Autoimmune Liver Disease: AIH, PSC and PBC

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DEFINITION

- **Autoimmune hepatitis:**
  - immune-mediated inflammatory disease of the liver
  - characterized by circulating autoantibodies
  - increased concentration of IgG
  - distinctive histological features.

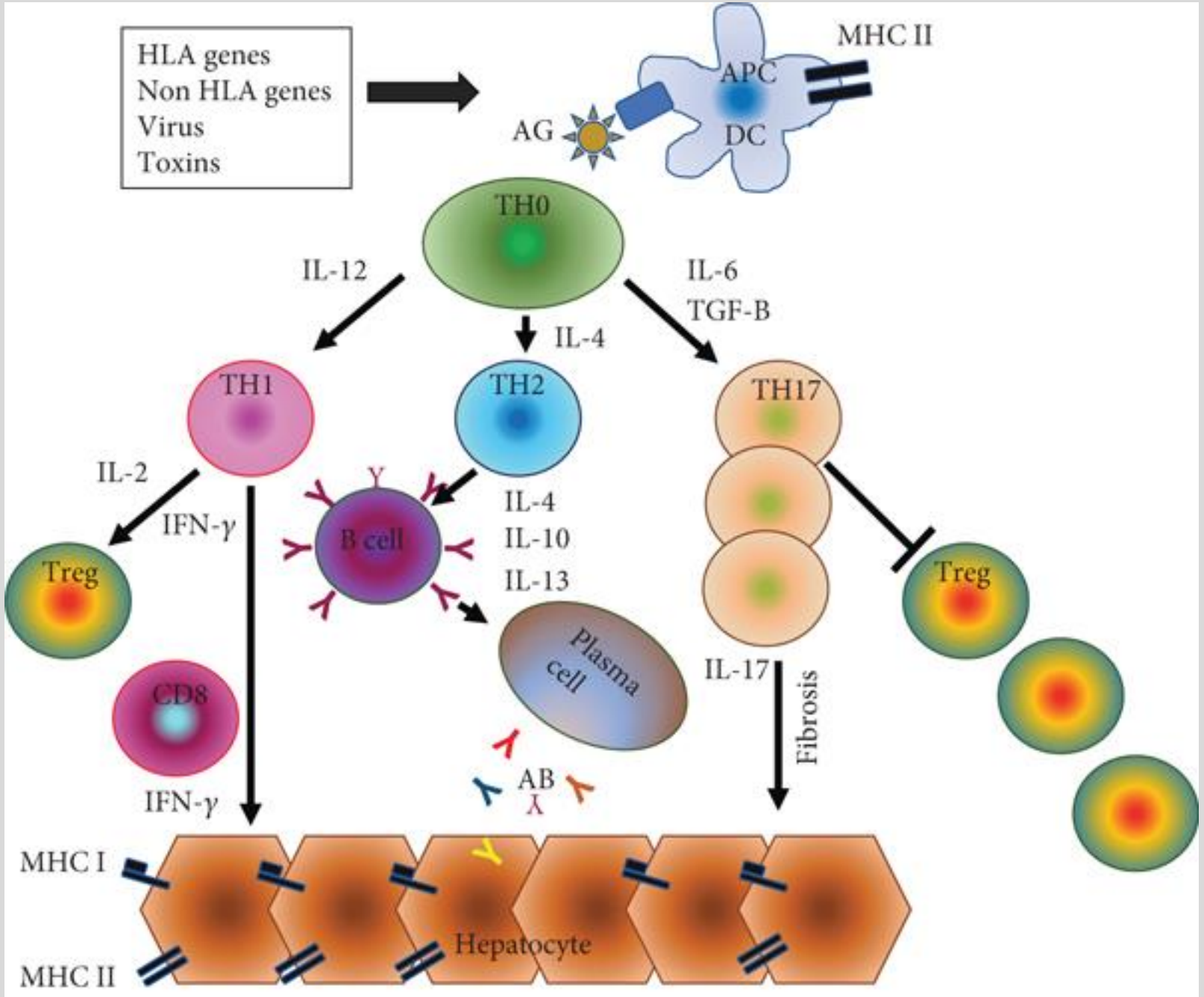
- It is a progressive disease that can lead to cirrhosis and liver failure if not treated appropriately.

EPIDEMIOLOGY

- Rare disease with incidence of 1.37 per 100 000 people
  - Increasing incidence documented over last decade
- Prevalence 17.44 per 100 000 people globally
- Female predominance
  - Type I: 4:1
  - Type II: 10:1
- Age of onset
  - **Bimodal:** Puberty and then in 4th and 6th decade – age at diagnosis increasing
  - Important to exclude in older patients with ‘new onset’ liver disease

PATHOPHYSIOLOGY

- Multifactorial: Genetic susceptibility + environmental triggers + immune dysregulation
- Genetic factors:
  - HLA genes (DR3 and DR4)
  - Non HLA genes involved in T-cell signalling and cytokine release
- Environmental factors
  - Drugs: Nitrofurantoin, minocycline, methyldopa
  - Hepatitis A
  - Diet
- Immunological factors
  - CD4+ T cells are thought to play a central role in AIH, as they become activated and differentiate into Th1 and Th17 cells



Sucher E et al. Autoimmune Hepatitis-Immunologically Triggered Liver Pathogenesis-Diagnostic and Therapeutic Strategies. J Immunol Res. 2019 Nov 25;2019:9437043.

CLINICAL PRESENTATION

- Very varied:
  - **Insidious onset with nonspecific symptoms**
    - **Fatigue, nausea, acne (in teenagers) , polyarthralgia, jaundice (may be fluctuating)**
    - **Cirrhosis +/- portal hypertension (1/3 adults and ½ children)**
  - Acute onset
    - Fulminant liver failure requiring transplant (1%)
    - True acute AIH without evidence of chronicity on biopsy
    - Acute flare of chronic disease process

ASSOCIATIONS

- Autoimmune conditions
  - Hashimoto's thyroiditis
  - Diabetes Mellitus T1
  - RA
  - SLE
  - Coeliac disease
- Overlap syndromes
  - PSC – AIH overlap
  - PBC – AIH overlap

DIAGNOSIS

- Clinical diagnosis supported by:
  - Raised aminotransferases
  - Elevated IgG levels (clue TP to Alb ratio)
  - Autoantibodies
  - Histology
  - Exclusion/testing for alternate diagnosis or co-factor

Simplified Diagnostic Criteria for AIH

Variable	Cutoff	Point
Autoantibodies	ANA or SMA 1:40	1
	ANA or SMA ≥1:80	2
	LKM (≥1:40) or SLA positive	2
IgG	>ULN	1
	>1.1×ULN	2
Liver histology	Compatible	1
	Typical	2
Absence of viral hepatitis	Yes	2

≥6, Probable autoimmune hepatitis (AIH); ≥7, definite AIH.

Table 1. Classification of Autoimmune Hepatitis.

