Autoimmune Potpourri

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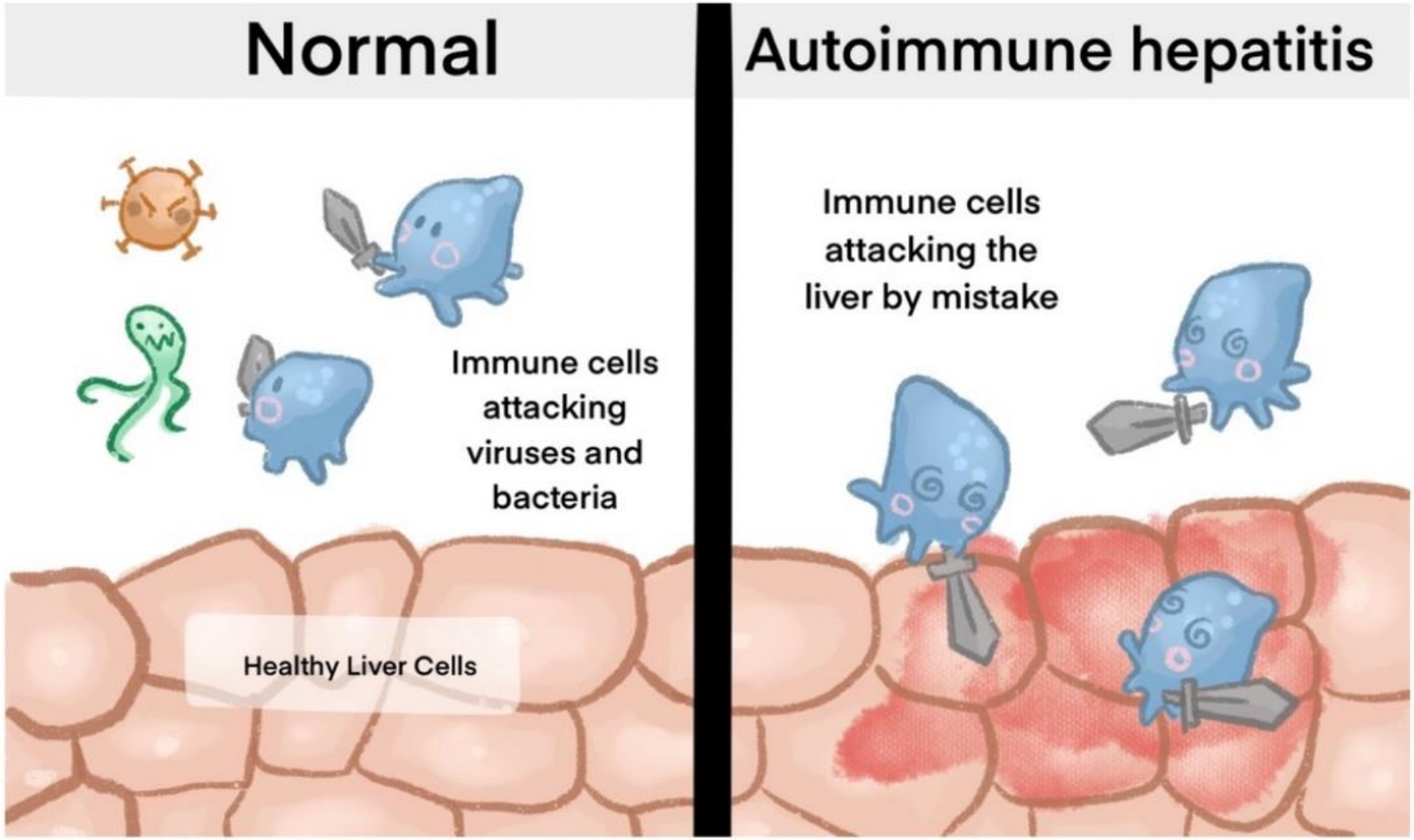
Autoimmune Potpourri

- Autoimmune Hepatitis (AIH)
- Primary Sclerosing Cholangitis (PSC)
- Primary Biliary Cholangitis (PBC)

What is Autoimmune Hepatitis (AIH)?

- Chronic, immune mediated inflammatory disease
- Elevated transaminase (AST, ALT)
- Elevated IgG levels
- + the presence of one or more autoantibody (ANA, SMA, SLA and LKM1)
- Liver biopsy: Interface hepatitis, plasma cell infiltration, lobular hepatitis



Mechanism of Autoimmune Hepatitis. Courtesy Aria Puri.

