

Primary biliary cholangitis

Small intrahepatic bile duct autoimmunity

Pathogenesis • morphologic recognition • clinicopathologic diagnosis

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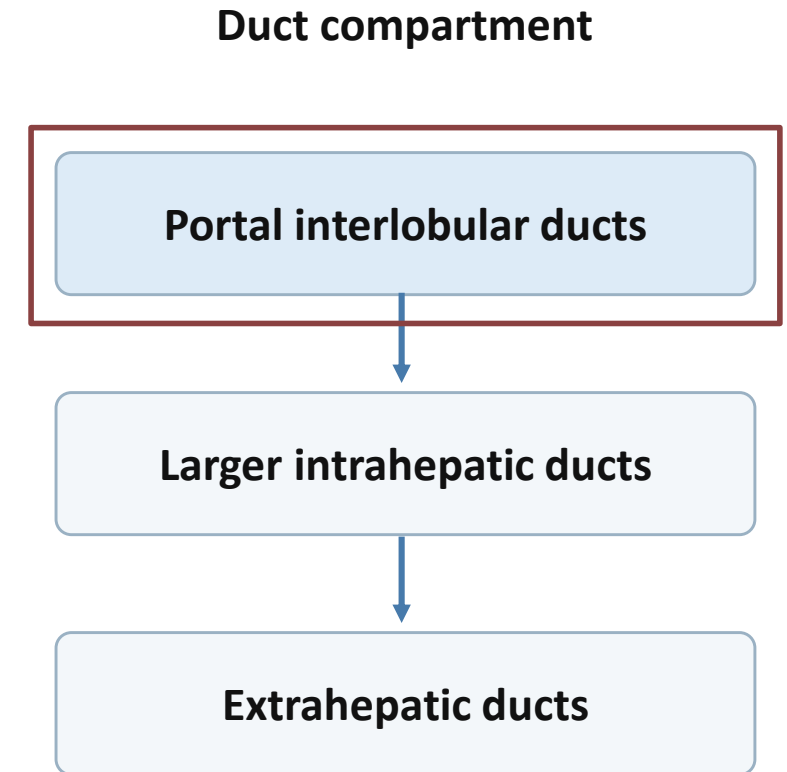
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Learning objectives

- Locate the biliary compartment targeted by PBC and explain its clinical consequences.
- Explain proposed immune mechanisms and interpret the diagnostic value of AMA.
- Recognize characteristic portal lesions, progressive ductopenia, and periportal cholestasis.
- Apply the Robbins diagnostic framework and distinguish PBC from PSC.

PBC is a small-duct autoimmune cholangiopathy

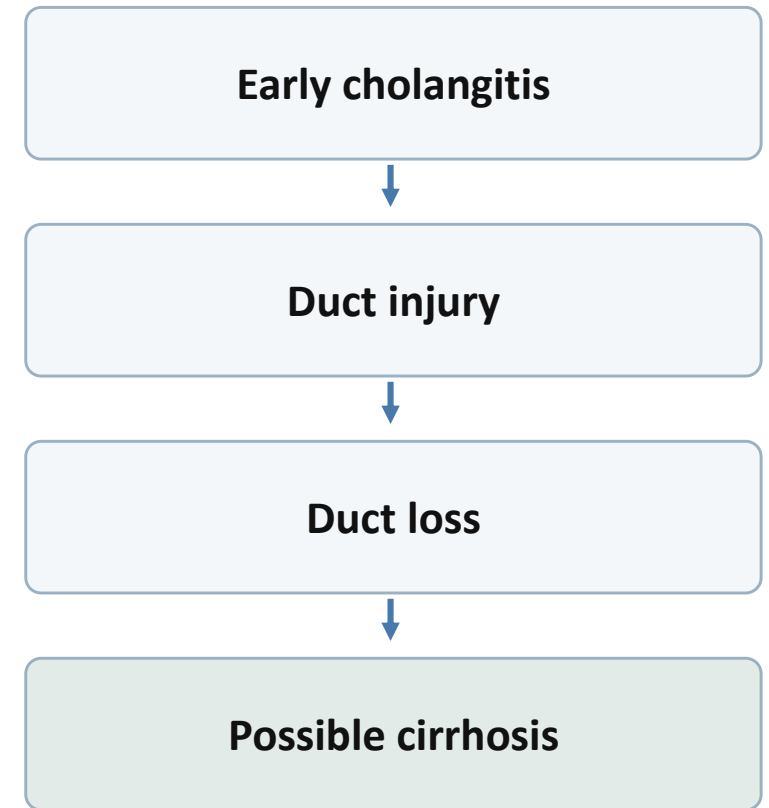
- Inflammatory destruction targets small- and medium-sized intrahepatic bile ducts.
- Large intrahepatic and extrahepatic bile ducts are generally not involved.
- Continued bile duct injury causes cholestasis and secondary hepatocellular damage.



PBC target: Upper compartment

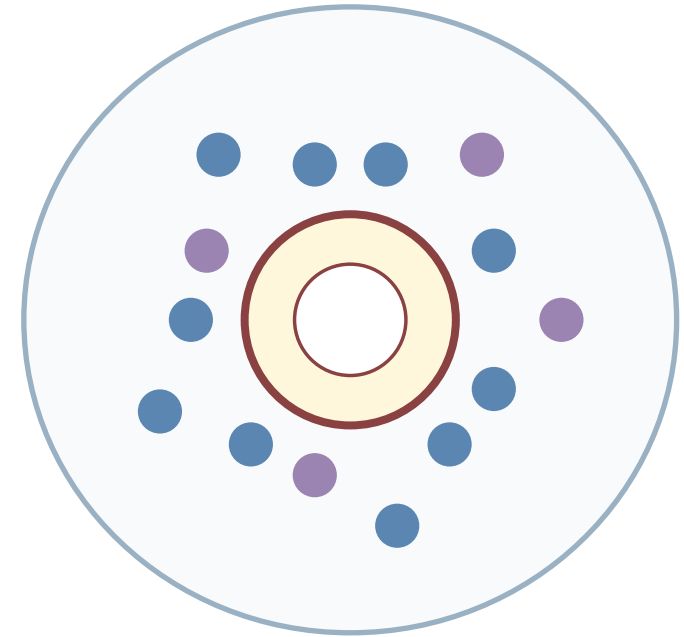
Why the disease is no longer named “biliary cirrhosis”

- Many patients are detected before advanced scarring develops.
- Cirrhosis is a possible late consequence, not a prerequisite for diagnosis.
- The term “primary biliary cholangitis” describes the characteristic inflammatory process.



Anatomical orientation: Where the injury begins

- The portal tract contains an interlobular bile duct beside vascular branches.
- Inflammation is directed at duct epithelium within portal tracts.
- A small-duct lesion may be present despite an unremarkable large-duct cholangiogram.



Small bile duct

Schematic — not a photomicrograph

Sex distribution: Marked female predominance

- Women account for roughly 90% of cases comparison.
- The reported female-to-male ratio is approximately 9:1.
- Sex predominance helps clinical suspicion but is not a diagnostic criterion.

