Primary Biliary Colangitis (PBC): Deciding Which Patients are Ursodiol Nonresponders

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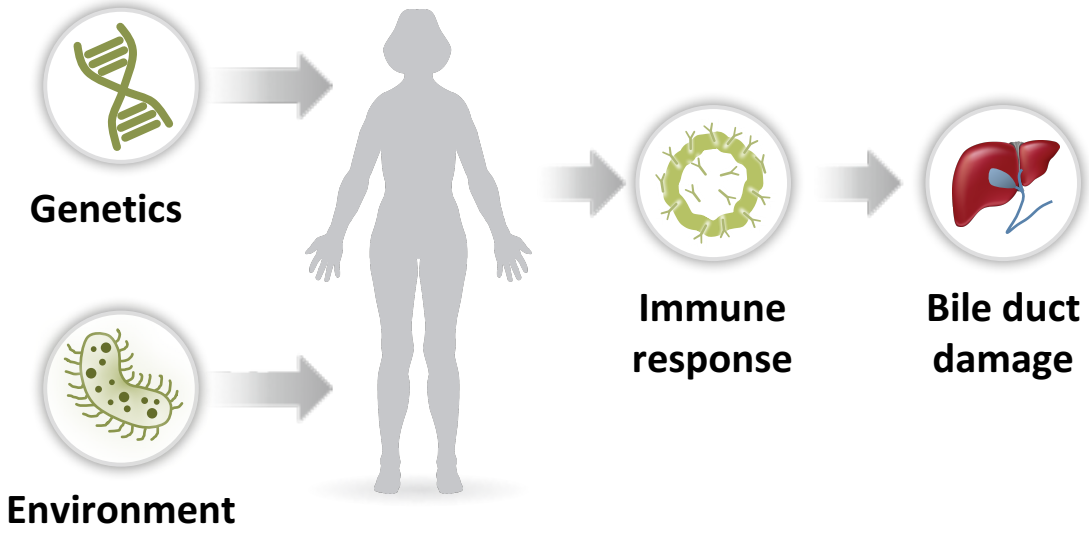
Case Study

- 57-year-old white female presents to you for routine annual exam
- Reports fatigue and intermittent itching
- Only medication is Synthroid; no OTC products
- BMI = 28; no metabolic syndrome

- ALP 300 IU/mL, AST 60 IU/mL, ALT 73 IU/mL, total bilirubin 0.7 mg/dL, hemoglobin 12.3 mg/dL, platelets 185K
- Viral hepatitis serologies negative
- Abdominal ultrasound shows normal liver/spleen morphology, no bile duct dilatation and normal gall bladder.

PBC is a Chronic, Progressive Autoimmune Disease

- PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis
- Factors possibly associated with onset and perpetuation of bile duct injury in PBC



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.

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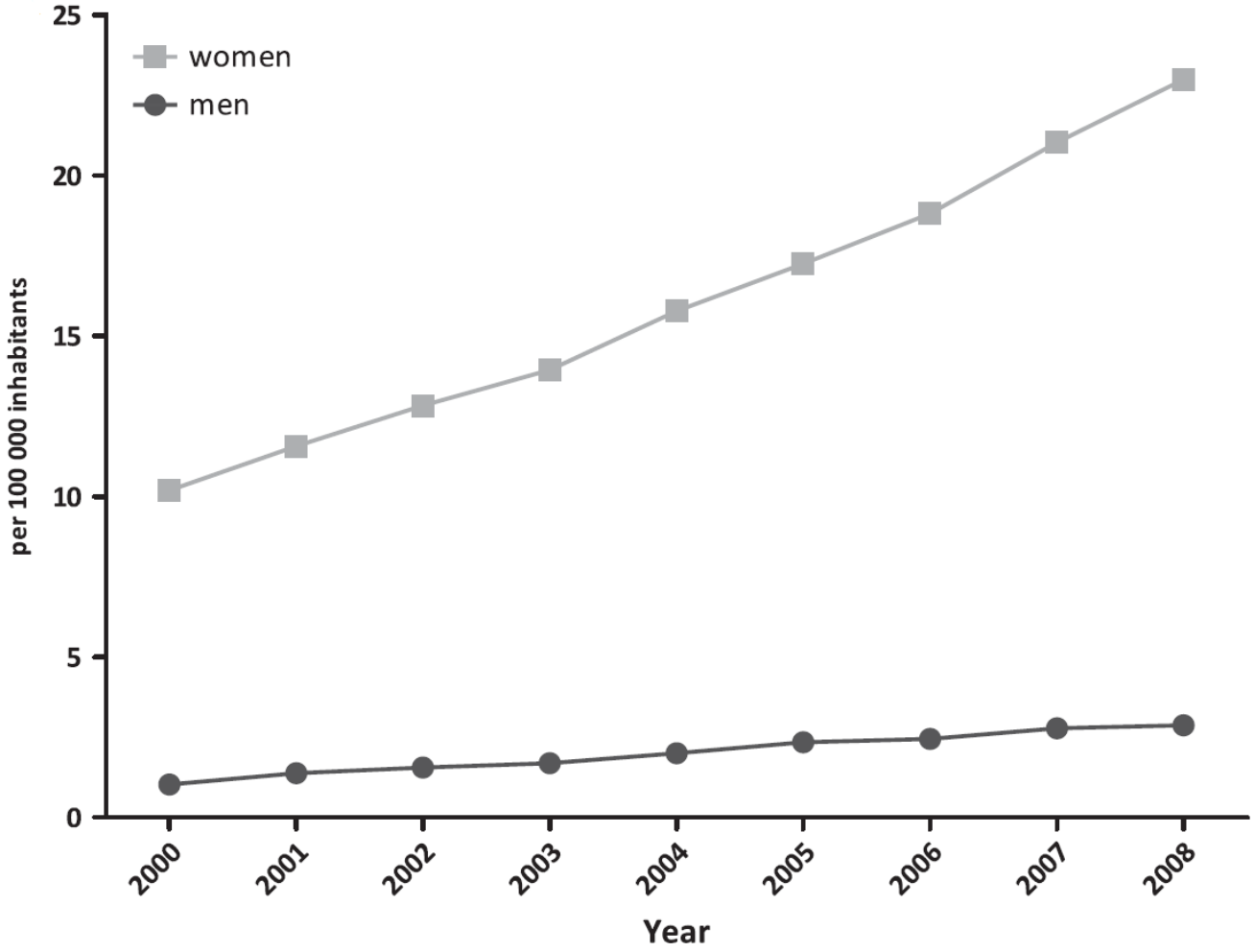
PBC Phenotype

Age	Usually >45 years
Gender	Female > Male (9:1)
Serology	AMA in ~95%; disease-specific ANA in ~30%-50%; ASMA may be present
Immunoglobulin	IgM typically elevated
MRCP	Normal
Liver Histology	Lymphocytic infiltrate; inflammatory duct lesion; granuloma may be present
Coexisting IBD	Not typical

Abbreviations: AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth-muscle antibody; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiography; PBC, primary biliary cirrhosis.

