4. Cook NF et al. *Br J Nurs*. 1997;6(14):811-815; 5. Graydon JE et al. *Cancer Nurs*. 1995;18(1):23-28; 6. Jones DEJ et al. *Aliment Pharmacol Ther*. 2007;25(4):471-476; 7. Ian Gan S et al. *Dig Dis Sci*. 2009;54(10):2242-2246;8. Babatin MA et al. *Aliment Pharmacol Ther*. 2006;24(5):813-820.

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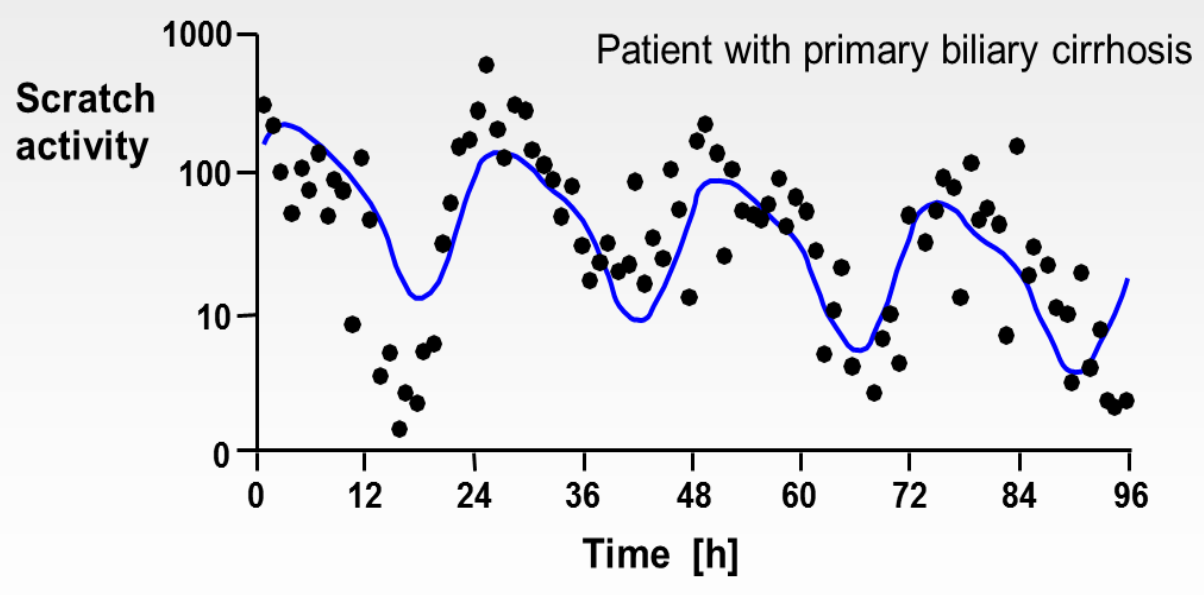
Cholestatic Pruritus – PBC

- Occurs in 20%-70% of patients with PBC
  - Among those reporting pruritus: 64.5% mild, 31.3% moderate and 4.2% severe
  - Intermittent; seasonal variation; worse in the heat, wool clothing
  - Diurnal variation, worse at night
  - Typically localized to limbs, soles of feet, and palms of hands



Talwalkar et al. *Clin Gastroenterol and Hepatol*. 2003; Carbone et al. *Gastro*. 2013.