Characteristic distribution

Women ~90%

Men ~10%

Descriptive values

Age and geographical patterns

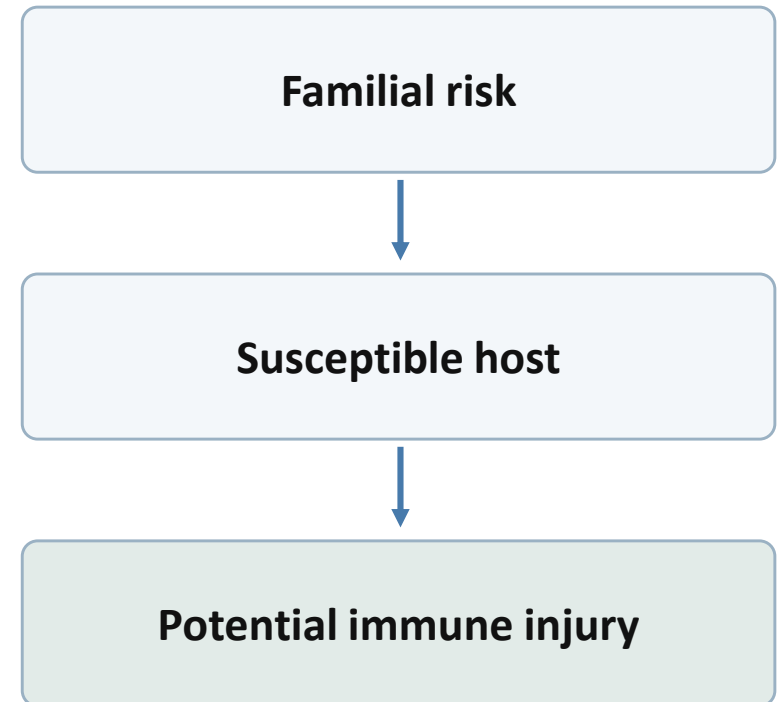
- Peak incidence is described between 40 and 50 years.
- The condition is more common in the United States and Northern Europe.
- Relatively low incidence in Africa and the Indian subcontinent.

Clinical and pathological context

Integrate history, serology, laboratory profile, and morphology.

Familial clustering indicates susceptibility

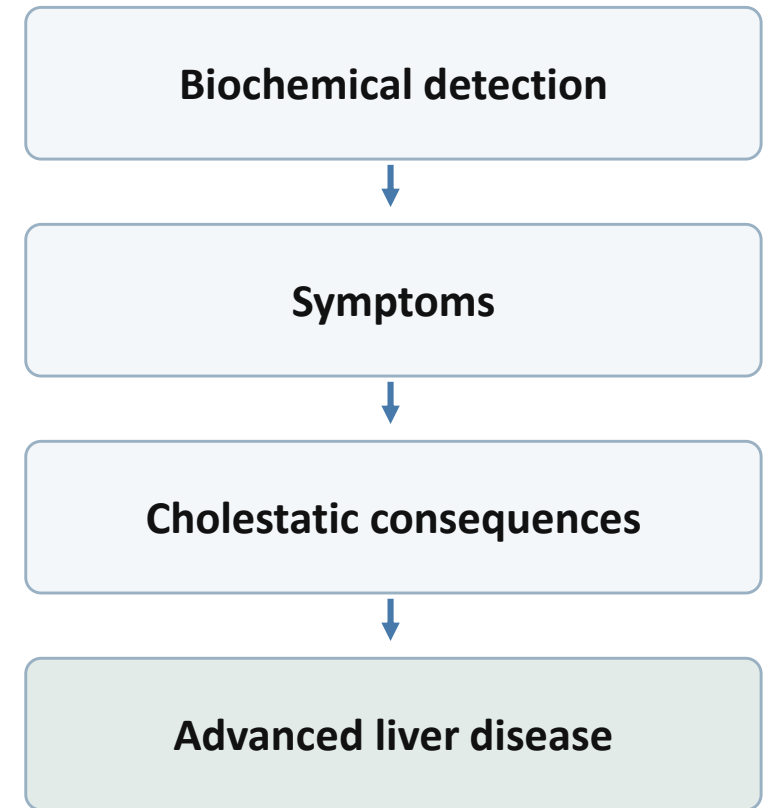
- Relatives of affected patients have an increased risk of PBC.
- Familial association supports inherited susceptibility rather than simple Mendelian transmission.
- Genetic background is considered alongside possible environmental exposures.



Conceptual mechanism

Clinical spectrum: Early detection versus advanced disease

- An asymptomatic patient may first be identified through an elevated alkaline phosphatase.
- Symptomatic patients most often report fatigue and pruritus.
- Jaundice, splenomegaly, and portal-hypertensive findings suggest later disease.



Where PBC fits within cholestatic liver disease

- Cholestasis reflects impaired bile formation or flow with retention of biliary constituents.
- PBC causes intrahepatic cholestasis through immune-mediated destruction of small ducts.
- Large-duct obstruction and PSC can produce cholestasis through different anatomical lesions.

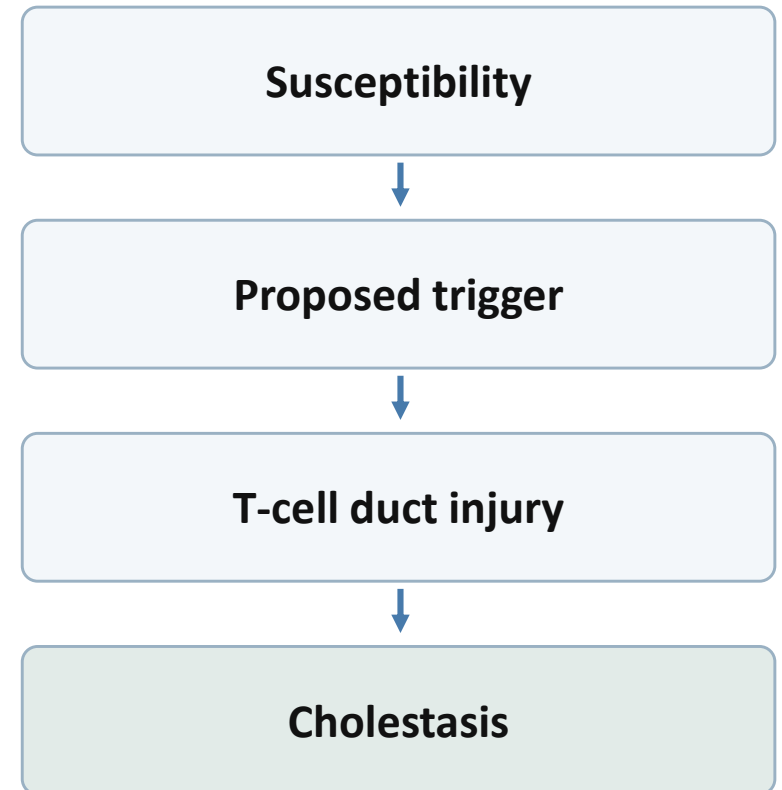
PBC: Small-duct destruction

**Other mechanisms:
Obstruction or large-duct
sclerosis**

Differential comparison

Immune pathogenesis: An integrated model

- Genetic susceptibility and proposed environmental triggers precede immune recognition.
- Autoreactive T lymphocytes target bile duct epithelial cells.
- Duct injury and loss impair bile drainage, causing cholestatic hepatocyte injury.



Conceptual mechanism

The initiating trigger remains unknown

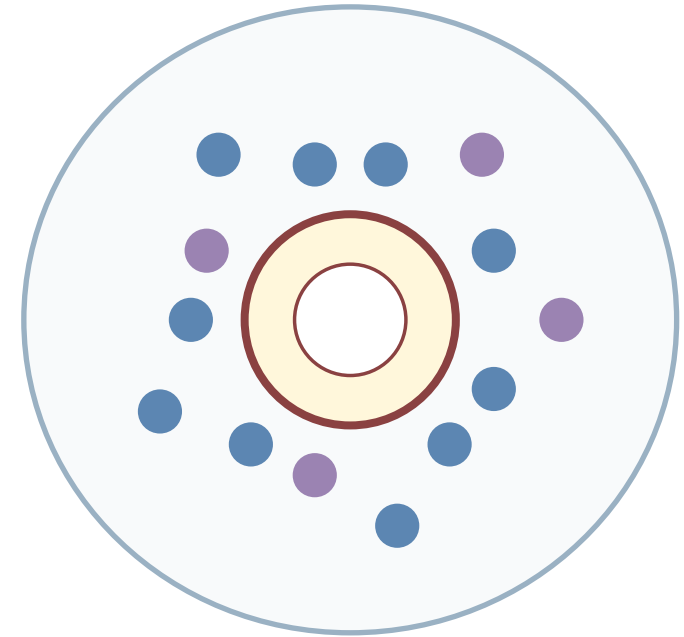
- Infectious exposures and toxic chemicals have been proposed as contributors.
- A specific initiating exposure has not been established.
- Avoid presenting a single infection or toxicant as the proven cause of PBC.

**Established observation
≠ complete mechanism**

Interpret proposed triggers
and causal links with caution.

