UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA
CLMMC V anno
Patologia Sistemica VI (M-Z)
AA 2023-24

Auroimmune liver diseases

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Testo consigliato Harrison's Principles of Internal Medicine – 19-20° Ed.

Chronic hepatitis classification by cause

Type of Hepatitis	Diagnostic Test(s)	Autoantibodies	Therapy
Chronic hepatitis B	HBsAg, IgG anti-HBc, HBeAg, HBV DNA	Uncommon [a]	IFN-, PEG IFN-, lamivudine, adefovir, entecavir,tenofovir, telbivudine
Chronic hepatitis C	Anti-HCV, HCV RNA	Anti-LKM1[a]	PEG IFN- plus ribavirin, telaprevir boceprevir
Chronic hepatitis D	Anti-HDV, HDV RNA, HBsAg, IgG anti-HBc	Anti-LKM3	IFN-, PEG IFN-[b]
Autoimmune hepatitis	ANA[c] (homogeneous), anti-LKM1(±), Hyperglobulinemia	ANA, anti-LKM1, anti-SLA[d]	Prednisone, azathioprine
Drug-associated	—	Uncommon	Withdraw drug
Cryptogenic	All negative	None	Prednisone (?), azathioprine (?)

Autoimmune liver diseases

Table 1 Autoimmune liver diseases: clinicopathologic features (adapted from Beuers[73])

	AIH	*PBC*	*PSC*	*AIC*[a]
Female:male	4:1	9:1	1:2	9:1
Predominant liver test elevation	AST, ALT	Alk phos, γ-GT	Alk phos, γ-GT	Alk phos, γ-GT
Serum Ig elevation	IgG	IgM	IgG, IgM	IgM
Autoantibodies	ANA, ASMA, LKM1, SLA/P, pANCA	AMA, AMA-M2, gp210	p-ANCA	ANA, ASMA
HLA association	A3, B8, DR3, DR4	DR8 (weak association)	DR52	B8, DR3, DR4
Histology	Interface and lobular hepatitis; prominent plasma cells	Florid bile duct lesion	Fibrosis and obliteration of large bile ducts; ductopenia	Florid bile duct lesion
Diagnosis	AIH score > 15 for diagnosis of definite AIH	AMA, cholestatic serum enzyme pattern, compatible histology	Biliary strictures and dilatation on cholangiography; cholestatic serum enzyme pattern, IBD, p-ANCA	Cholestatic serum enzyme pattern, AMA neg, ANA or ASMA positive; histology c/w PBC
First-line medical therapy	Immunosuppression (corticosteroids+ azathioprine)	Ursodeoxycholic acid (UDCA)	UDCA	UDCA

[a]Autoi

AIH: Autoimmune hepatitis
PBC: Primary biliary cholangitis (cirrhosis)
PSC: Primary sclerosing cholangitis
AIC: Autoimmune cholangitis

Autoimmune hepatitis

- Autoimmune hepatitis is a chronic disorder characterized by continuing hepatocellular **necrosis and inflammation, usually with fibrosis**, which can progress to cirrhosis and liver failure.
- Based on contemporary estimates of the natural history of treated autoimmune hepatitis, the **10-year survival is 80–90%.**
- The prominence of extrahepatic features of autoimmunity as well as seroimmunologic abnormalities in this disorder supports an autoimmune process in its pathogenesis;
- Autoantibodies and other typical features of autoimmunity, however, do not occur in all cases;

Autoimmune hepatitis

C*linical features* of autoimmune hepatitis are similar to those described for chronic viral hepatitis.

- The onset of disease may be insidious or abrupt; the disease may **present initially like an acute viral hepatitis;**
- A subset of patients with autoimmune hepatitis has distinct features**.** This is the group with positive **lupus erythematosus (LE) antibodies** (initially labeled "lupoid" hepatitis) in whom other autoimmune features are common. **Such patients are predominantly young to middle-aged women with marked hyperglobulinemia and high-titer circulating ANAs.**
- **Fatigue, malaise, anorexia, amenorrhea, acne, arthralgias, and jaundice are common.**
- Occasionally arthritis, maculopapular eruptions (including cutaneous vasculitis), erythema nodosum, colitis, pleurisy, pericarditis, anemia, azotemia, and sicca syndrome (keratoconjunctivitis, xerostomia) occur.

Autoimmune hepatitis: laboratory findings

***Laboratory features* of autoimmune hepatitis are similar to those seen in chronic viral hepatitis.**

- Liver biochemical tests are invariably abnormal but may not correlate with the clinical severity or histopathologic features in individual cases.
- **Serum AST and ALT levels are increased and fluctuate in the range of 100–1000 units.**
- In severe cases, the **serum bilirubin** level is moderately elevated (3–10 mg/dL)].
- Hypoalbuminemia occurs in patients with very active or advanced disease. Serum alkaline phosphatase levels may be moderately elevated or near normal.
- In a small proportion of patients, marked elevations of **alkaline phosphatase activity occur**; in such patients, clinical and **laboratory features overlap** with those of primary biliary cirrhosis.
- The prothrombin time is often prolonged, particularly late in the disease or during active phases.

Autoimmune hepatitis: laboratory findings

Hypergammaglobulinemia (>2.5 g/dL) is common in autoimmune hepatitis.

Rheumatoid factor is common

- As noted above, **circulating autoantibodies are also prevalent. The most characteristic are ANAs** in a homogeneous staining pattern. Smooth-muscle antibodies are less specific, seen just as frequently in chronic viral hepatitis.
- Because of the high levels of globulins achieved in the circulation of some patients with autoimmune hepatitis, occasionally the globulins may bind nonspecifically in solid-phase binding immunoassays for viral antibodies. This has been recognized most commonly in tests for antibodies to hepatitis C virus, as noted above. In fact, studies of autoantibodies in autoimmune hepatitis have led to the recognition of new categories of autoimmune hepatitis.

Autoimmune hepatitis

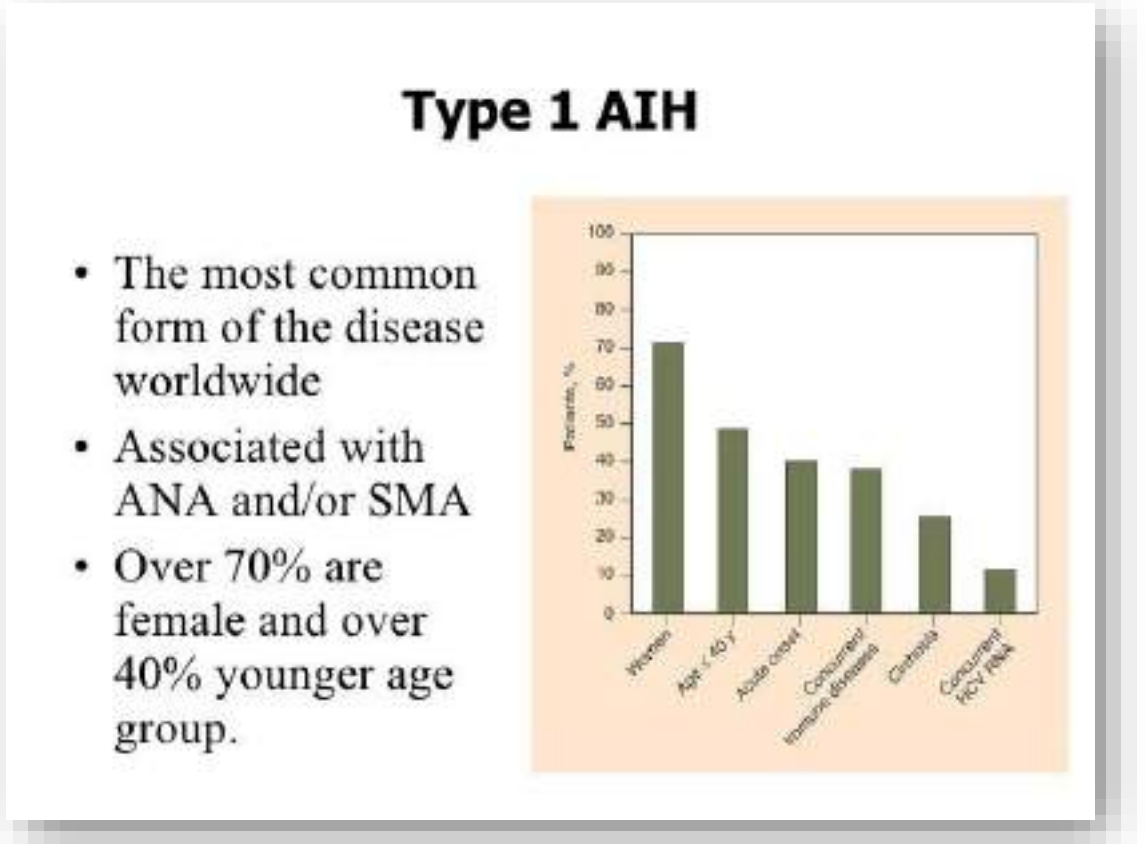
Table 1. Comparison of Type 1 and Type 2 AIH

	Type 1	Type 2
Female to male ratio	4:1	10:1
Age distribution	Infancy to elderly adulthood	Childhood to young adulthood
Geographic distribution	Global	Global but with geographic differences in adult prevalence: Southern Europe > Northern Europe and Europe > United States[a]
Clinical presentation and course	ALF rare	ALF rare
	Indolent presentation more frequent than severe presentation	Severe presentation, especially in children and adolescents
Signature autoantibodies	ANA	Anti-LKM1
	SMA	Anti-LC1
	Anti–F-actin[b]	Anti-LKM3
Overlapping autoantibodies	Anti-SLA/LP	Anti-SLA/LP
	Anti-ASGPR	Anti-ASGPR
Histology at presentation	Spectrum ranging from ALF with massive hepatocellular necrosis, mild disease to active cirrhosis	ALF with massive hepatocellular necrosis rare
		Often high-grade inflammation
		Cirrhosis common
Response to steroid and AZA	Excellent in majority	Excellent in minority
	Failure in minority	Failure common
Requirement for long-term immunosuppression	Sustained withdrawal successful in minority	Sustained withdrawal rare
	Majority require long-term therapy	Nearly universal need for long-term therapy

Autoimmune hepatitis

Type I autoimmune hepatitis **is the classic syndrome occurring in young women, associated with marked hyperglobulinemia, lupoid features, circulating ANAs, and HLA-DR3 or HLA-DR4.**

Also associated with type I autoimmune hepatitis **are autoantibodies against actin (anti-SMA)** as well as atypical perinuclear antineutrophilic cytoplasmic antibodies **(pANCA).**

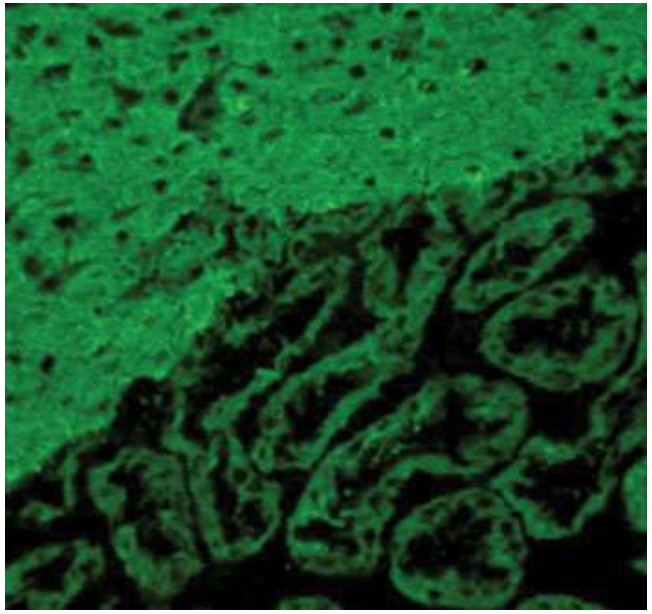


Autoimmune hepatitis

***Type II autoimmune hepatitis*, often** seen in children, more common in Mediterranean populations, and linked to HLA-DRB1 and HLA-DQB1 haplotypes, **is associated not with ANA but with anti-LKM.**

Actually, **anti-LKM represent a heterogeneous group of antibodies**.

In type II autoimmune hepatitis, the antibody **is anti-LKM1,** directed against **cytochrome P450 2D6**. This is the same anti-LKM seen in some patients **with chronic hepatitis C**. Anti-LKM2 is seen in drug-induced hepatitis, and anti-LKM3 is seen in patients with chronic hepatitis D.