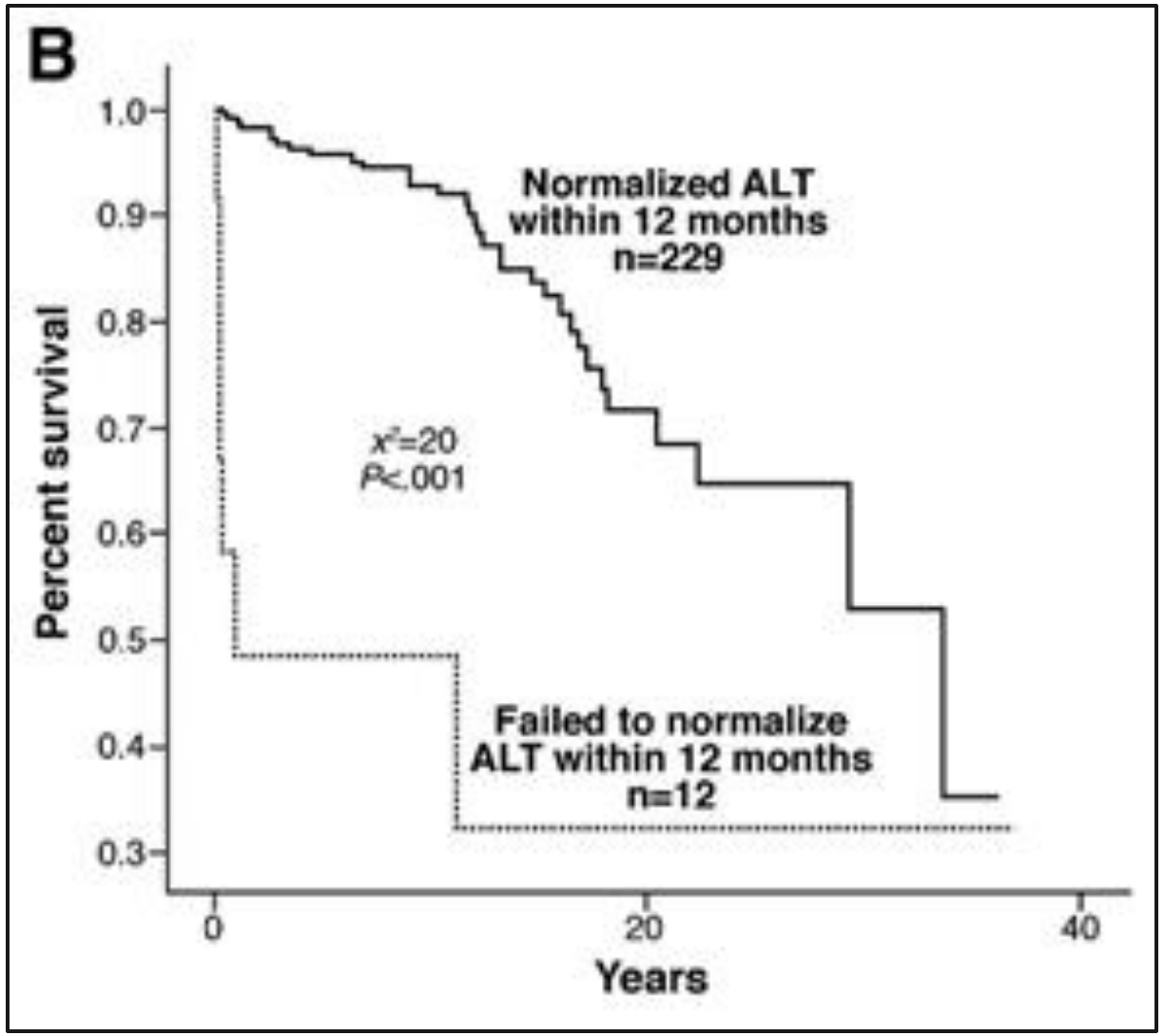
Liver Diseases That Resemble AIH

Viral hepatitis
Drug-induced liver injury
Wilson’s disease
Hereditary hemochromatosis
PBC
PSC
MASLD/MASH

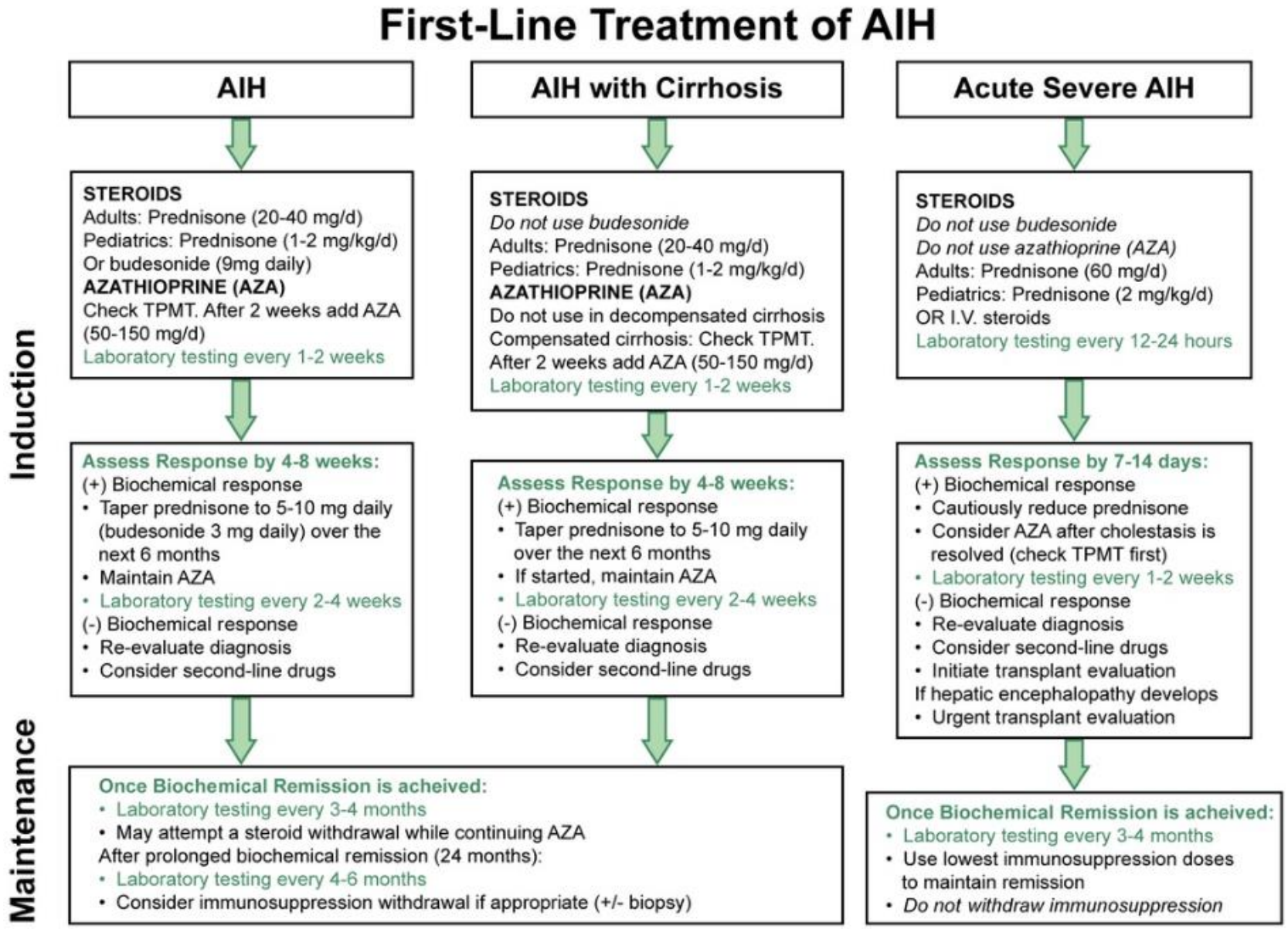
Goal of Treatment for AIH

- Improve symptoms, control hepatic inflammation
- Achieve biochemical remission (normalization of AST, ALT, IgG)
- Promote the regression of fibrosis at the lowest risk of drug-induced complication
- Prevent disease progression