The T-cell component of duct injury

- PBC is considered a T-cell-mediated autoimmune disorder.
- Lymphocytes infiltrate and damage the epithelium of small interlobular ducts.
- PDC-E2-specific T cells support immune recognition of a mitochondrial autoantigen.

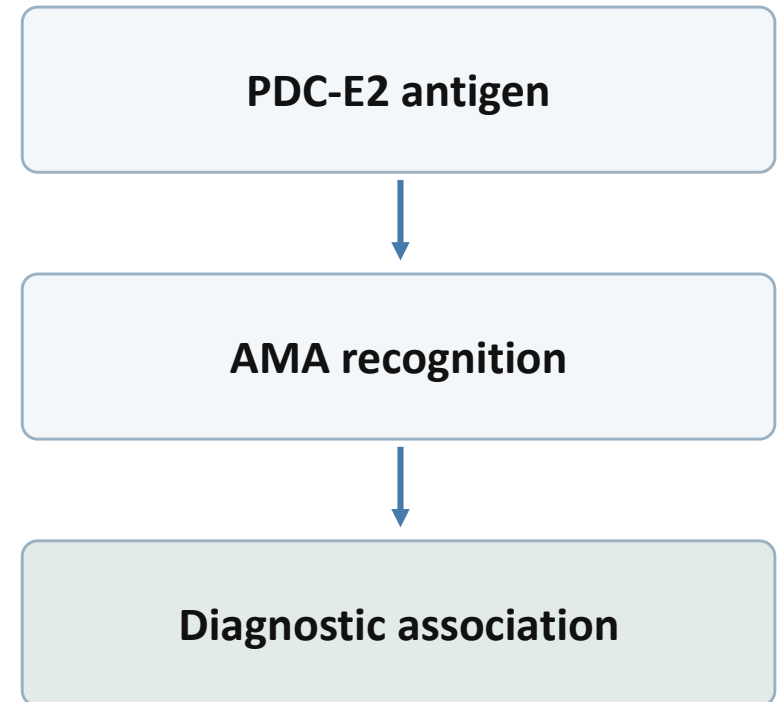


Small bile duct

Schematic — not a photomicrograph

PDC-E2 defines the characteristic autoimmune target

- PDC-E2 is the E2 subunit of the pyruvate dehydrogenase complex.
- Antimitochondrial antibodies in PBC characteristically recognize this component.
- Its antigenic recognition is diagnostically important, even though the full injury mechanism remains uncertain.



Conceptual mechanism

AMA is a marker—not a measured injury severity scale

- Antimitochondrial antibodies are highly characteristic of PBC.
- AMA titers do not correlate reliably with disease severity or progression.
- AMA titers also do not predict response to therapy.

Characteristic marker

Not a severity measure

Not a response predictor

Why AMA cannot be assumed to cause duct destruction

- A minority of otherwise typical patients have no detectable AMA.
- PDC-E2-directed T cells provide independent evidence of cellular autoimmunity.
- The causal role of the circulating autoantibody itself remains uncertain.

**Established observation
≠ complete mechanism**

Interpret proposed triggers
and causal links with caution.

Additional autoantibodies may accompany PBC

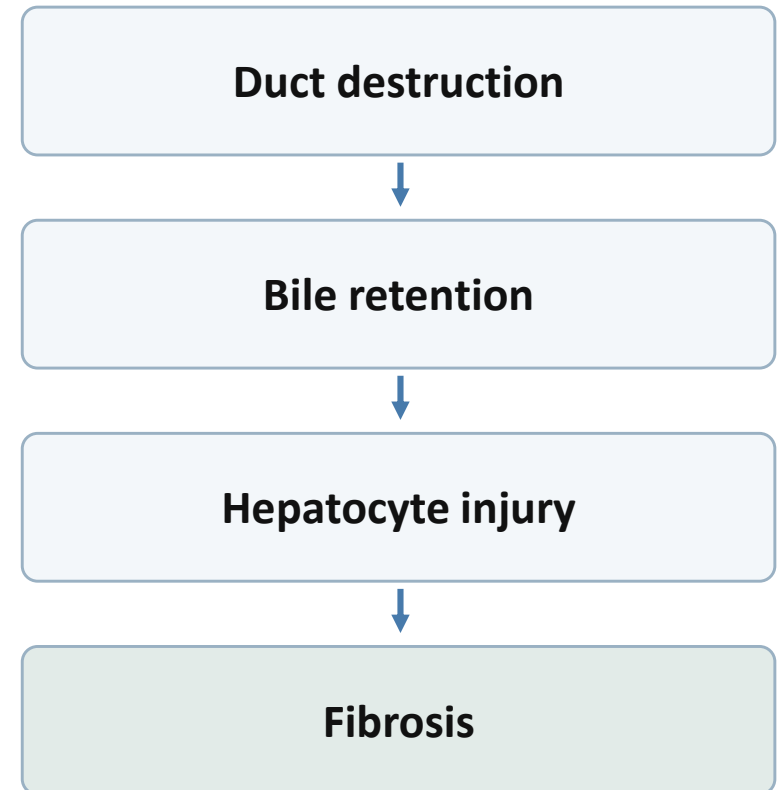
- Autoantibodies against nuclear pore proteins are described.
- Anticentromere and other antinuclear reactivities may also occur.
- These findings supplement—not replace—the textbook’s standard diagnostic framework.

Clinical and pathological context

Integrate history, serology, laboratory profile, and morphology.

Loss of bile ducts creates a cholestatic cascade

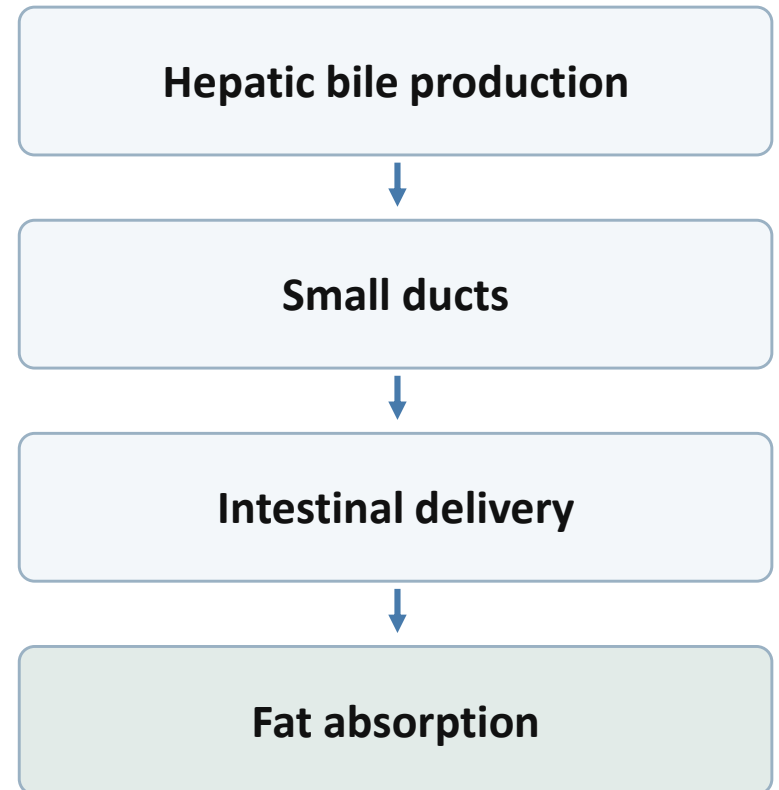
- Immune destruction reduces effective bile duct drainage.
- Retained bile salts and other biliary constituents injure adjacent liver parenchyma.
- Chronic injury can produce ductular response, fibrosis, and eventually cirrhosis.



Conceptual mechanism

Normal bile supports excretion and fat absorption

- Bile carries bilirubin, cholesterol, and other solutes toward the intestine.
- Bile acids help emulsify dietary fat to permit absorption.
- PBC-related impairment can therefore affect both hepatic tissue and intestinal nutrient handling.