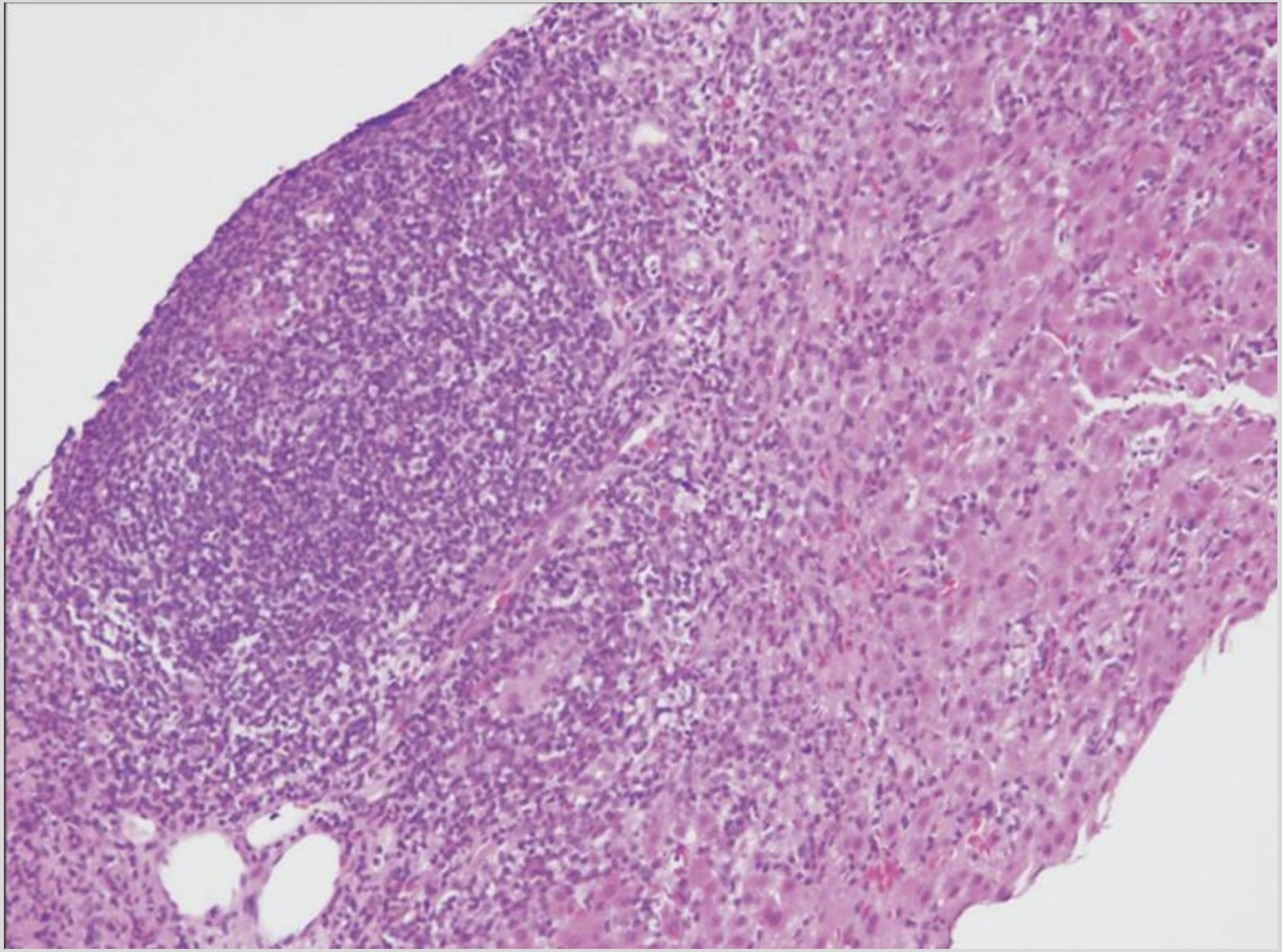
Variable	Type 1 Autoimmune Hepatitis	Type 2 Autoimmune Hepatitis
Characteristic autoantibodies	Antinuclear antibody* Smooth-muscle antibody* Antiactin antibody† Autoantibodies against soluble liver antigen and liver–pancreas antigen‡ Atypical perinuclear antineutrophil cytoplasmic antibody	Antibody against liver–kidney microsome 1* Antibody against liver cytosol 1*
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Predominantly childhood and young adulthood
Sex of patients	Female in approximately 75% of cases	Female in approximately 95% of cases
Association with other autoimmune diseases	Common	Common§
Clinical severity	Broad range	Generally severe
Histopathologic features at presentation	Broad range	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	Approximately 100%

* The conventional method of detection is immunofluorescence.
† Tests for this antibody are rarely available in commercial laboratories.
‡ This antibody is detected by enzyme-linked immunosorbent assay.
§ Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy is seen only in patients with type 2 disease.[47]

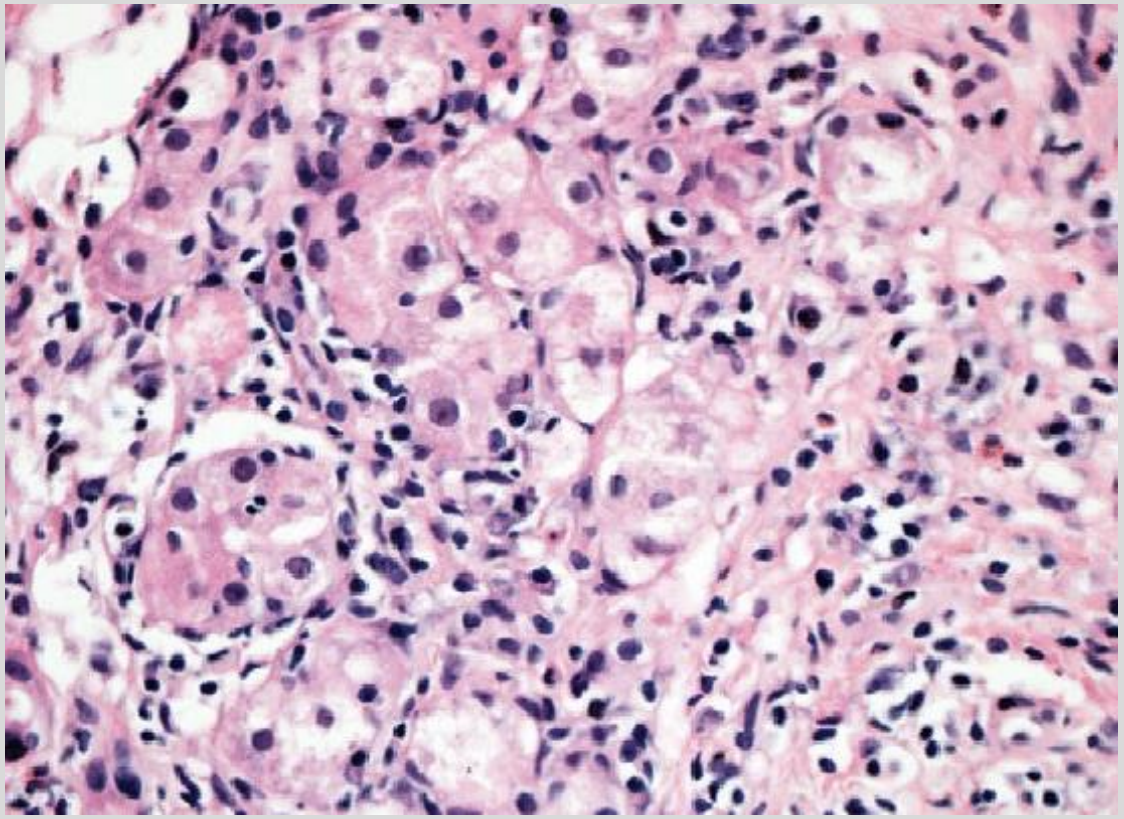
Krawitt EL. Autoimmune hepatitis. N Engl J Med. 2006 Jan 5;354(1):54-66. doi: 10.1056/NEJMra050408.

HISTOLOGY

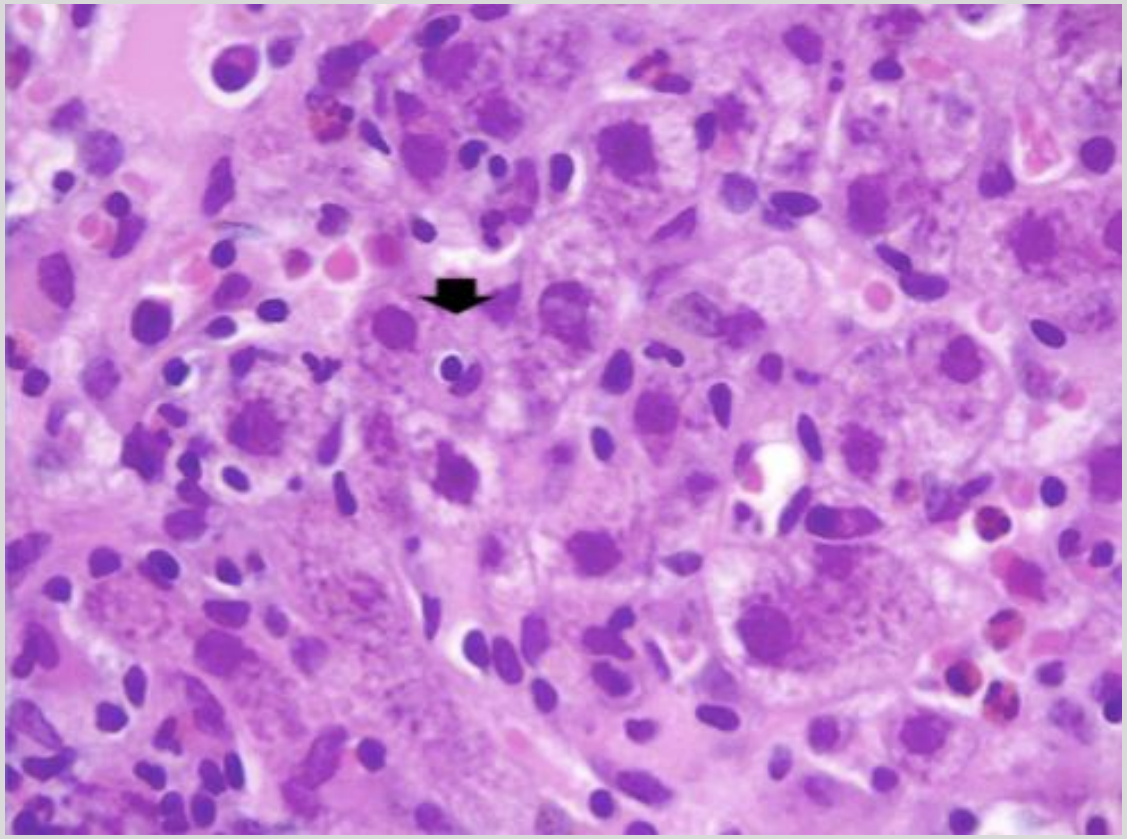
- Mandatory where possible.
  - Assists in making diagnosis
  - Assess degree of fibrosis and inflammatory activity
  - Aid in exclusion or confirmation of alternate causes/overlap
- Typical histology (2 out of 3)
  - Interface hepatitis with plasmalymphocytic infiltrate
  - Emperipolesis
  - Rosetting of hepatocytes