Biochemical Response is Associated With Improved Survival



First Line Treatment for AIH



AASLD AIH 2019 Guidelines

First Line Treatment for AIH

Steroids

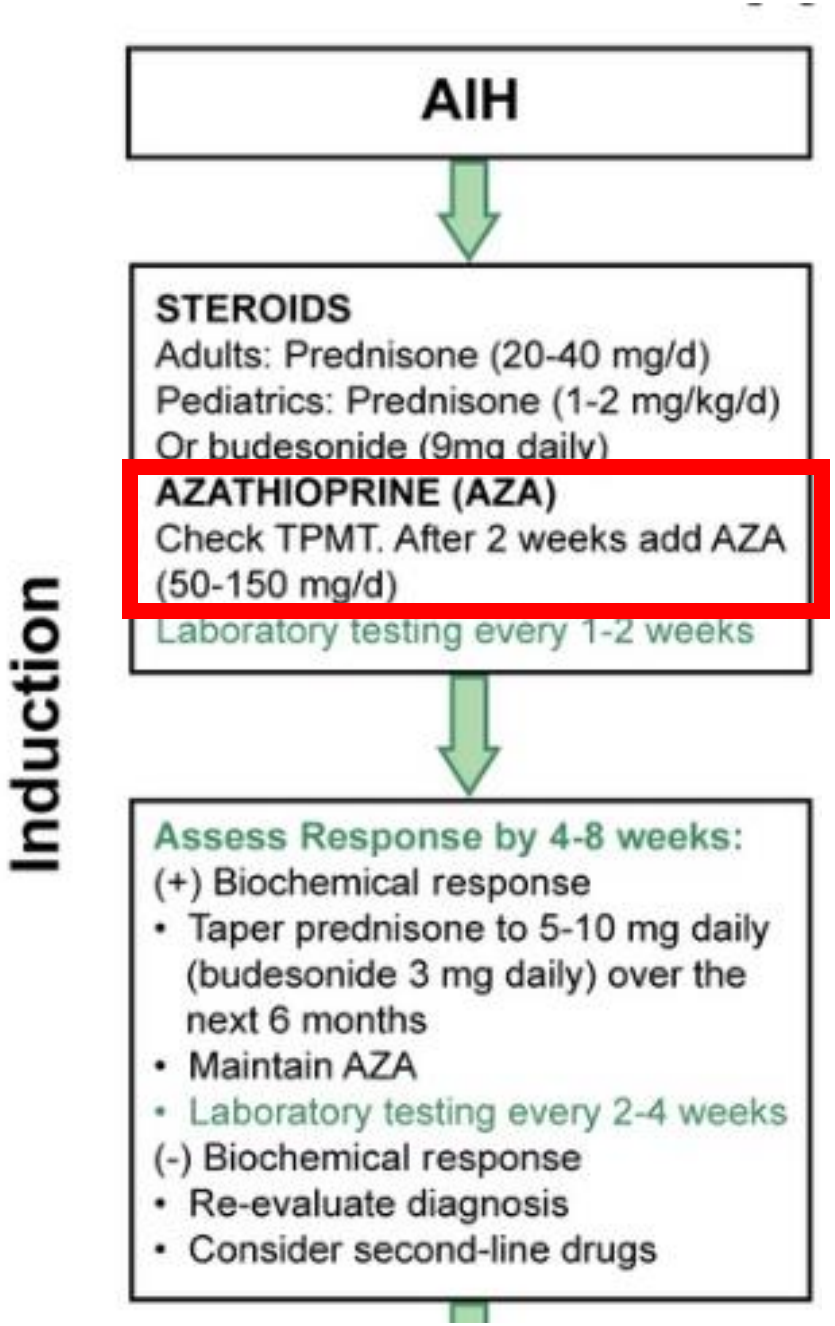
- Prednisone 20-40 mg/day
- Budesonide 9 mg daily

Immunosuppression

- Azathioprine 50-150 mg daily or 1-2 mg/kg/day

Side Effects of First Line Drugs in AIH

Drug	Side Effects	Management Options
Prednisone	Weight gain, glucose intolerance/diabetes, HTN, fatty liver, osteoporosis, opportunistic infections, psychosis, depression, anxiety	Lifestyle interventions for metabolic syndrome, bone density monitoring, Vitamin A/D, proactive screening for mental health symptoms
Budesonide	Unable to reach the liver with portal hypertensive shunts, portal vein thrombosis in cirrhosis	Should not be prescribed in cirrhotic patients
Azathioprine (AZA)	Mild cytopenia, severe leukopenia, bone marrow failure, cholestatic liver changes, nonmelanoma skin cancer	Reduce dose if mild cytopenia, discontinue in severe cytopenia, GI intolerance, and screening for skin CA



Checking AZA Metabolite

- Patients with zero or near zero TPMT activity are at risk for **myelosuppression**
- Absent or near absent TPMT activity occurs in 0.3-0.5% of the population
- Screening for TPMT does not reduce the frequency of other side effects to AZA

Second Line Treatment for AIH

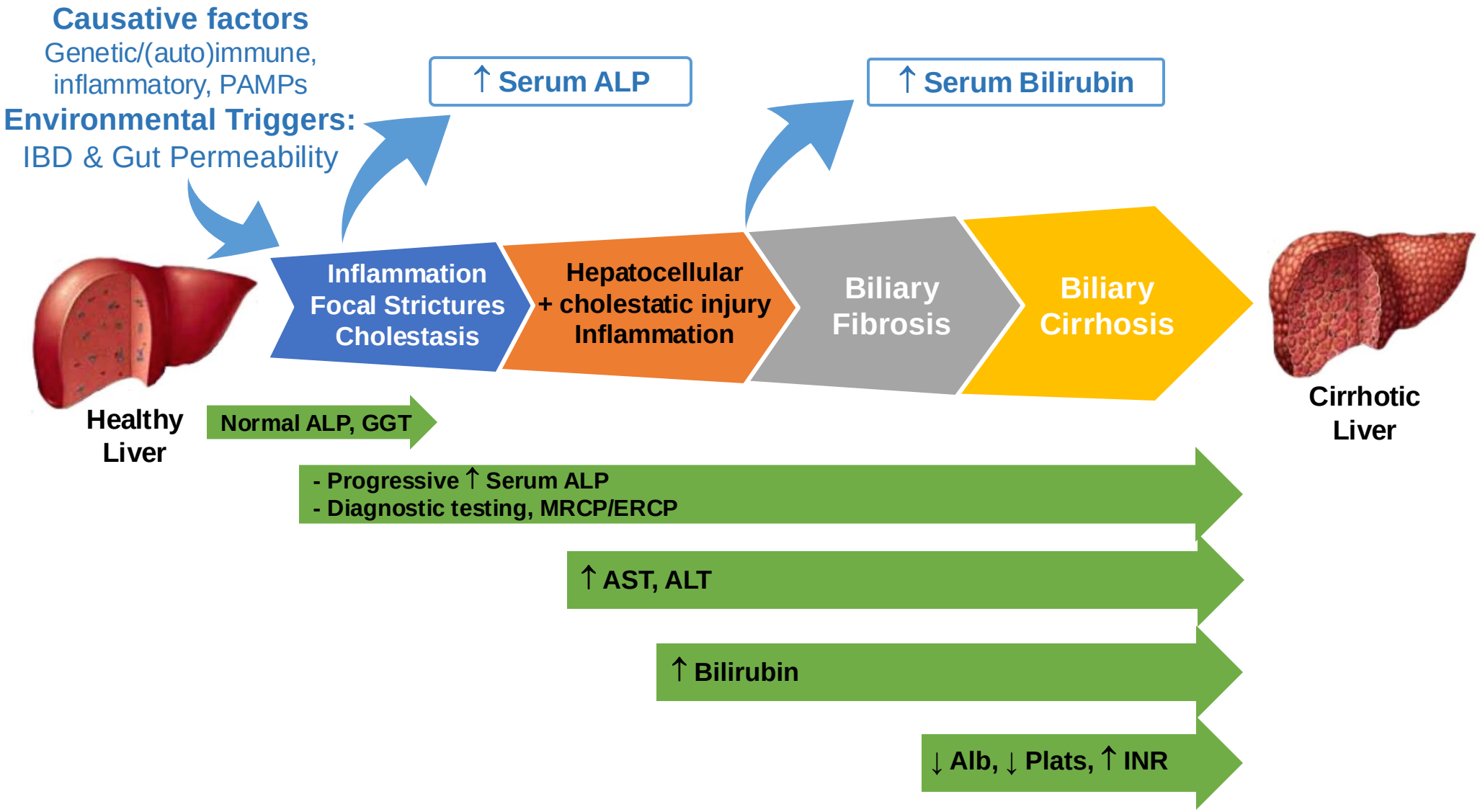
- Mycophenolate mofetil (MMF)
- Calcineurin inhibitors (tacrolimus)
- Mercaptopurine
- Biologics (rituximanb and infliximab)