Conceptual mechanism

Laboratory cholestasis reflects disturbed biliary physiology

- Canalicular and biliary epithelial injury is associated with elevated alkaline phosphatase.
- Gamma-glutamyl transferase is another characteristic cholestatic enzyme.
- A cholestatic enzyme pattern does not, by itself, establish PBC as the cause.

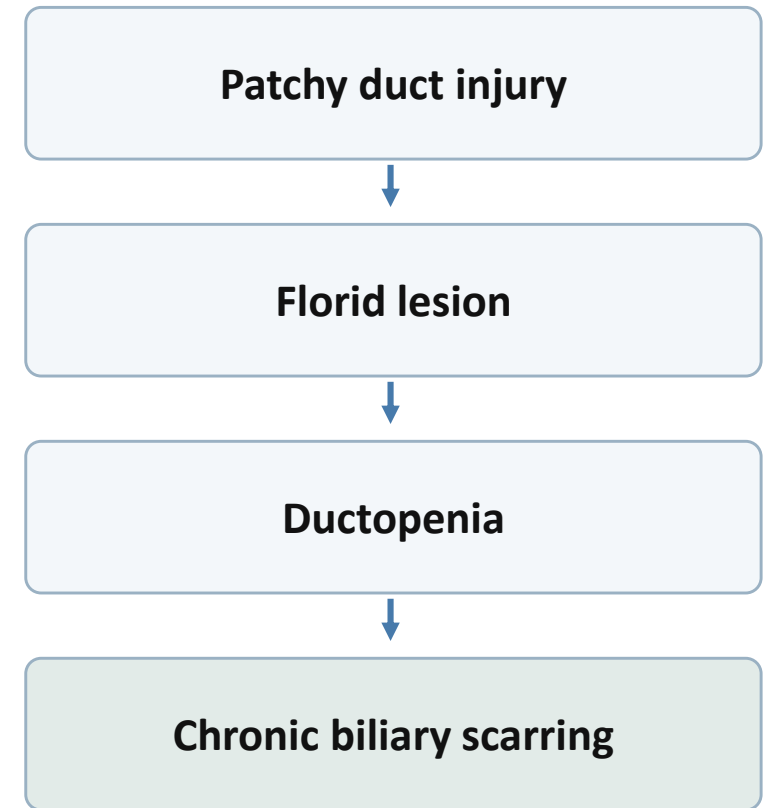
ALP elevation

GGT elevation

Cause still requires evaluation

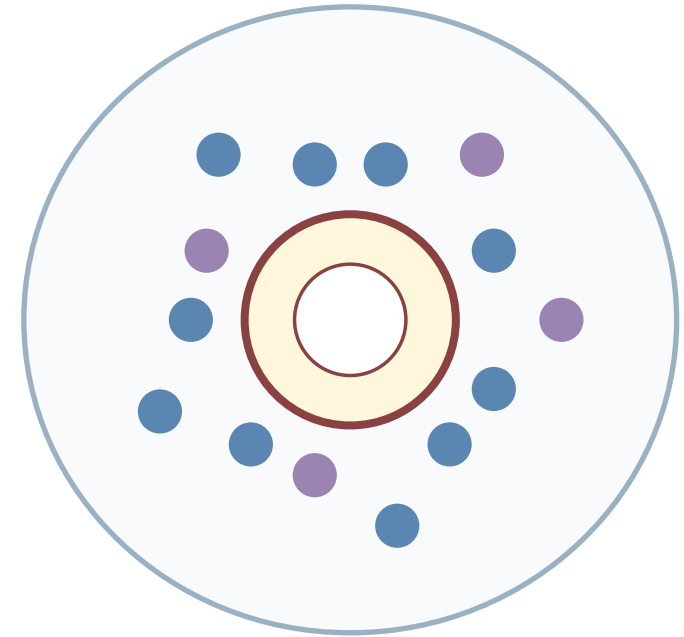
Morphologic sequence: Injury to duct loss

- Early disease may involve only a subset of portal tracts.
- The characteristic inflammatory duct lesion precedes progressive disappearance of small ducts.
- Long-standing cholestasis creates secondary parenchymal changes and fibrosis.



The diagnostic target is the interlobular bile duct

- Small bile duct epithelium is directly damaged by inflammatory infiltrates.
- The duct lumen and epithelial continuity may become difficult to recognize.
- Portal inflammatory changes must be interpreted relative to an actual duct profile.

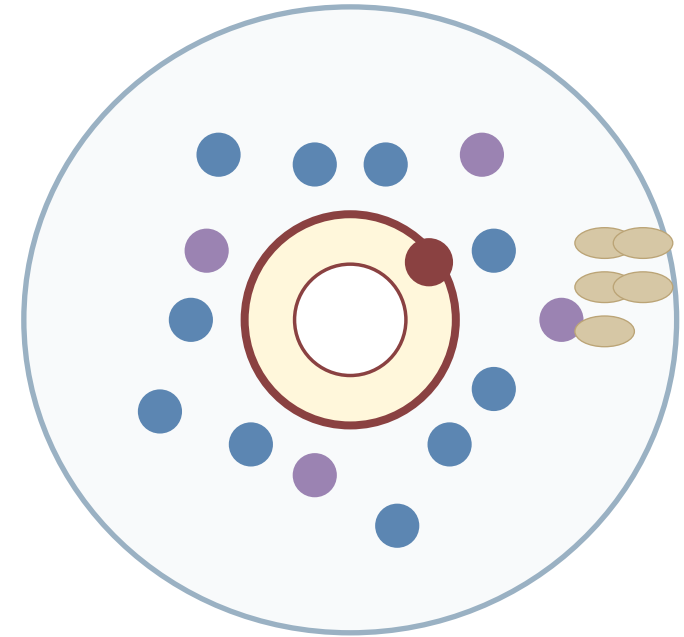


Small bile duct

Schematic — not a photomicrograph

Florid duct lesion: Defining microscopic pattern

- Lymphocytes infiltrate and injure a small interlobular bile duct.
- Granulomatous inflammation may surround or center on the damaged duct.
- The combination is highly characteristic of PBC when present.

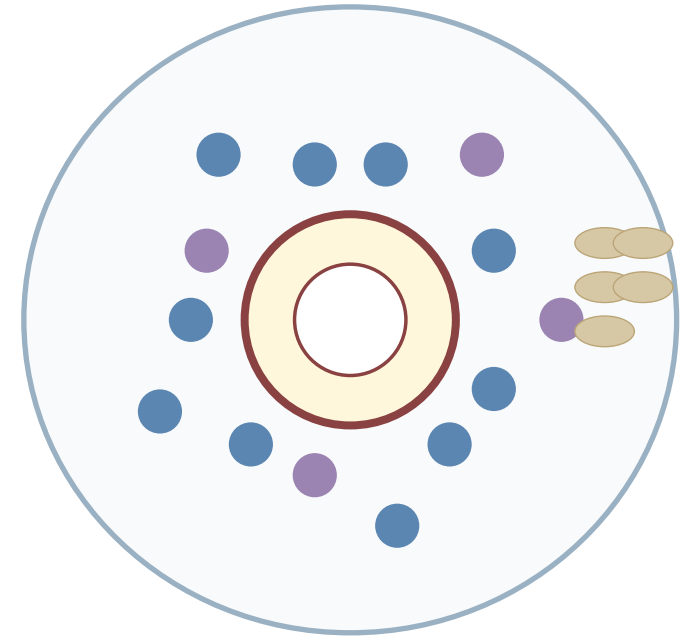


Small bile duct

Schematic — not a photomicrograph

Granulomas in PBC are often poorly formed

- Epithelioid granulomas may be identified within portal tracts.
- Some granulomatous reactions are centered specifically on damaged bile ducts.
- A portal granuloma alone is not diagnostic without bile duct injury context.