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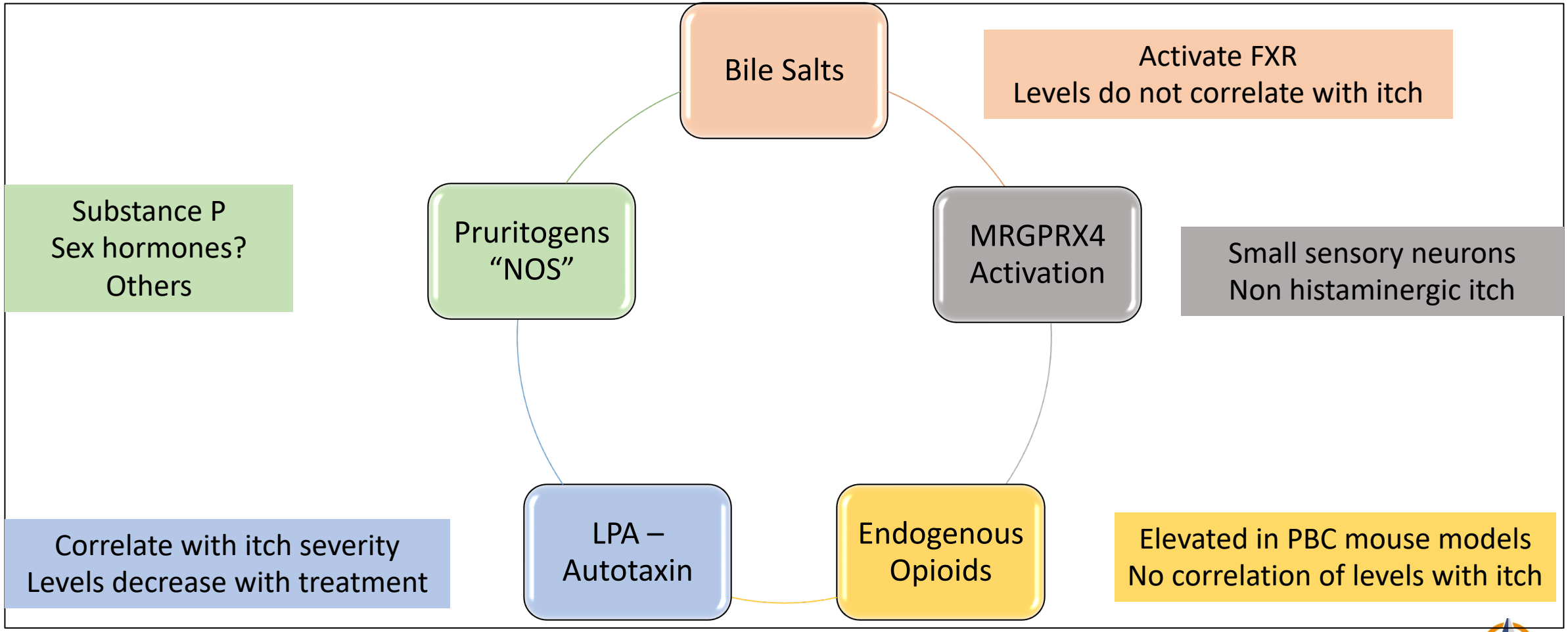
Pathogenesis of Pruritus



Doll MM. Kremer AE. Curr Gastroentere! Res 2019

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Stepwise Approach to Pruritus


HEPATOLOGY

AASLD

Practice Guidance | Free Access

Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases

Keith D. Lindor, Christopher L. Bowlus, James Boyer, Cynthia Levy, Marlyn Mayo

First published: 02 August 2018 | https://doi.org/10.1002/hep.30145 | Cited by: 1

General advice

First-line agent:
Cholestyramine

Second-line agents:
Rifampin
Naltrexone
Sertraline

Other treatments:
Fibrates
IBATs
Nasobiliary drainage
MARS
Phototherapy
Plasmapheresis
**Active area of clinical research

Liver Transplantation
Patients without significant hepatic dysfunction will need exemption points

De Vries et al. *Gastroenterology*. 2021; Golpanian, Yosipovitch and Levy. *Dig Dis Sci*. 2021; Lindor et al. *Hepatology*. 2019.