Anti-liver kidney microsomal

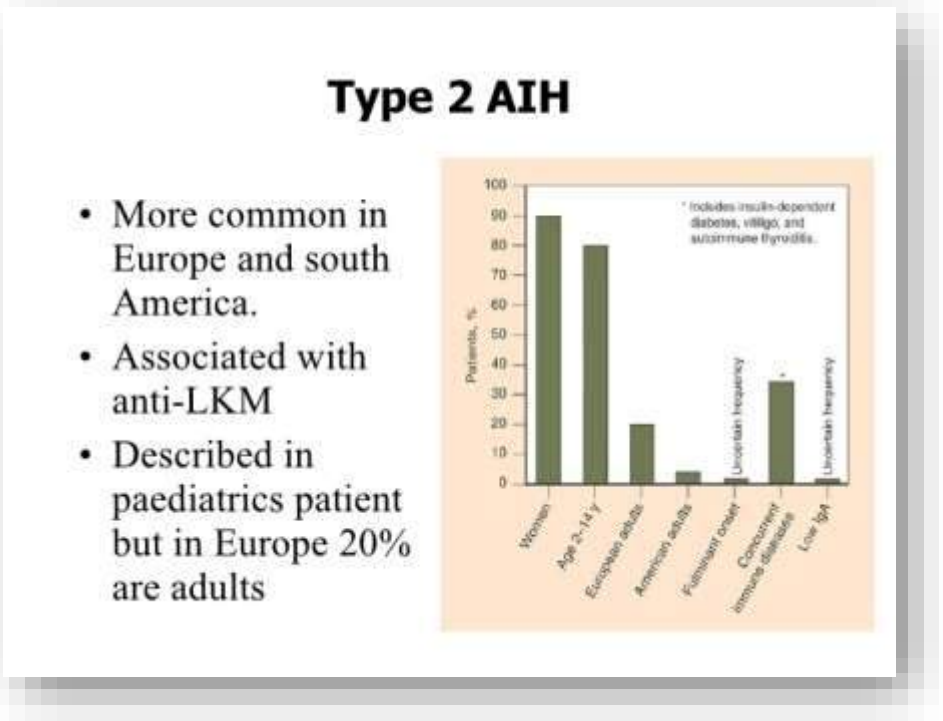
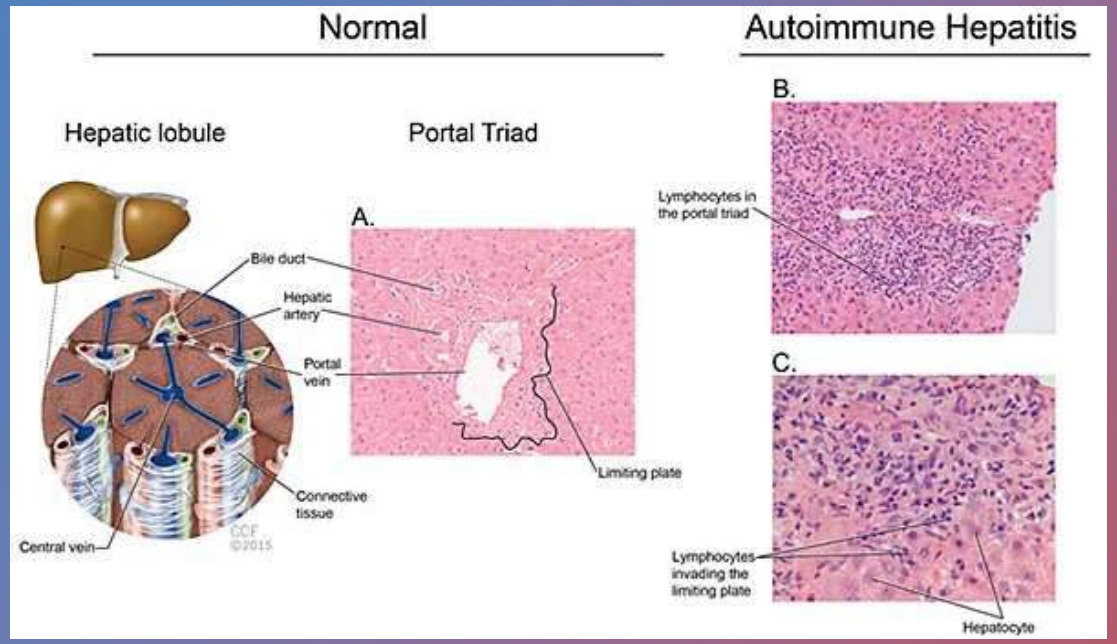
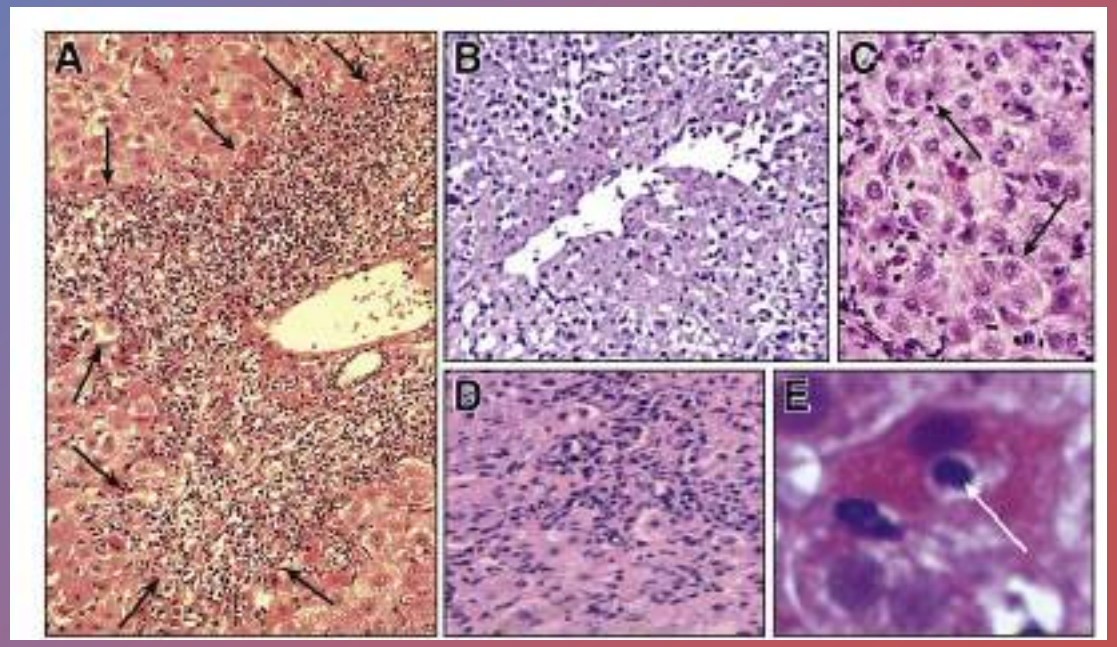


Table 2. Autoantibodies and Differential Diagnosis of AIH

Autoantibody	Autoantigen	Liver diseases	Utility
ANA	Chromatin, ribonucleoproteins, ribonucleoprotein complexes (gp210 and Sp100 in PBC)	AIH, PBC, PSC, DILI, chronic HBV, HCV infections, WD, NAFLD	Compatible with type 1 AIH Must exclude other diseases
SMA	Microfilaments: filamentous actin (F-actin), intermediate filaments: vimentin, desmin	AIH, PBC, PSC, DILI, HBV, HCV, WD, NAFLD	Compatible with type 1 AIH Must exclude other diseases
pANCA	Beta-tubulin isotype 5, mimicry with bacterial precursor protein FtsZ	AIH, PSC, IBD AIH-PSC OS?	Compatible with type 1 AIH AIH-PSC OS? Must exclude other diseases
AMA	2-oxo-acid dehydrogenase complex (E2 subunit lipodryl domains)	PBC, rarely AIH AIH-PBC OS?	Rarely observed in type 1 AIH AIH-PBC OS?
LKM-1	Epitopes of cytochrome P450 2D6 (CYP2D6)	AIH, chronic HCV infection, halothane-induced hepatitis	Diagnostic of type 2 AIH if HCV infection excluded
LKM-3	Family 1 UDP-glucuronosyltransferases (UGT1A)	AIH, chronic HDV	Diagnostic of type 2 AIH if chronic HDV infection excluded
LC-1	Formiminotransferase cyclodeaminase (FTCD)	AIH type 2	Diagnostic of type 2 AIH Liver specific
LM	Epitopes of cytochrome P450 2A6 (CYP2A6)	APECED HCV	APECED Must exclude HCV infection
SLA/LP	tRNA-selenocysteinyl-tRNA synthase (SepSecS protein)	AIH type 1 or 2	Diagnostic of AIH Compatible with either type 1 or 2 AIH Prognostic for severe disease, relapse after withdrawal of immunosuppression, fetal loss
ASGPR	Asialoglycoprotein receptor	AIH, PBC, DILI, chronic HBV, HCV, HDV infections	Liver specific Compatible with type 1 or 2 AIH. Prognostic for severe disease, histopathologic activity and relapse after withdrawal of immunosuppression

NOTE. New autoantigens being investigated in AIH include α-actinin, a ubiquitous cytoskeletal cross-linking protein within the family of filamentous actin (F-actin)[214]; phosphoenolpyruvate carboxykinase 2[215]; ribosomal P[216]; nucleosome[217]; programmed cell death-1[218]; and interleukin-4 receptor.[219] APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; ASGPR, anti-asialoglycoprotein receptor antibody; HDV, hepatitis D virus; IBD, inflammatory bowel disease; LC-1, anti-liver cytosol type 1 antibody; NAFLD, nonalcoholic fatty liver disease; pANCA, perinuclear neutrophil cytoplasmic antibody; tRNA, transfer RNA; UDP, uridine diphosphate; UGT, uridine diphosphate glucuronosyltransferase.





Autoimmune hepatitis

Liver biopsy abnormalities are similar to those described for chronic viral hepatitis. Expanding portal tracts and extending beyond the plate of periportal hepatocytes into the parenchyma (designated *interface hepatitis* or *piecemeal necrosis*) is a mononuclear cell infiltrate that, in autoimmune hepatitis, may include the presence of plasma cells.

Necroinflammatory activity characterizes the lobular parenchyma, and evidence of hepatocellular regeneration is reflected by "rosette" formation, the occurrence of thickened liver cell plates, and regenerative "pseudolobules.

Septal fibrosis, bridging fibrosis, and cirrhosis are frequent. Bile duct injury and granulomas are uncommon; however, a subgroup of patients with autoimmune hepatitis have histologic, biochemical, and serologic features overlapping those of primary biliary cirrhosis

Autoimmune hepatitis

Exclusion of liver disease caused by genetic disorders, viral hepatitis, drug hepatotoxicity, and alcohol are linked with such inclusive diagnostic criteria as hyperglobulinemia, autoantibodies, and characteristic histologic features.

Factors in favor of the diagnosis

include **female gender**; **predominant aminotransferase elevation**; presence and level of globulin elevation; **presence of nuclear, smooth muscle, LKM1, and other autoantibodies**;

concurrent other autoimmune diseases;

characteristic histologic features (interface hepatitis, plasma cells, rosettes);

HLA DR3 or DR4 markers;

and response to treatment (see below).

Weighing against the diagnosis are predominant alkaline phosphatase elevation, mitochondrial antibodies, markers of viral hepatitis, history of hepatotoxic drugs or excessive alcohol, histologic evidence of bile duct injury, or such atypical histologic features as fatty infiltration, iron overload, and viral inclusions.

Autoimmune hepatitis

Clinical feature	Points
ANA or SMA	
• ≥1:40	+1
• ANA or SMA ≥1:80 or LKM1 ≥1:40 or SLA-positive	+2
Serum IgG	
• >upper limit of normal	+1
• >1.1 times upper limit of normal	+2
Histologic findings	
• Compatible with AIH	+1
• Typical of AIH	+2
Hepatitis viral markers	
• Negative	+2
Aggregate score without treatment	
• Definite AIH	≥7
• Probable AIH	≥6

ANA=antinuclear antibody; SMA=smooth muscle antibody; LKM1=liver kidney microsomal antibody; SLA=soluble liver antigen antibody; IG=immunoglobulin.

Reproduced from Hennes EM, et al.[15]

Autoimmune hepatitis

Differential Diagnosis

- Early during the course of chronic hepatitis, autoimmune hepatitis may resemble typical *acute viral hepatitis*.
- In adolescence, ***Wilson's disease*** may present with features of chronic hepatitis long before neurologic manifestations become apparent and before the formation of **Kayser-Fleischer rings. In this age group, serum ceruloplasmin** and **serum and urinary copp**er determinations plus measurement of liver copper levels will establish the correct diagnosis.

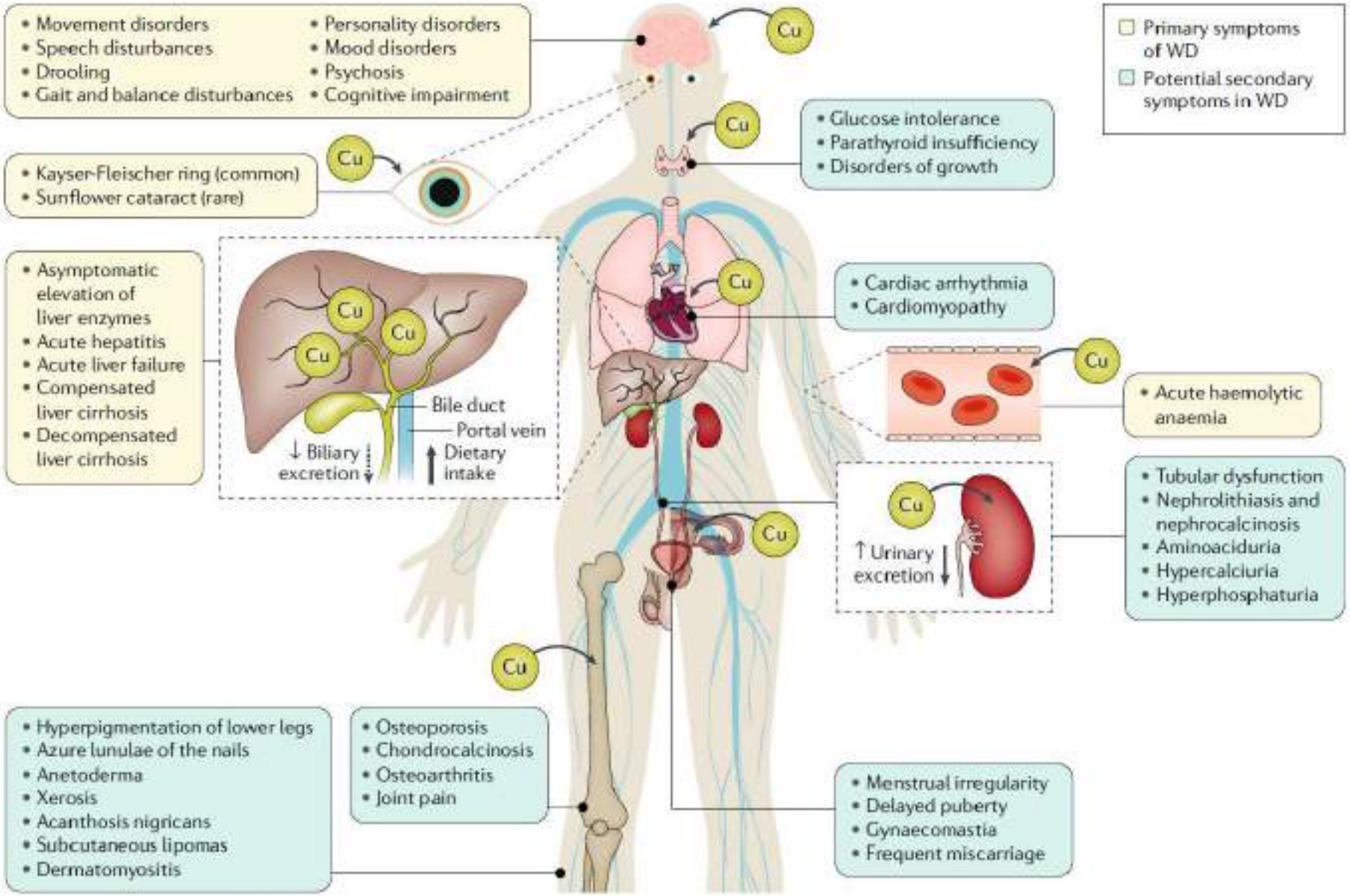


Fig. 3 | **Copper toxicity in the pathogenesis of WD.** Dietary copper (Cu) is transported via the portal vein and

Wilson’s disease

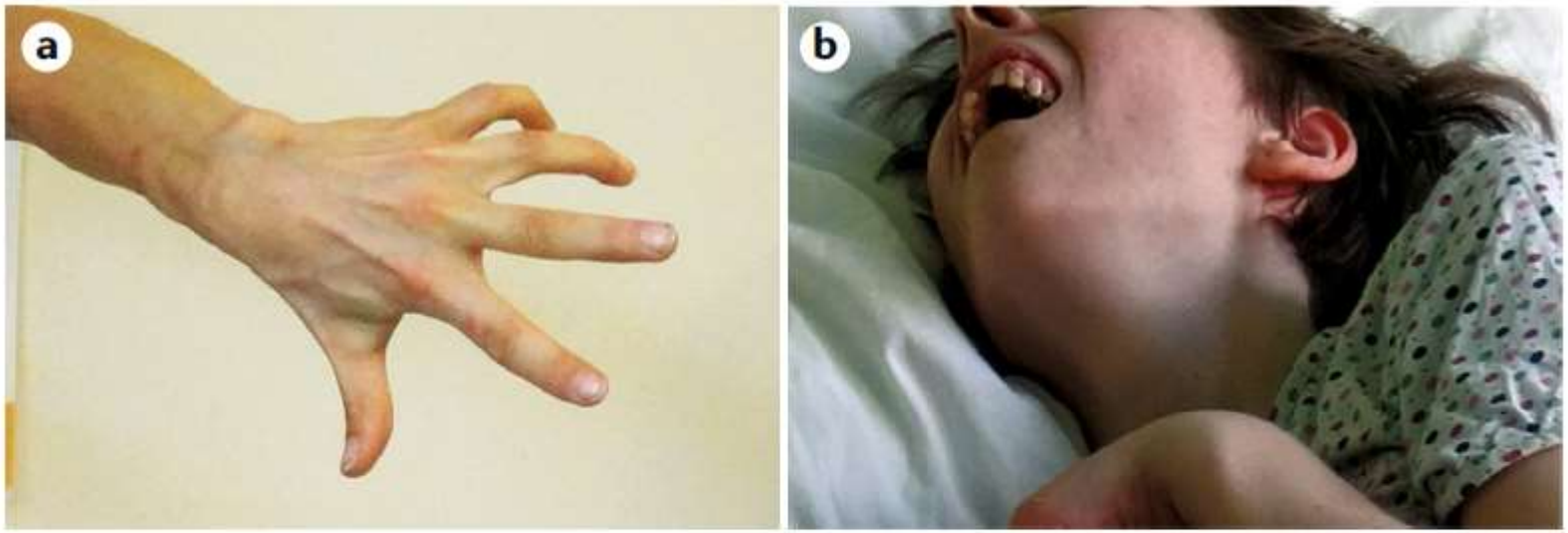


Fig. 6 | **Dystonia, a characteristic symptom in WD.** Dystonia is present in at least one-third of all patients with a neurological presentation of Wilson disease (WD) and can be generalized, segmental, multifocal or focal[1]. Part **a** shows focal hand dystonia. The most characteristic WD dystonic presentation is abnormal facial expression or risus sardonicus, which presents as a fixed smile due to dystonia of the risorius muscle, as shown in part **b**, severe dystonia.