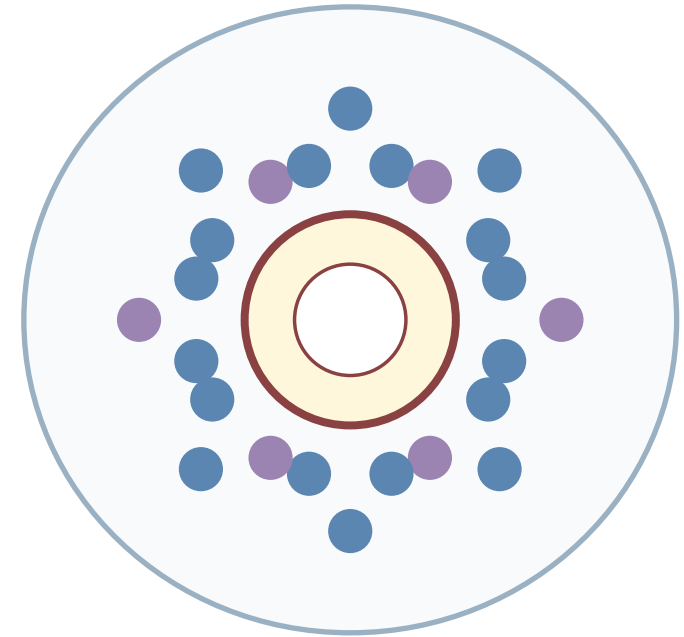


Small bile duct

Schematic — not a photomicrograph

Portal lymphoplasmacytic inflammation accompanies duct injury

- Portal tracts commonly contain lymphocytes and plasma cells.
- The inflammatory infiltrate may be extensive even when a florid lesion is focal.
- Interpret inflammation alongside duct epithelial injury and loss.

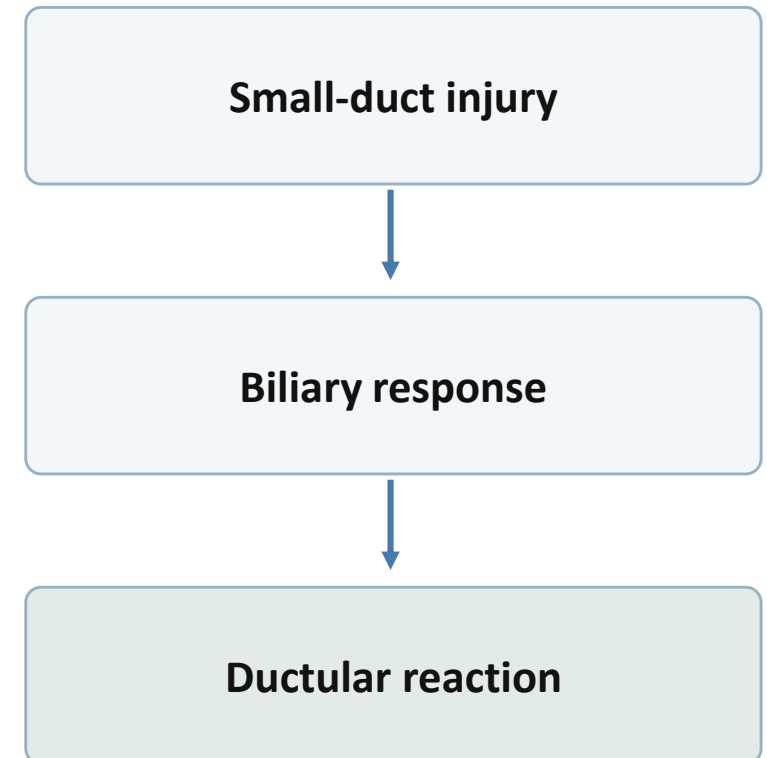


Small bile duct

Schematic — not a photomicrograph

Ductular reaction represents a response to injury

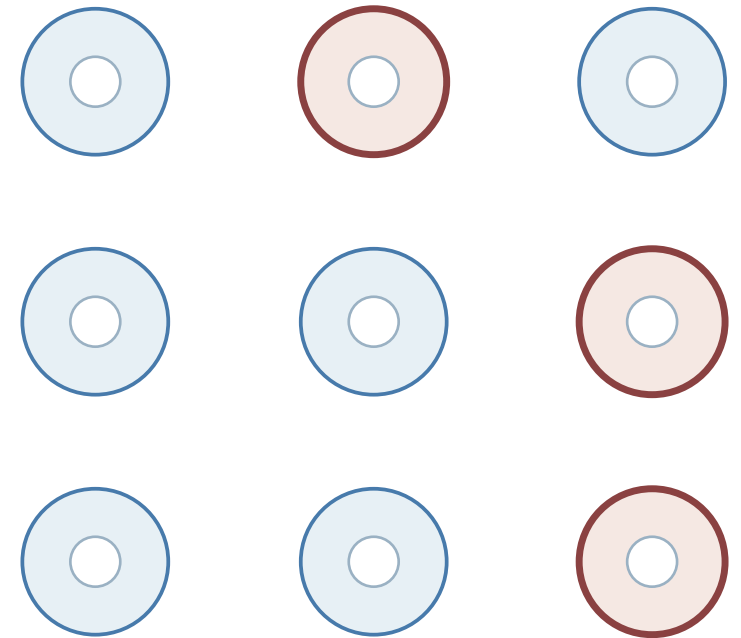
- Ductular proliferation may be seen in inflamed portal regions.
- It accompanies chronic disturbance of the small-duct compartment.
- Ductular reaction alone is not specific for PBC.



Patchiness makes a biopsy vulnerable to sampling error

- Early injury often affects a minority of portal tracts.
- A core may miss the most characteristic granulomatous duct lesion.
- The absence of a florid lesion in one sample does not exclude PBC.

Patchy portal tract involvement

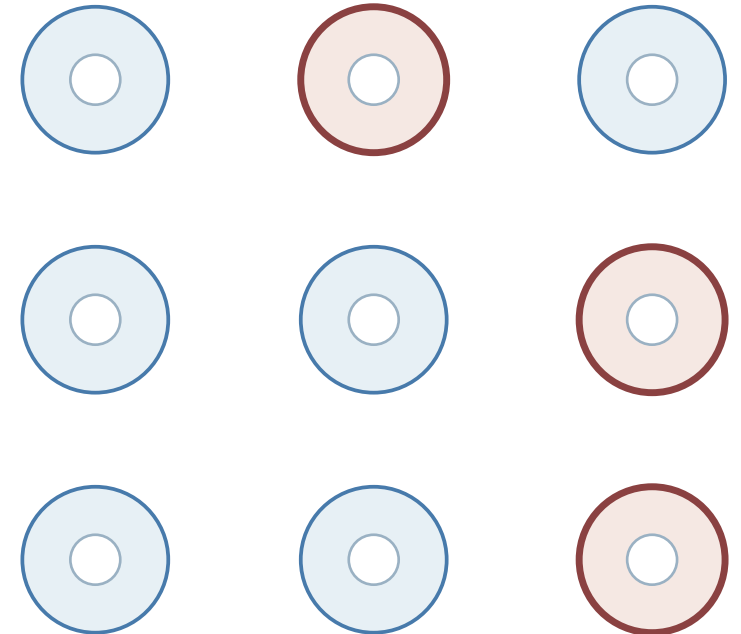


Schematic: Selected ducts injured; Sampling matters

Portal tract sampling: Intact ducts versus injured ducts

- Review multiple portal tracts rather than focusing on a single dramatic area.
- Distinguish preserved ducts from actively injured ducts and absent ducts.
- Link morphologic interpretation to biochemical and serologic findings.