AIH: Key Takeaways

- Chronic liver disease with an immune-mediated pathogenesis.
- Characterized by elevated liver enzymes, autoantibodies (ANA, SMA, LKM), and liver histology with inflammatory changes.
- Treated with immunosuppressive therapy (prednisone, azathioprine).

Primary Sclerosing Cholangitis (PSC)

Primary Sclerosing Cholangitis (PSC): Autoimmune Disease

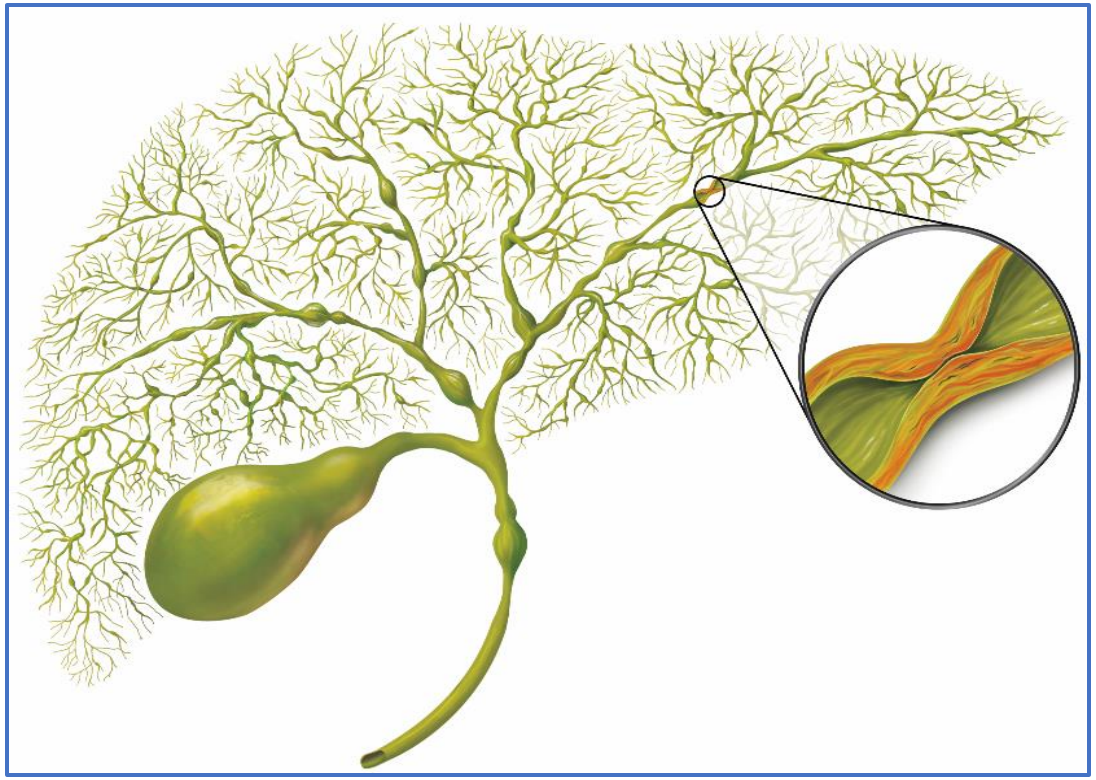


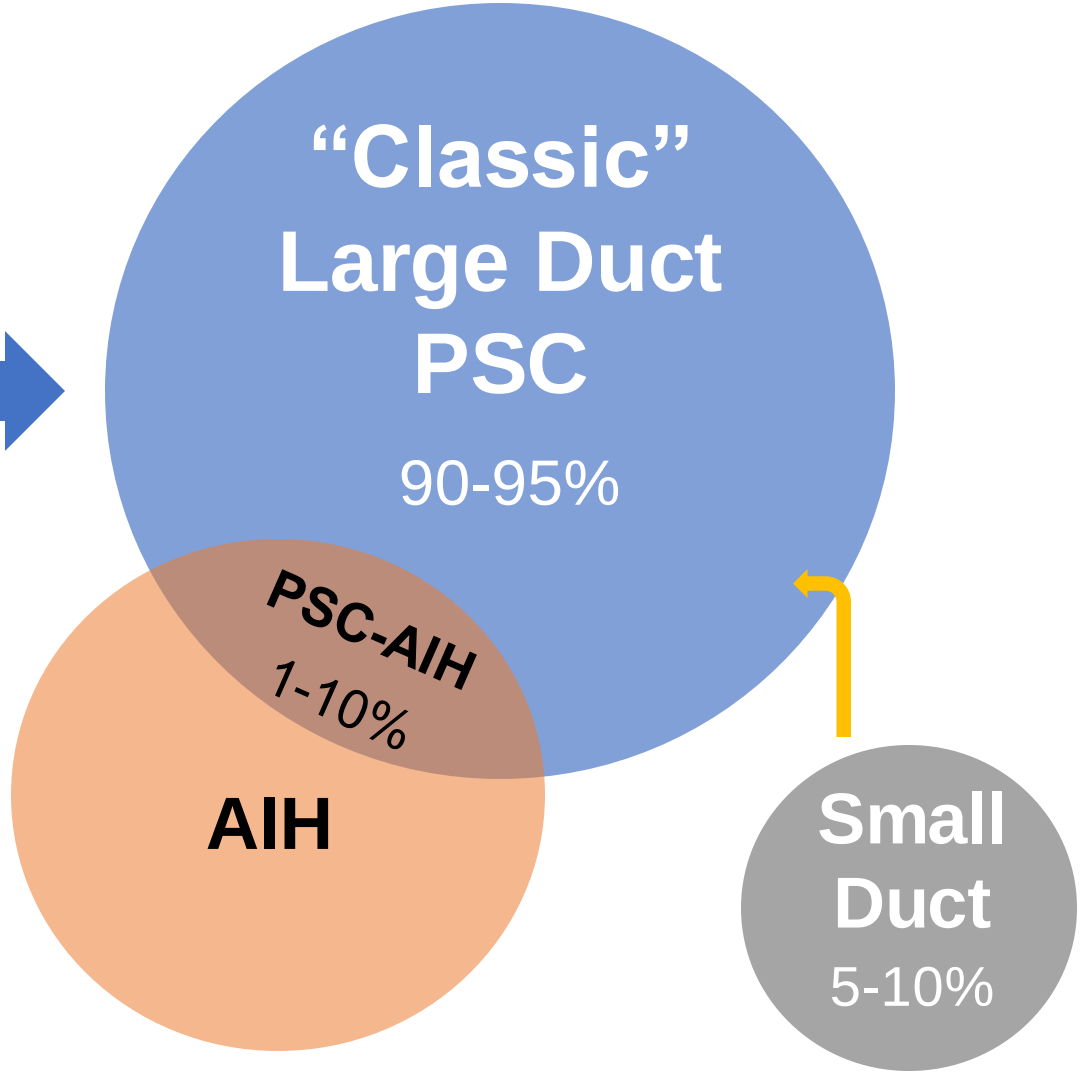
Demographics and Epidemiology of PSC

