# Primary Sclerosing Cholangitis (PSC) and Autoimmune Hepatitis (AIH): What You Need to Know

Katherine Wilks, PA

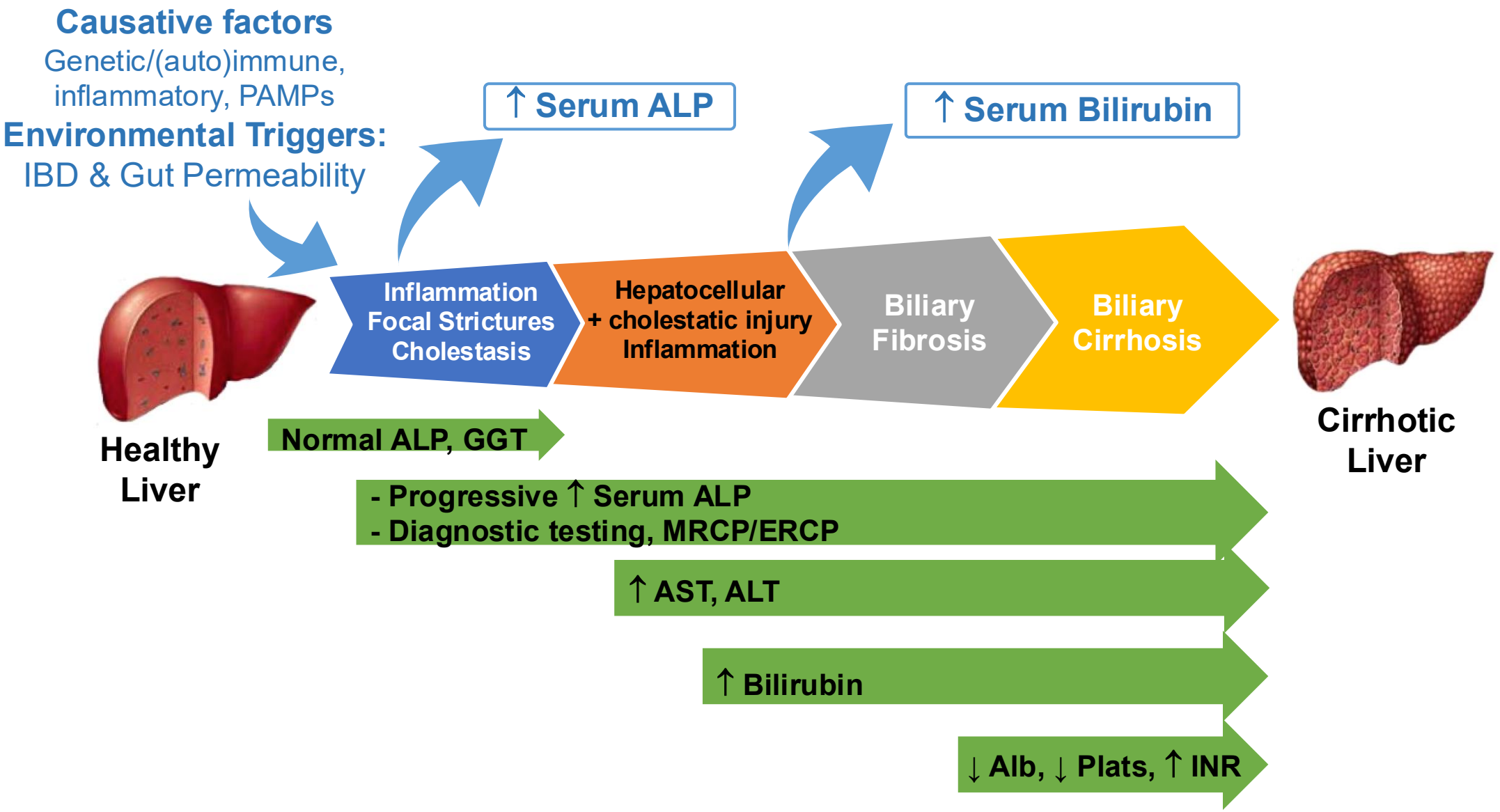
Texas Liver Institute

San Antonio, Texas

# Primary Sclerosing Cholangitis (PSC)

- Long natural history
- Median survival free of transplant 15-20 years
- Small-duct and large duct varieties
- Genetic and autoimmune associations
- Presence and type of IBD may influence clinical events
- Possible association with IgG4 autoimmune cholangiopathy
- Histologic features may be non-specific, sampling and biological variability