Wilson’s disease

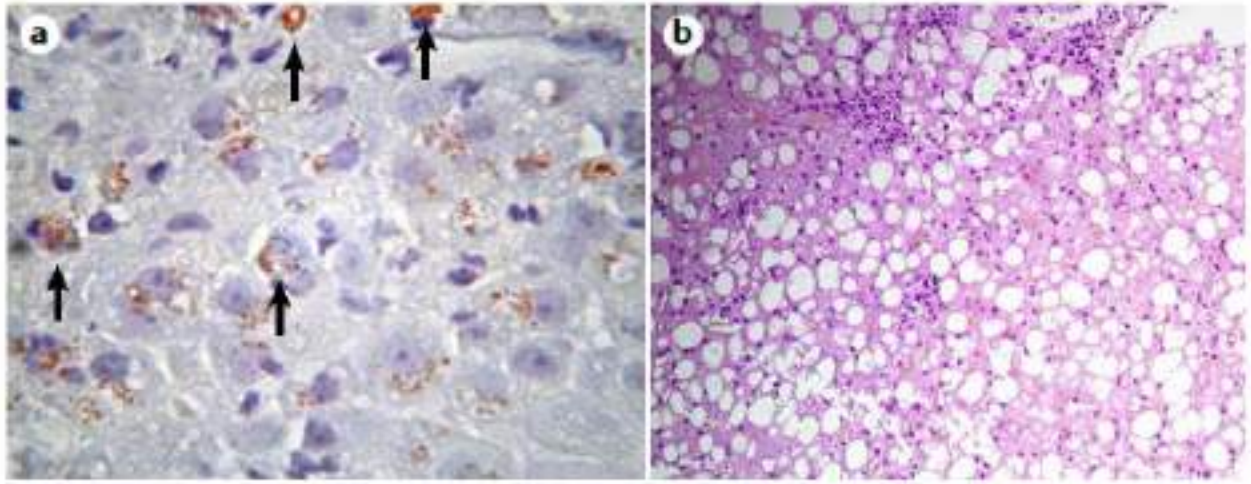
Diagnostic recommendations in Wilson's disease

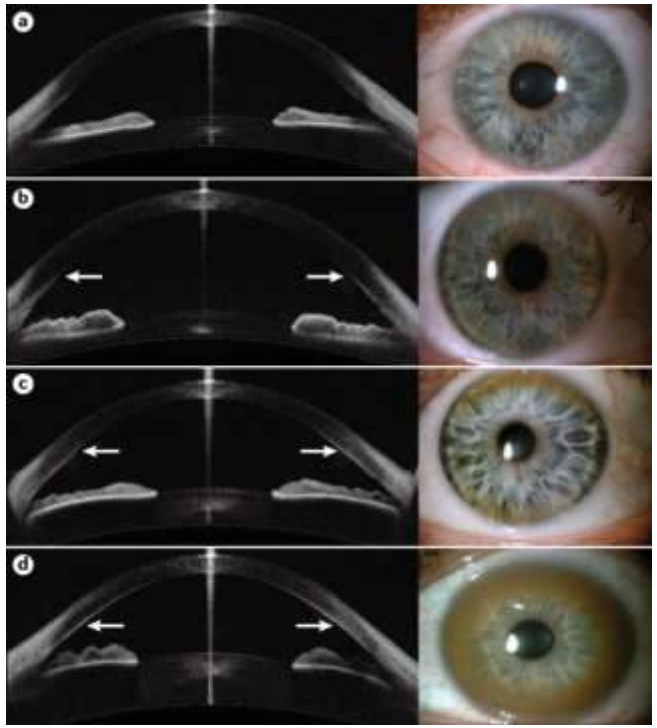
•Wilson's disease should be considered in any individual with liver abnormalities of uncertain cause and those with new onset movement disorders.

•Assessment should include history, physical examination, liver function tests, full blood count, serum copper and caeruloplasmin, and 24-h urinary copper excretion. Liver biopsy quantitative copper concentrations remain the best biochemical evidence for Wilson's disease.

•Kayser-Fleischer rings should be sought using slit-lamp examination by a skilled examiner.

•Family screening of first-degree relatives must be undertaken. When possible, genetic diagnosis should be used, especially in patients with indeterminate clinical and biochemical features.





Wilson's disease

Table 1 | **Routine tests for the diagnosis of Wilson disease**

Test	Typical finding	False 'negative'	False 'positive'
Serum ceruloplasmin	Decreased in patients with WD compared with healthy controls	• Normal levels in patients with marked hepatic inflammation • Overestimation by immunological assay • Pregnancy • Oestrogen therapy	Low levels in patients with malabsorption, malnutrition and/or aceruloplasminemia and in heterozygotes
24 h urinary copper	• Adults: >100 μg (1.6 μmol) per 24 h • Child: >40 μg (0.64 μmol) per 24 h	• Normal levels caused by incorrect collection • Normal levels in children without liver disease	• Increased in hepatocellular necrosis • Increased in cholestasis • May appear increased owing to sample contamination
Non-ceruloplasmin-bound copper	>10 μg dl^{-1} (1.6 μmol per litre)	May appear normal or negative if ceruloplasmin is measured by immunological assay	NA
Hepatic copper	250 μg (4 μmol) g^{-1} dry weight	• Regional variation in patients with active liver disease • Regional variation in patients with regenerative nodules	• Increased in cholestatic syndromes • Increased in idiopathic copper toxicosis disorders
Kayser-Fleischer rings by slit-lamp examination	Present	• Absent in up to 50% of patients with hepatic WD • Absent in most asymptomatic siblings	May be present in primary biliary cholangitis (primary biliary cirrhosis)

Diagnostic scores

Test	Parameter	Score
Typical clinical signs and symptoms		
Kayser-Fleischer rings	Present	2
	Absent	0
Neurological symptoms[a]	Severe	2
	Mild	1
	Absent	0
Serum ceruloplasmin	Normal (>0.2 g per litre)	0
	0.1–0.2 g per litre	1
	<0.1 g per litre	2
Coombs-negative haemolytic anaemia	Present	1
	Absent	0
Other tests		
Liver copper (in the absence of cholestasis)	>250 µg (>4 µmol) g^{-1} dry weight	2
	50–249 µg (0.8–4 µmol) g^{-1}	1
	Normal: <50 µg (<0.8 µmol)	−1
	Rhodanine-positive granules[b]	1
Urinary copper (in the absence of acute hepatitis)	Normal	0
	1–2 × ULN	1
	>2 × ULN	2
	Normal but >5 × ULN after D-penicillamine	2
Mutation analysis	On both chromosomes detected	4
	On one chromosome detected	1
	No mutations detected	0
Total score	*Evaluation*	
≥4	Diagnosis established	
3	Diagnosis possible; more tests needed	
≤2	Diagnosis very unlikely	

Wilson's disease

Table 3 | **Drugs used in the treatment of Wilson disease**

Drug	Mode of action	Interactions	Frequency of AEs leading to treatment discontinuation	Assessment of treatment effectiveness and adherence
DPA	Promotes urinary excretion of copper	• Do not combine with myelosuppressive agents, cytostatic agents, antimalarials, gold therapy, oxyphenbutazone or phenylbutazone • DPA interacts with heavy metals	• 20–30% during treatment[174,179] • 'Early' AEs (first 3 weeks) include fever, cutaneous manifestations, lymphadenopathy, arthralgia, leukopenia, thrombocytopenia and proteinuria • 'Late' AEs (3 weeks to years) include paradoxical neurological worsening, renal insufficiency, fatal glomerulonephritis, intra-alveolar haemorrhage, myasthenia-like syndrome, lupus-like syndrome, fatal bone marrow aplasia, gastric symptoms, hair loss or loss of taste	• Copper urinary excretion 200–500 µg per 24 h (at the beginning of the treatment >1,000 µg per 24 h) • Serum NCC[a] 5–15 µg dl^{-1} • Normalization of copper urinary excretion 2 days after stopping the treatment with DPA
Trientine	Promotes urinary excretion of copper	• Mineral supplements should be avoided	• 7.1%[179] • Gastritis • Sideroblastic anaemia • Lupus-like reactions • Loss of taste	• Copper urinary excretion 200–500 µg per 24 h (at the beginning of the treatment >1,000 µg per 24 h) • Serum NCC 5–15 µg dl^{-1} • Normalization of copper urinary excretion 2 days after stopping the treatment with trientine

DPA, penicillamine

Autoimmune hepatitis

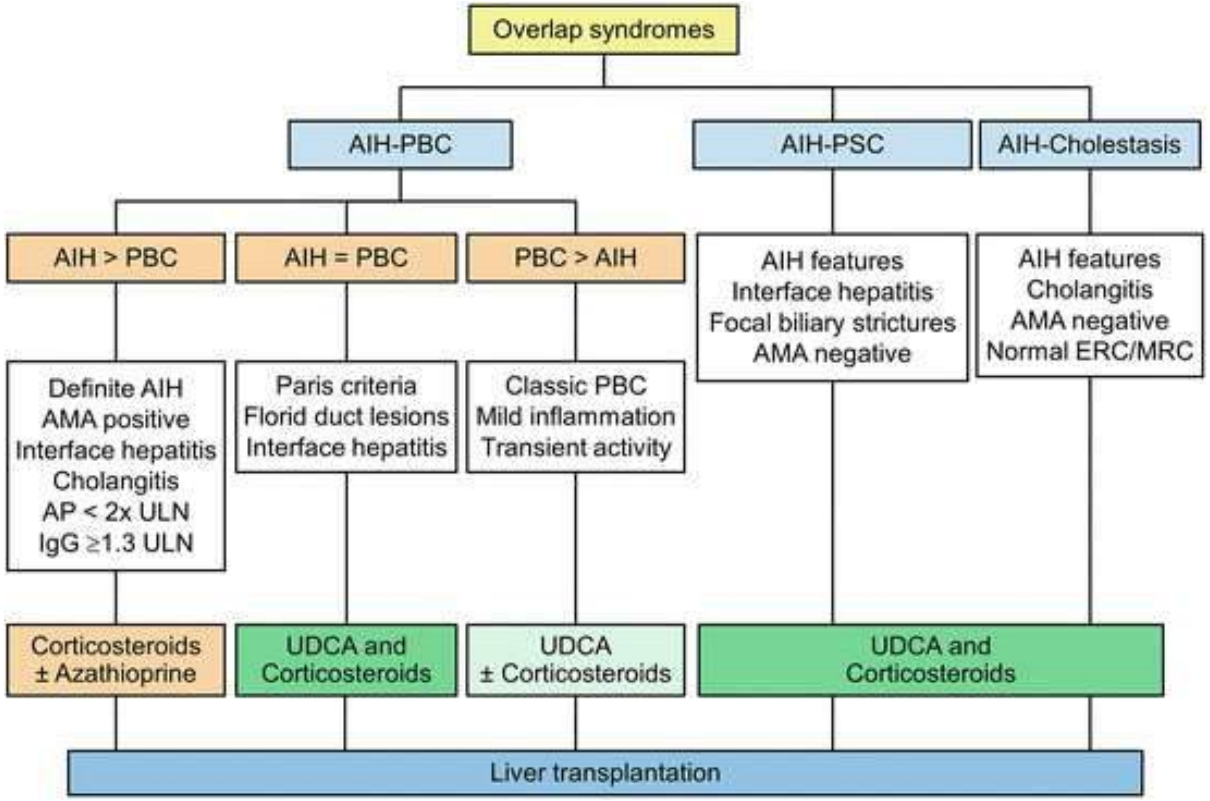
Differential Diagnosis

- ***Primary biliary cholangitis (PBC)*** share clinical features with type 1 autoimmune hepatitis, and both alcoholic hepatitis and nonalcoholic steatohepatitis may present with many features common to autoimmune hepatitis; historic, biochemical, serologic, and histologic assessments are usually sufficient to allow these entities to be distinguished from autoimmune hepatitis.
- Of course, the distinction between autoimmune and chronic viral hepatitis is not always straightforward, especially when viral antibodies occur in patients with autoimmune disease or when autoantibodies occur in patients with viral disease.