Rosettes



Emperipolesis



TREATMENT: INDUCTION

- **AIM: induce remission with normalisation of aminotransferases and IgG by 6 months** (achieved in 2/3)
- Steroids
  - Response is universal in AIH
  - Often rapid but remission can take up to 6 months
  - Poor response: consider alternate diagnosis or **compliance**
  - Dose is individualised
    - 0,5mg/kg – 1mg/kg prednisone dly in guidelines
  - Budesonide alternative in those without cirrhosis

TREATMENT: INDUCTION

- Budesonide:
  - Alternate steroid regimen
  - Fewer side effects (acne and moon face) but slower response rate
  - Start 9mg/day
  - Not for use in cirrhosis
  - Recent data (2023) suggests poorer response rate

- Acute severe liver failure:
  - Early consideration of transplant workup

TREATMENT: MAINTENANCE

- Azathioprine
  - 50 – 100mg/day (1-2mg/kg)
  - Start low dose and titrated slowly
  - Bilirubin must be <100 micromol/L (metabolism altered)
- Antimetabolites
  - TPMT - Thiopurine methyltransferase – HIGHLY polymorphic
  - Risk for increased levels of metabolites and adverse effects (eg: severe neutropenia) not as high risk as in IBD due to dosing differences
- If intolerant to AZA, not necessarily intolerant to 6MP

ALTERNATIVE OPTIONS

- Second line:
  - Mycophenolate Mofetil – 2g/day
  - Teratogenic – Must discuss contraception

- Third line: need to interrogate compliance
  - Cyclosporin A, Tacrolimus, 6 – Mercaptopurine, Infliximab

PROGNOSIS

- Untreated AIH carries a significant morbidity and mortality – death within 5 yrs
- Steroid treatment improves survival
- Addition of azathioprine improves the rate of maintenance of remission
- Well treated AIH shows survival benefit even if significant fibrosis at diagnosis
- Liver transplant:
  - Indication: Acute liver failure, decompensated cirrhosis, HCC
  - Survival of >80% at 5 years
  - AIH recurrence 8-12% within 1 year, 36 – 68% at 5 years

TO STOP OR NOT TO STOP

- Patients should be in remission for at least 2 years (normal IgG and transaminases)
- Patients should have been on treatment for a minimum of 3 years and have biopsy proven remission
- Relapse occurs in 50 – 90% of patients with treatment withdrawal
- Most relapse within 12 months
- Need lifelong surveillance as relapse can occur at any point
- After a single relapse drug withdrawal should **never** be attempted again

SUPPORTIVE CARE

- Malignancy screening
  - HCC screening for all those with cirrhosis 6 monthly
  - UV protection and monitoring for non melanoma skin cancer
- Bone protection
  - DEXA scans
  - Calcium & Vit D supplementation +/-bisphosphonates
- Vaccination
  - Influenza
  - COVID-19
  - Hepatitis A and B

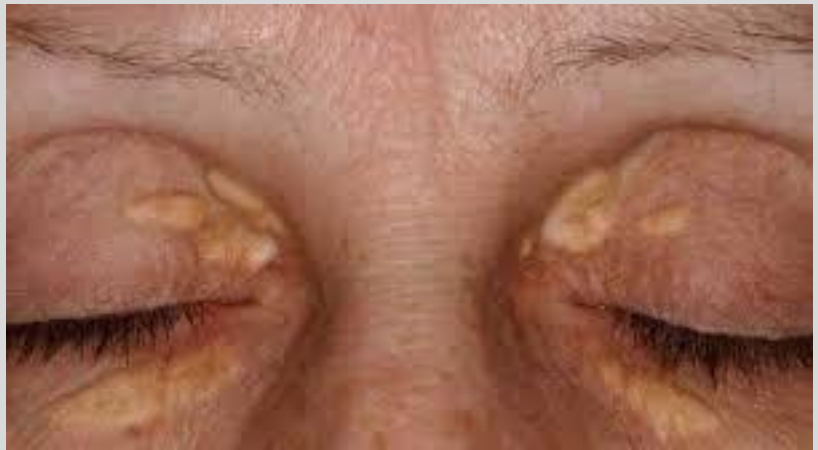
PREGNANCY

- AIH is not a contraindication to pregnancy BUT patient should be stable on treatment and in remission
  - 10-20% risk of foetal and maternal complications if flare
- Prednisone and azathioprine safe in pregnancy
- MMF contraindicated in pregnancy
- May flare post delivery – require higher doses of steroids for a short time
- Need closer monitoring post delivery to monitor for flare
  - 2 weeks post delivery
  - Monthly for 3-6 months

DEFINITION

Primary Biliary Cholangitis is a chronic, progressive, autoimmune disease:

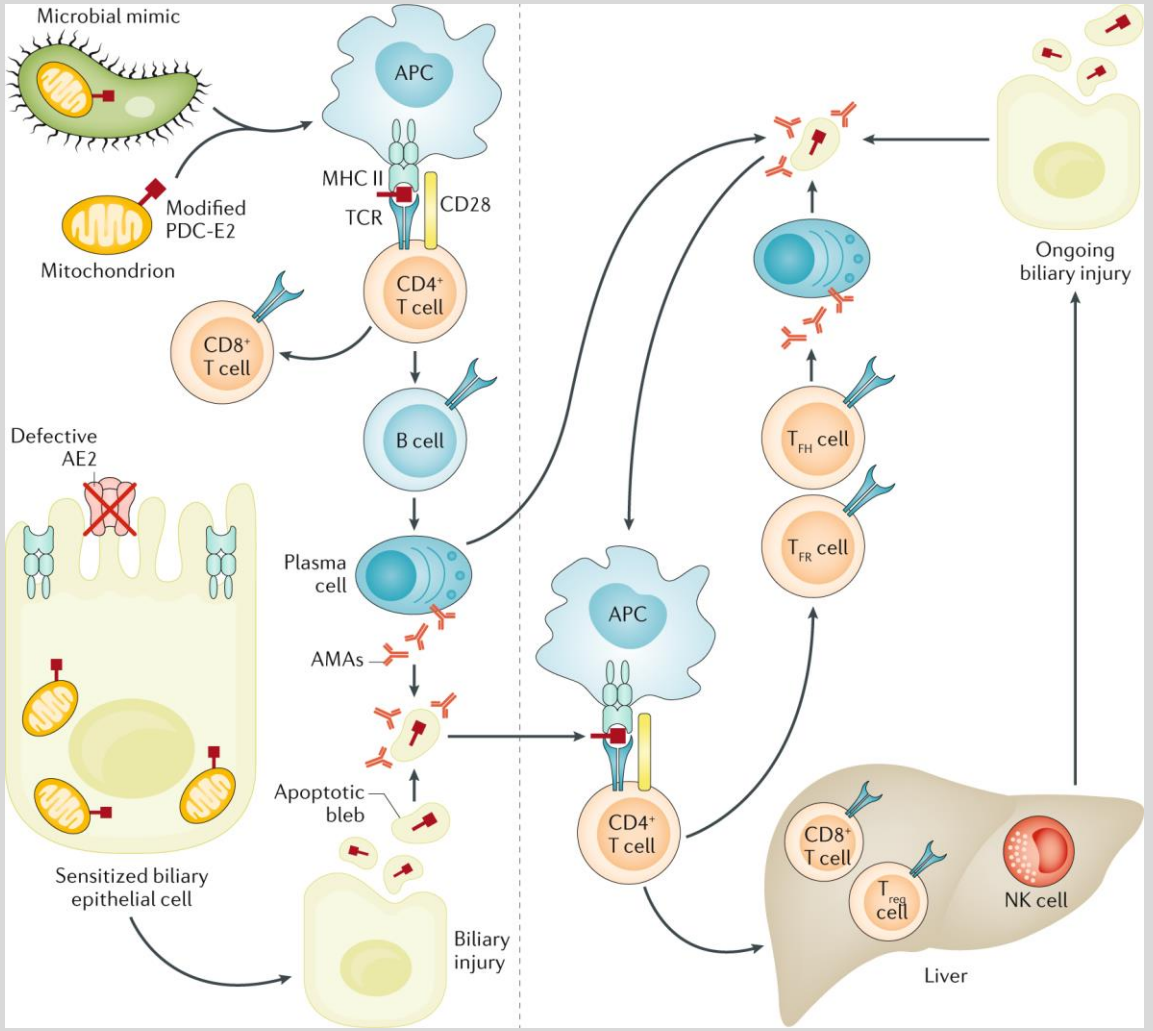
- destruction of small intrahepatic bile ducts
- leads to cholestasis, inflammation and ultimately cirrhosis
- antimitochondrial antibody positive in >90%