# 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%

# PSC: Strong Association with Inflammatory Bowel Disease (IBD)

## Association with colitis:

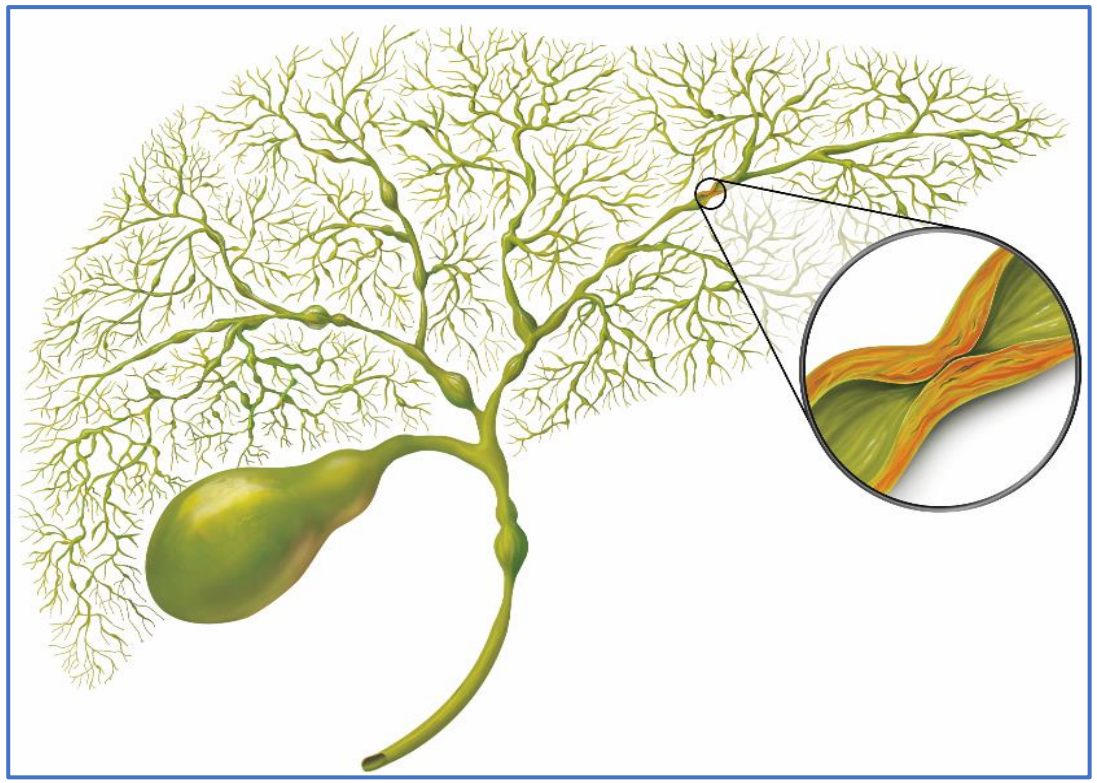
- Ulcerative colitis: 70-98%, often with a rarer UC phenotype
  - Rectal sparing (52% vs 6%)
  - Backwash ileitis (51% vs 7%)
- Crohn's colitis or ileocolitis: 3-13%