Trivedi PJ, et al. *Aliment Pharmacol Ther*. 2012;36:517-533.

PBC Prevalence



Boonstra K, Kunst A, Stadhouders P, et al. *Liver International*. 2014;34:e35.

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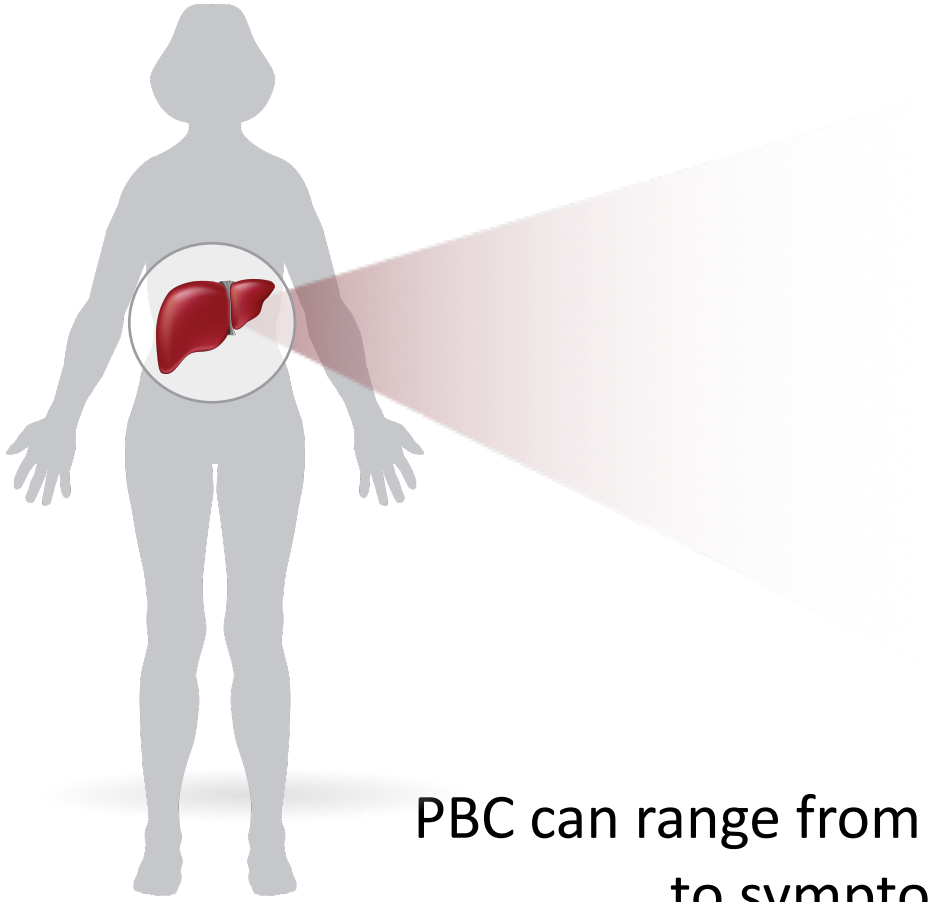
Clinical Features Vary Greatly Between Patients



- Fatigue[1,2]
- Pruritus[1,2]
- Concurrent autoimmune diseases[1,2]
- Reduced bone density[1,2]
- Hypercholesterolemia[1,2]
- Xanthoma and Xanthelasma[2,3]

PBC can range from asymptomatic and slowly progressive to symptomatic and rapidly evolving.[1]

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*. 2009;50(1):291-308.

Diagnostic Considerations

Spectrum of Autoimmune Liver Injuries[1]

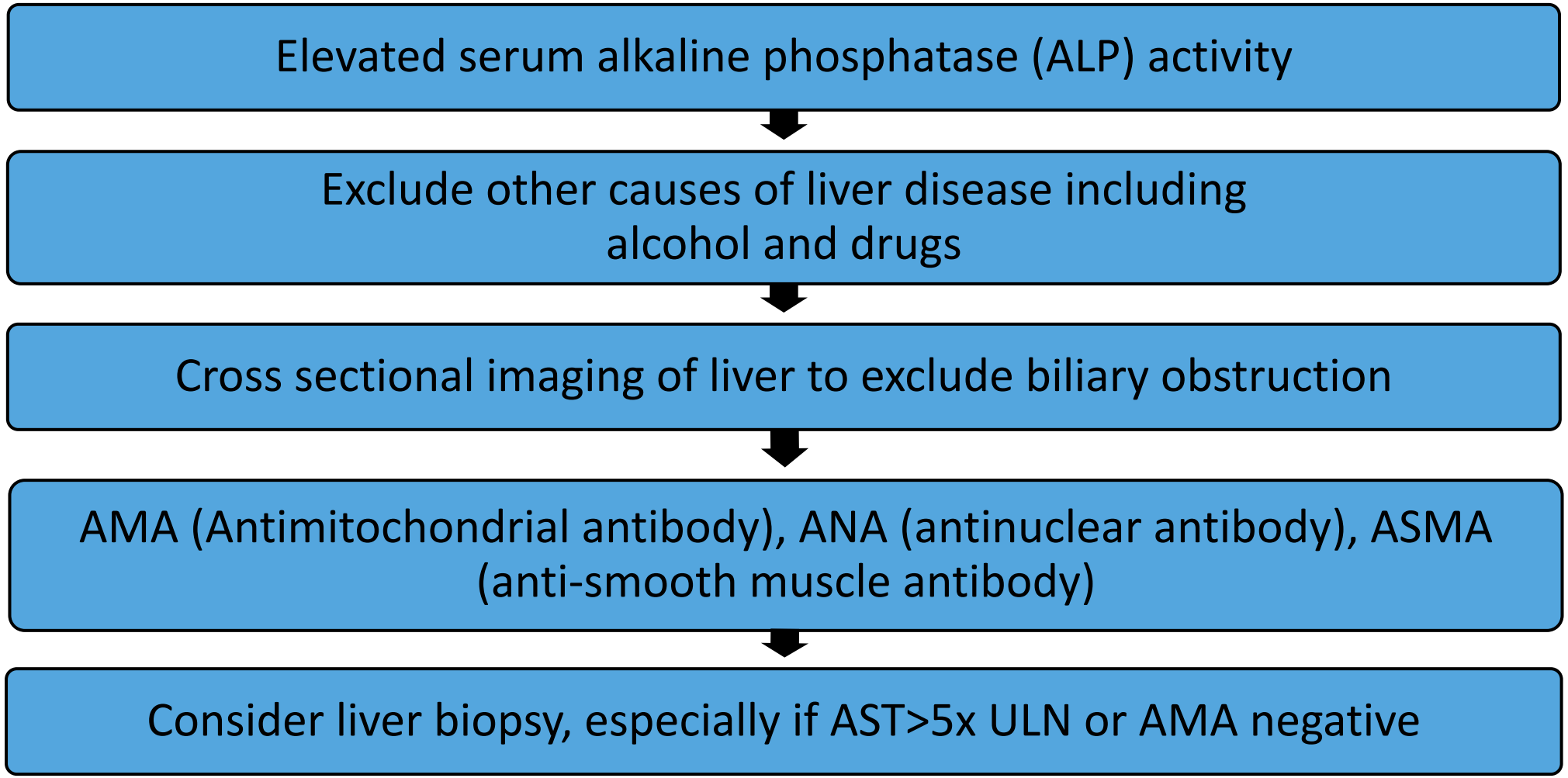
- Autoimmune hepatitis[1]
- Primary biliary cholangitis[1]
- Primary sclerosing cholangitis[1]
- IgG4-related disease[2]