Autoimmune hepatitis

Differential Diagnosis

Finally, occasionally, features of autoimmune **hepatitis overlap** with features of autoimmune biliary disorders such as **primary biliary cirrhosis, primary sclerosing** cholangitis, or, even more rarely, mitochondrial antibody-negative autoimmune cholangitis. **Such overlap syndromes are difficult to categorize,** and often response to therapy may be the distinguishing factor that establishes the diagnosis**.**



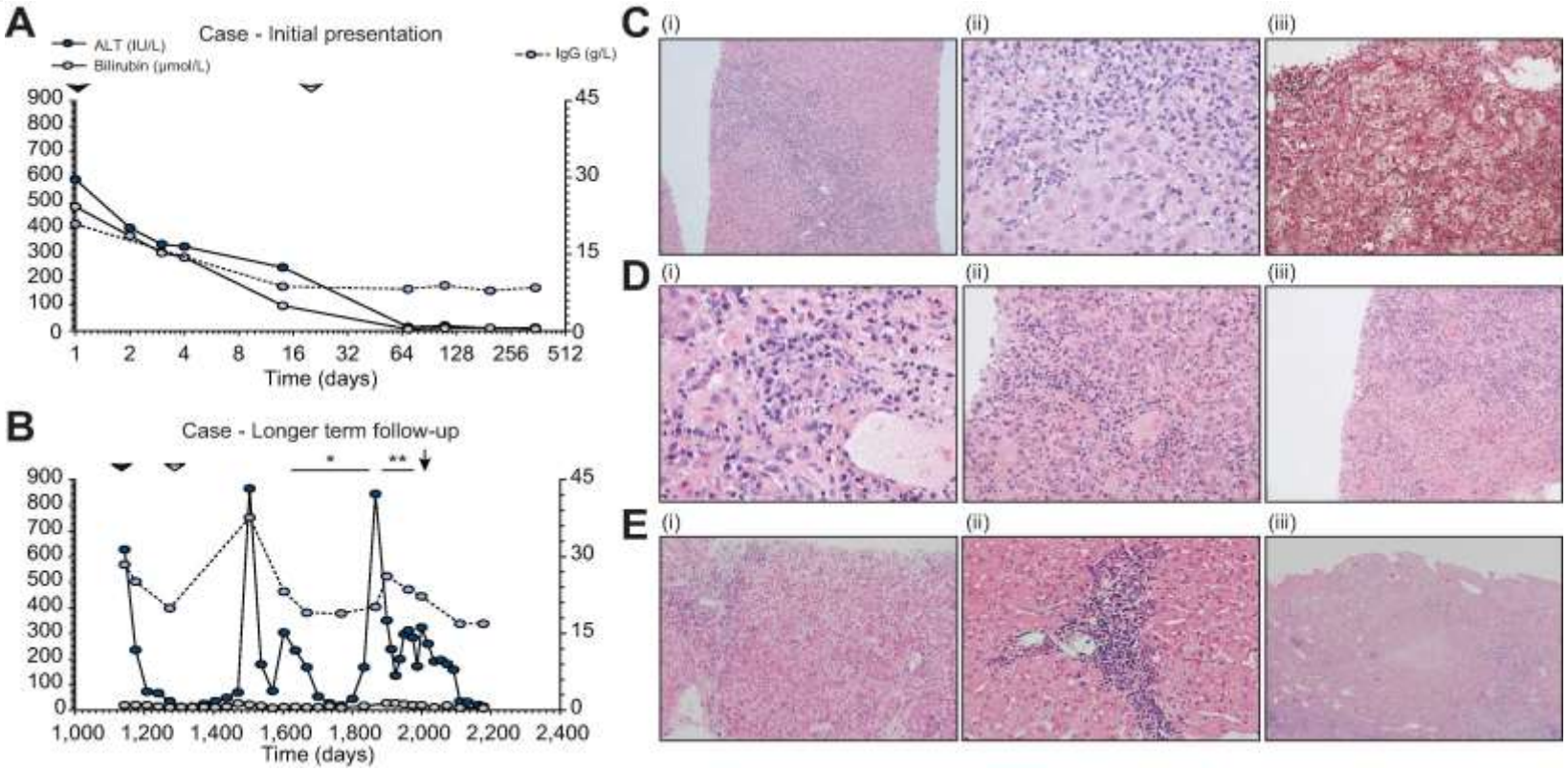
Autoimmune hepatitis: aggressive clinical feature

- The course of autoimmune hepatitis may be variable. In those with mild disease or limited histologic lesions (e.g., piecemeal necrosis without bridging), progression to cirrhosis is limited.
- In those with severe symptomatic autoimmune hepatitis (aminotransferase levels >10 times normal, **marked hyperglobulinemia, "aggressive" histologic lesions—bridging** necrosis or multilobular collapse, cirrhosis), the 6-month mortality without therapy may be as high as 40%.

- **Such severe disease accounts for only 20% of cases**; the natural history of milder disease is variable, often accentuated by spontaneous remissions and exacerbations.

- Especially **poor prognostic sign**s include the presence **histologically of multilobular collapse** at the time of initial presentation and **failure of the bilirubin to improve after 2 weeks of therapy**. Death may result from complications of cirrhosis

Ig totali: 600-2300 mg/dl
IgG: 800-1800 mg/dl
IgA: 90-400 mg/dl
IgM: 60-280 mg/dl
IgE: 0-180 UI/ml; 20-440 mg/dl

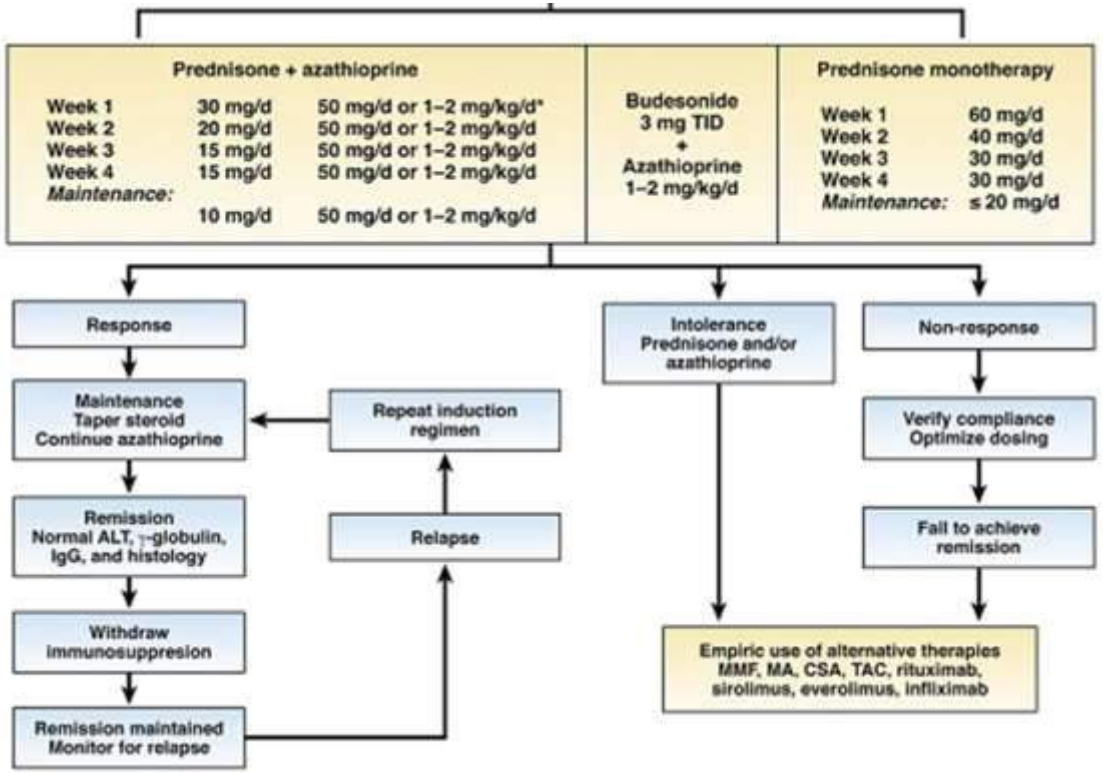


Timeline graph of laboratory parameters from the case is shown during the patient's initial presentation and phase of treatment, with black arrowheads indicating the start date of oral **prednisolone at 20 mg** once daily, and white arrowhead the introduction of **azathioprine**. (B) A timeline graph of laboratory parameters from the same patient, who presented again after a period of non-attendance to clinic. Black arrowhead indicates re-initiation of prednisolone and white arrowhead azathioprine. Single and double asterisks indicate the duration of **tacrolimus therapy (without azathioprine)**, respectively, and the black arrow the first infusion of **rituximab**. (C) Representative images showing typical features of chronic AIH.

Rituximab anti-CD20

Autoimmune hepatitis:treatment

- The mainstay of management in autoimmune hepatitis is **glucocorticoid therapy.**
- **A) prednisone dose (30 mg/d) with azathioprine (50 mg/d).**
- **B) of prednisone 60 mg/d.** This high dose is tapered successively over the course of a month down to a maintenance level of 20 mg/d.
- **C) An alternative but equally effective approach is Budesonide 3 mg/TID + azathioprine**



Primary biliary cholangitis (cirrhosis)

- **The major causes of intrahepatic cholestatic syndromes are primary biliary cirrhosis (PBC), autoimmune cholangitis, primary sclerosing cholangitis (PSC), and idiopathic adulthood ductopenia.**
- These syndromes are usually clinically distinguished from each other by antibody testing, cholangiographic findings, and clinical presentation. However, they all share the histopathologic features of chronic cholestasis, such as **cholate stasis, copper deposition, xanthomatous transformation of hepatocytes, and irregular so-called biliary fibrosis.** In addition, there may be chronic portal inflammation, interface activity, and chronic lobular inflammation.
- Ductopenia is a result of this progressive disease as patients develop cirrhosis

Autoimmune liver diseases

Table 1 Autoimmune liver diseases: clinicopathologic features (adapted from Beuers[73])

	AIH	*PBC*	*PSC*	*AIC*[a]
Female:male	4:1	9:1	1:2	9:1
Predominant liver test elevation	AST, ALT	Alk phos, γ-GT	Alk phos, γ-GT	Alk phos, γ-GT
Serum Ig elevation	IgG	IgM	IgG, IgM	IgM
Autoantibodies	ANA, ASMA, LKM1, SLA/P, pANCA	AMA, AMA-M2, gp210	p-ANCA	ANA, ASMA
HLA association	A3, B8, DR3, DR4	DR8 (weak association)	DR52	B8, DR3, DR4
Histology	Interface and lobular hepatitis; prominent plasma cells	Florid bile duct lesion	Fibrosis and obliteration of large bile ducts; ductopenia	Florid bile duct lesion
Diagnosis	AIH score > 15 for diagnosis of definite AIH	AMA, cholestatic serum enzyme pattern, compatible histology	Biliary strictures and dilatation on cholangiography; cholestatic serum enzyme pattern, IBD, p-ANCA	Cholestatic serum enzyme pattern, AMA neg, ANA or ASMA positive; histology c/w PBC
First-line medical therapy	Immunosuppression (corticosteroids+ azathioprine)	Ursodeoxycholic acid (UDCA)	UDCA	UDCA

[a]Autoimmune cholangitis.

Primary biliary cholangitis

- Point **prevalence of PBC in Italy is was calculated as 27.90 per 100,000 inhabitants** and incidence of PBC as 5.31 per 100,000 inhabitants/year.
- A **strong female preponderance and a median age of around 50 years at** the time of diagnosis.

A.

	ISTAT 2015 (n=60,795,612)	LPD 2015 (n= 1,204,216)
North	45.8%	44.9%
Center	20%	18.4%
South	23.1%	25.3%
Islands	11.1%	11.5%

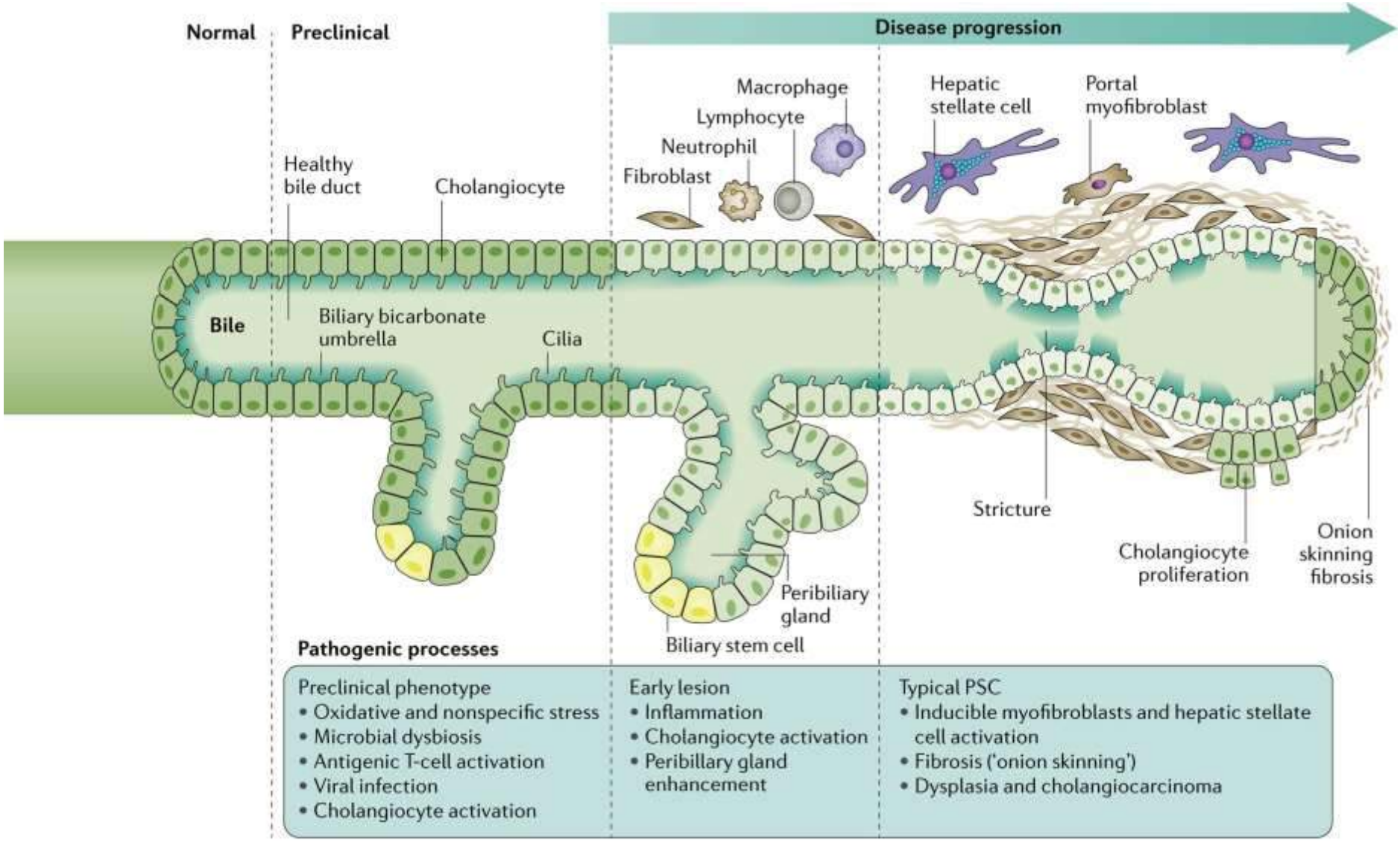
Primary biliary cholangitis

The cause of PBC is unknown; it is characterized by portal inflammation and necrosis of cholangiocytes in small and medium-sized bile ducts.