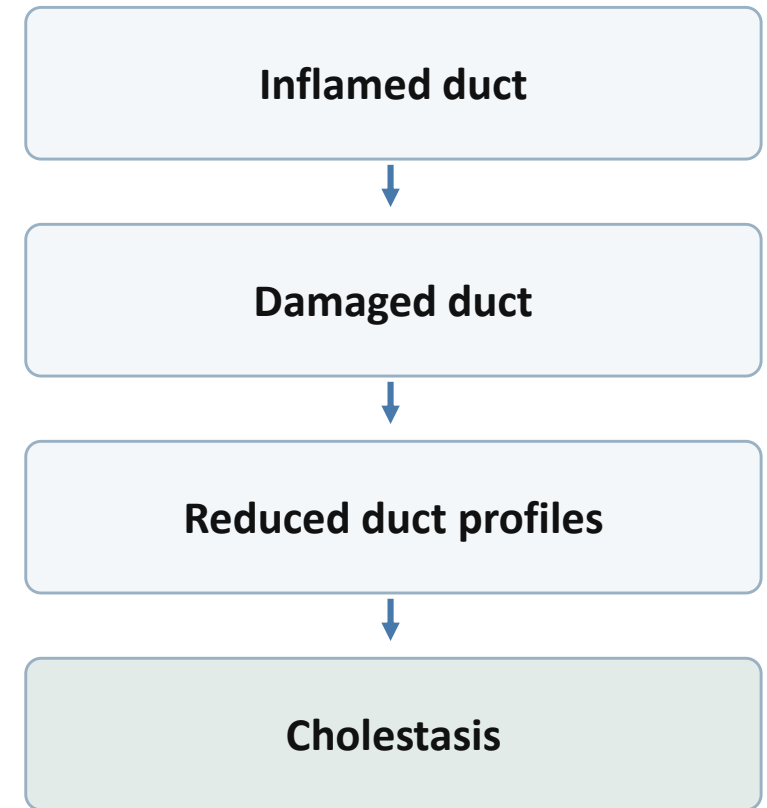
Patchy portal tract involvement



Schematic: Selected ducts injured; Sampling matters

Ductopenia emerges with disease progression

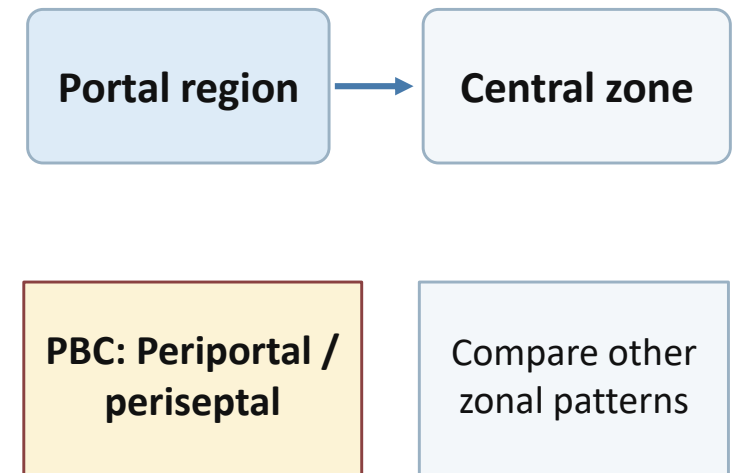
- Progressive loss of intrahepatic small ducts is a major late morphologic change.
- Duct loss worsens impaired bile drainage and supports chronic cholestasis.
- Ductopenia occurs in other disorders, so its cause requires clinicopathologic correlation.



PBC cholestasis tends to be periportal or periseptal

- Bile accumulation in PBC is not typically centered in the centrilobular zone.
- The source emphasizes periportal/periseptal distribution.
- This localization can help distinguish patterns of cholestatic injury.

Schematic hepatic acinar axis

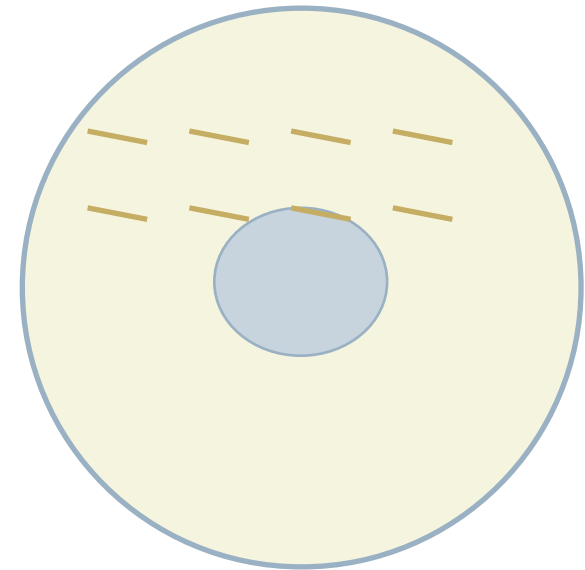


Conceptual distribution; Not tissue scale

Cholate stasis changes periportal hepatocytes

- Bile salt retention produces swollen hepatocytes with pale cytoplasm.
- Fine granular cytoplasmic strands produce the appearance termed feathery degeneration.
- This reaction is associated with chronic biliary injury rather than exclusively with PBC.

Cholate-stasis hepatocyte

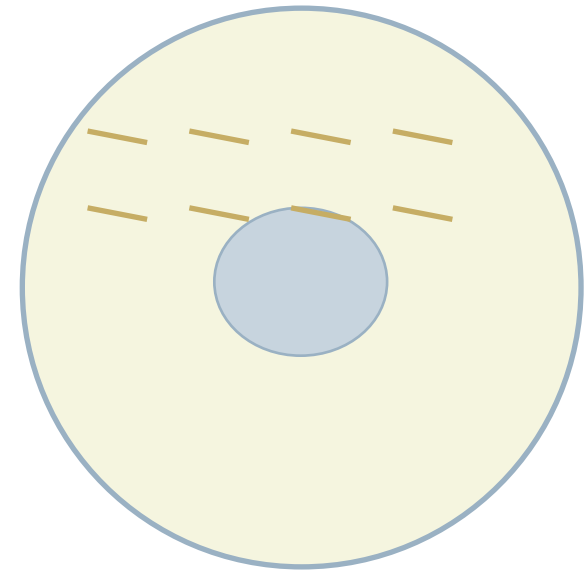


Schematic — not an H&E specimen

Mallory hyaline may occur in chronic cholestatic injury

- Periportal hepatocytes with cholate stasis may develop Mallory hyaline.
- The inclusion is not unique to PBC or to alcoholic liver injury.
- Its significance depends on the surrounding biliary pattern.

Cholate-stasis hepatocyte



Schematic — not an H&E specimen

Cholate stasis is a pattern, not a specific diagnosis

- Periportal feathery degeneration points to a chronic biliary process.
- Similar hepatocellular changes can appear across chronic biliary disorders.
- A diagnosis of PBC still depends on serology, clinical evidence, and duct-specific lesions.

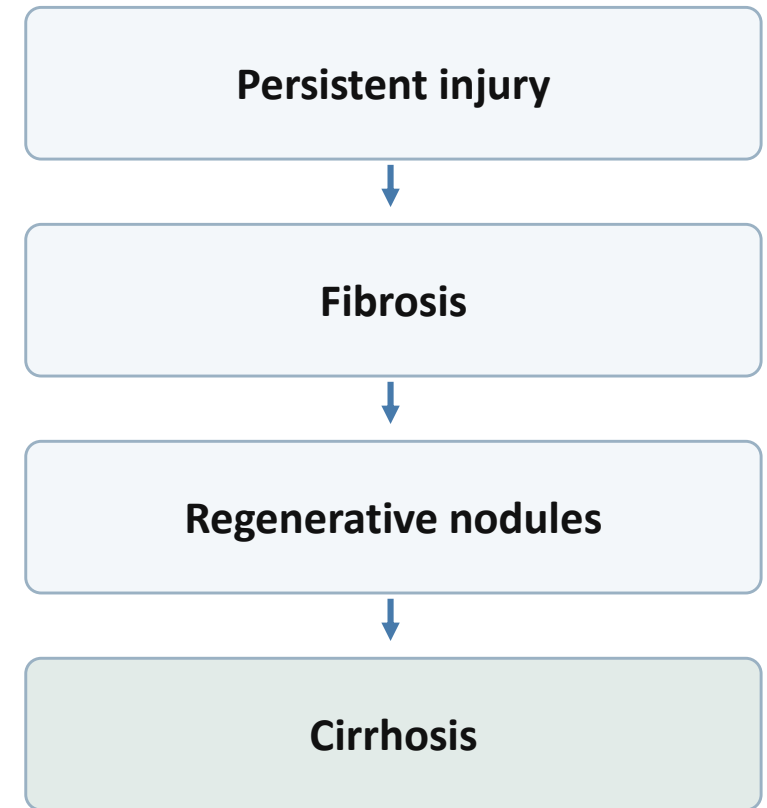
Cholate stasis

Chronic biliary injury

Not PBC-specific

Fibrosis and nodular regeneration are late consequences

- Persistent cholestasis may culminate in cirrhosis.
- Biliary cirrhotic nodules may be elongated or garland-shaped.
- The textbook contrasts this pattern with rounder nodules in hepatitic cirrhosis.