Differential for Cholestatic Liver Biochemistry[3]

- Drug-induced liver injury
- Inherited cholestasis
- Idiopathic ductopenia
- Malignant infiltration
- Nonalcoholic fatty liver disease
- Obstructive biliary lesion
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Sarcoidosis

1. Trivedi PJ, et al. *Aliment Pharmacol Ther.* 2012;36:517-533; 2. Joshi D, et al. *Aliment Pharmacol Ther*. 2014;40:1251-1261;
3. Hirschfield GM, et al. *Best Pract Res Clin Gastroenterol.* 2011;25:701-712.

AASLD Suggested Diagnostic Algorithm for Patients with Suspected PBC



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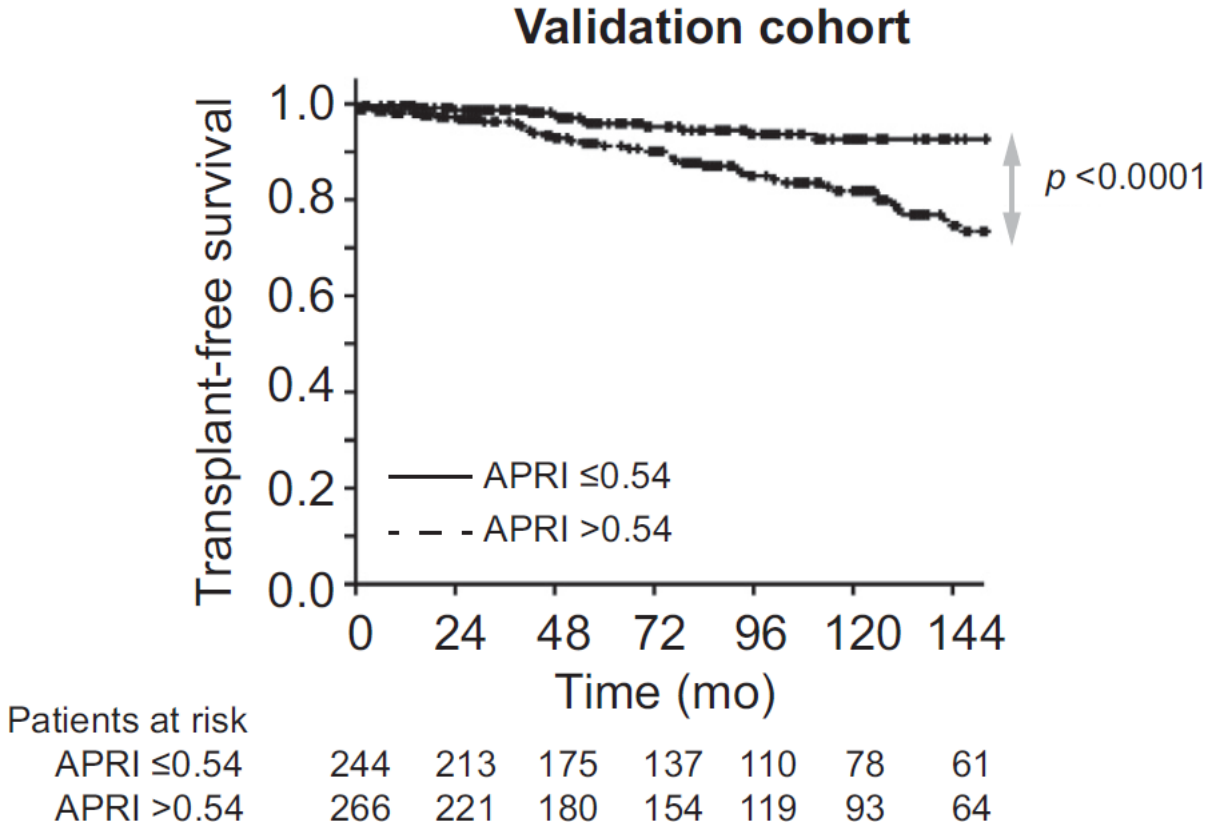
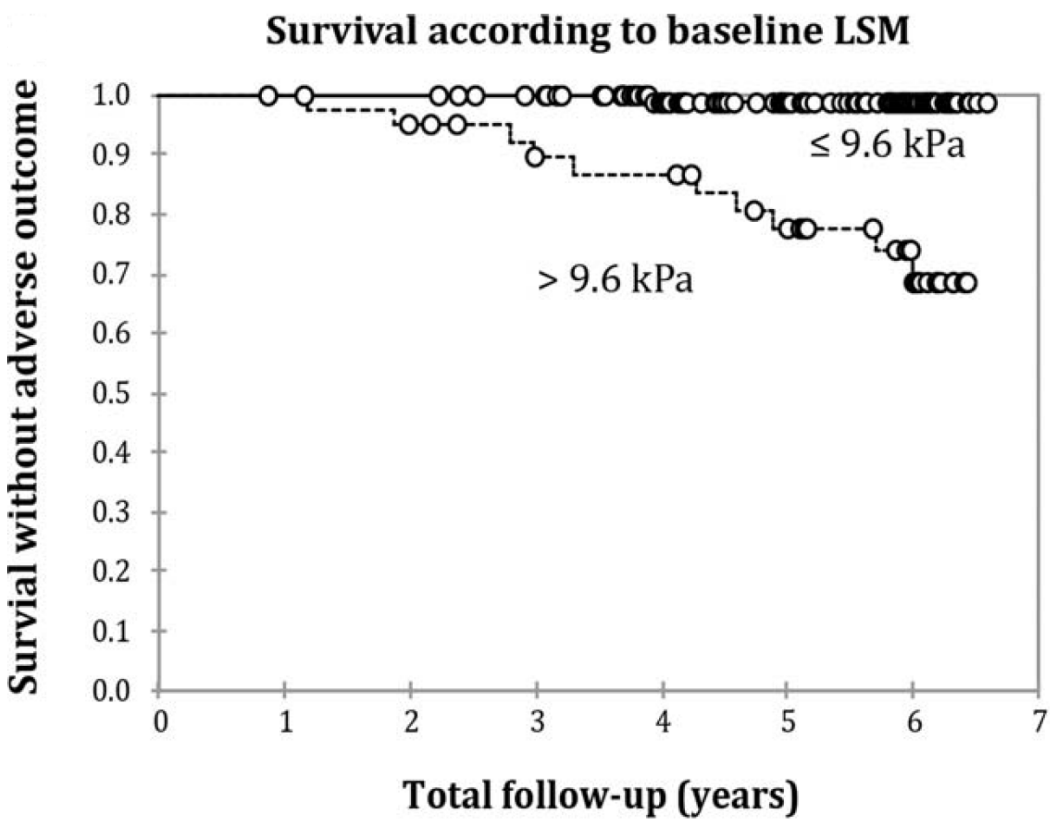
Higher APRI and Elastography Associated with Poor Survival