EPIDEMIOLOGY

- Rare disease
- Remains a female predominant disease
  - 9:1 female: male
  - Mainly >40 years
- Globally: 20-40 per 100 000 people are affected
- Annual incidence 2-3 per 100 000 people

PATHOGENESIS



Gulamhusein, A.F., Hirschfield, G.M. Primary biliary cholangitis: pathogenesis and therapeutic opportunities. Nat Rev Gastroenterol Hepatol 17, 93–110 (2020).

PRESENTATION

- Symptomatic
  - **Fatigue** – very common (to to 80%)
  - **Pruritis** (early – often precedes jaundice)
  - Jaundice (marker of advanced disease)
  - Sicca syndrome (30%)
  - Metabolic bone disease
  - Hyperlipidaemia

- Incidental
  - Often incidental finding of abnormal LFTs (50 – 60%)

- Cirrhosis and portal hypertension with associated complications

ASSOCIATIONS

- PBC is commonly associated with other autoimmune conditions
  - **Sjogren syndrome** 7-34%
  - Raynaud 9-13%
  - **Hashimoto's thyroiditis** 11-13%
  - RA 3-8%
  - Psoriasis 6%
  - **IBD** 1%
  - Scleroderma or CREST 1-2%

DIAGNOSIS

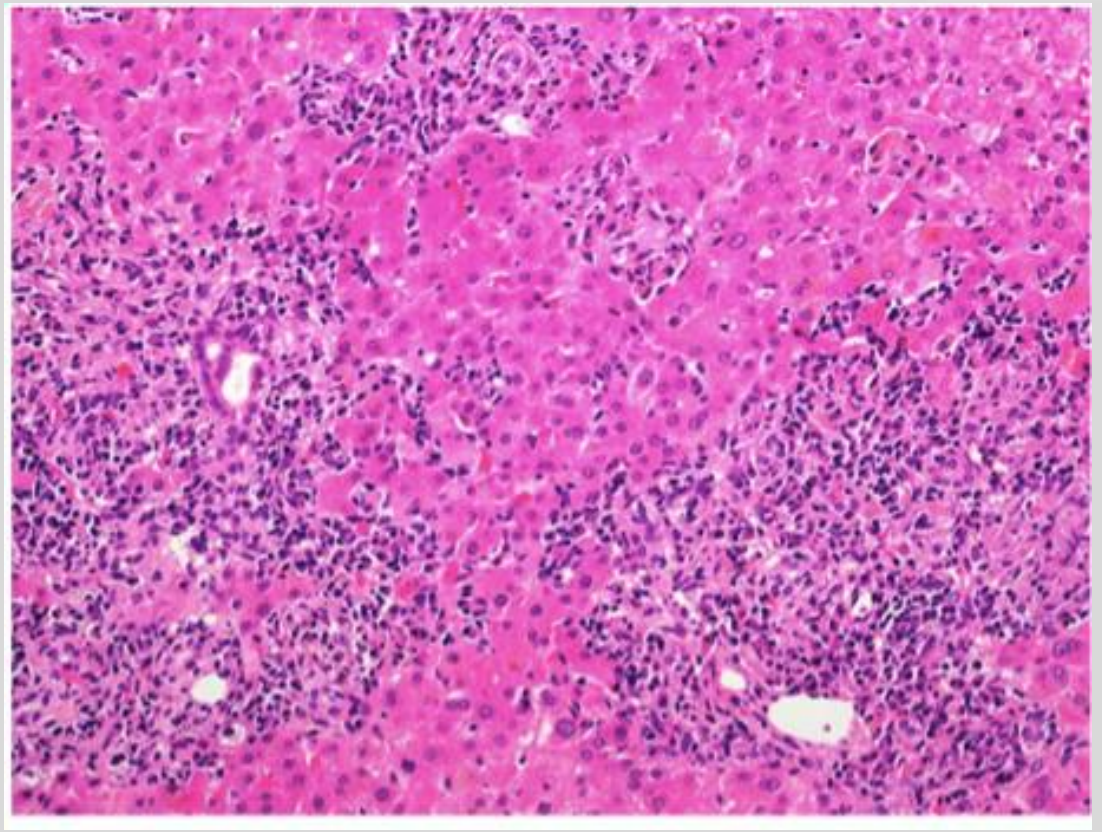
- Diagnosis is considered in the correct clinical context
  - No extrahepatic biliary obstruction
  - Often an older lady with pruritis and fatigue

- Need 2 of 3 criteria
  - ALP 2x ULN or GGT 5x ULN
  - **AMA positive at >1:40** (or other PBC specific antibodies if AMA negative)
  - Histology suggestive of PBC: Florid bile duct lesions and granulomas

  - **AMA**: Against M2 component of pyruvate dehydrogenase enzyme on inner membrane of mitochondria: Very specific but not itself pathogenic

HISTOLOGY

- Florid duct lesions
  - **Granuloma** formation
  - Lymphocytic infiltrate
- Lymphocytic cholangitis



MANAGEMENT

- Guided by stage of disease
- Early diagnosis can have excellent outcomes
- Fibrosis without cirrhosis: conservative treatment
- Once decompensated and cirrhotic – transplant work up

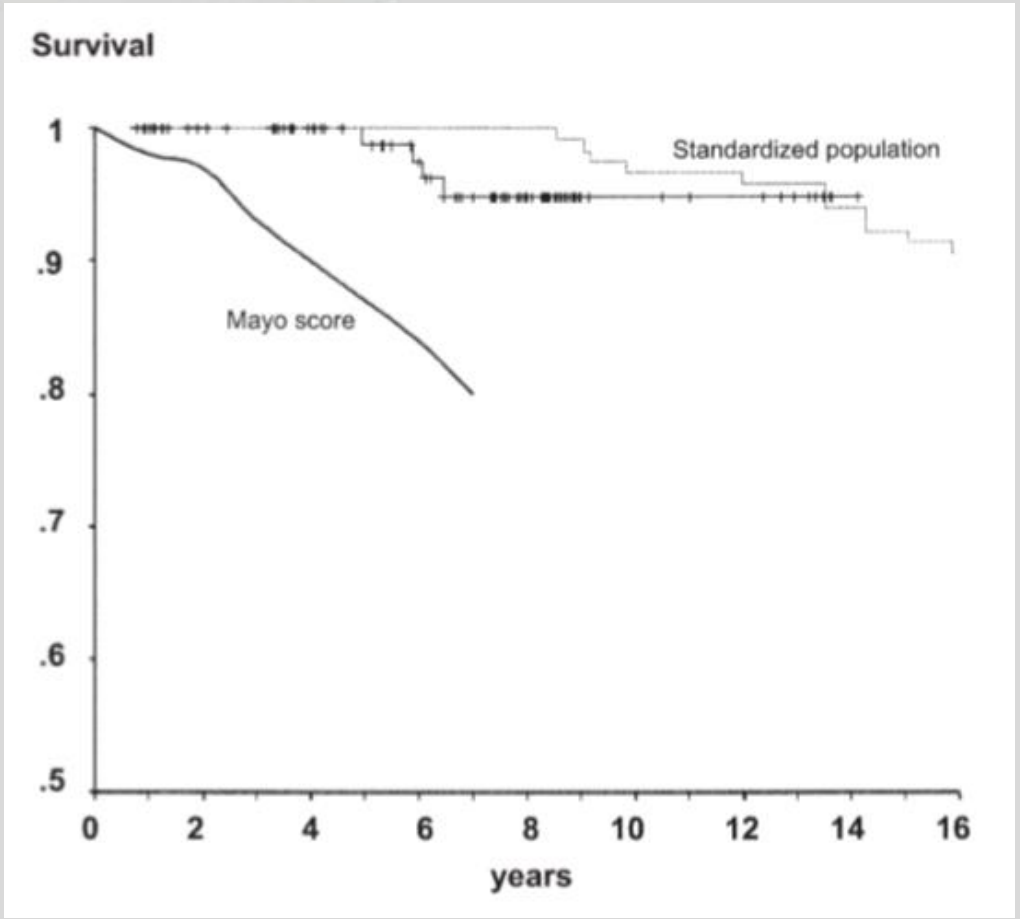
- AMA negative PBC has a similar course and prognosis