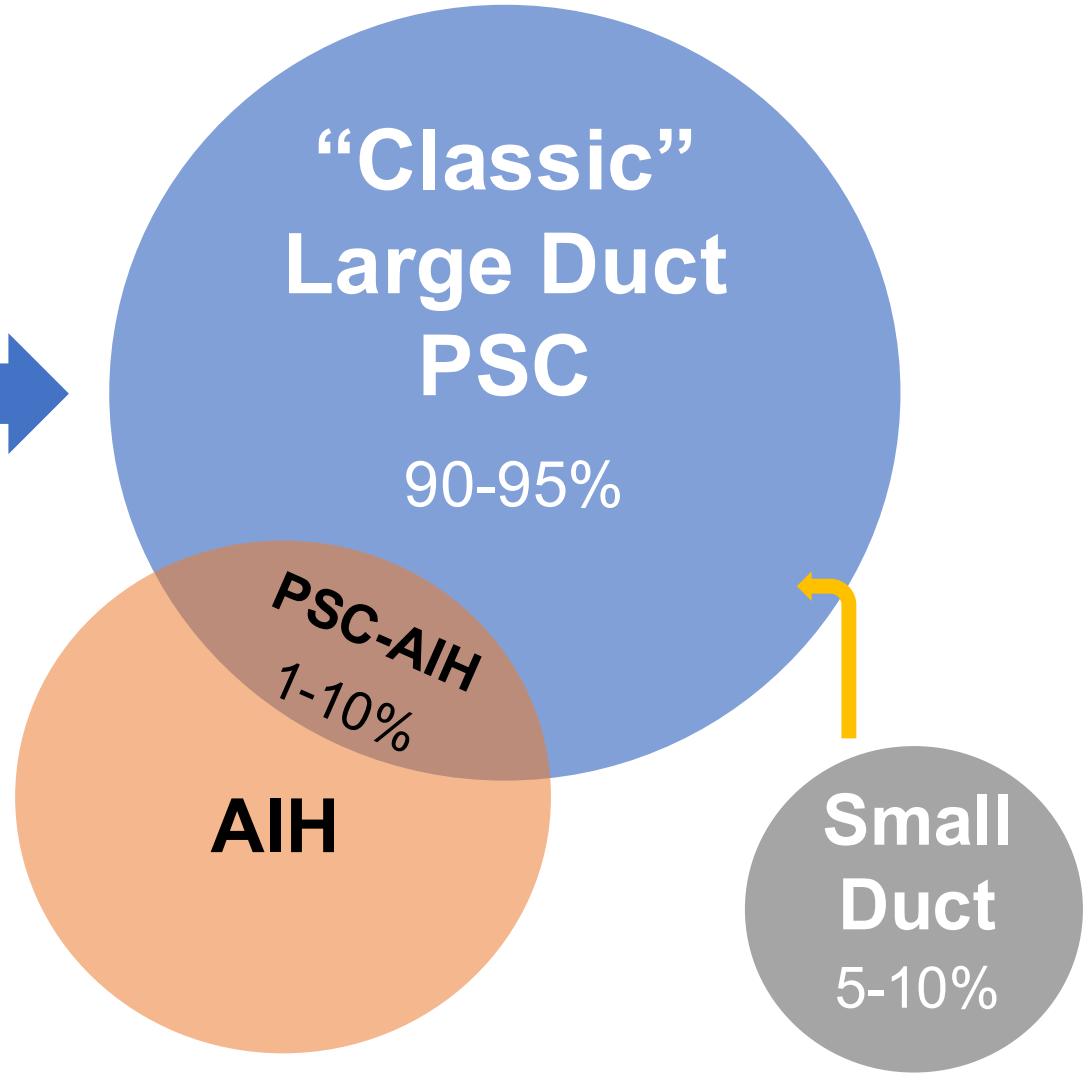
## Prevalence of IBD colitis:

- 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)

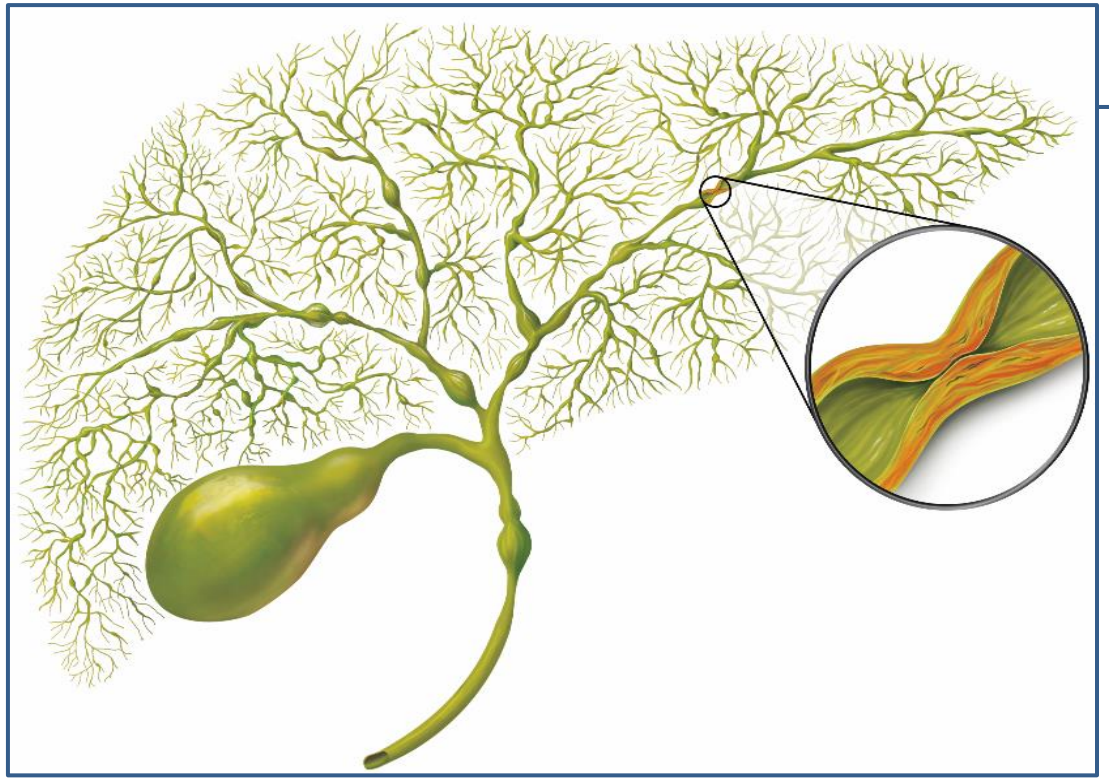
Vierling JM. PSC. *Schiff's Liver Diseases*. 12th Ed. 2017.