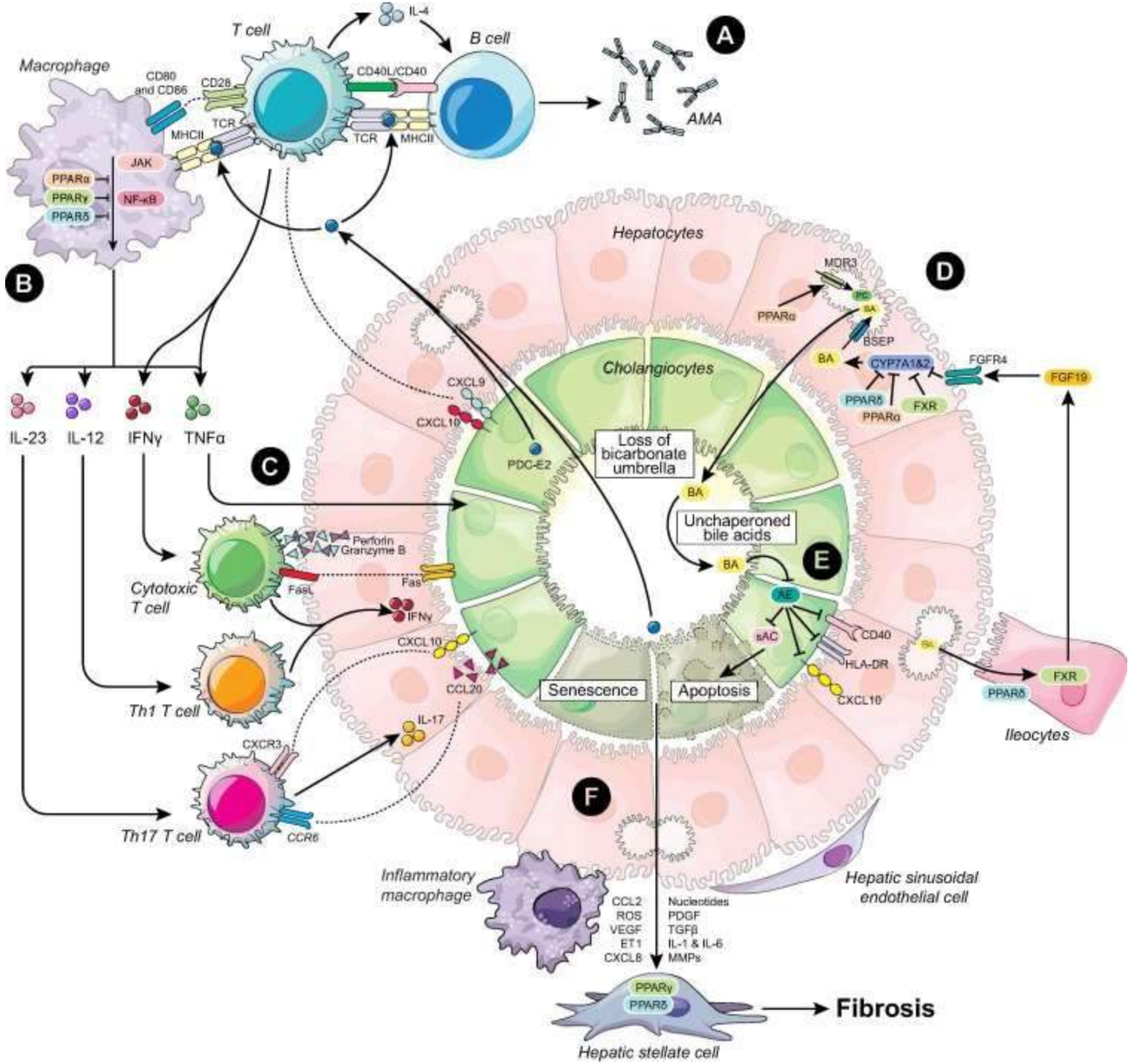
Cholestatic features prevail, and biliary cirrhosis is characterized by an elevated bilirubin level and progressive liver failure.

Antimitochondrial antibodies (AMA) are present in about 90% of patients with PBC. These autoantibodies recognize intermitochondrial membrane proteins that are enzymes of the pyruvate dehydrogenase complex (PDC), the branched chain–2-oxoacid dehydrogenase complex, and the 2-oxogluterate dehydrogenase complex.

Primary biliary cholangitis



Nature Reviews | Gastroenterology & Hepatology

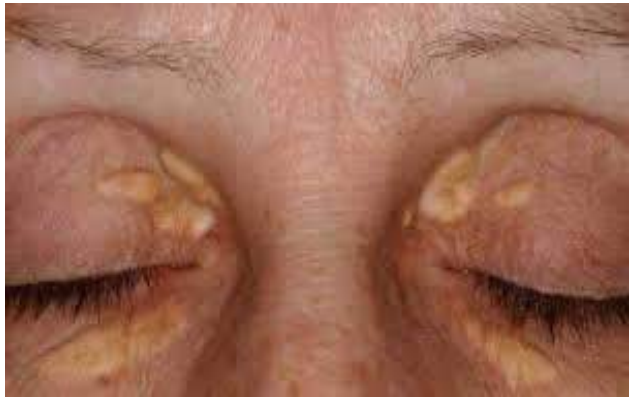

A
T cell
IL-4
B cell
Macrophage
CD80 and CD86
CD28
CD40L/CD40
TCR
MHCII
TCR
MHCII
AMA
JAK
PPARα
PPARγ
PPARδ
NF-κB
B
Hepatocytes
D
MDR3
PC
PPARα
BA
BSEP
BA
CYP7A1&2
FGFR4
FGF19
PPARδ
PPARα
FXR
Cholangiocytes
CXCL9
CXCL10
PDC-E2
Loss of bicarbonate umbrella
IL-23
IL-12
IFNγ
TNFα
C
BA
Unchaperoned bile acids
BA
E
Perforin
Granzyme B
Fas
FasL
Cytotoxic T cell
IFNγ
AE
sAC
CD40
HLA-DR
CXCL10
CXCL10
CCL20
Senescence
Apoptosis
FXR
PPARδ
Ileocytes
Th1 T cell
IL-17
CXCR3
F
Th17 T cell
CCR6
Inflammatory macrophage
Hepatic sinusoidal endothelial cell
CCL2
ROS
VEGF
ET1
CXCL8
Nucleotides
PDGF
TGFβ
IL-1 & IL-6
MMPs
PPARγ
PPARδ
Fibrosis
Hepatic stellate cell

Primary biliary cholangitis

- Histopathologic analyses of liver biopsies of patients with PBC have resulted in identifying four distinct stages of the disease as it progresses. The earliest lesion is termed *chronic nonsuppurative destructive cholangitis* and is a necrotizing inflammatory process of the portal tracts. Medium and small bile ducts are infiltrated with lymphocytes and undergo duct destruction. Mild fibrosis and sometimes bile stasis can occur.
- With progression, the inflammatory infiltrate becomes less prominent, **but the number of bile ducts is reduced and there is proliferation of smaller bile ductules.**
- Increased fibrosis ensues with the expansion of periportal fibrosis to bridging fibrosis.
- Finally, cirrhosis, which may be micronodular or macronodular, develops.

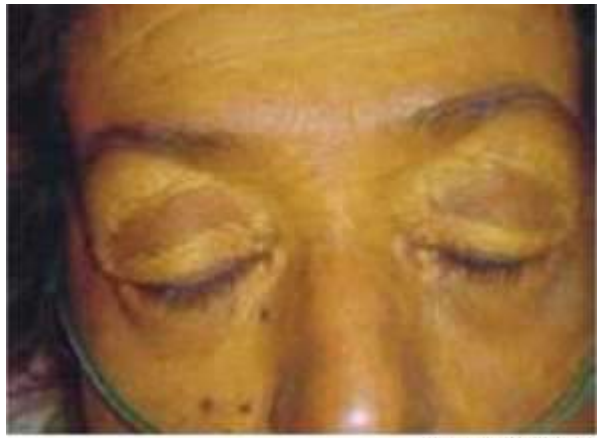
Primary biliary cholangitis

Currently most patients with PBC are asymptomatic.



When symptoms are present, they most prominently include a significant degree of **fatigue** out of proportion to what would be expected for either the severity of the liver disease or the age of the patient.

Pruritus is seen in approximately 50% of patients at the time of diagnosis and can be debilitating.



Physical examination can **show jaundice and other complications of chronic liver disease including hepatomegaly, splenomegaly, ascites, and edema**.

Other features that are unique to **PBC include hyperpigmentation, xanthelasma, and xanthomata**, which are related to the altered cholesterol metabolism seen in this disease.

Hyperpigmentation is evident on the trunk and the

Primary biliary crirrhosis

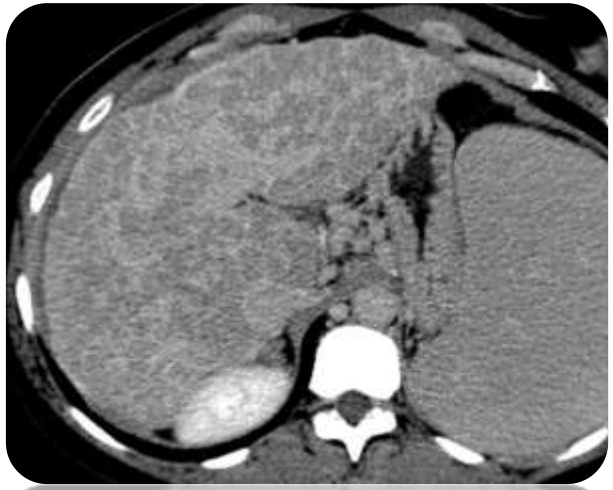
- Laboratory findings in PBC show cholestatic liver enzyme abnormalities with an elevation in γ-glutamyl transpeptidase and alkaline phosphatase (ALP) along with mild elevations in aminotransferases (ALT and AST).

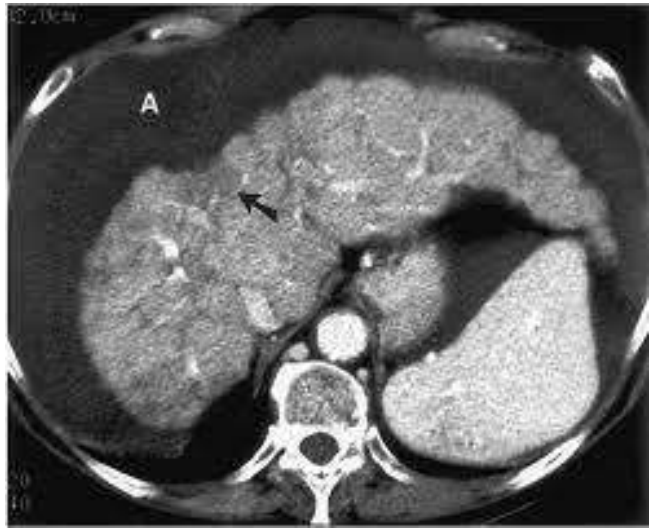
- Immunoglobulins, particularly IgM, are typically increased.

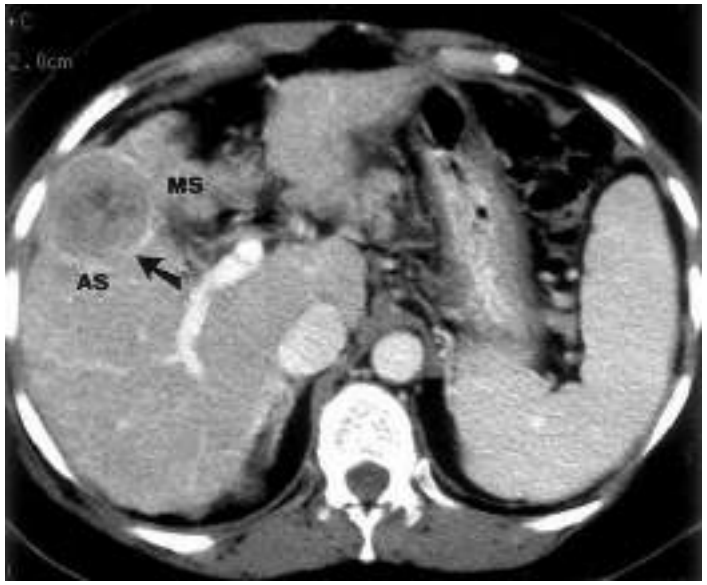
- **PBC patients are AMA positive (90%)**

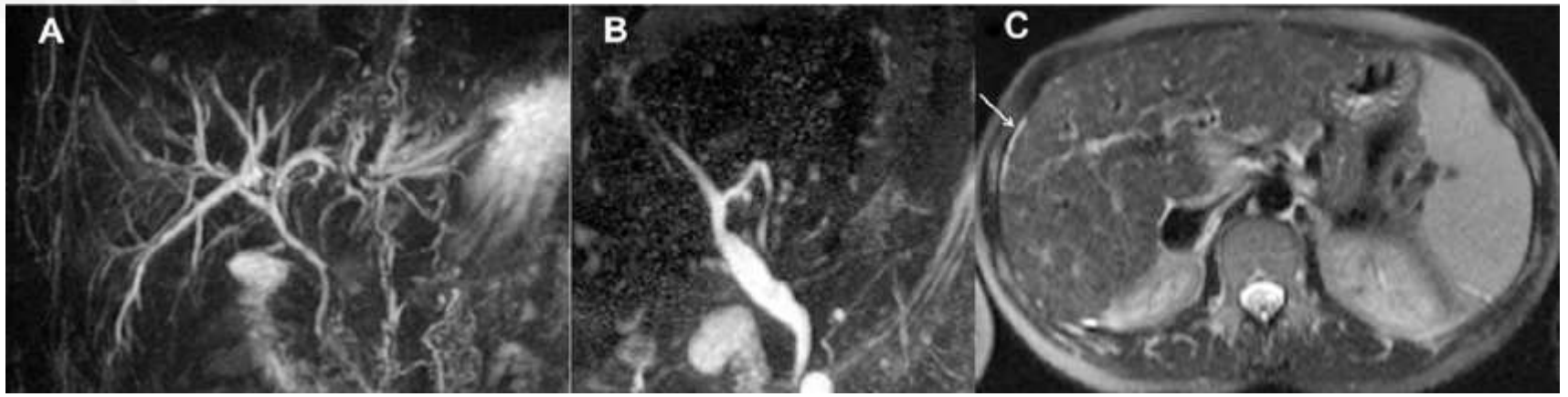
- Hyperbilirubinemia usually is seen once cirrhosis has developed.
- Thrombocytopenia, leukopenia, and anemia may be seen in patients with portal hypertension and hypersplenism.