Trivedi PJ et al. *J Hepatol*. 2014;60(6):1249-58; Corpechot C et al. *Hepatology*. 2012;56(1):198-208.

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Disease Management

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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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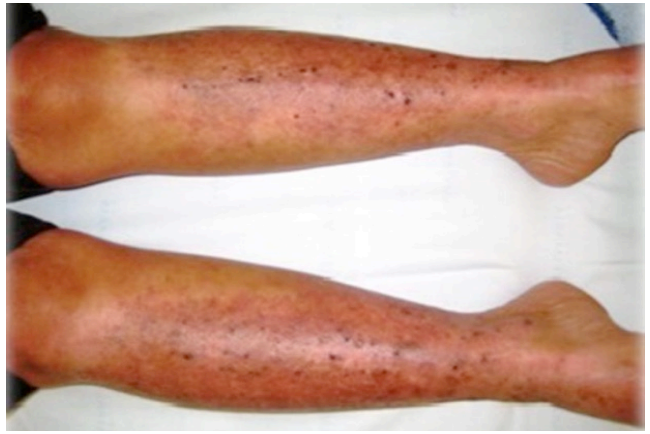
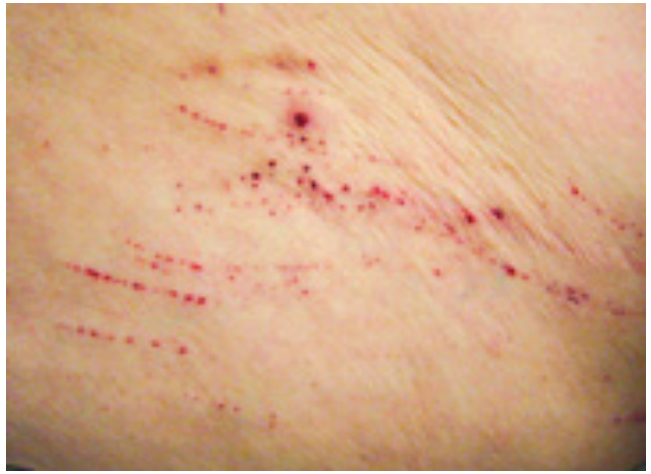
Pruritus Is Common Among PBC Patients

- Prevalence reported as high as 69%[1]
- Unknown etiology[1,2]
  - Bile salts, endogenous opioids, histamine, serotonin, progesterone/estrogen, and autotaxin/lysophosphatidic acid are suspected pruritogens[2]
- Diurnal variation – most intense itch in the late evening[2]
- Localization reported at limbs – soles of feet, palms of hands[2]
- Exacerbated by contact with wool, heat, or pregnancy[3]





1. Imam MH, et al. *J Gastroenterol Hepatol*. 2012;27(7):1150-1158;
2. Beuers U, et al. *Hepatology*. 2014;60(1):399-407;
3. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308.

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Numerous Treatment Options Exist to Help Patients Manage Their Pruritus

General Recommendations[1]	• Skin moisturizer • Wet, cooling, or moist wraps • Topical agents with symptomatic relief (eg, camphor, menthol) • Relaxation techniques • Training to stop the cycle of itch, scratch, itch
First-line[2-4]	Bile acid sequestrants: •Cholestyramine •Colestipol, colesevelam
The following agents may be used for pruritus that is refractory to bile acid sequestrants:	
Second-line[2-4]	Rifampicin
Third-line[2-4]	Oral opioid antagonists: •Naltrexone •Nalmefene
Fourth-line[2-4]	Selective serotonin reuptake inhibitors: •Sertraline

1. Weisshaar E, et al. *Acta Derm Venereol*. 2012;92(5):563-581; 2. European Association for the Study of the Liver. *J Hepatol*. 2009;51(2):237-267; 3. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308. 4. Hohenester S, et al. *Semin Immunopathol*. 2009;31(3):283-307.