# PSC: Three Distinct Clinicopathological Entities

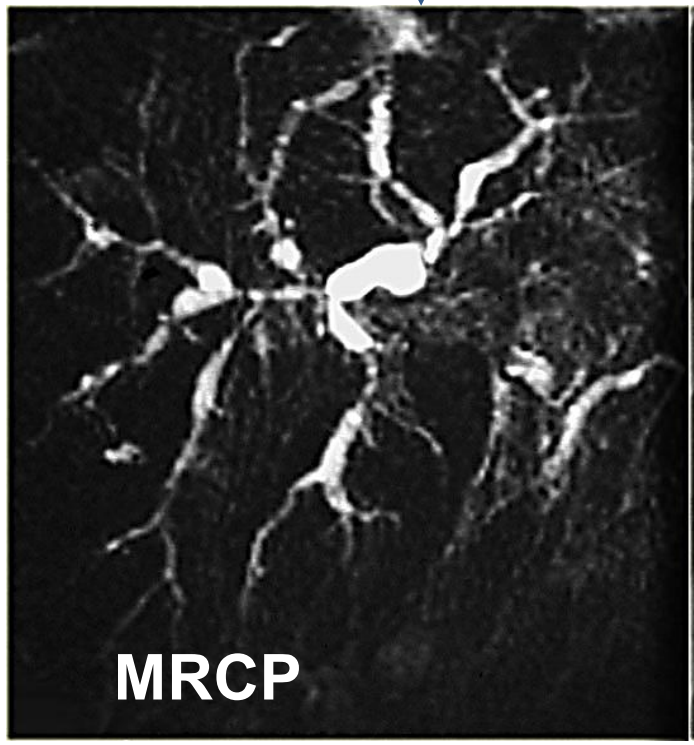


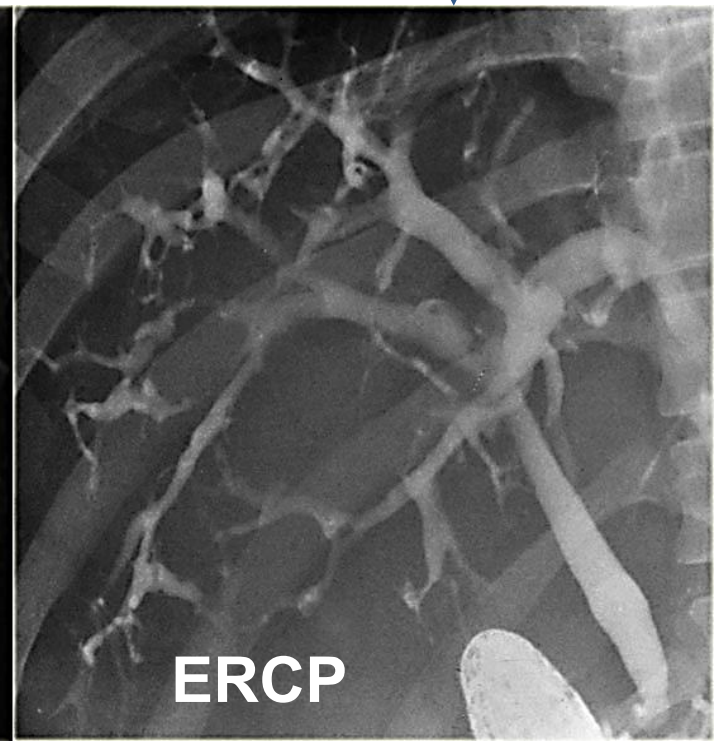


# PSC: Cholangiography for Detection of Large Duct Disease



Cholangiography for Detection of Large Duct Disease




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

# Indications for ERCP

*Review MRI/MRCP prior to ERCP*

- New-onset or worsening pruritus
- Unexplained weight loss
- Worsening serum liver test abnormalities
- Elevated serum CA 19-9
- Concern for relevant stricture or CCA

**2-8% risk of cholangitis**

- **Periprocedural antibiotic prophylaxis for 1-3 days**

**1-9% risk of pancreatitis**

- **Indomethacin, Lactated Ringer's, PD stent**

**Replace plastic stents every 4 weeks**

Bowlus C et al. *Hepatology*. 2023.

# Treatment Options 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 13-15 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<br>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 UDCA is commonly prescribed.
- Excellent candidates for living donor liver transplant.