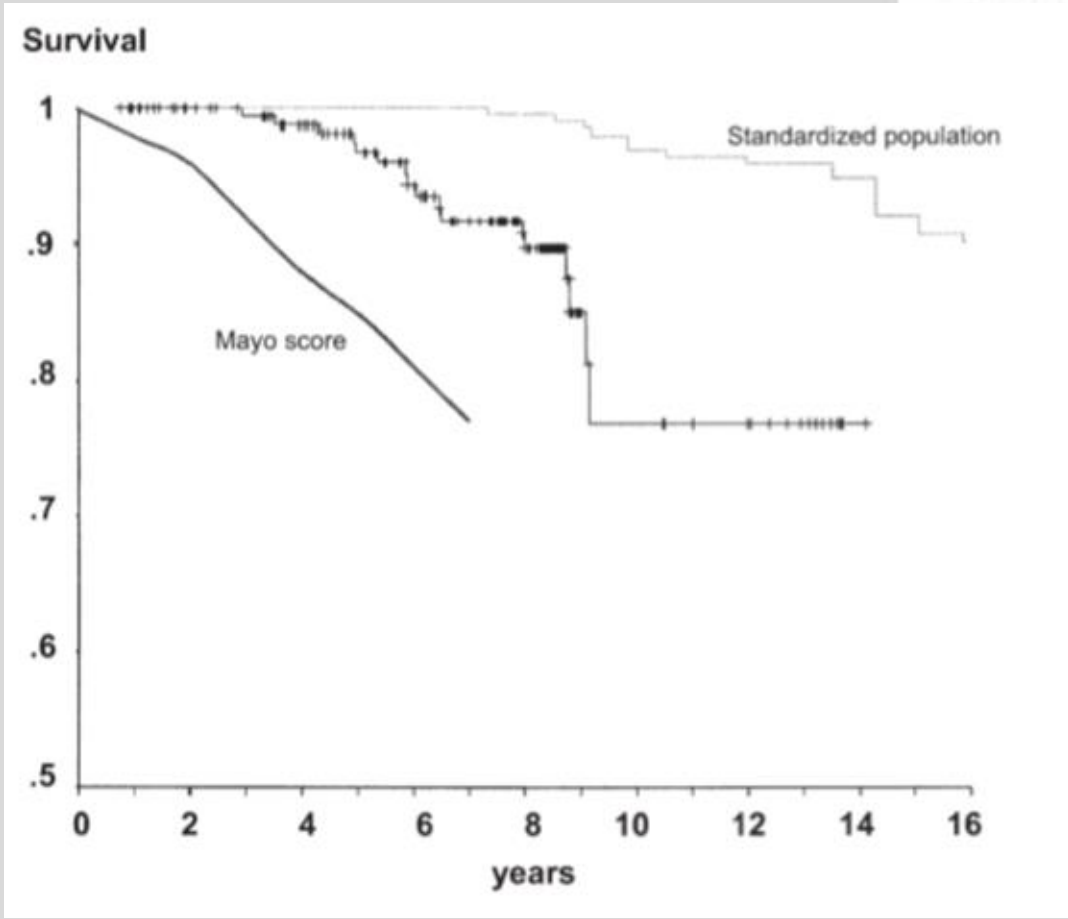
MANAGEMENT

- Ursodeoxycholic acid remains the drug of choice due to it's hepatoprotective effect
  - 13 – 15mg/kg/day
- Drug effects:
  - Improve liver chemistry results
  - Delay histologic progression
  - Prolong transplant free survival
- Vital to assess response at 6 -12 months
  - ALP >1.67x ULN &/or T bili <2x ULN – high risk
  - RCT evidence for addition of second agent

- Up to 30 – 50 % of patients are incomplete responders to URDA
- All patients, however, show benefit
- If started early in disease process, survival may approximate unaffected population
- Remains the backbone of treatment

URSODEOXYCHOLIC ACID RESPONSE





Parés A, Caballería L, Rodés J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology. 2006 Mar;130(3):715-20

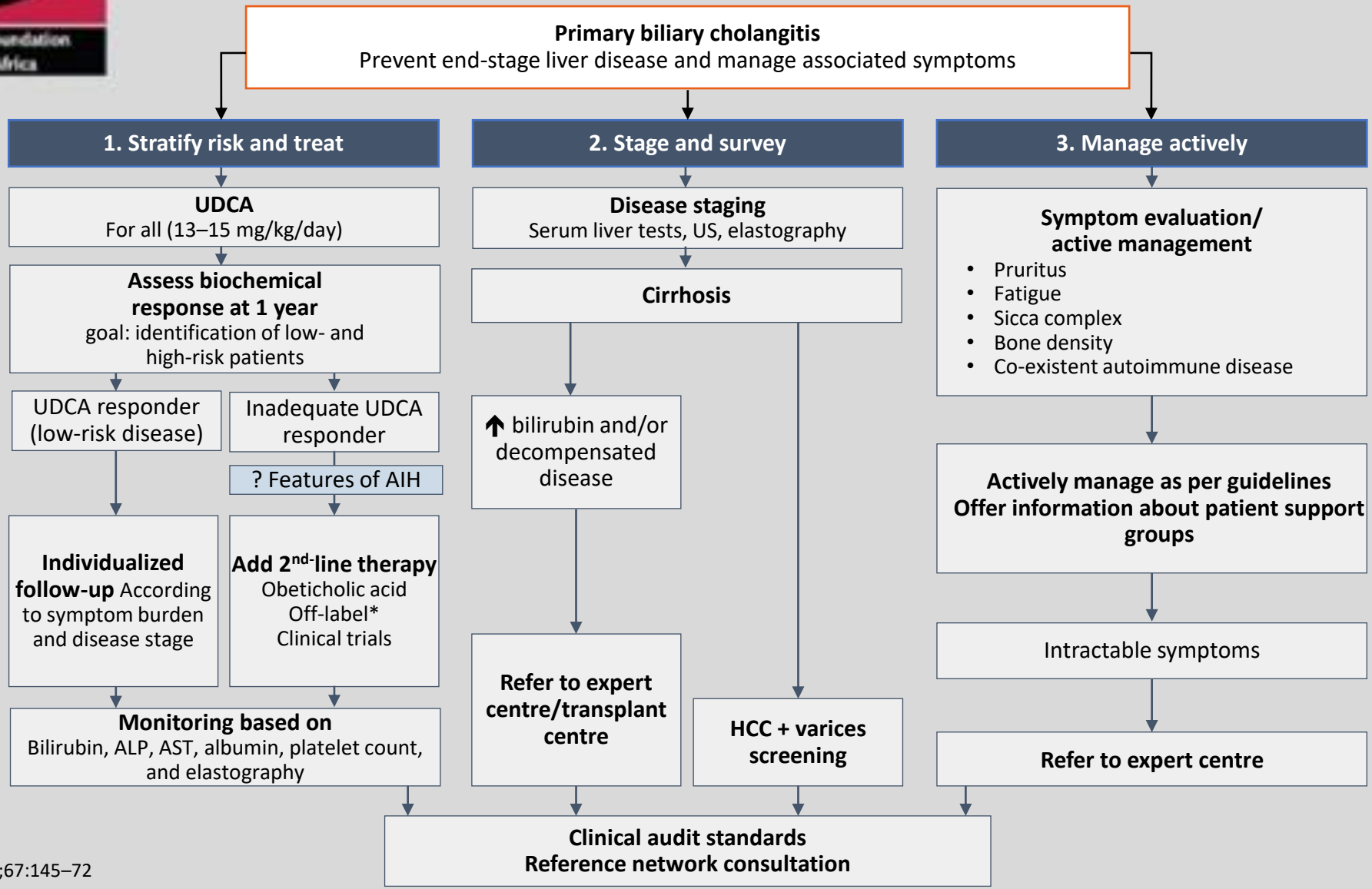
OBETICHOLIC ACID

- Works via farnesoid X receptor pathway
- POISE Trial: 2016 in NEJM
  - Significant improvement at 12 months for OCA vs placebo
- Obeticholic acid (OCA) approved as second line treatment for incomplete responders in combination with URDA
- Monotherapy if intolerant of URDA
- Contraindicated in those with decompensated cirrhosis or portal hypertension
- Need to monitor lipid profile
- Concern of increasing pruritis