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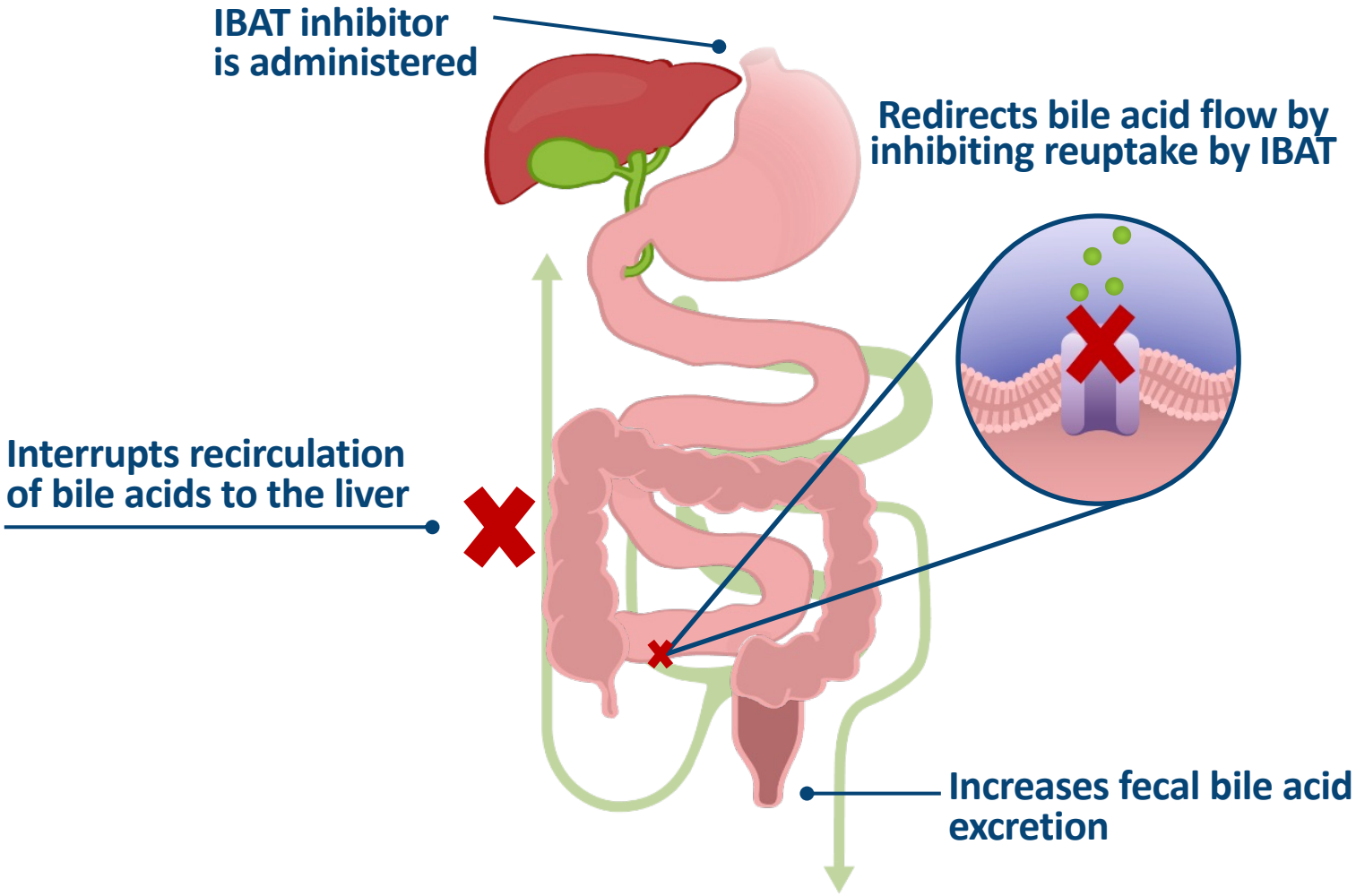
IBAT Inhibitors: Pharmacologic Inhibition of Bile Acid Recirculation



Clinical effects of IBATi in cholestasis:

- ✓ Improvements in pruritus (itch)
- ✓ Reductions in sBA
- ✓ Improved transplant-free survival

FDA Approved IBAT Inhibitors

- Maralixibat (Livmarli) for Alagille Syndrome
- Odevixibat (Bylvay) for PFIC

IBAT(i), ileal bile acid transporter (inhibitor); sBA, serum bile acid.

Gonzales E, *et al. Lancet* 2021; **398**:1581–1592; Tiessen RG *et al. BMC Gastroenterology* 2018; **18**:3. Figure adapted from: Slijepcevic D & van de Graaf SFJ. *Dig Dis* 2017;35:251–258.