# Autoimmune Hepatitis (AIH)

# Clinical Presentation

- Chronic, autoimmune mediated inflammatory disease
- Fatigue is the main complaint in 85% of patients
- Asymptomatic in 25-34% of patients
- ANA, SMA and anti-LKM1 are absent in 19-34% of North American patients
- Concurrent autoimmune disease are present in 14-44% of patients with AIH
  - Autoimmune thyroid disease is the most common

Mack CL et al, AASLD Practice Guideline. *Hepatology* 2020; 72:671-722.

# AIH: Demographics and Epidemiology

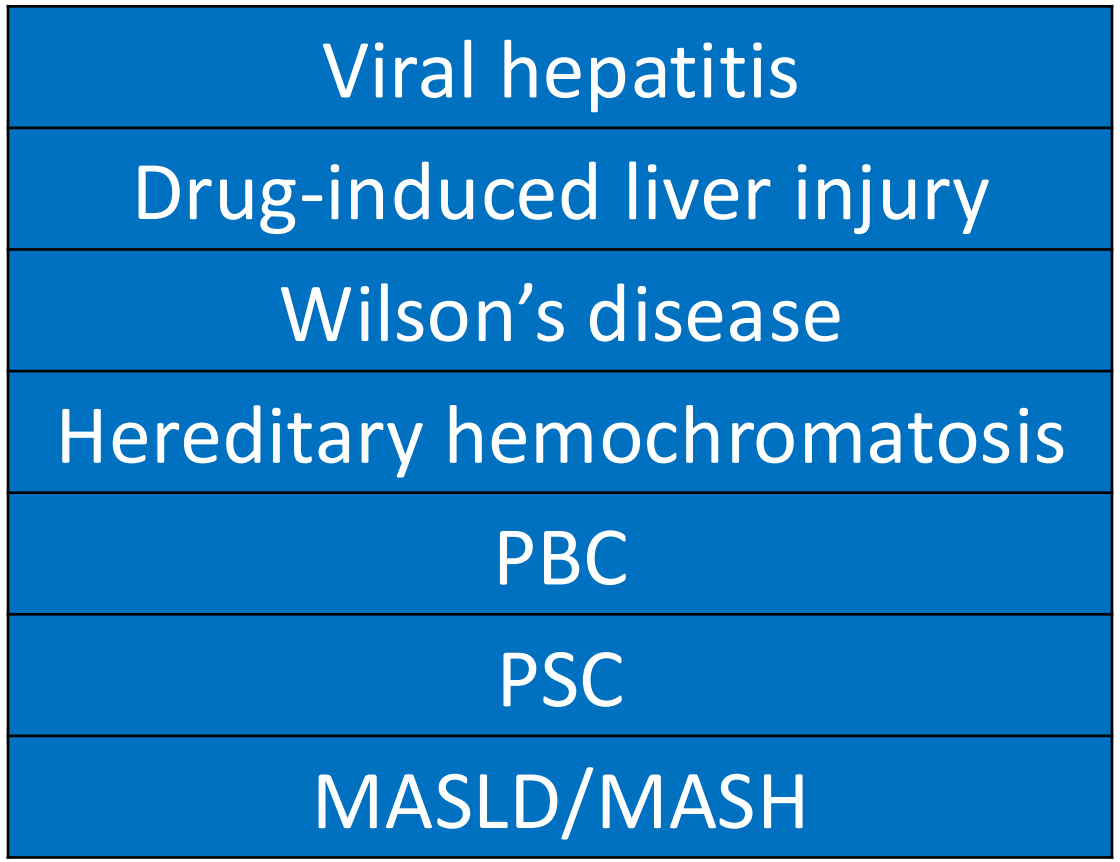
- Afflicts ~200,000 in US
- Female to male ratio= 4-6:1
- Afflicts both children and adults
- Bimodal age distribution: 10-20 vs. 45-75 yrs
- ~6% liver transplants in US
- 40% mortality in symptomatic patients
- ≤6 months in severe untreated disease