FIBRATES

- Act as PPAR agonists
  - Increase secretion of phospholipids in bile canaliculi
  - Decrease bile acid synthesis
  - Reduce bile acid toxicity
  - Anti-inflammatory effect
- Bezafibrate and fenofibrate have been studied
- Improved biochemistry (ALP and bilirubin), improved markers of fibrosis and improved pruritis
- Not studied in those with advanced liver disease
- May be effective as part of ‘triple therapy’ in difficult to treat patients

THREE PILLARS OF PBC MANAGEMENT



*E.g. Fibrates, budesonide

EASL CPG PBC. J Hepatol 2017;67:145–72

MONITORING

- Serum biochemistry:
  - ALP
  - Bilirubin
- Liver stiffness with transient elastography
- Cirrhosis:
  - Endoscopy for varices
  - HCC monitoring
- Metabolic bone disease and vitamin deficiencies

TRANSPLANT

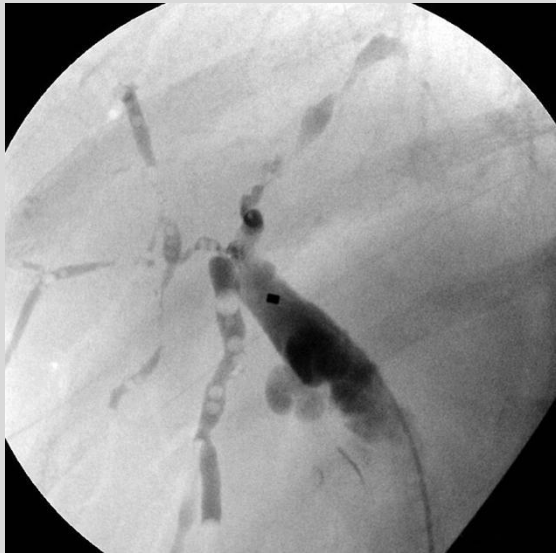
- Decreasing number of patients with PBC being listed for transplant
  - Likely secondary to ursodeoxycholic acid treatment
- Consideration for transplant assessment
  - MELD score >15
  - Complications of cirrhosis
- Outcomes
  - 80 – 85% survival at 5 years post transplant
  - Recurrence of 15 - 20% at 5 years – Need biopsy to prove it

SYMPTOM MANAGEMENT

- Pruritis
  - Pharmacological
    - Cholestyramine 4g 1-2x/d
    - Rifampicin 150-300mg/day
    - Naltrexone-opioid antagonist- 12.5-50mg/day
    - Sertraline 75-100mg nocte
    - Antihistamine-sedative type
  - Non-pharmacological
    - Short nails
    - Light/cotton clothing
    - Calamine or aqueous lotion
    - Avoid hot showers
    - Possible role for UVA therapy – isomerisation of bile acids to make them more water soluble

DEFINITION

- **Primary sclerosing cholangitis (PSC**) is a chronic cholestatic liver disease characterized by -
  - chronic inflammation and fibrosis of both the intrahepatic and extrahepatic bile ducts
  - formation of multifocal bile duct damage and strictures
  - frequently associated with inflammatory bowel disease (IBD)
  - not secondary to another cause

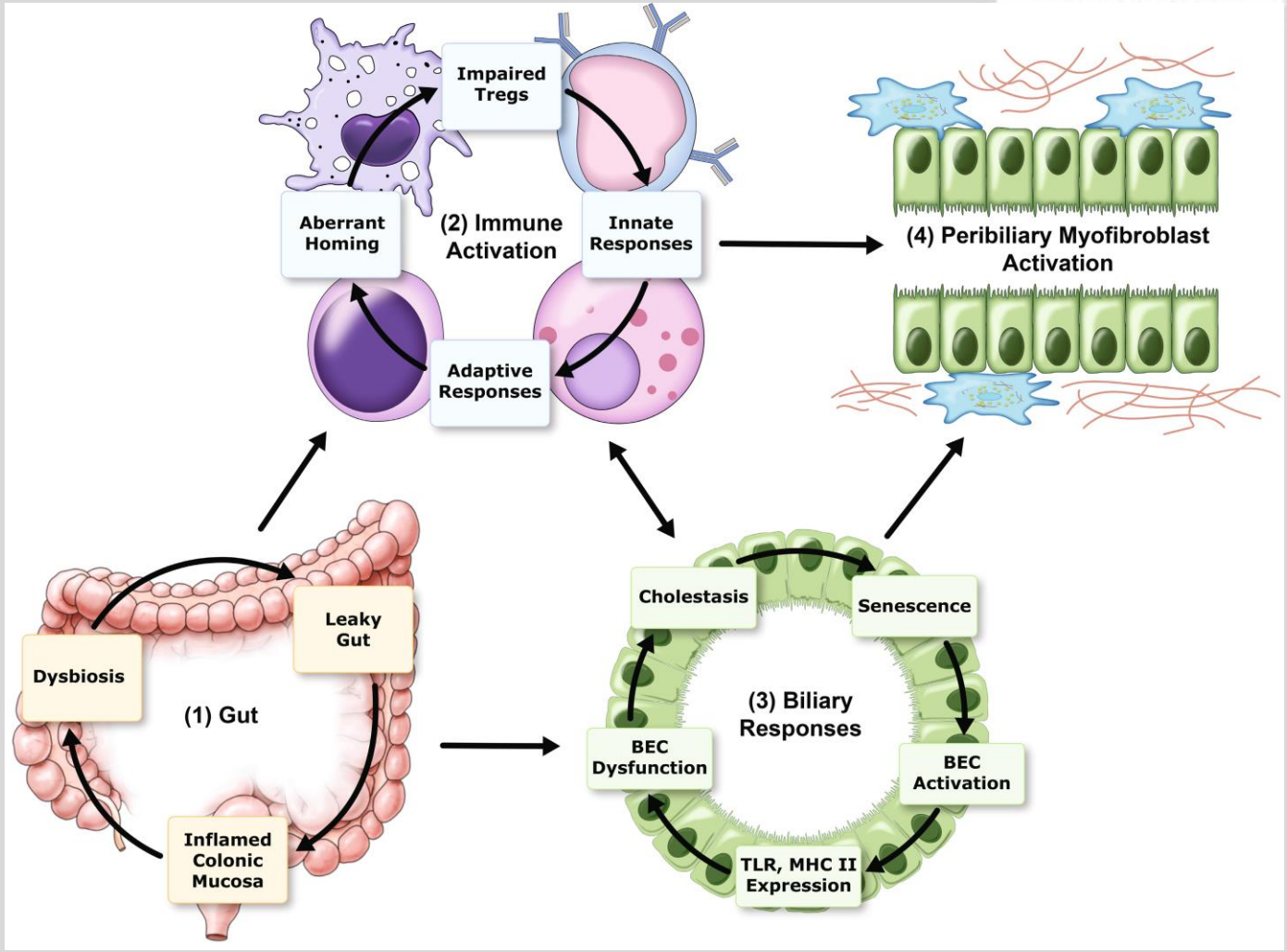


PSC EPIDEMIOLOGY

- Predominantly in men with a 3:2 ratio
- 70 – 80% of those with PSC have associated IBD
- Incidence of PSC is 6 – 16 per 100 000 people
  - Peak incidence: 25 – 45 years
  - Mean age at diagnosis: 36 - 39 years
- Africa
  - Significant lack of data
  - Top reason for liver transplant in South Africa

PATHOPHYSIOLOGY

- Genetically susceptible host
- Environmental triggers
- Immune activation



Bowlus, Christopher L et al. "AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma." Hepatology (Baltimore, Md.) vol. 77,2 (2023): 659-702

SUBTYPES OF PSC

- Classic or Large duct PSC (90%)
  - Typical features diagnosed on MRCP
- Small Duct PSC (10%)
  - Normal cholangiogram
  - Biochemical features of PSC +/- IBD
  - Biopsy diagnosis: typical of PSC
- Paediatric PSC
  - Often with inflammation consistent with AIH