- Afflicts all ages and races
- Prevalence ~ 40 per million with familial predisposition
  - 0.7% among 1st degree relatives (100-fold ↑)
  - 1.5% among siblings
- Male: Female Ratio: 1.5:1 (60% males)
- Diagnosis <45 years of age in 67%

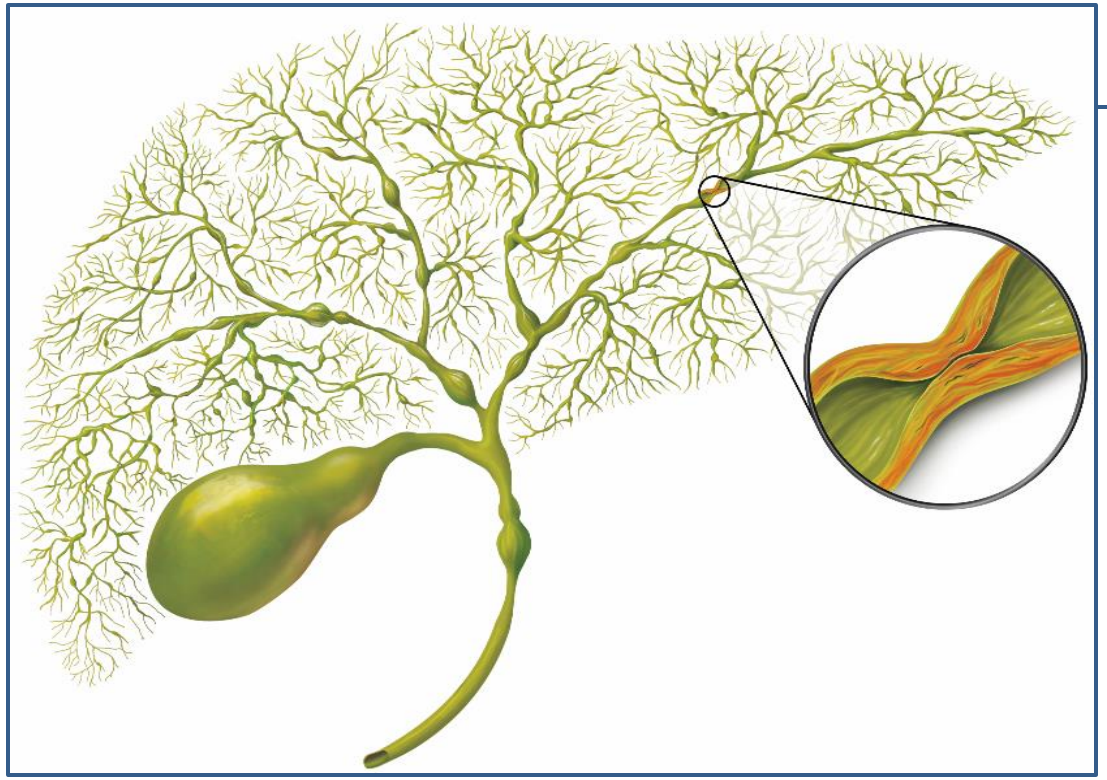
Primary Sclerosing Cholangitis (PSC)

Three Distinct Clinicopathological Entities

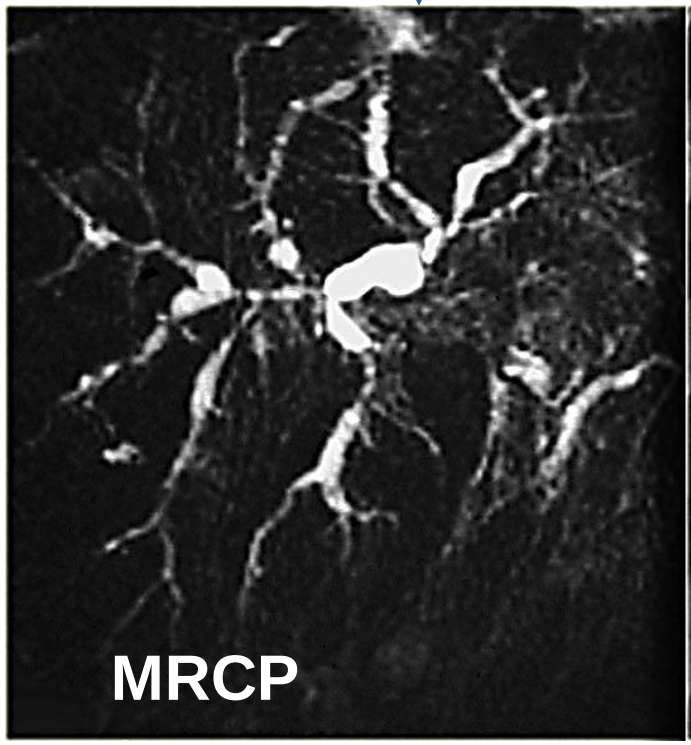


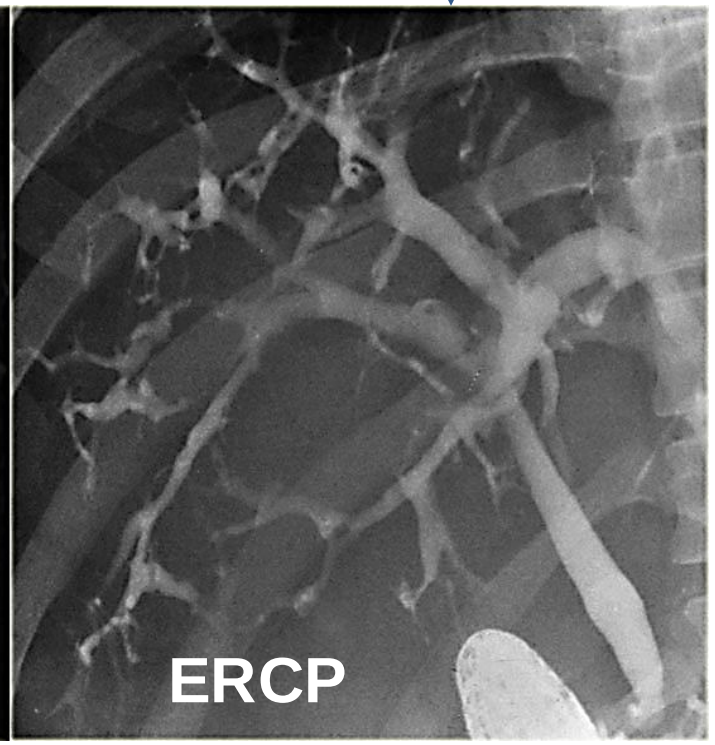


Primary Sclerosing Cholangitis (PSC)