Primary biliary cholangitis



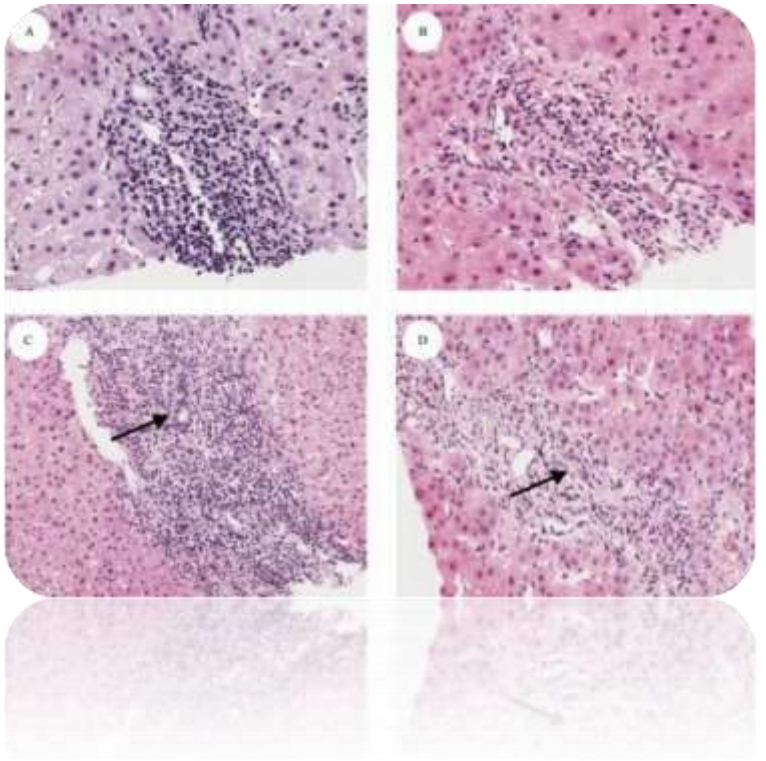






Primary biliary cholangitis

- Liver biopsy shows characteristic features
- Up to 10% of patients with characteristic PBC will have features of AIH as well and are defined as having "overlap" syndrome.
- These patients are treated as PBC patients and may progress to cirrhosis with the same frequency as typical PBC patients.
- As many as 10% of patients with PBC may be AMA-negative.
- Liver biopsy is most important in this setting of AMA-negative PBC. In patients who are AMA-negative with cholestatic liver enzymes, PSC should be ruled out by way of cholangiography.



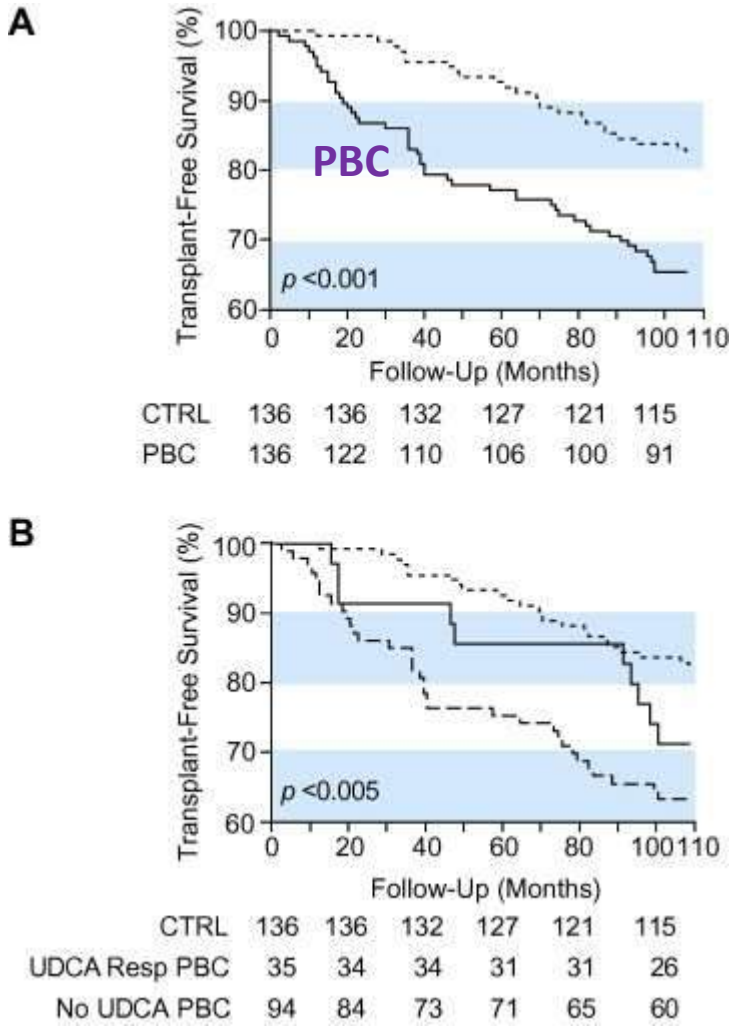
Primary biliary cholangitis

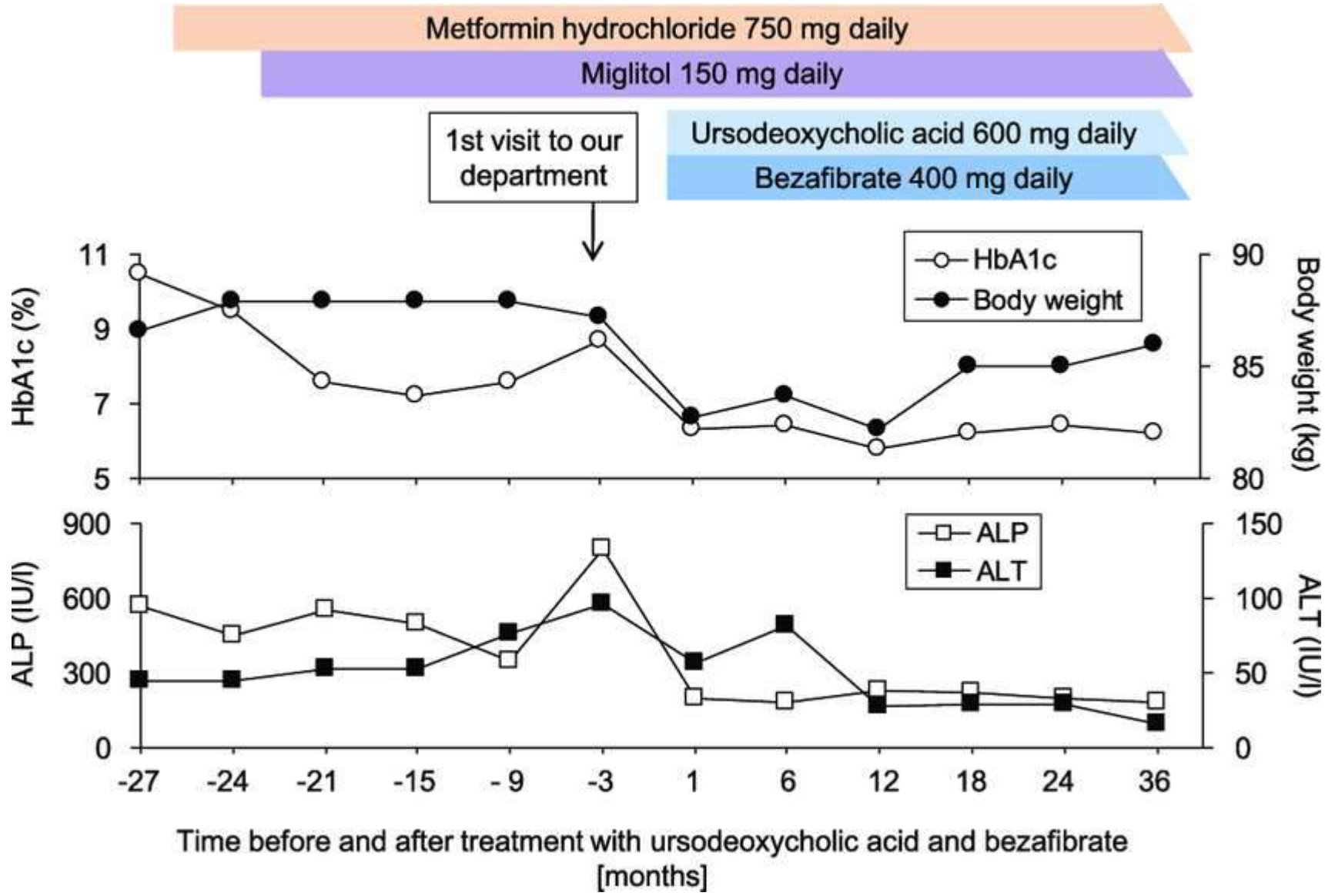
Treatment of the typical manifestations of cirrhosis are no different for PBC than for other forms of cirrhosis.

UDCA has been shown to improve both biochemical and histologic features of the disease.

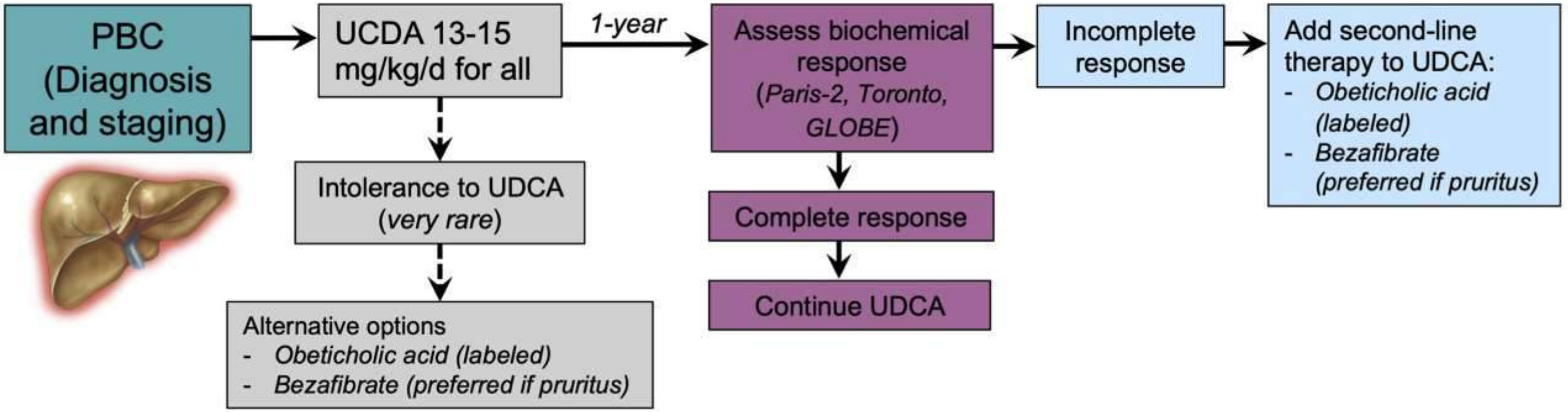
Improvement is greatest when therapy is initiated early; the likelihood of significant improvement with UDCA is low in patients with PBC who present with manifestations of cirrhosis.

UDCA is given in doses of 13–15 mg/kg per day




Metformin hydrochloride 750 mg daily
Miglitol 150 mg daily
1st visit to our department
Ursodeoxycholic acid 600 mg daily
Bezafibrate 400 mg daily
HbA1c
Body weight
HbA1c (%)
Body weight (kg)
11
9
7
5
90
85
80
ALP
ALT
ALP (IU/l)
ALT (IU/l)
900
600
300
0
150
100
50
0
-27
-24
-21
-15
- 9
-3
1
6
12
18
24
36
Time before and after treatment with ursodeoxycholic acid and bezafibrate
[months]

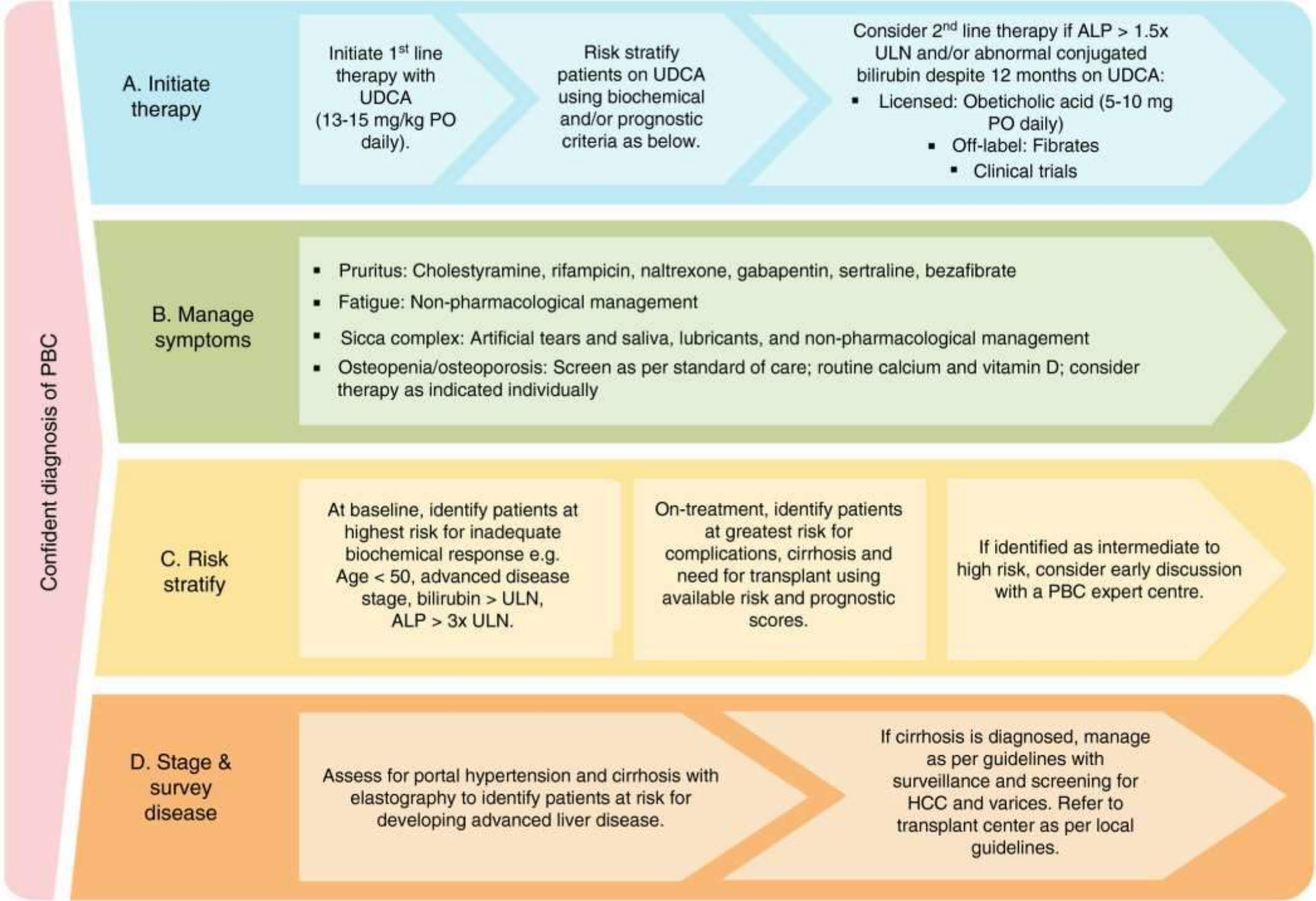
Primary biliary cholangitis: Treatment algorithm for incomplete responders