PRESENTATION

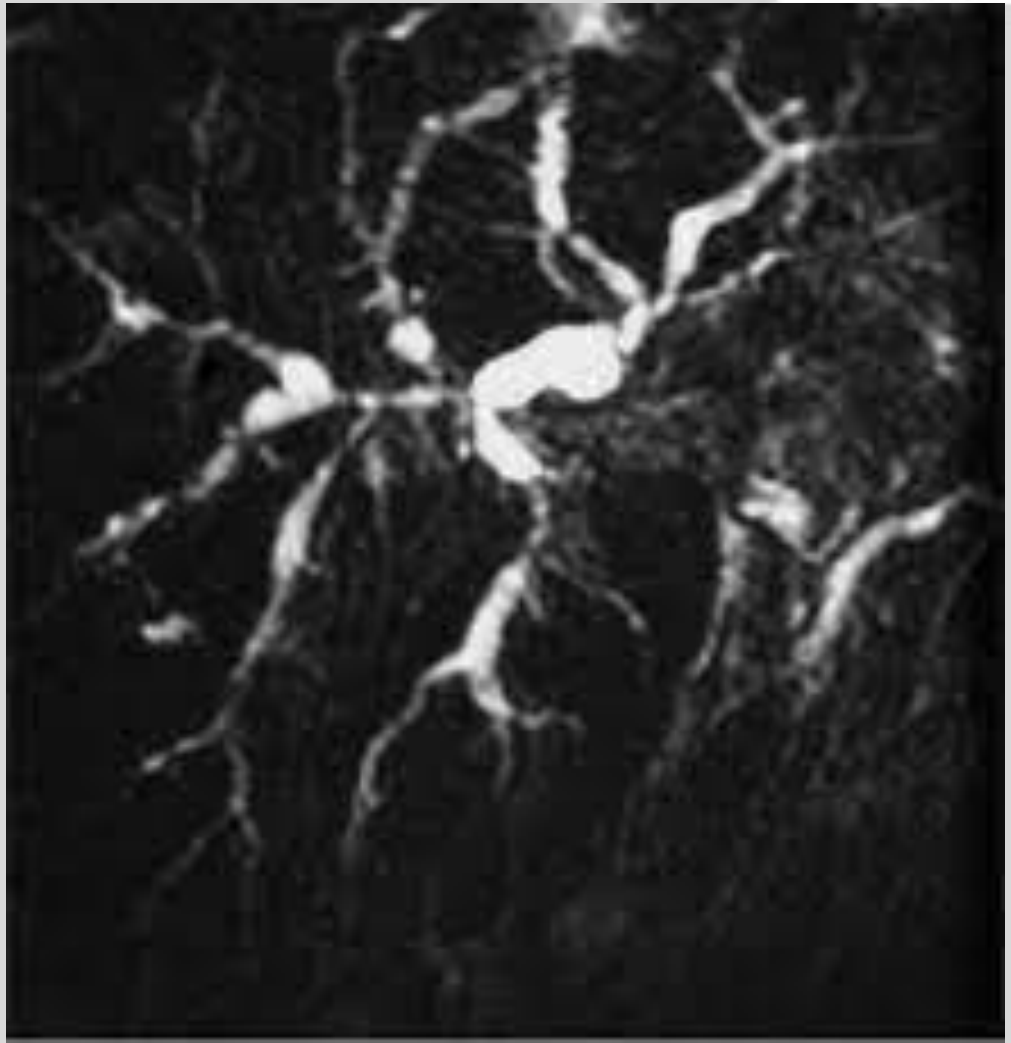
- Asymptomatic 15 – 55%
- Jaundice: concern for stricture ?benign vs malignant
- Right upper quadrant pain
- Fatigue, Pruritis, Loss of weight
- Cholangitis
- Complications of biliary cirrhosis: ascites, hypersplenism, variceal bleed

DIAGNOSIS

- MRCP is diagnostic
- Biochemistry:
  - ALP and GGT may be raised in isolation leading to further workup
  - Raised aminotransaminases: consider AIH if >5x ULN
  - Serum autoantibodies are not specific and their presence in PSC is highly variable
- Biopsy in specific clinical scenario
- Transient shear wave elastography - staging

MRCP

- Sensitivity of > 85 %
- Specificity of > 90%
- Diagnostic in ‘classic’ or large duct PSC
  - Involvement of intra- and extra-hepatic bile ducts
  - Strictures and dilatation
  - Beaded appearance
  - Floating ducts



BIOPSY

- Not routinely required
- Useful in diagnosis of small duct PSC
- Characteristic ‘onion skin’ appearance surrounding bile ducts
- May help if concern of AIH overlap syndrome

ASSOCIATION WITH IBD

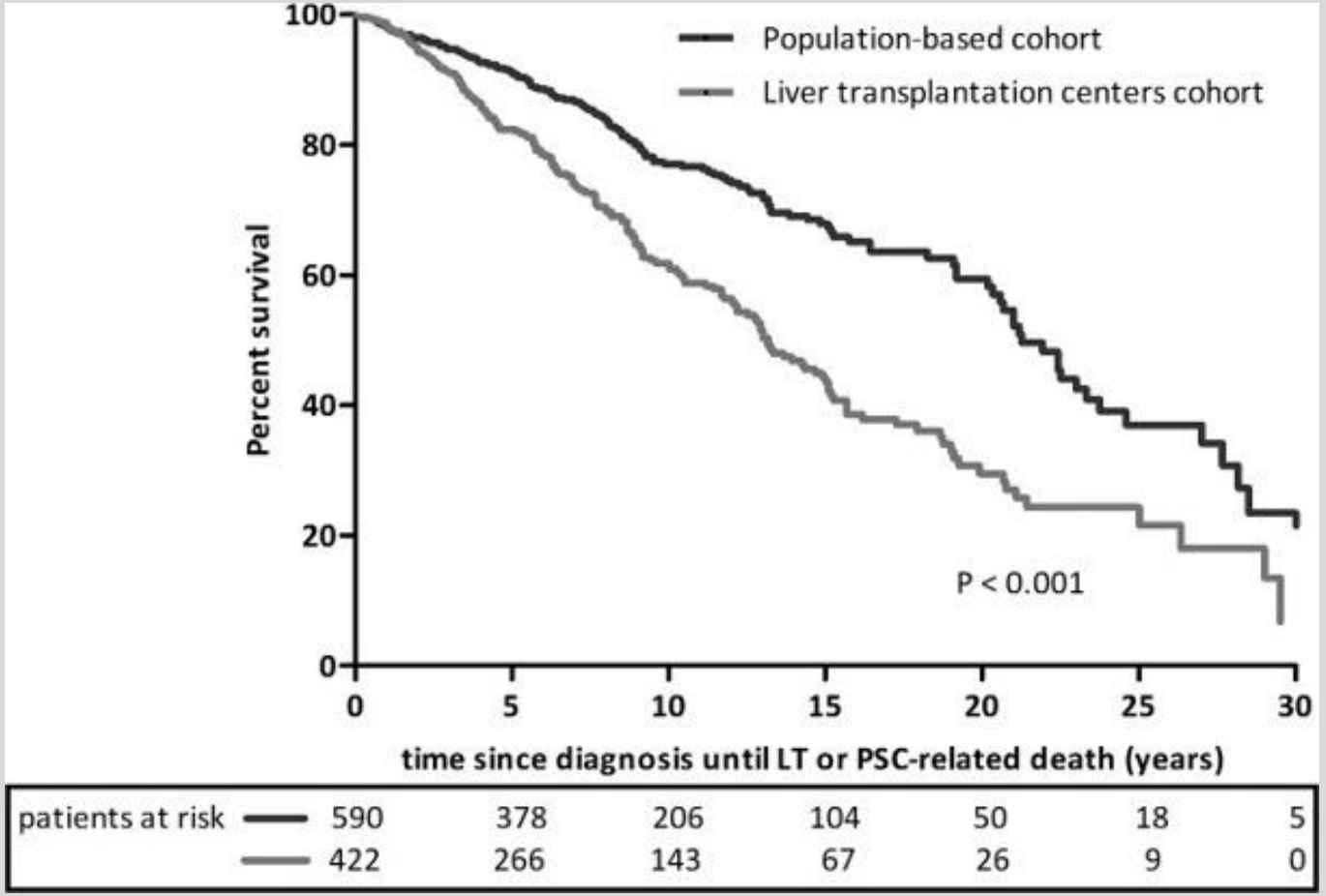
- Strong association with IBD
- 70 – 80% of those with PSC will have IBD
  - Ulcerative colitis most common
    - Often pancolitis or more right sided disease with backwash ileitis
    - Milder UC phenotype
  - Chron's Disease –usually Chron's colitis
  - May occur at any time in disease course, including post transplant
- PSC/UC overlap has a significantly greater risk of colorectal cancer
  - Need annual surveillance

TREATMENT

- No proven, effective medical treatment
- Multiple medications being trialled
- Ursodeoxycholic acid
  - 13-15mg/kg/day
  - Higher doses harmful
  - If ALP improves in 6 months can continue -if no change then consider stopping
  - May decrease risk of colorectal cancer in PSC/UC patients
- Transplant only modality that prolongs survival
  - Jaundice (T bili >100) often a trigger to consider transplant
  - Complications of cirrhosis
  - Recurrent cholangitis
  - PSC recurrence in 35% at 5 yrs post transplant

Sedki M, Levy C. Update in the Care and Management of Patients with Primary Sclerosing Cholangitis. Curr Gastroenterol Rep. 2018 Jun 9;20(7):29.