Long Term Management

- Liver chemistry tests every 3-6 months
- Thyroid status (TSH) annually
- Bone mineral densitometry every 2-4 years
- Vitamins A, D, K annually if bilirubin >2.0
- Upper endoscopy every 1-3 years if cirrhotic or Mayo risk score >4.1
- Ultrasound ± AFP every 6 months in patients with known or suspected cirrhosis

Ursodeoxycholic Acid (UDCA) and Treatment Response

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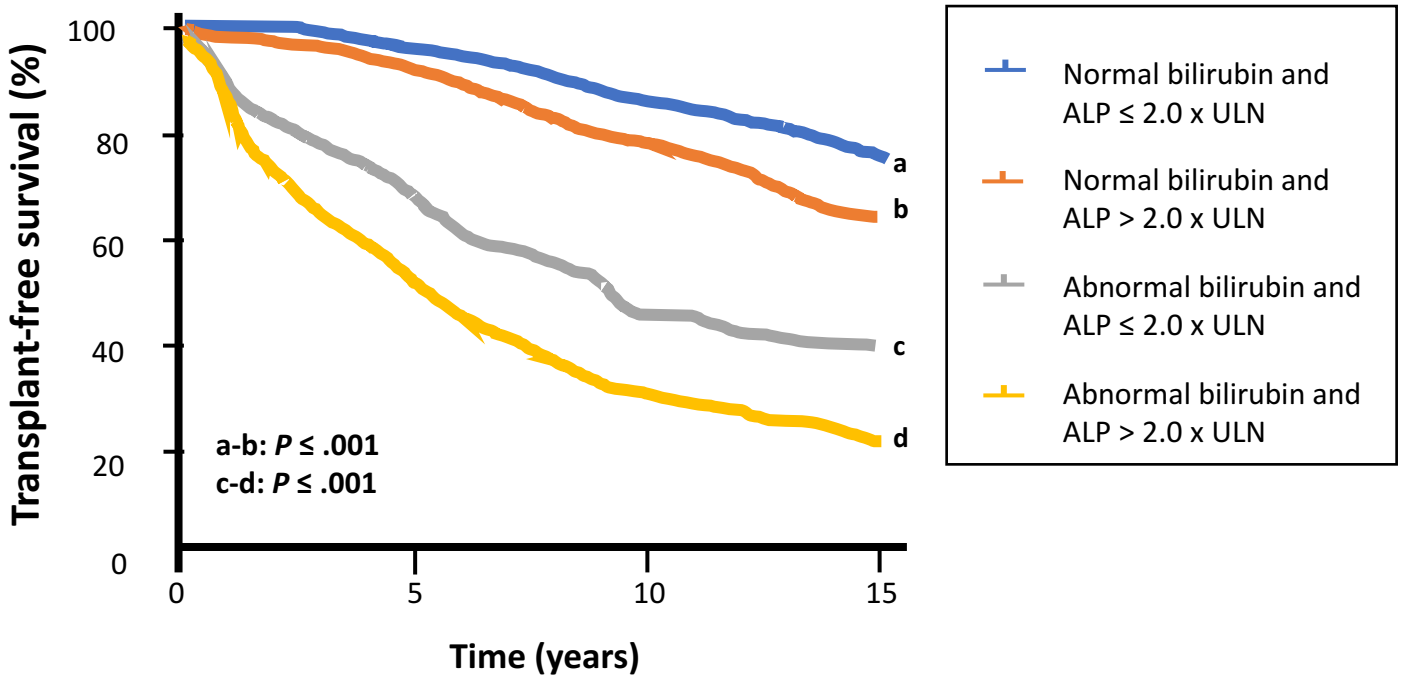
First Line: Ursodeoxycholic Acid (UDCA)

- UDCA is the only FDA-approved first-line PBC therapy
- Recommended adult dosage is 13–15 mg/kg/day
- Orally administered, naturally occurring, hydrophilic secondary bile acid
- Typically administered in 2 divided doses

Abbreviations: FDA, Food and Drug Administration; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

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

UDCA: Bilirubin and Alkaline Phosphatase at 1 Year Follow-up



a	2112	1482	887	504
b	681	489	337	228
c	271	193	153	137
d	400	345	302	283

Lammers, et al. *Gastroenterology*. 2014; 147:1338-1349.