# AIH: Ethnic Notations

- Blacks are younger at presentation, commonly have cirrhosis (57%-85% vs 38%), higher frequencies of liver failure (38% vs 9%), require liver transplant more commonly (52% vs 23%), and have greater mortality (24% vs 6%).
- Asians with AIH have a higher mortality (29%) than Hispanic Americans (5%) and white Americans (8%) with AIH.

Wong RJ, *J Clin Gastroenterol* 2012;46:155-161.

# Exclude Liver Diseases That Resemble AIH



# Drug-induced AIH-like Injury

- Drug-induced liver injury can mimic AIH
- Unpredictable idiosyncratic or hypersensitivity drug reaction has been implicated in 2-17% of patients with classical features of AIH
- Minocycline, nitrofurantoin and infliximab have been most incriminated

Mack CL et al, AASLD Practice Guideline. *Hepatology* 2020; 72:671-722.

# Drugs Associated with Liver Injuries Resembling AIH

| Definite Association | Probable Association | Possible Association |
|---|---|---|
| Minocycline[187,192-198] | Propylthiouracil[579,580] | Ipilimumab (anti-CTLA-4)[581] |
| Nitrofurantoin[187,199-205] | Isoniazid[582] | Tremelimumab (anti-CTLA-4)[581] |
| Infliximab[206-221] | Diclofenac[583,584] | Nivolumab (anti-PD-1)[581] |
| Alpha-methyldopa[585-587] | Etanercept[216,432,433] | Pembroluzimab (anti-PD-1)[230,588] |
| Adalimumab[216,433,589-591] | Atorvastatin[592-595] | Atezolizumab (anti-PD-L1)[581] |
| Halothane[596,597] | Rosuvastatin[598] | Black cohosh (herbal medicine)[599,600] |
| Oxyphenisatin*[601] | Clometacine[602,603] | Dai-saiko-to (herbal medicine)[604] |
| Dihydralazine*[573,574,605] | | Germander (herbal medicine)[606] |
| Tienilic acid*[607] | | Hydroxycut (nutritional supplement)[608] |
| | | Trichloroethylene (toxin)[609] |
| | | Papaverine[610] |
| | | Indomethacin[611] |
| | | Imatinab[612] |

*Removed from marketplace.
Abbreviation: anti-PD-L1, antibody to programmed death protein ligand 1.

Mack CL et al, AASLD Practice Guideline. *Hepatology* 2020; 72:671-722.

# Histological Findings

- Diagnosis of AIH cannot be made without liver biopsy and compatible histological findings.
- Interface hepatitis is the histological hallmark of AIH accompanied by
  - Plasma cell infiltration in 66%
  - Lobular hepatitis in 47%
  - Centrilobular necrosis in 29%
- Cirrhosis present in 28-33% of adults at presentation, especially in the elderly, as well as in 38% of children.

Mack CL et al, AASLD Practice Guideline. *Hepatology* 2020; 72:671-722.

# Goal of Treatment for AIH

- No cure
- Improve symptoms, control hepatic inflammation
- Achieve biochemical remission (normalization of AST, ALT, IgG)
- Prevent disease progression