Cholangiography for Detection of Large Duct Disease





Vierling JM. PSC. *Schiff's Liver Diseases.* 12th Ed. 2017.

Primary Sclerosing Cholangitis (PSC)

Association with colitis:

- Ulcerative colitis: 70-98%, often with a rarer UC phenotype
  - Rectal sparing (52% vs 6%)
  - Backwash ileitis (51% vs 7%)
- Crohn's colitis or ileocolitis: 3-13%

Prevalence of IBD Colitis:

- 50% at time of PSC diagnosis
- Increases to ≥80% with time
- Prevalence of PSC in IBD Centers
  - USA using ERCP for elevated ALP:
    - 2.3-4.6% in UC
    - 1.2-3.6% in CD
- Systematic MRCP screening: PSC in 8.1% (65% had liver tests WNL)

*** Strong Association with Inflammatory Bowel Disease (IBD)

Vierling JM. PSC. *Schiff's Liver Diseases.* 12th Ed. 2017.

Treatment for PSC

- No proven pharmacological therapy for PSC
- UDCA is not approved for PSC, but commonly used
- High doses of UDCA are contraindicated
- If ALP remains elevated it is reasonable to try 13-23 mg/kg/day, and it can be continued if improvement in ALP or symptoms improve
- Current management is tailored to the individual, remains compassionate and supportive

PSC Management

- Endoscopic therapy of dominant strictures
  - Short-term stenting of 2-3 weeks vs. balloon dilation
  - Routine administration of prophylactic antibiotics before ERCP
- Liver transplantation
  - Survival 70-80% over 10 years
  - Disease recurrence in ~20%
  - Good candidates for living donor liver transplant with excellent outcomes

EASL Guidelines. *J Hep*. 2017;1265-81.

Surveillance for Cancer in PSC

Cancer	Imaging and/or Endoscopy	Laboratory Testing
Colorectal carcinoma	Annual colonoscopy	CEA
Cholangiocarcinoma	Annual MRCP ERC & cholangioscopic biopsies of suspicious strictures	CA-19-9
Gallbladder carcinoma	Annual US or cross-sectional imaging	No defined or exploratory biomarkers

Vierling JM. PSC. *Schiff's Liver Diseases.* 12th Ed. 2017.

PSC: Key Takeaways

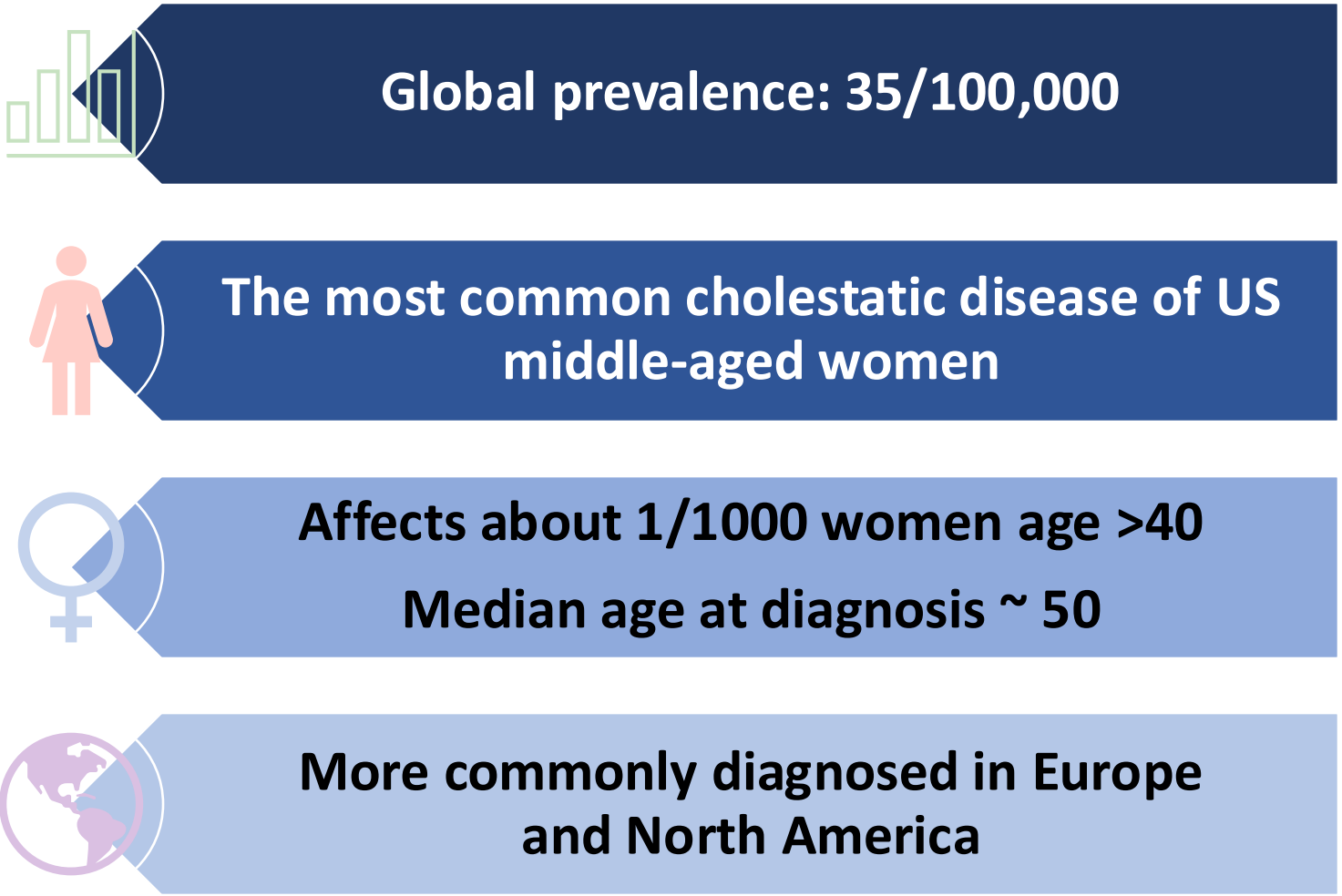
- Progressive, inflammatory disease of the bile ducts, often associated with IBD (especially ulcerative colitis).
- Leads to bile duct strictures, cholestasis, and eventual liver cirrhosis.
- No definitive treatment but can lead to liver transplantation for advanced cases.
- Excellent candidates for living donor liver transplant.