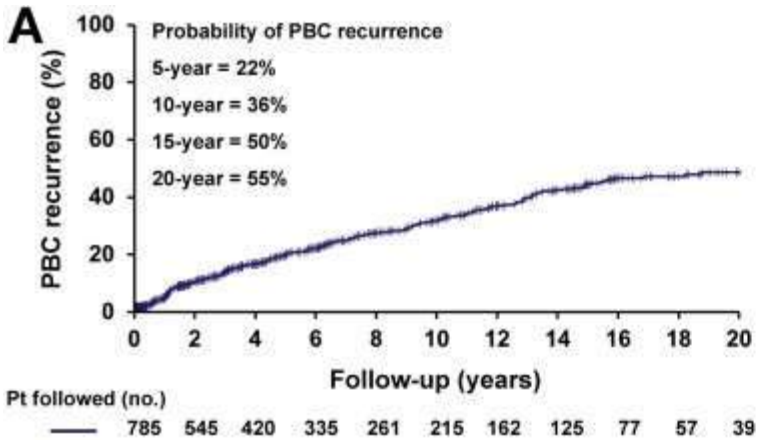
Clinical Gastroenterology and Hepatology

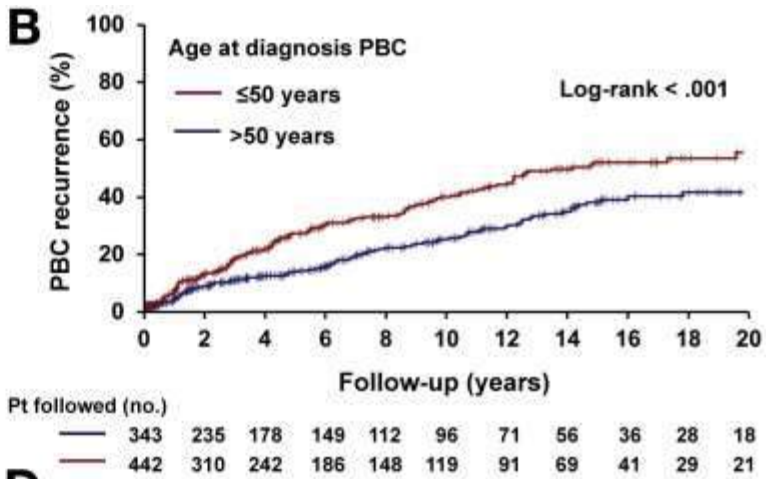
Clinical Gastroenterology and Hepatology
Volume 19, Issue 11, November 2021, Pages 2241-2251.e1

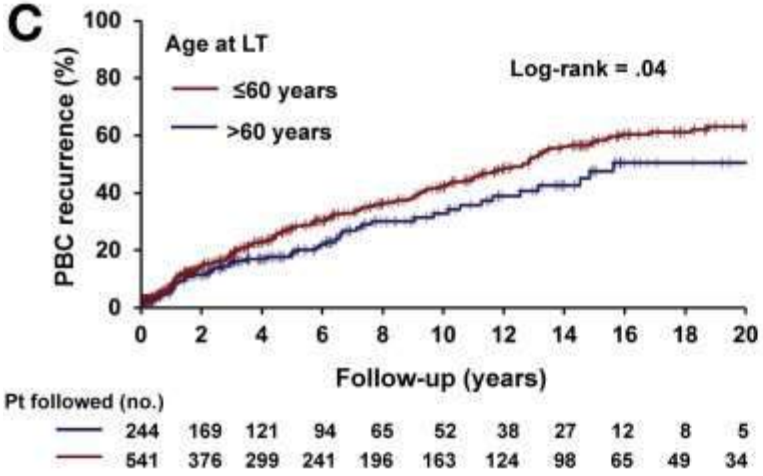
R. Pellicciari, S. Fiorucci, E. Camaioni, *et al.* **6alpha-ethyl-chenodeoxycholic acid (6-ECDCA), a potent and selective FXR agonist endowed with anticholestatic activity**
J Med Chem, 45 (2002), pp. 3569-3572

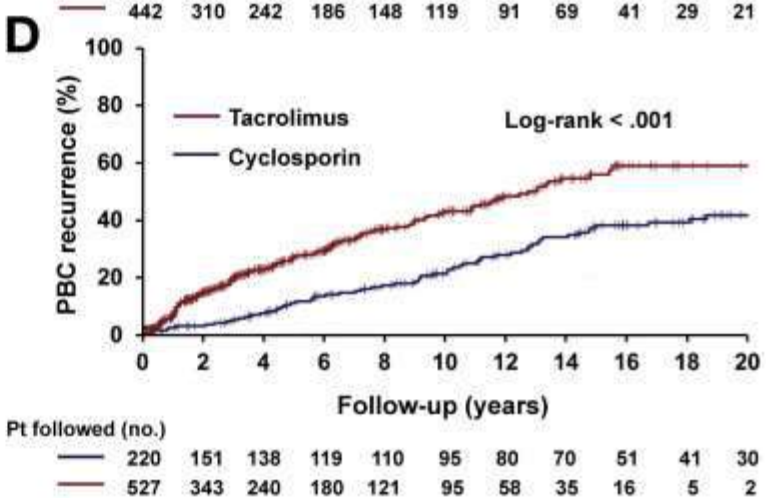

Confident diagnosis of PBC
A. Initiate therapy
Initiate 1st line therapy with UDCA (13-15 mg/kg PO daily).
Risk stratify patients on UDCA using biochemical and/or prognostic criteria as below.
Consider 2nd line therapy if ALP > 1.5x ULN and/or abnormal conjugated bilirubin despite 12 months on UDCA:
Licensed: Obeticholic acid (5-10 mg PO daily)
Off-label: Fibrates
Clinical trials
B. Manage symptoms
Pruritus: Cholestyramine, rifampicin, naltrexone, gabapentin, sertraline, bezafibrate
Fatigue: Non-pharmacological management
Sicca complex: Artificial tears and saliva, lubricants, and non-pharmacological management
Osteopenia/osteoporosis: Screen as per standard of care; routine calcium and vitamin D; consider therapy as indicated individually
C. Risk stratify
At baseline, identify patients at highest risk for inadequate biochemical response e.g. Age < 50, advanced disease stage, bilirubin > ULN, ALP > 3x ULN.
On-treatment, identify patients at greatest risk for complications, cirrhosis and need for transplant using available risk and prognostic scores.
If identified as intermediate to high risk, consider early discussion with a PBC expert centre.
D. Stage & survey disease
Assess for portal hypertension and cirrhosis with elastography to identify patients at risk for developing advanced liver disease.
If cirrhosis is diagnosed, manage as per guidelines with surveillance and screening for HCC and varices. Refer to transplant center as per local guidelines.

PBC recurrence after Liver transplanation









Primary sclerosing cholangitis

- **PSC is a chronic cholestatic syndrome that is characterized by diffuse inflammation and fibrosis involving the entire biliary tree, resulting in chronic cholestasis**.

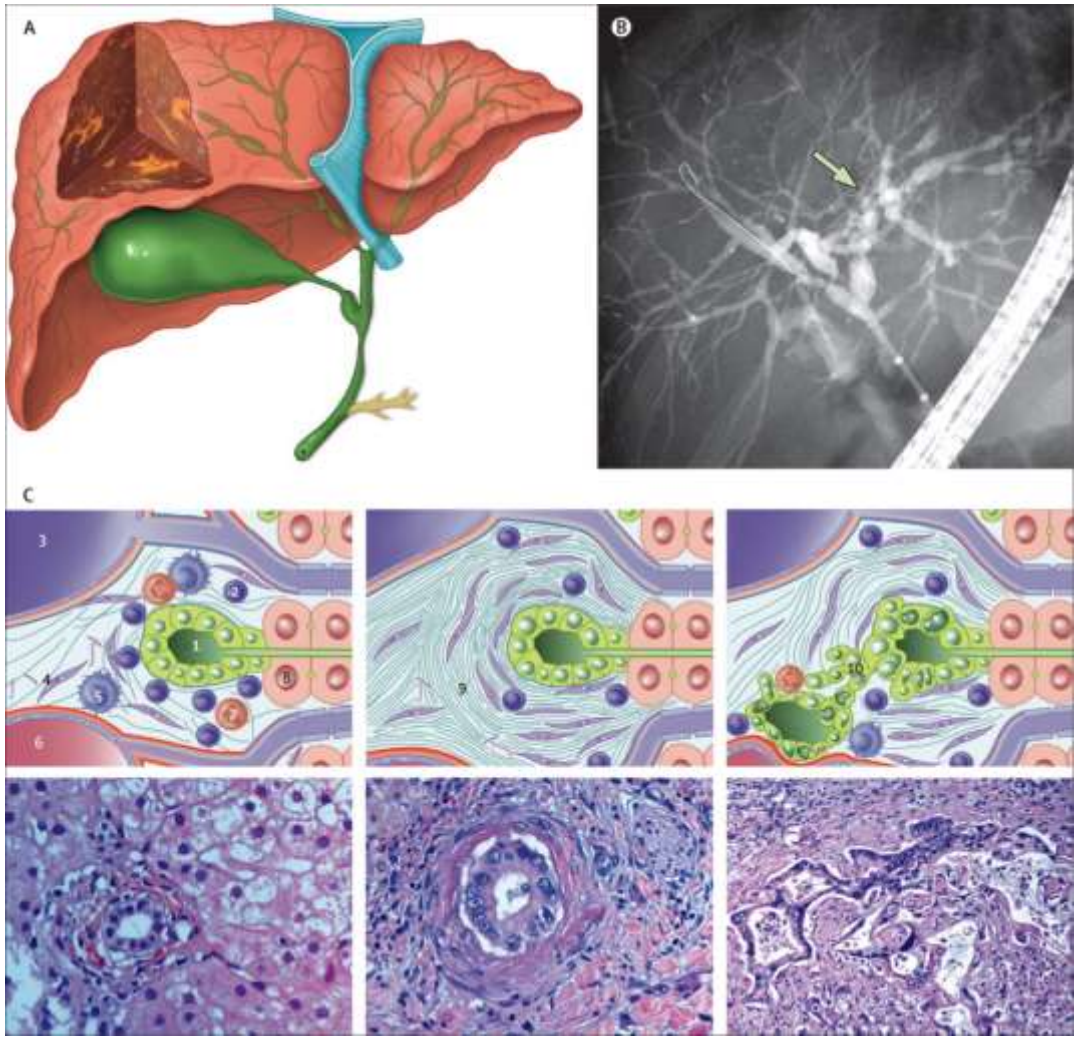
- This pathologic process ultimately results in obliteration of both the **intra- and extrahepatic biliary tree**, leading to biliary cirrhosis, portal hypertension, and liver failure.

- The cause of PSC remains unknown despite extensive investigation into various mechanisms related to bacterial and viral infections, toxins, genetic predisposition, and immunologic mechanisms, all of which have been postulated to contribute to the pathogenesis and progression of this syndrome.

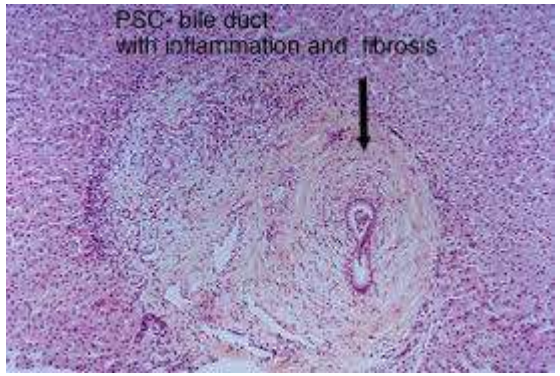
Primary sclerosing cholangitis

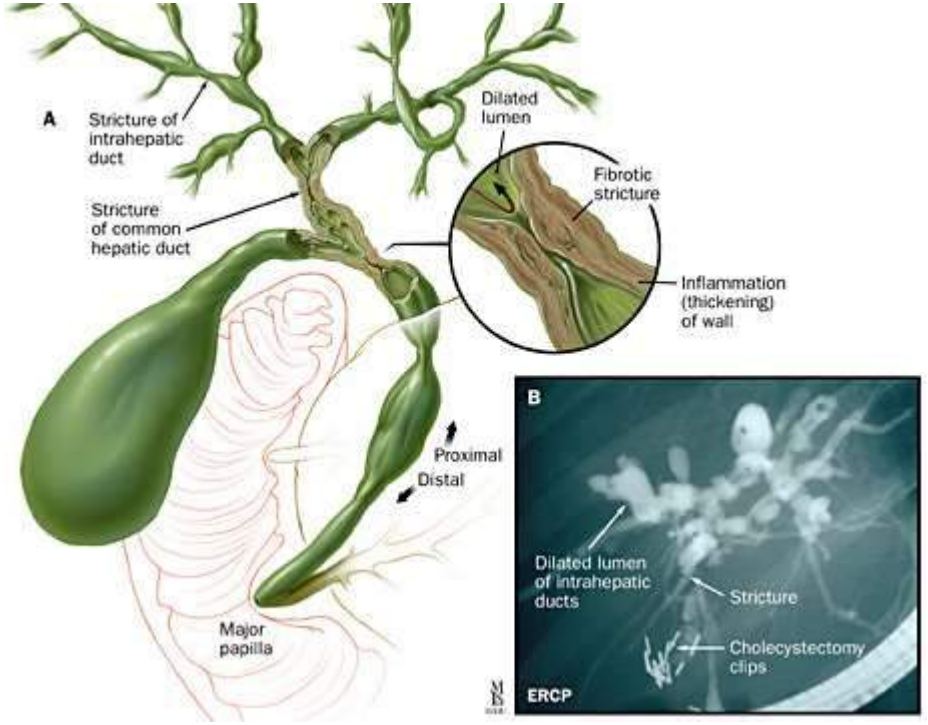
- **Pathologic changes that can occur in PSC show bile duct proliferation as well as ductopenia and fibrous cholangitis (pericholangitis).**
- Liver biopsy changes in PSC **are not pathognomonic,** and establishing the diagnosis of PSC must involve **imaging of the biliary tree**.
- Periductal fibrosis is occasionally seen on biopsy specimens and can be quite helpful in making the diagnosis. As the disease progresses, biliary cirrhosis is the final end-stage manifestation of PSC.