Portal hypertension may develop without established cirrhosis

- Some patients develop nodular regenerative hyperplasia.
- This may produce portal hypertension despite the absence of conventional fibrotic cirrhosis.
- The basis of nodular regenerative hyperplasia in PBC remains uncertain.

**Established observation
≠ complete mechanism**

Interpret proposed triggers
and causal links with caution.

Histology: What is characteristic and what is nonspecific?

- Highly characteristic: Destructive lymphocytic/granulomatous small-duct lesion.
- Supportive: Portal inflammation, ductular reaction, patchy duct loss.
- Nonspecific chronic consequences: Feathery degeneration, fibrosis, regenerative change.

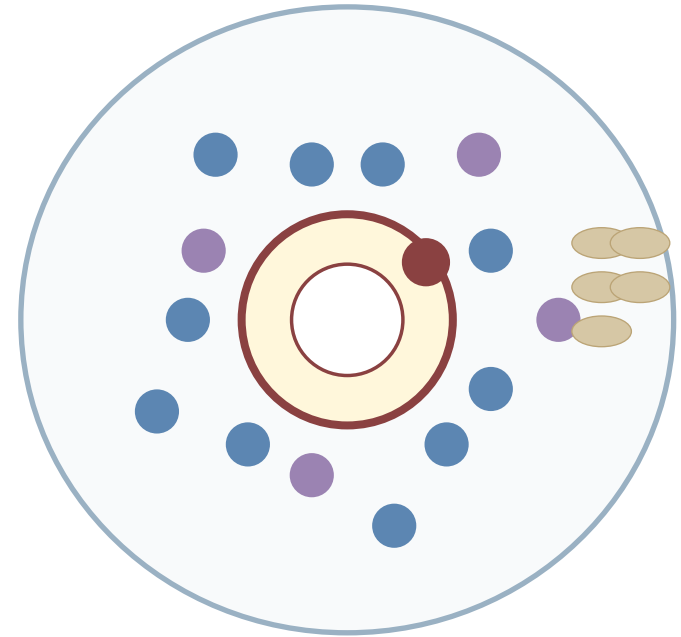
Florid lesion: Characteristic

Duct loss: Supportive

Cholate stasis: Nonspecific

The textbook lesion in one conceptual view

- Inflamed portal tract with destruction centered on a small bile duct.
- Lymphocytes and plasma cells surround the duct; Granulomatous reaction may coexist.
- This is the lesion described in the source's Fig. 18.36— not a reproduced photomicrograph.



Small bile duct

Schematic — not a photomicrograph

Fatigue and pruritus are the common symptomatic presentation

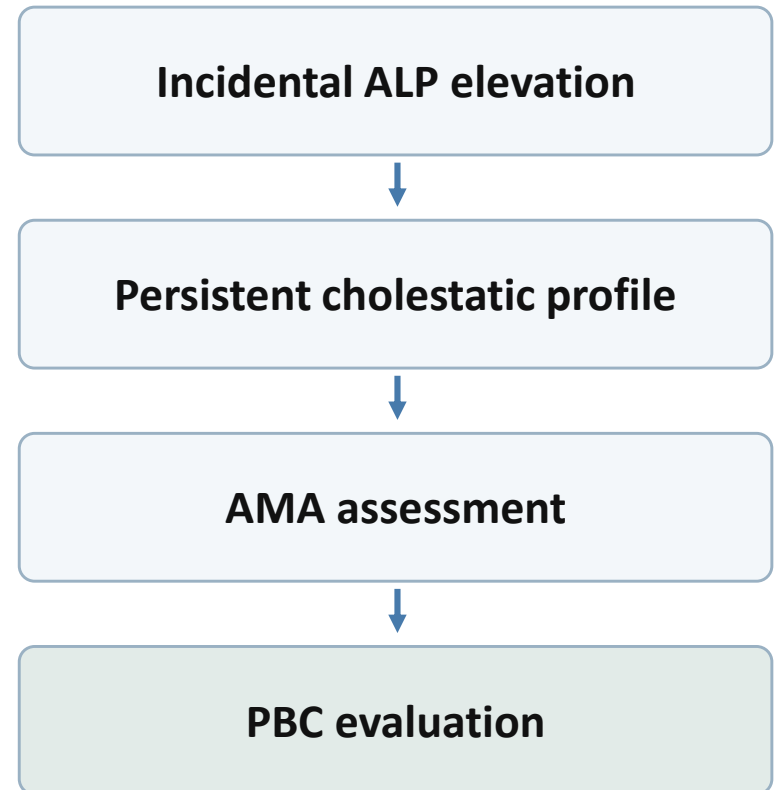
- Both symptoms may develop insidiously and progress gradually.
- They reflect a disease that may be biochemically apparent before advanced structural injury.
- Symptom severity alone does not define the microscopic stage.

Clinical and pathological context

Integrate history, serology, laboratory profile, and morphology.

Asymptomatic PBC is an important detection pathway

- Increasing numbers of cases are identified by persistently elevated serum alkaline phosphatase.
- Patients may have no jaundice or other obvious signs of advanced disease.
- Serologic evaluation becomes important when a persistent cholestatic profile is detected.



Conceptual mechanism

Pruritus is a cholestatic clinical clue

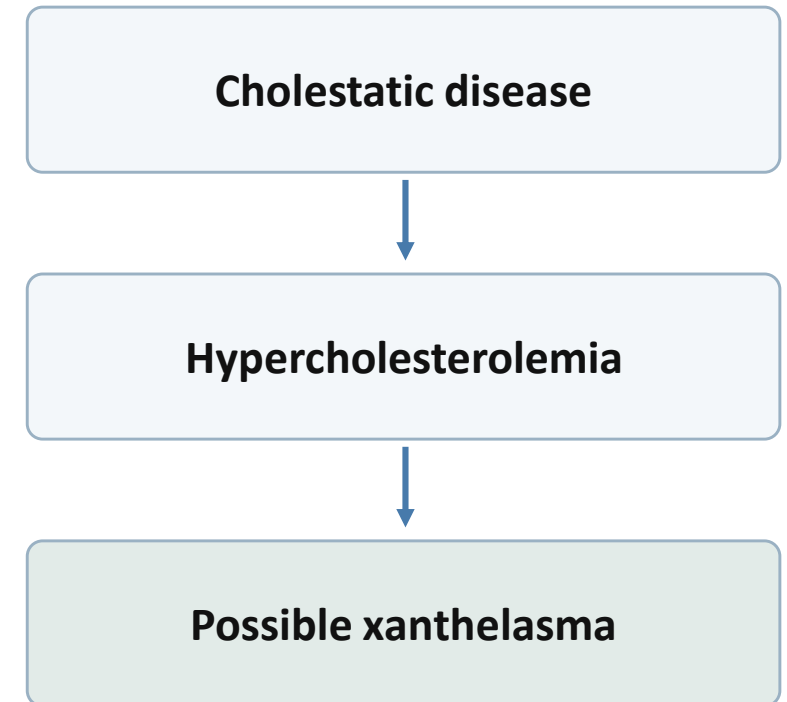
- Pruritus is among the characteristic early symptoms.
- It may occur before clinically evident jaundice.
- Its presence should be considered alongside biochemical and autoimmune findings.

Clinical and pathological context

Integrate history, serology, laboratory profile, and morphology.