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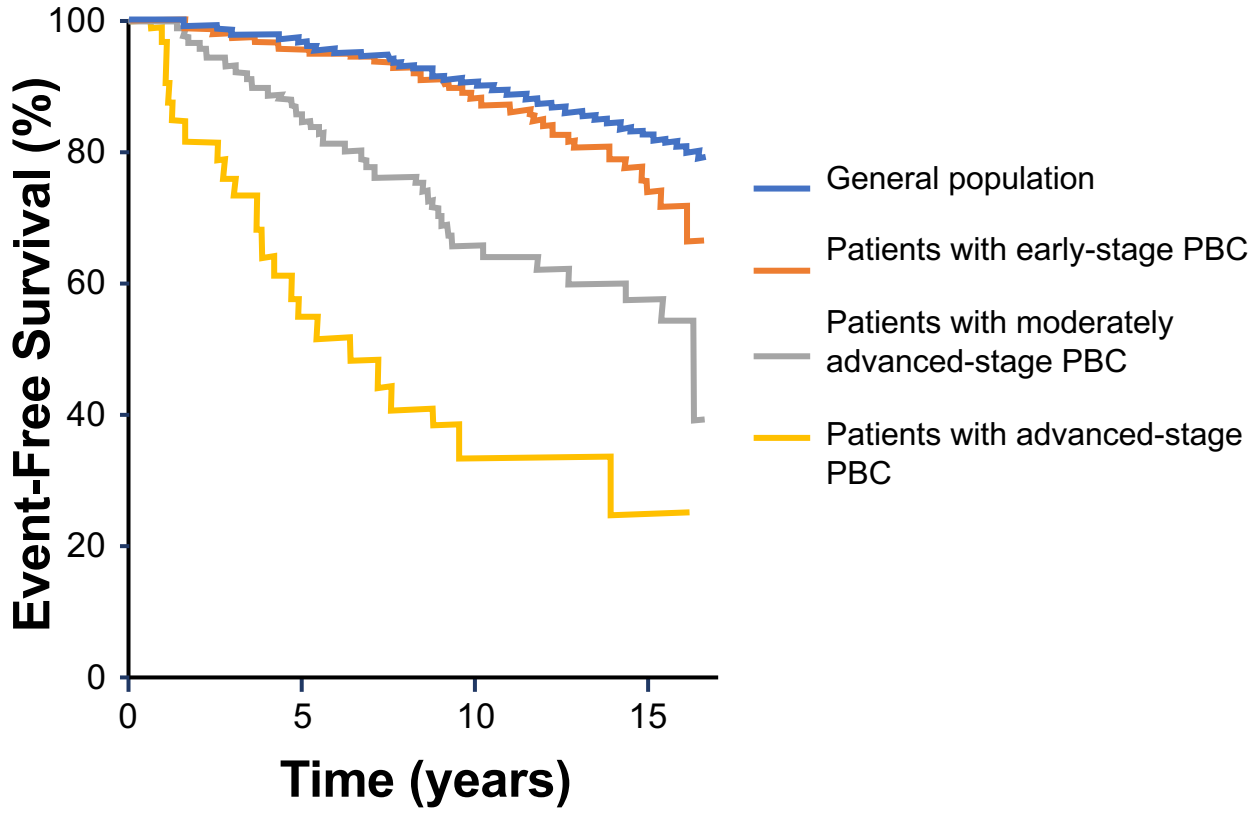
Treatments for PBC

First Line Therapy

First line therapy: Ursodeoxycholic acid/Ursodiol (UDCA)

- Dose: 13-15 mg/kg/day
- Improvement in liver tests may be seen within a few weeks and 90% of the improvement usually occurs within 6-9 months



- Survival of patients with early-stage PBC comparable to survival of the general population (p=.254)
- Survival in advanced-stage PBC significantly worse (p<0.001)

Lindor K, et al. *Hepatology.* 2009;50:291-308.

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Second Line Therapy

- Obeticholic acid (OCA)
  - Can be added to UDCA in cases of inadequate response or replace UDCA in cases of UDCA intolerance.
  - Dose: Start at 5 mg once a day. If adequate response is not achieved with 5 mg/day and OCA is well tolerated, increase to 10 mg/day after 3 months
  - **Contraindication**: Cirrhosis Child-Pugh Class B or C. PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension

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Future Therapeutic Targets

- Fibrates -Peroxisome proliferator-activated receptor (PPAR)
  - **Bezafibrate**: Weak pan-PPAR
  - **Fenofibrate:** PPARα
- Non-Fibrates - Peroxisome proliferator-activated receptor (PPAR)
  - **Elafibranor** : Dual PPAR-α/δ agonist
  - **Seladelpar:** PPAR-δ agonist
  - **Saroglitazar:** Dual PPAR-α/γ agonist
- Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase
  - Inflammation and fibrosis

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Next Steps for Patient

- HCV: Cured!
- PBC treatment: UDCA 13-15 mg/kg/day
  - 64 kg (832-960 mg)
  - Started on 300 mg TID
- Pruritus treatment: Cholestyramine 4 g/day (up to 16 g/day)
- DEXA for bone density
- Repeat labs in 3 months

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Case #2: Q&A/Panel Discussion

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Closing Remarks

Eugenia Tsai, MD

Director, Hepatobiliary Cancer & Resident/Fellow Education
The Texas Liver Institute
Assistant Professor of Medicine
Assistant Program Director, Transplant Hepatology Fellowship
UT Health San Antonio
San Antonio, Texas

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Closing Remarks

- Please answer the 7 post-test questions and hand to our staff before leaving.
- Downloadable slide decks will be available through www.txliver.com website within 5 days.
- Claiming credit: Follow instructions on page 9 in the meeting guide.

- Drawing for $50 gift card!

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