# First Line Treatment for AIH

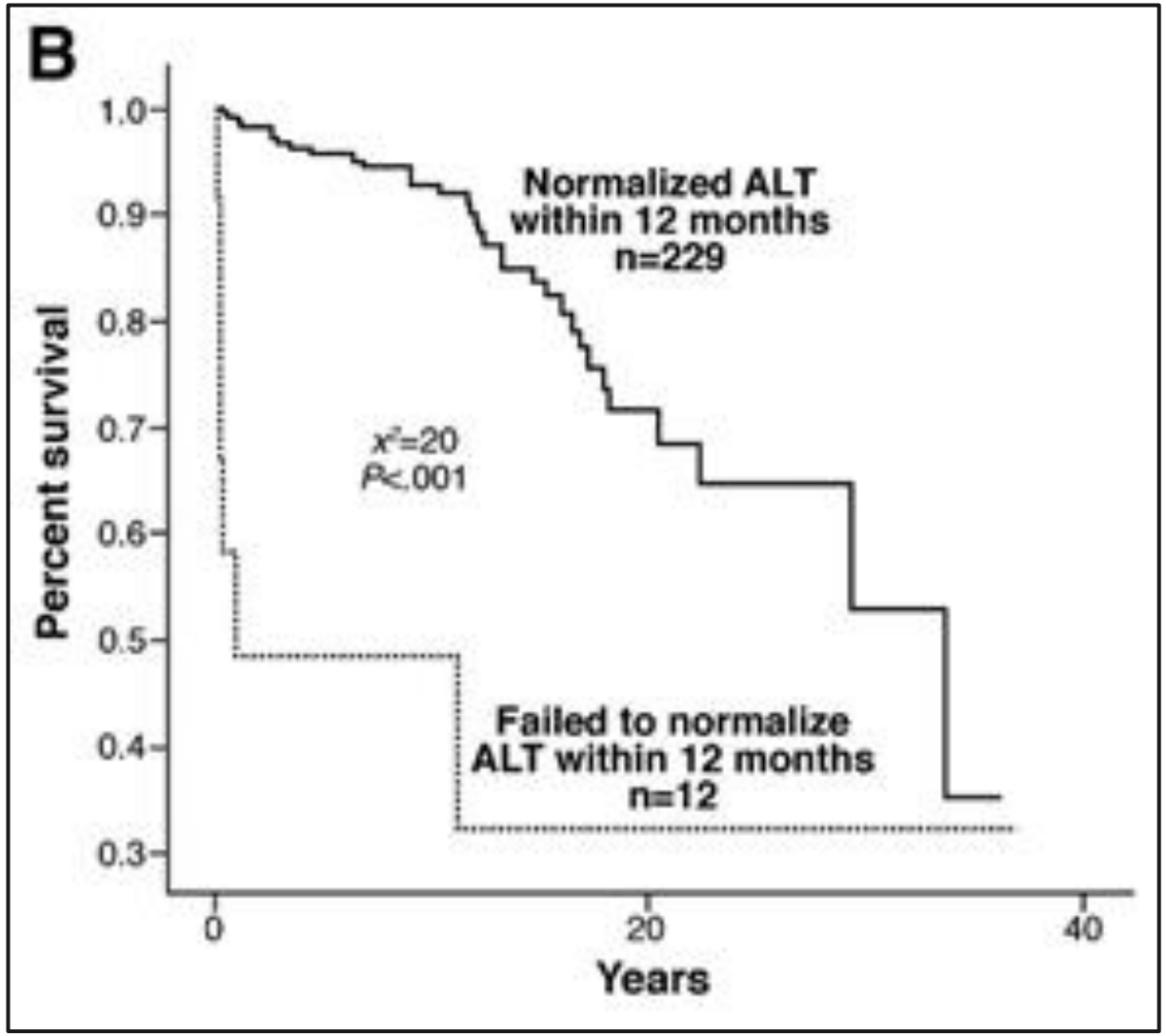
Steroids (induction)

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

Immunosuppression (maintenance)

- Azathioprine 50-150 mg/day or 1-2 mg/kg/day
- ? Mycophenolate mofetil (250-1,000 mg BID)