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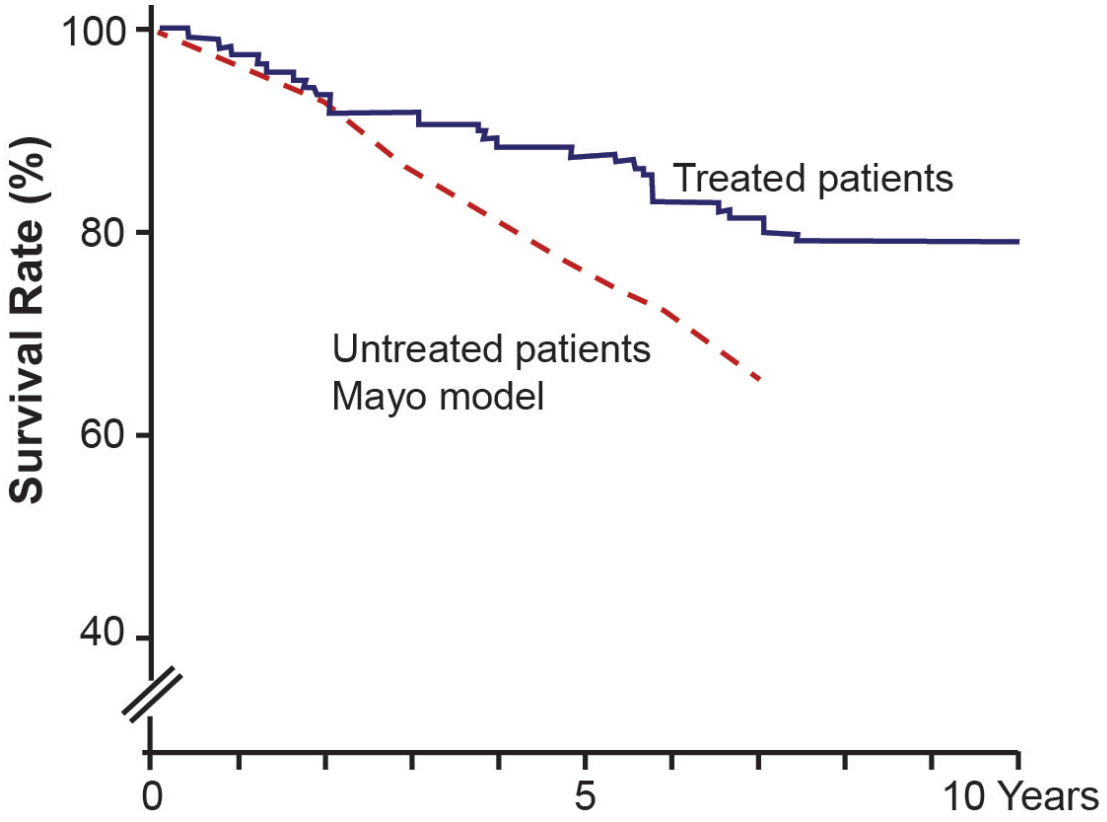
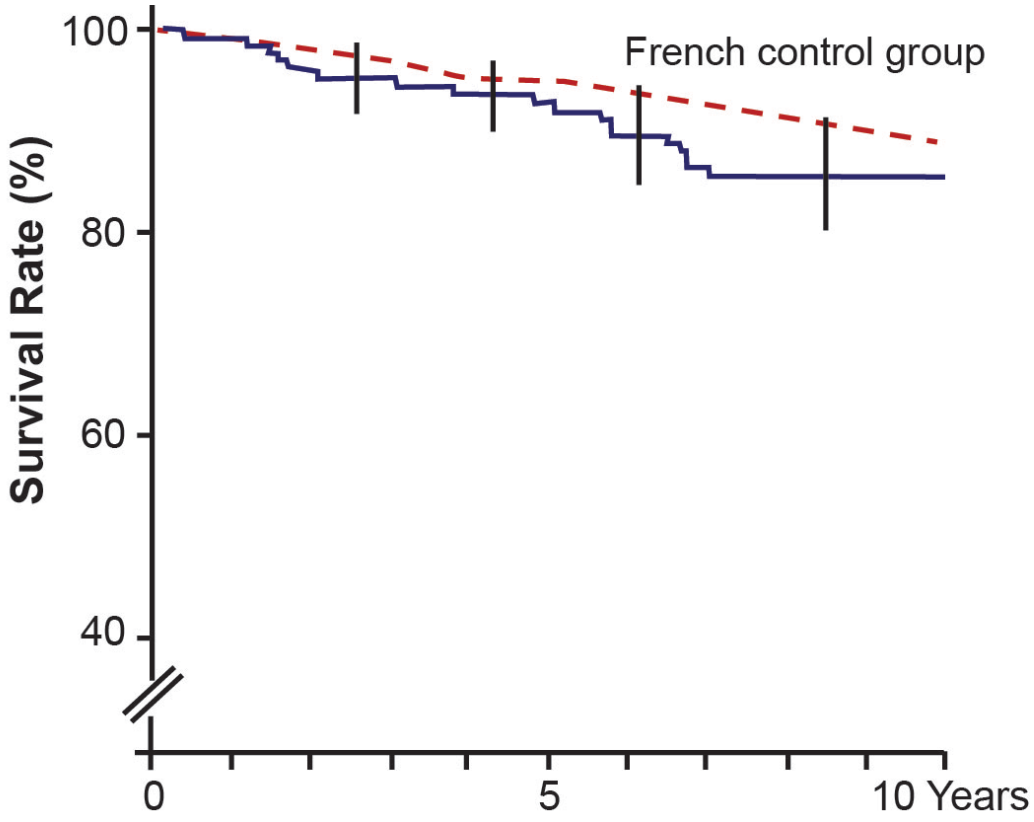
UDCA: Overall Survival

UDCA Treated vs. Untreated



UDCA Treated vs. Healthy Control



Poupon RE, Bonnand AM, Chretien Y, et al. *Hepatology*. 1999; 29(6):1668-1671

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UDCA Treatment Failure: Depends on Definition

Study	Treatment Failure (%)
Pells et al, 2013[1] (UK-PBC group)	• 60% of patients presenting at age <40 years • 10% of patients presenting at age >70 years
Corpechot et al, 2011[2]	• 13%–37%*
Kuiper et al, 2009[3]	• 34%–38%*
Corpechot et al, 2008[4]	• 35%–39%*

*Depending on criteria used.

1. Pells G, et al. *J Hepatol.* 2013;59:67-73; 2. Corpechot C, et al. *J Hepatol.* 2011;55:1361-1367;
3. Kuiper EM, et al. *Gastroenterology.* 2009;136:1281-1287; 4. Corpechot C, et al. *Hepatology.* 2008;48:871-877.

Established Response Criteria Models (2006-2010)

Barcelona[1] (2006)	ALP decreased by >40% from baseline or normalized after 1 year UDCA
Paris-I[2] (2008)	All 3 of the following: ALP ≤3 x ULN; AST ≤2 x ULN; and bilirubin ≤1 mg/dL after 1 year UDCA
Rotterdam[3] (2009)	Albumin and bilirubin normalization when 1 or both were abnormal at baseline; albumin OR bilirubin normalization when both were abnormal at baseline after 1 year UDCA
Toronto[4] (2010)	ALP <1.67 x ULN after 2 years UDCA

1. Parés A, et al. *Gastroenterology.* 2006;130:715-720; 2. Corpechot C, et al. *Hepatology.* 2008;48:871-877;
3. Kuiper EM, et al. *Gastroenterology.* 2009;136:1281-1287; 4. Kumagi T, et al. *Am J Gastroenterol.* 2010;105:2186-2194.

Modifications of Biochemical Response Criteria Models (2011-2013)

Paris-II[1] (2011)	All 3 of the following: ALP ≤1.5 x ULN; AST ≤1.5 x ULN; and bilirubin ≤1 mg/dL after 1 year UDCA
Early Biochemical Response[2] (2013)	Barcelona, Paris-I, or Toronto criteria met at 6 months UDCA