TRANSPLANT FREE SURVIVAL



Boonstra, Kirsten et al. “Population-Based Epidemiology, Malignancy Risk, and Outcome of Primary Sclerosing Cholangitis.” Hepatology (Baltimore, Md.) 58.6 (2013): 2045–2055.

COMPLICATIONS

- PSC recurrence in 35% post transplant by 5 years
- Cirrhosis and portal hypertension
  - Ascites
  - Variceal bleeds
  - Encephalopathy
- Recurrent cholangitis
  - Early treatment with antibiotics
  - Consider PTC if appropriate
  - Dominant stricture: may benefit from balloon dilatation
- Fat soluble vitamin deficiencies

MALIGNANCY

- Major increased lifetime risk of hepatobiliary and colorectal cancer
- Hepatobiliary cancers: 161 x greater risk } compared to
- Colorectal cancer: 10 x greater risk } general population
- Overall frequency of malignancy is 13%
- 40% of mortality in PSC from associated malignancy
  - Cholangiocarcinoma
  - Colorectal cancer
  - Gall bladder adenocarcinoma
  - Hepatocellular carcinoma

Sedki M, Levy C. Update in the Care and Management of Patients with Primary Sclerosing Cholangitis. Curr Gastroenterol Rep. 2018 Jun 9;20(7):29.

SCREENING

- Cholangiocarcinoma
  - Increased risk in older age, male
  - Increased risk within the first year
  - Dominant stricture should raise concern (<25% will be malignant)
  - Annual imaging with MRCP +/- USS
  - Serum Ca 19-9
- Gall Bladder Carcinoma
  - Increased benign and malignant lesions in PSC
  - Cholecystectomy for all gallbladder lesions regardless of size (8mm cutoff may be used if aim to avoid surgery)

Sedki M, Levy C. Update in the Care and Management of Patients with Primary Sclerosing Cholangitis. Curr Gastroenterol Rep. 2018 Jun 9;20(7):29.

SCREENING

- Hepatocellular carcinoma
  - Biannual USS and AFP in all cirrhotic patients
- Colorectal carcinoma
  - PSC-IBD patients have 20-30% risk of colorectal cancer at 20 year follow up
  - Need annual colonoscopy with 4 quadrant biopsies
  - PSC is an independent risk factor for colorectal ca in IBD (UC>CD)
  - PSC with no IBD – Follow up unclear. Some guidelines say 5 years

Sedki M, Levy C. Update in the Care and Management of Patients with Primary Sclerosing Cholangitis. Curr Gastroenterol Rep. 2018 Jun 9;20(7):29.

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Primary Biliary Cholangitis (PBC) vs Primary Sclerosing Cholangitis (PSC)

Primary Biliary Cholangitis (PBC)		Primary Sclerosing Cholangitis (PSC)
Inflammation of **intrahepatic bile ducts** which may lead to fibrosis and cirrhosis	**Site of Involvement**	Inflammation of both **intra and extrahepatic bile ducts** (10-15% only intrahepatic affected)
♀ Female > male (9:1 ratio)	**Gender**	♂ Male > female
Often asymptomatic; Pruritus, fatigue, abdominal pain; Jaundice after years	**Features**	Pruritus, fatigue, cholangitis
Cholestatic picture with raised ALP, GGT	**Liver function tests**	Cholestatic picture with raised ALP, GGT
Anti-mitochondrial antibody (AMA) M2 subtype positive in 98% of PBC	**Investigation**	ERCP/MRCP shows **beaded appearance** of bile ducts
Sjogren's syndrome (seen in 80% of PBC) Rheumatoid arthritis Systemic sclerosis	**Associated conditions**	80% of those with PSC have inflammatory bowel disease (usually UC)
Cirrhosis	**Complications**	↑ Risk of cholangio and colorectal carcinoma Cirrhosis
• Cholestyramine for pruritus • Ursodeoxycholic acid – **improves survival** and delay transplantation • Liver transplantation	**Treatment**	• Cholestyramine for pruritus • Ursodeoxycholic acid – may improve LFTs but **does not improve survival** • Liver transplantation

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GRAM PROJECT

REFERENCES

- EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol. 2015 Oct;63(4):971-1004. doi:10.1016/j.jhep.2012.04.004
- Muratori L, Lohse AW, Lenzi M. Diagnosis and management of autoimmune hepatitis. BMJ. 2023 Feb 6;380:e070201. doi: 10.1136/bmj-2022-070201. Erratum in: BMJ. 2023 Feb 10;380:p330. PMID: 36746473.
- Tanaka A. Autoimmune Hepatitis: 2019 Update. Gut Liver. 2020 Jul 15;14(4):430-438. doi: 10.5009/gnl19261. PMID: 32301319; PMCID: PMC7366136.
- Sucher E, Sucher R, Gradistanac T, Brandacher G, Schneeberger S, Berg T. Autoimmune Hepatitis-Immunologically Triggered Liver Pathogenesis-Diagnostic and Therapeutic Strategies. J Immunol Res. 2019 Nov 25;2019:9437043. doi: 10.1155/2019/9437043. PMID: 31886312; PMCID: PMC6899271.
- Covelli C, Sacchi D, Sarcognato S, Cazzagon N, Grillo F, Baciorri F, Fanni D, Cacciatore M, Maffeis V, Guido M. Pathology of autoimmune hepatitis. Pathologica. 2021 Jun;113(3):185-193. doi: 10.32074/1591-951X-241. PMID: 34294936; PMCID: PMC8299324.
- Komori A. Recent updates on the management of autoimmune hepatitis. Clin Mol Hepatol. 2021 Jan;27(1):58-69. doi: 10.3350/cmh.2020.0189. Epub 2020 Dec 10. PMID: 33291862; PMCID: PMC7820207.
- Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Autoimmmune hepatitis. Cell Mol Immunol. 2022 Feb;19(2):158-176. doi: 10.1038/s41423-021-00768-8. Epub 2021 Sep 27. PMID: 34580437; PMCID: PMC8475398.

- Hirschfield GM et al. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. Gut. 2018 Sep;67(9):1568-1594. doi: 10.1136/gutjnl-2017-315259.
- Bowlus, Christopher L et al. “AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma.” Hepatology (Baltimore, Md.) vol. 77,2 (2023): 659-702
- Sedki M, Levy C. Update in the Care and Management of Patients with Primary Sclerosing Cholangitis. Curr Gastroenterol Rep. 2018 Jun 9;20(7):29. doi: 10.1007/s11894-018-0635-8. PMID: 29886518.
- Hasegawa S, Yoneda M, Kurita Y, Nogami A, Honda Y, Hosono K, Nakajima A. Cholestatic Liver Disease: Current Treatment Strategies and New Therapeutic Agents. Drugs. 2021 Jul;81(10):1181-1192. doi: 10.1007/s40265-021-01545-7. Epub 2021 Jun 17. PMID: 34142342; PMCID: PMC8282588.
- EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017 Jul;67(1):145-172. doi: 10.1016/j.jhep.2017.03.022. Epub 2017 Apr 18. PMID: 28427765.
- Parés A, Caballería L, Rodés J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid. Gastroenterology. 2006 Mar;130(3):715-20. doi: 10.1053/j.gastro.2005.12.029. PMID: 16530513.
- Floreani A, De Martin S. Treatment of primary sclerosing cholangitis. Dig Liver Dis. 2021 Dec;53(12):1531-1538. doi: 10.1016/j.dld.2021.04.028. Epub 2021 May 16. PMID: 34011480.
- Purohit T, Cappell MS. Primary biliary cirrhosis: Pathophysiology, clinical presentation and therapy. World J Hepatol. 2015 May 8;7(7):926-41. doi: 10.4254/wjh.v7.i7.926. PMID: 25954476; PMCID: PMC4419097.