Primary Biliary Cholangitis (PBC)

What is Primary Biliary Cholangitis (PBC)?

- Chronic, progressive, cholestatic autoimmune disease
- Lymphocytic destruction of intralobular bile ducts resulting in periportal inflammation, bile duct damage, fibrosis and progression to cirrhosis
- Previously referred to as “primary biliary cirrhosis”

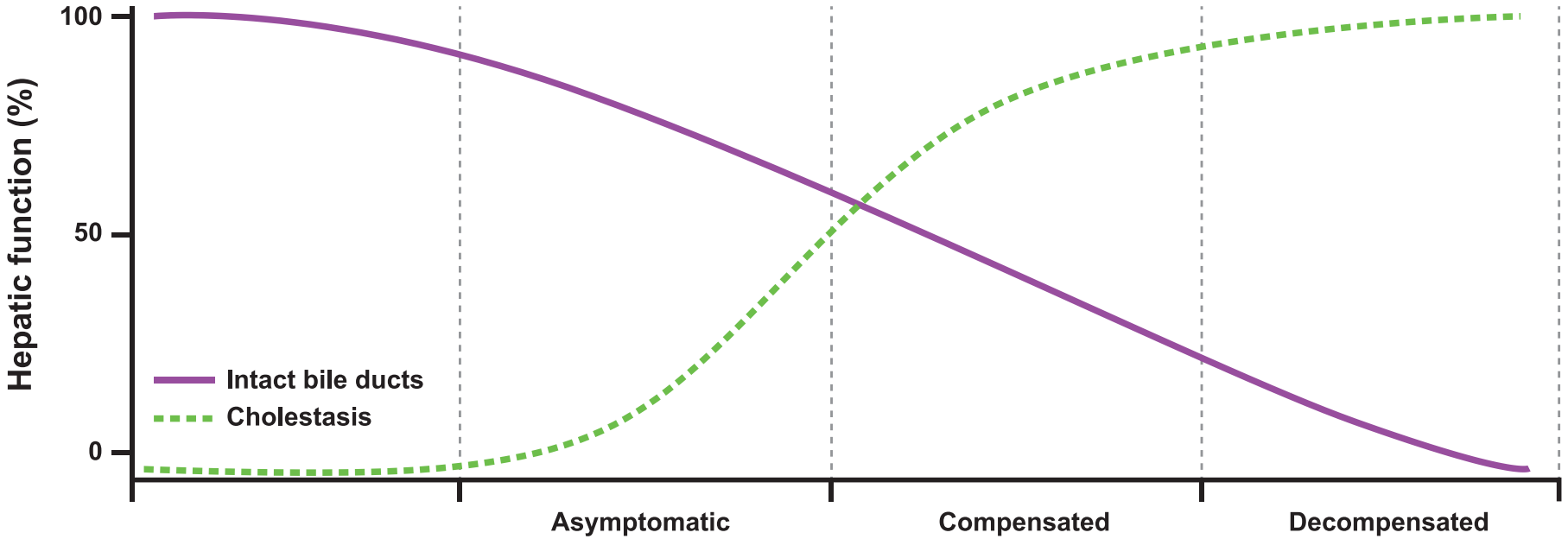
Epidemiology



EASL. *J Hepatol.* 2017; 67(1):145-172; Lammers et al. 2014.

The Natural History of PBC

PBC is commonly characterized by slow progression of cholestasis, fibrosis, followed by hepatic dysfunction and decompensation



Widespread use of AMA testing enables the diagnosis of PBC patients before they develop symptoms of cholestasis or hepatic decompensation

Younossi Z et al. *AJG*. 2019; 114:48-63.

PBC Phenotype

Age	Typically >45 years
Gender	Female > Male (9:1)
Serology	AMA in ~95%; disease-specific ANA in ~30%-50%; ASMA may be present, ANA specific anti-GP210, anti-sp-100
Immunoglobulin	IgM typically elevated
MRCP	Normal
Liver Histology	Lymphocytic infiltrate; inflammatory duct lesion; granuloma may be present
Coexisting IBD	Not typical

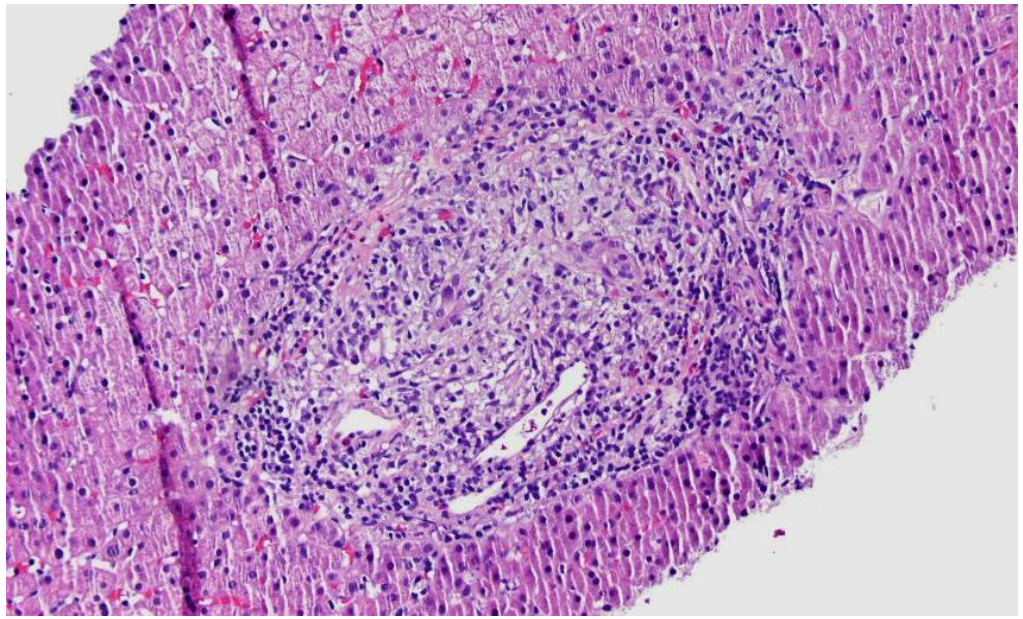
Abbreviations: AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth-muscle antibody; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiography; PBC, primary biliary cholangitis.