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

1. Corpechot C. *J Hepatol.* 2011;55:1361-1367; 2. Zhang LN, et al. *Hepatology*. 2013;58:264-272.

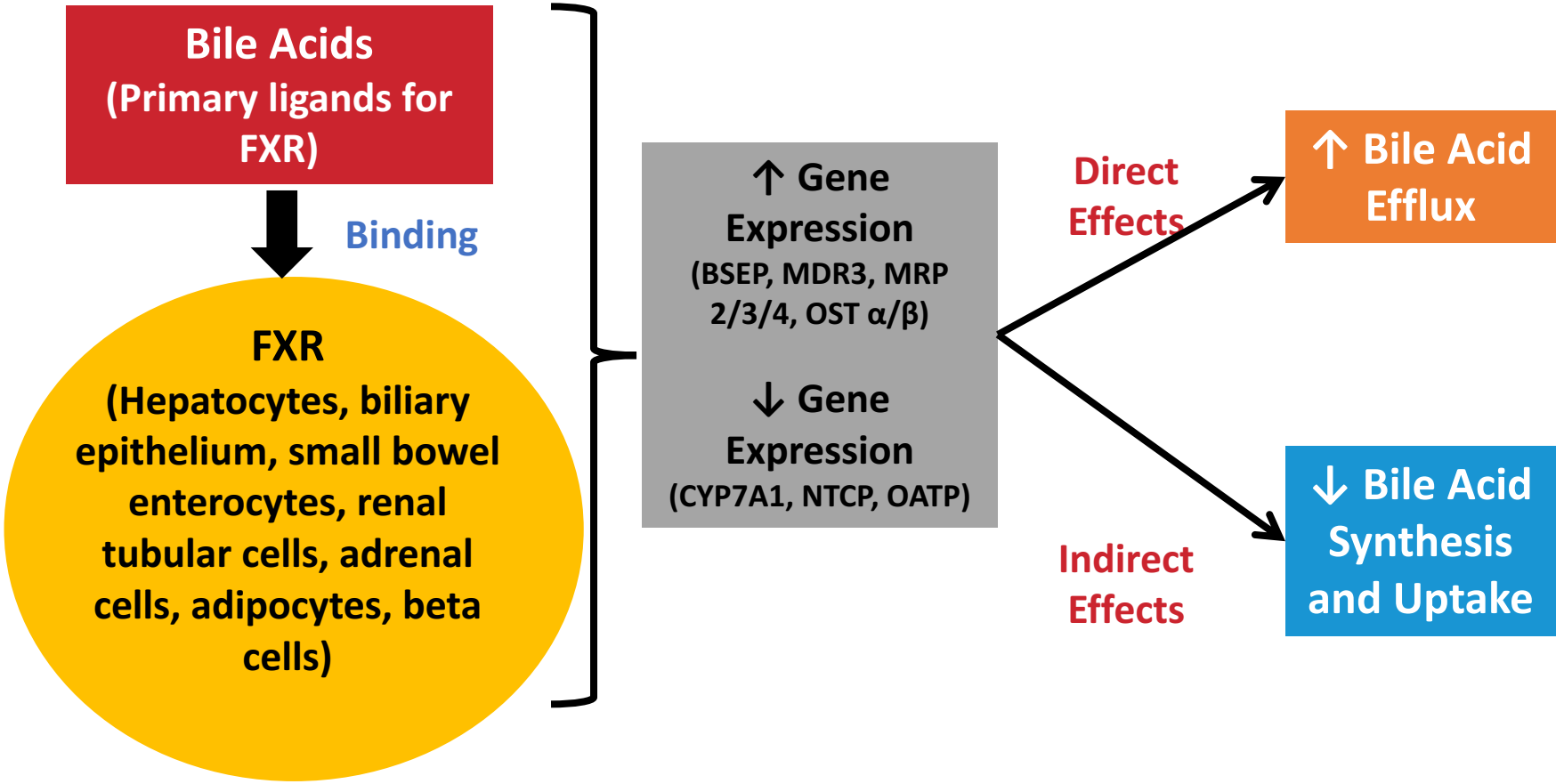
Optimized Response Criteria Models (2014-2015)

Biochemical + APRI[1] (2014)	Biochemical response (Barcelona, Paris-I/II, or Toronto) and APRI ≤0.54 after 1 year UDCA
UK-PBC Risk Score[2] (2015)	Prognostic index comprising baseline albumin and platelet count, plus bilirubin, ALT or AST, and ALP after 1 year UDCA
GLOBE Score[3] (2015)	Prognostic index comprising baseline age, and bilirubin, ALP, albumin, and platelet count after 1 year UDCA

1. Trivedi PJ, et al. *J Hepatol.* 2014;60:1249-1258; 2. Carbone M, et al. *Hepatology.* 2015 Jul 29; 3. Lammers WJ, et al. *Gastroenterology.* 2015 Aug 7.

Treating Those with an Inadequate Response to UDCA

Farnesoid X Receptor Signaling



Abbreviations: BSEP, bile salt export pump; FXR, farnesoid X receptor; MRP 2/3/4, multidrug resistant protein 2/3/4; NTCP, sodium/taurocholate cotransporting polypeptide; OATP, organic anion transporting polypeptide; OST α/β, organic soluble transporter α/β.

Neuschwander-Tetri BA. *Curr Gastroenterol Rep.* 2012;14:55-62.

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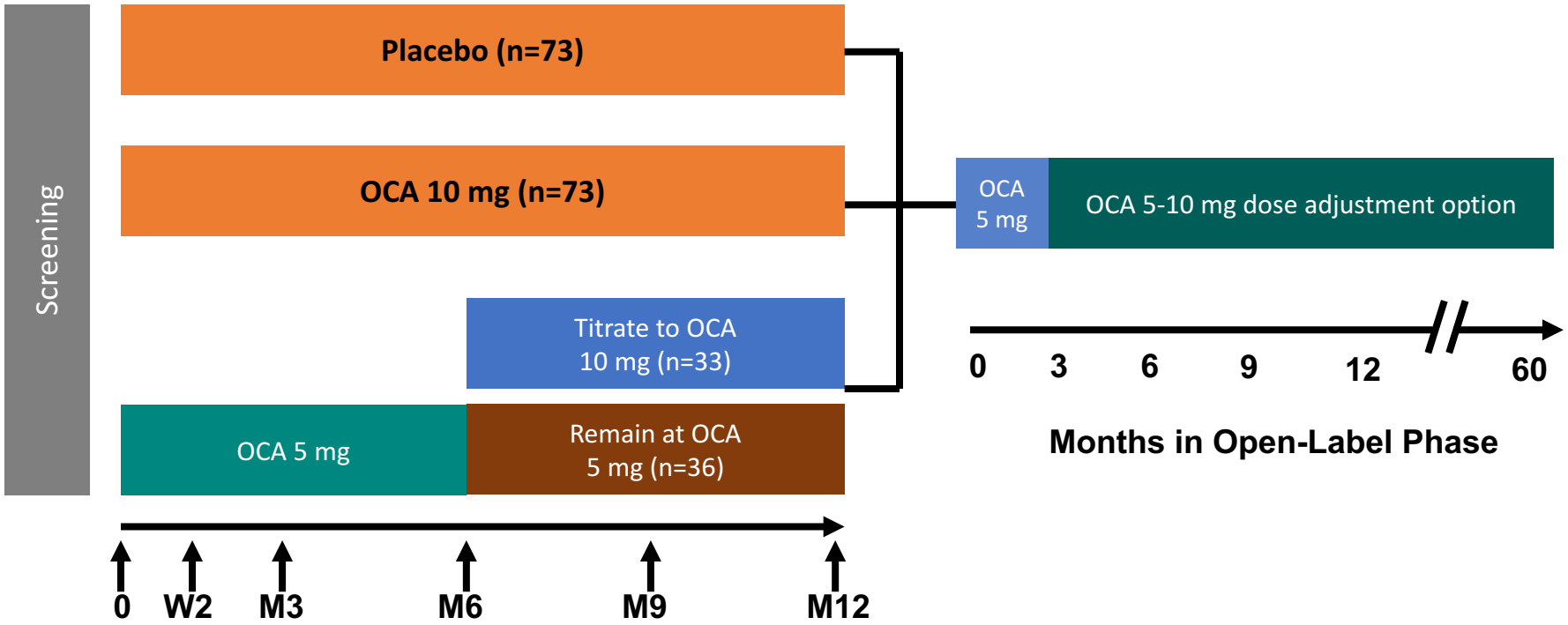
OCA in Patients with PBC: POISE Study Design