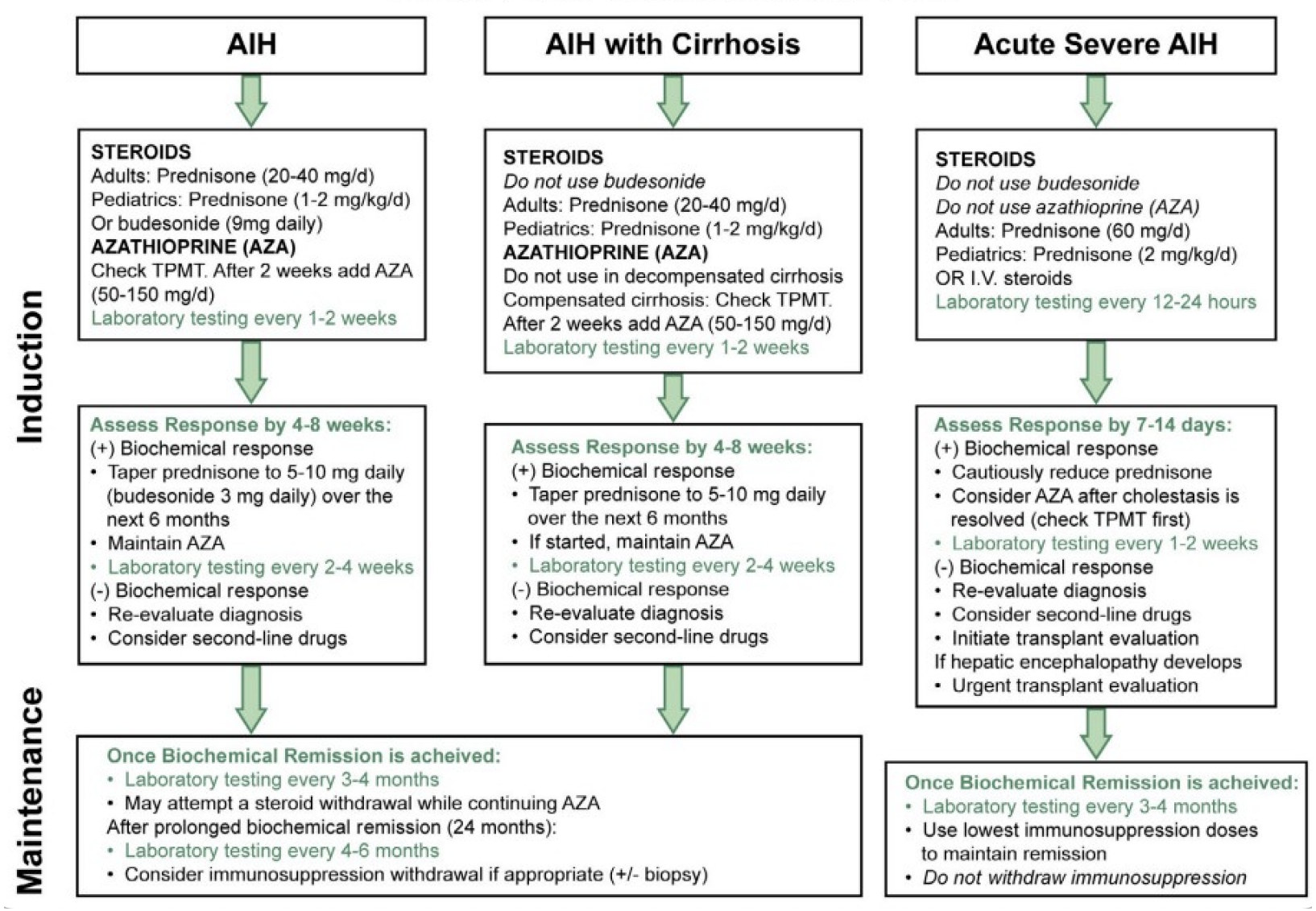
# Biochemical Response is Associated With Improved Survival



# Treatment Response

- The rapidity of response to treatment is the most important index of outcome, and ALT should improve within 2 weeks.
- Elevated serum ferritin and low IgG values (<1.9-fold ULN) at baseline predict good response.
- IgG normalizes with therapy but may not with cirrhosis (gammopathy of cirrhosis).

# First-Line Treatment of AIH




Mack et al., 2019 AASLD Guidelines. *Hepatology* 72(2): 671-722.

# Treatment Withdrawal: Not a Good Idea

- Sustained normal AST, ALT, and IgG for at least 2 years have been proposed as requisites before attempting treatment withdrawal.
- Normal histology reduces the risk of subsequent relapse to 28%,and liver biopsy prior to drug withdrawal has been the preferred strategy.
- Relapse in up to 90% of adults, 80% of children
  - Usually respond to retreatment

Hartl J, et al. *J Hepatol* 2015;62: 642-646

# AIH: Summary

- 63% 10-year transplant free survival with treatment
- 27% without therapy
- Diagnosis is based on histology and IgG mainly
- Serologies usually positive but not always reliable

- Therapy: Pred 20 mg/d + Aza 1-2 mg/kg/d
  - Wean prednisone slowly over several months after ALT normalizes
  - Histology lags behind ALT but useful guide on therapy
- Relapse rate off therapy 70-90% within 2 years

# AIH and PSC: Summary

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