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

PBC Diagnostic Criteria

PBC Diagnosis

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



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

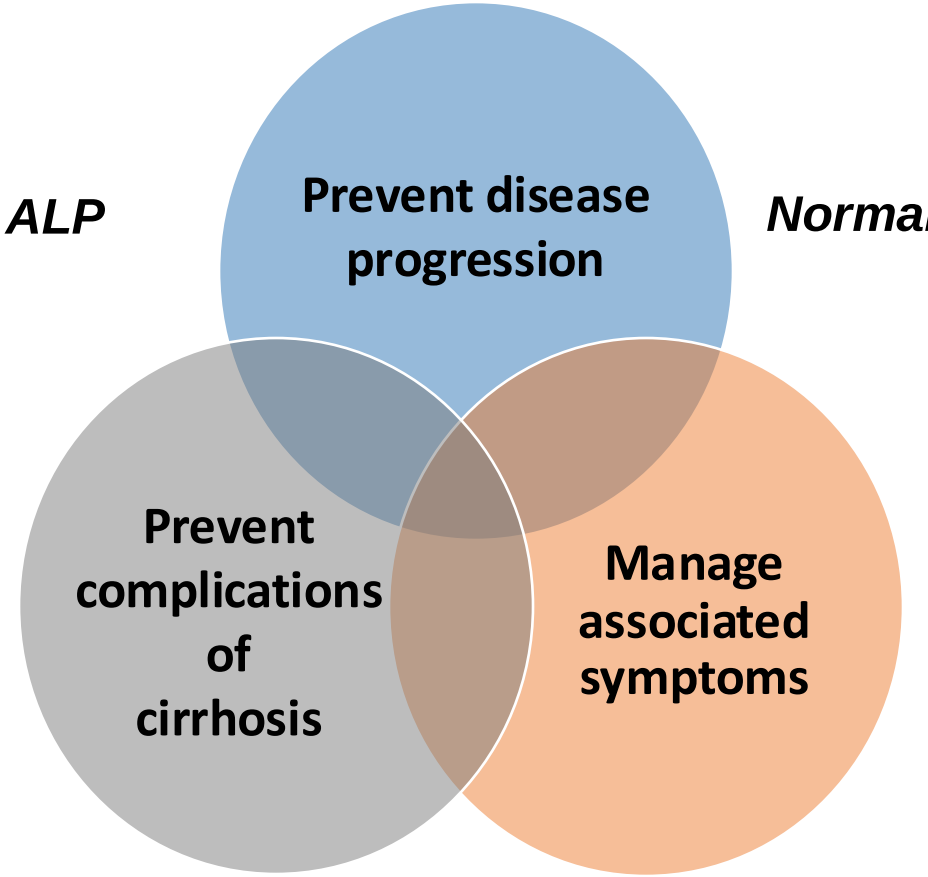
AASLD Criteria

Clinical Manifestations of PBC

- Fatigue
- Pruritus (hands &feet)
- RUQ abdominal pain
- Other autoimmune conditions
- Excoriations
- Xanthelasma
- Xanthoma

Treatment Goals

Reduce ALP → Normalize ALP



Normalize bilirubin → Bilirubin <0.6

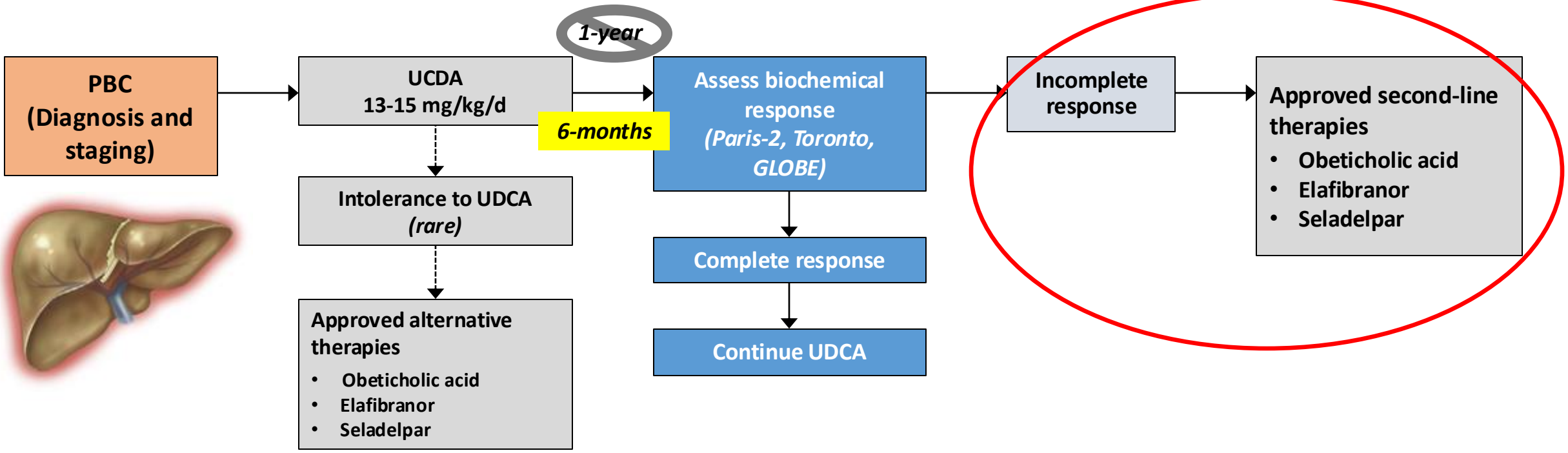
The goal of lifelong therapy is to prevent progressive liver disease and ameliorate disease-associated symptoms that reduce patient QoL[8]

8. European Association for the Study of the Liver. *J Hepatol*. 2017; 67:145–72; 9. Lindor KD et al. *Hepatology*. 2022; 75:1012-1013.

FDA Approved Therapy for PBC

- First Line Treatment
  - Ursodeoxycholic acid (UDCA)
- Second Line Treatment
  - Obeticholic acid (OCA)
  - Elafibranor
  - Seladelpar

PBC Treatment Algorithm



Modified from Montano-Loza AJ et al. *Clin Gastroenterol Hepatol*. 2021; 19:2241-2251.e1.

PBC: Key Takeaways

- Chronic autoimmune disorder affecting small bile ducts, leading to cholestasis and progressive liver damage.
- Key features include elevated alkaline phosphatase (ALP) and positive antimitochondrial antibodies (AMA).
- Ursodeoxycholic acid (UDCA) is the first line treatment to slow progression.
- 2nd line therapies for PBC
  - Obeticholic acid (OCA)
  - Elafibranor
  - Seladelpar

Key differences

- **AIH**: Primarily affects hepatocytes with inflammation and autoantibodies.
- **PSC**: Involves large and small bile ducts resulting in strictures and cholangitis. Strongly associated with inflammatory bowel disease (IBD) and hallmark feature is beading appearance on MRCP.
- **PBC**: Affects small bile ducts with a hallmark AMA positivity.

Summary

- Early diagnosis and treatment are essential to prevent progression to cirrhosis.
- Regular monitoring for liver function, complications, and liver transplantation when indicated.