- If patients were on UDCA at baseline, they were allowed to continue throughout the course of therapy.

Modified from Nevens F et al. *N Engl J Med* 2016;375:631-643.

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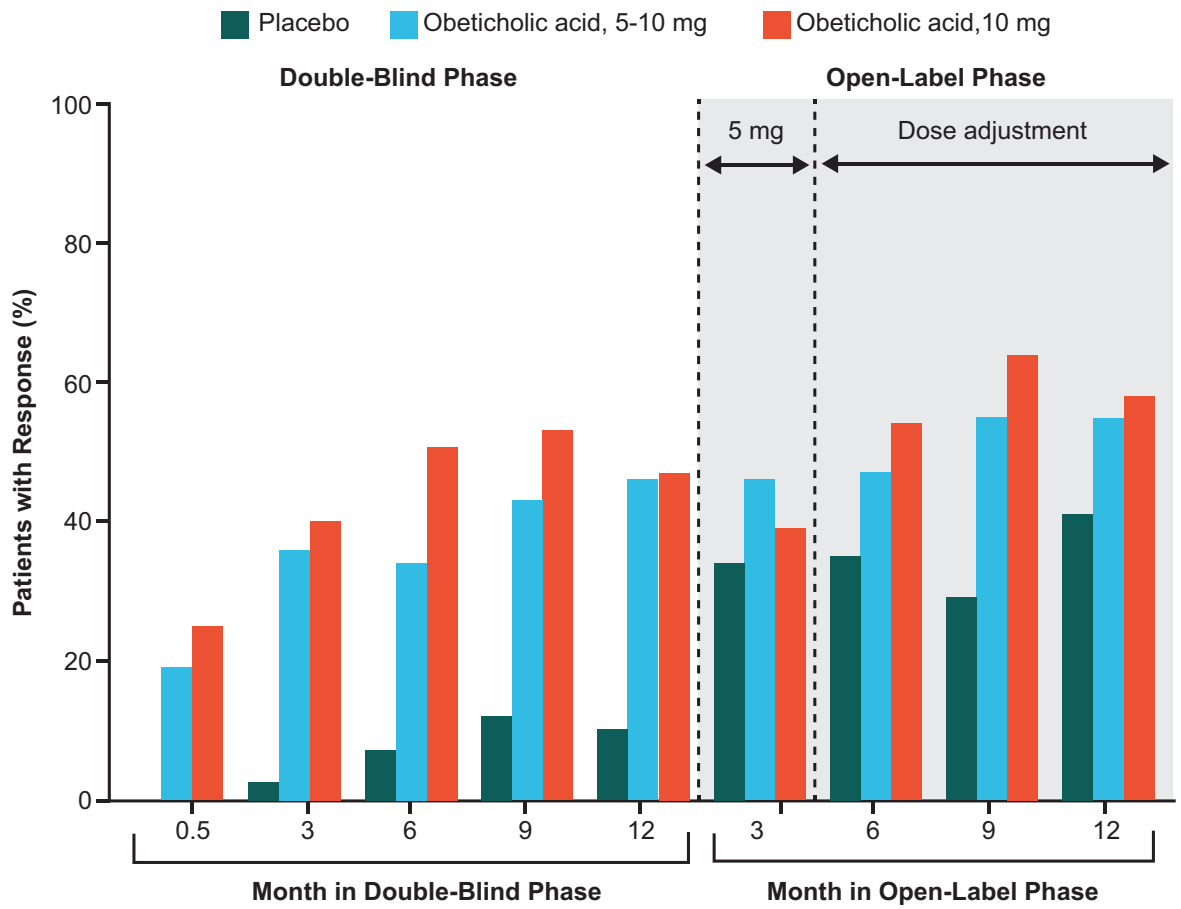
Primary Endpoint: POISE Study

Positive response at 12 months defined as:

- ALP <1.67 x ULN and
- bilirubin WNL and
- ≥15% ALP reduction

Both OCA 10 mg and OCA 5-10 mg titration arm significantly better than placebo arm (p<0.0001)



No. of Patients									
Placebo	73	73	73	73	73	64	60	59	59
Obeticholic acid, 5-10 mg	70	70	70	70	70	63	62	62	60
Obeticholic acid, 10 mg	73	73	73	73	73	64	59	61	59

Nevens F, et al. *N Engl J Med.* 2016;375:631-643.

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Adverse Events in POISE and Open-Label Extension

Event	Placebo N=73 n (%)	OCA 5 -10 mg N=70 n (%)	OCA 10 mg N=73 n (%)	Open Label N=193 n (%)
Pruritus	28 (38)	39 (56)	50 (68)	138 (72)
Nasopharyngitis	13 (18)	17 (24)	13 (18)	45 (23)
Headache	13 (18)	12 (17)	6 (8)	36 (19)
Fatigue	10 (14)	11 (16)	17 (23)	50 (26)
Nausea	9 (12)	4 (6)	8 (11)	28 (15)
Serious Adverse Events	3 (4)	11 (16)	8 (11)	27 (14)

Modified from Nevens F, et al. *N Engl J Med.* 2016;375:631-643.

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Conclusions

- PBC is a slowly progressive disease that is associated with morbidity and mortality
- Fatigue and pruritus limit health-related quality of life
- UDCA has been a mainstay of therapy
- Definition of UDCA nonresponse still not standardized
- OCA given to those with an inadequate response to or unable to tolerate UDCA produced a significant clinically meaningful improvement in liver biochemistry, which have been shown to correlate strongly with clinical benefit.

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