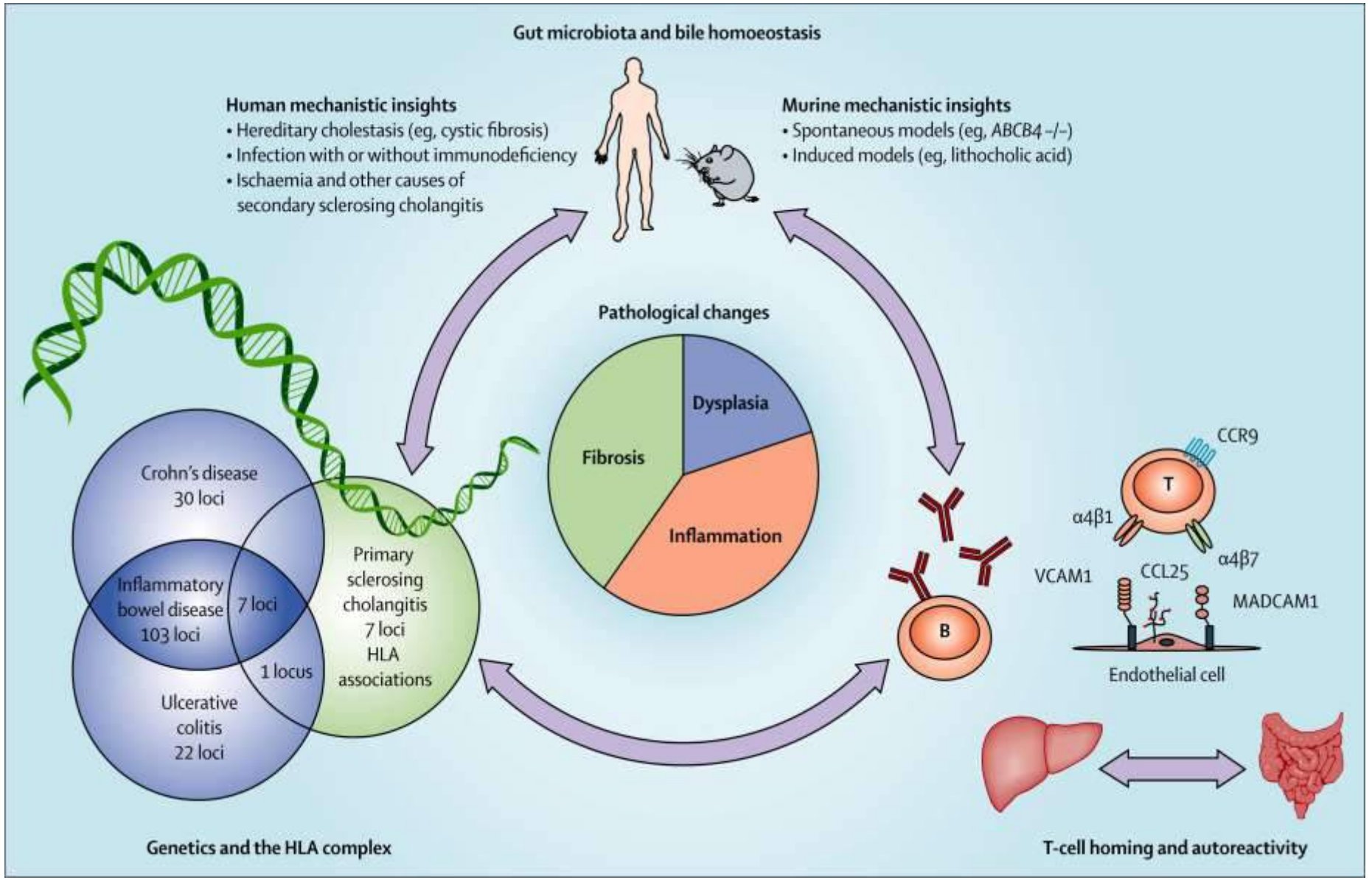
PSC- histology and ERCP



PSC- histology and ERCP

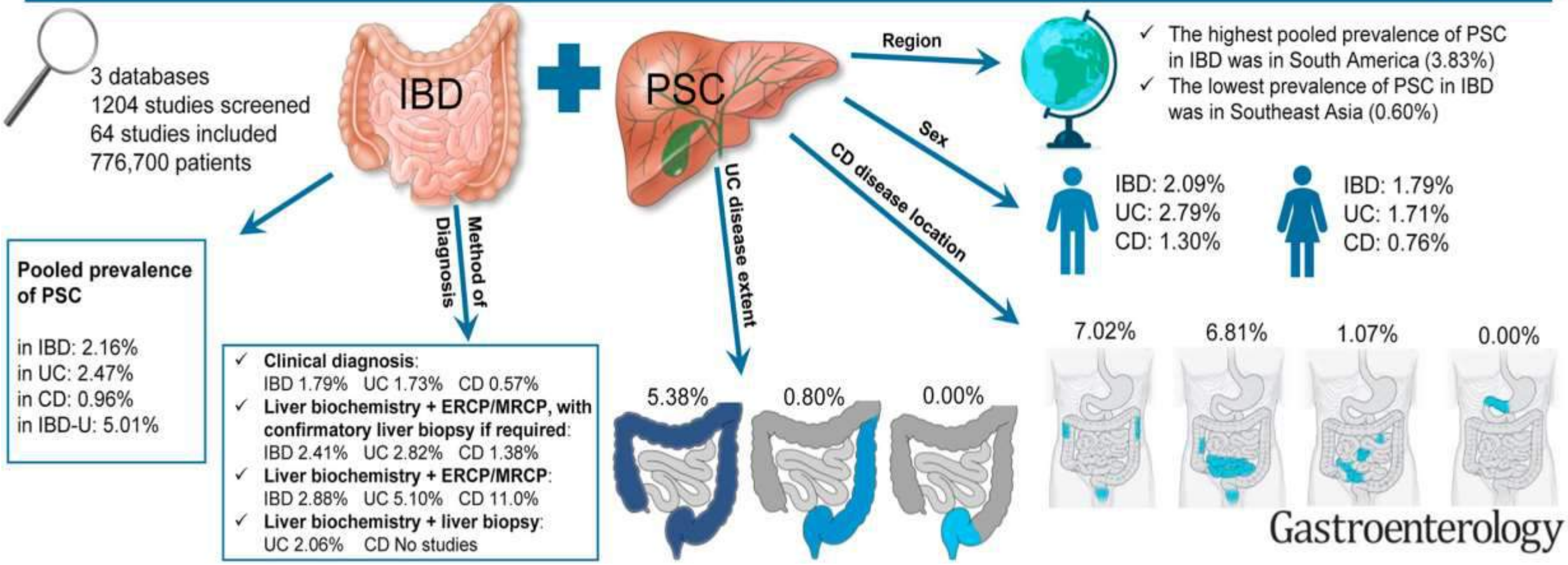






The Lancet 2013 3821587-1599DOI: (10.1016/S0140-6736(13)60096-3)

Prevalence of Primary Sclerosing Cholangitis in Patients with Inflammatory Bowel Disease: Systematic Review and Meta-analysis



Gastroenterology 2021 1611865-1877DOI: (10.1053/j.gastro.2021.08.032)

Primary sclerosing cholangitis

Clinical Features

- The usual clinical features of PSC are those found in cholestatic liver disease, with **fatigue, pruritus, steatorrhea, deficiencies of fat-soluble vitamins, and the associated consequences.**
- As in **PBC, the fatigue is profound** and nonspecific.
- **Pruritus** can often be debilitating and is related to the cholestasis.
- The severity of **pruritus does not correlate with the severity of the disease.** Metabolic bone disease, as seen in PBC, can occur with PSC

Primary sclerosing cholangitis

Laboratory Findings

- Patients with PSC typically are identified in the course of an evaluation of abnormal liver enzymes. **Most patients have at least a twofold increase in ALP and may have elevated aminotransferases as well.**
- Albumin levels may be decreased, and prothrombin times are prolonged in a substantial proportion of patients at the time of diagnosis. Some degree of correction of a prolonged prothrombin time may occur with parenteral vitamin K.

Primary sclerosing cholangitis

Laboratory Findings

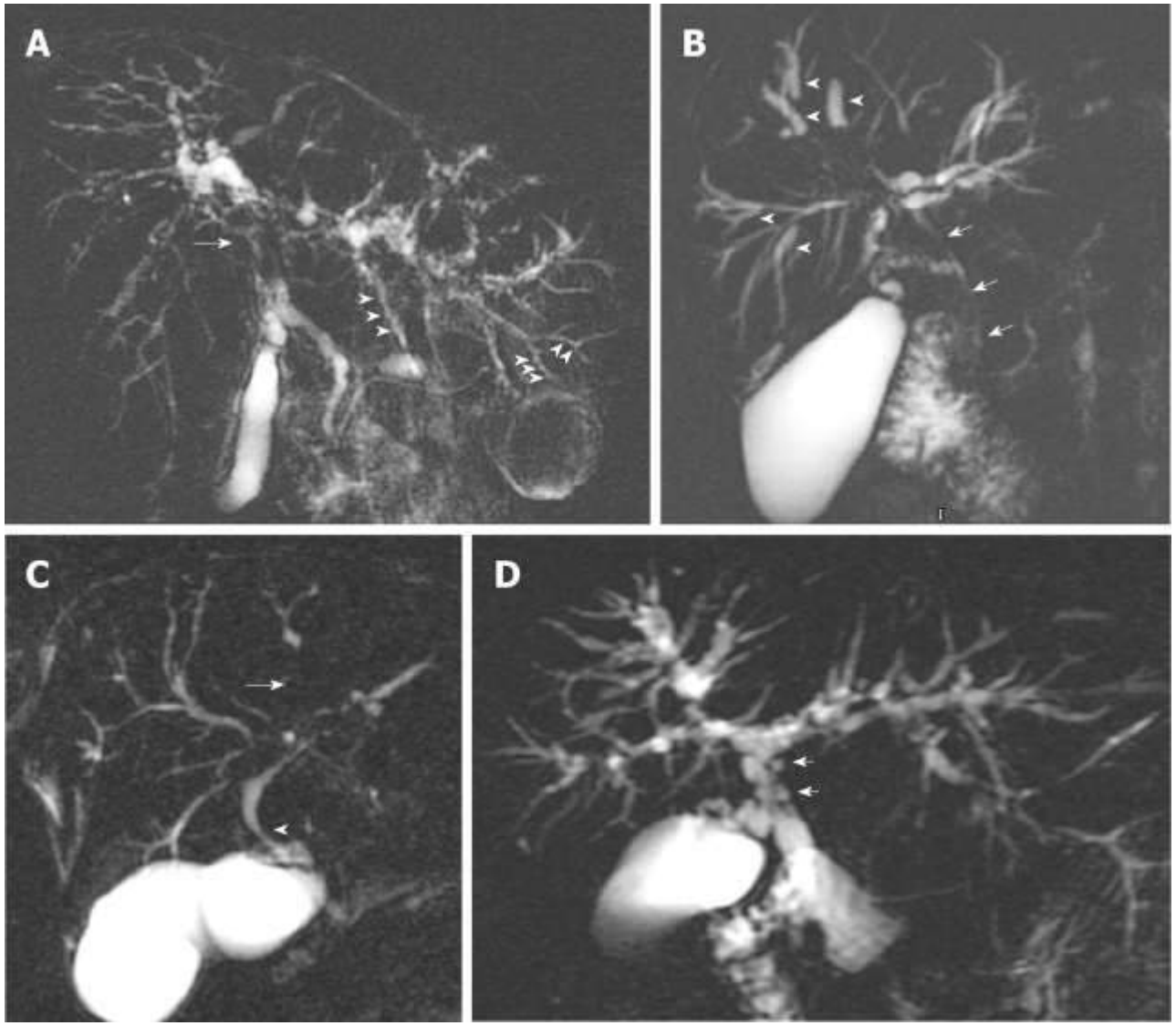
- A small subset of patients have aminotransferase elevations greater than five times the upper limit of normal and may have features of AIH on biopsy. **These individuals are thought to have an overlap syndrome between PSC and AIH.**
- Autoantibodies are frequently positive in patients with the overlap syndrome but are typically negative in patients who only have PSC.
- One autoantibody, the perinuclear antineutrophil cytoplasmic antibody **(P-ANCA)** is positive in about 65% of patients with PSC. Over 50% of patients with PSC also have ulcerative colitis.

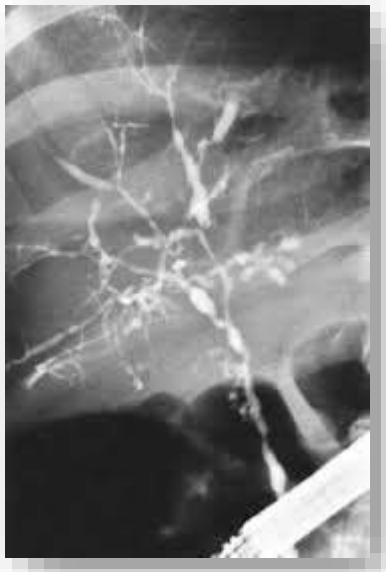
Primary sclerosing cholangitis

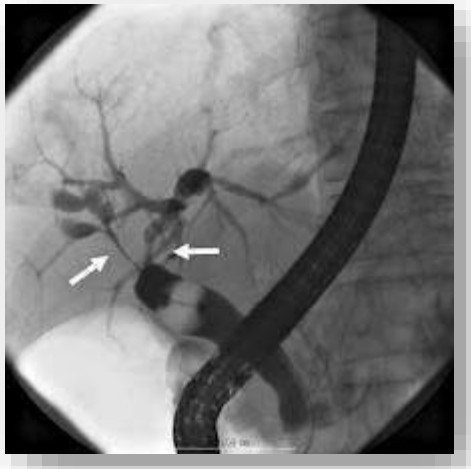
- The definitive diagnosis of PSC requires **cholangiographic imaging**.
- Over the last several years, MRI with magnetic resonance cholangiopancreatography (MRCP) has been utilized as the imaging technique of choice for initial evaluation.
- Some investigators feel that endoscopic retrograde cholangiopancreatography (ERCP) should also be performed to be certain whether or not a dominant stricture is present.

Primary sclerosing cholangitis

MR







Primary sclerosing cholangitis

Treatment

- There is no specific proven treatment for PSC, although studies are currently ongoing using high-dose (20 mg/kg per day) UDCA to determine its benefit.
- **Endoscopic dilatation of dominant strictures** can be helpful, but the ultimate treatment is liver transplantation.
- A complication of PSC is the development of **cholangiocarcinoma,** which is a relative contraindication to liver transplantation.
- Symptoms of pruritus are common, and the approach is as mentioned previously for this problem in patients with PBC (see above).

Biliary intervention	
Antibiotic prophylaxis during endoscopic retrograde cholangiography	**Absolute necessity (eg, ciprofloxacin)**
Long-term antibiotics	**Unproven; consider in recurrent cholangitis; consider rotating antibiotics (eg, amoxicillin–clavulanic acid, ciprofloxacin, co-trimoxazole)**
Endoscopic treatment	**Centre-specific practice; risk of biliary sepsis (concurrent and future) *vs* benefit of early diagnosis of malignancy; intervention for dominant biliary strictures**
Transplantation	
Liver transplantation	**Established indications include decompensated cirrhosis , intractable cholangitis, biliary obstruction, hepatocellular carcinoma; debated indications include biliary dysplasia, hilar cholangiocarcinoma, pruritus**
Surveillance	
Colonoscopy	**Increased risk of colon cancer in patients with concomitant inflammatory bowel disease necessitates annual colonoscopy with screening biopsies**
Ultrasonography	**Annual imaging of gallbladder; six monthly surveillance for hepatocellular carcinoma once patient is cirrhotic**
Cholangiocarcinoma	**Consensus not reached; challenges with performance characteristics of carbohydrate antigen 19-9 and cytology in particular**
Bone density	**Increased prevalence of low bone mass; consider estimation of overall fracture risk**
Family	**Not recommended (familial disease is rare)**

Indication for liver transplantation in Europe