Hypercholesterolemia and xanthelasma

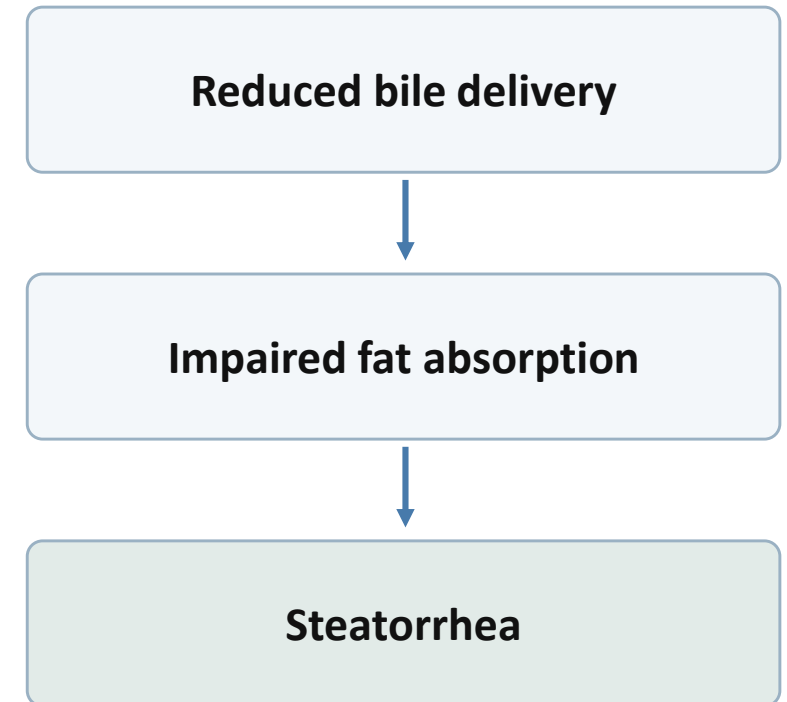
- Disturbed bile-related cholesterol handling is often accompanied by hypercholesterolemia.
- Xanthelasmas can become a visible manifestation of lipid deposition.
- Neither hypercholesterolemia nor xanthelasma alone establishes the diagnosis.



Conceptual mechanism

Malabsorption reflects reduced effective bile delivery

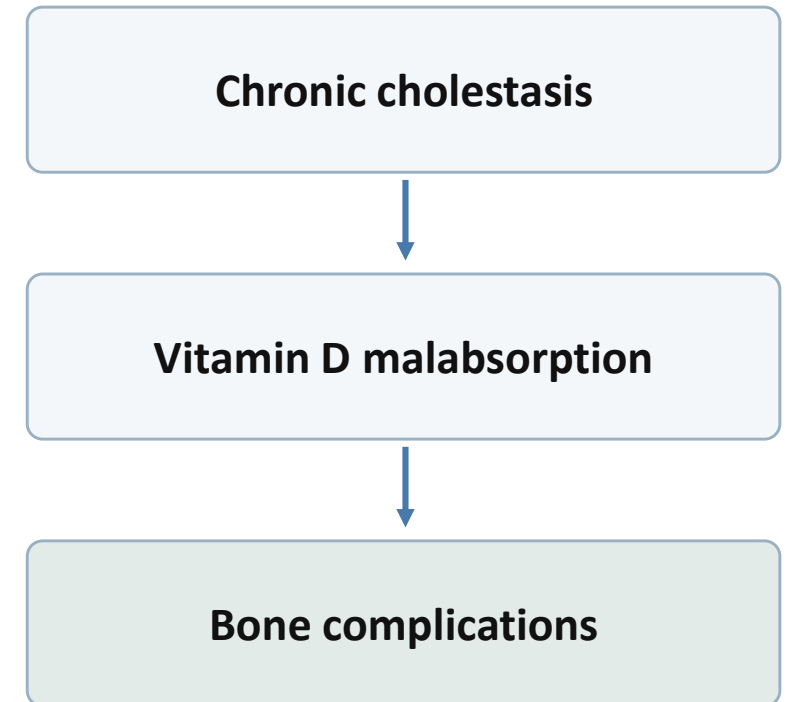
- Steatorrhea may accompany cholestasis as intestinal fat handling becomes impaired.
- Failure of adequate fat emulsification can affect absorption of fat-soluble nutrients.
- Such consequences become clinically relevant in sustained disease.



Conceptual mechanism

Vitamin D deficiency links cholestasis to bone disease

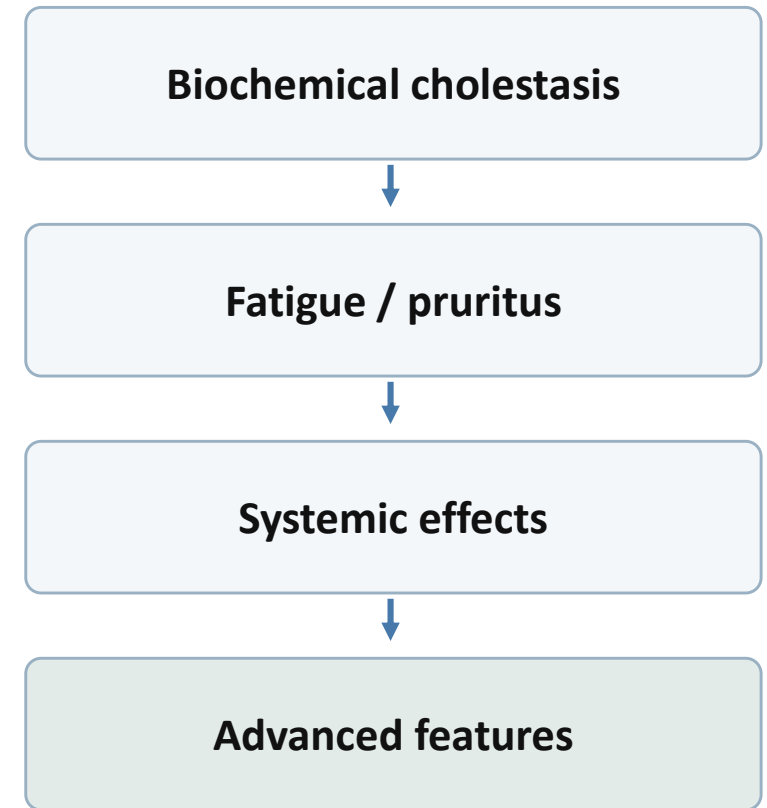
- Vitamin D malabsorption is described in PBC.
- Osteomalacia and osteoporosis may follow impaired vitamin D and skeletal homeostasis.
- Bone disease is part of the systemic clinical impact of chronic cholestasis.



Conceptual mechanism

Progression produces additional systemic manifestations

- Skin hyperpigmentation may be present.
- Jaundice and splenomegaly are emphasized in more advanced disease.
- These findings suggest progression beyond isolated biochemical cholestasis.



Autoimmune disease associations are diagnostically useful

- Sjögren syndrome, thyroiditis, and systemic sclerosis are prominent associations.
- Rheumatoid arthritis, Raynaud phenomenon, and celiac disease may coexist.
- Associated autoimmunity increases clinical suspicion but is not a substitute for PBC criteria.

Sjögren / thyroiditis

Systemic sclerosis

Other autoimmune disorders

PBC versus autoimmune hepatitis: Different primary targets

- PBC centers on destruction of small interlobular bile ducts.
- Autoimmune hepatitis centers on hepatocellular inflammation and interface injury.
- Overlap is possible, so atypical biochemical and histologic patterns require broader consideration.

PBC: Bile duct injury

AIH: Hepatocyte/interface injury

Differential comparison

First diagnostic clue: A persistent cholestatic enzyme pattern

- Elevated alkaline phosphatase for more than 6 months is one textbook criterion.
- A single abnormal result does not satisfy the stated persistence requirement.
- The biochemical pattern establishes a cholestatic phenotype, not the etiology by itself.

ALP elevated

Persistence >6 months

Evaluate etiology

Antimitochondrial antibodies provide strong serologic support

- AMA is detected in approximately 90%–95% of patients.
- It can be present at all stages of the disease.
- Its high disease association makes it especially useful with persistent cholestatic enzymes.

Characteristic serology

AMA-positive ~90–95%

AMA-negative minority

Descriptive values

AMA testing methods: Immunofluorescence versus ELISA

- Indirect immunofluorescence can detect characteristic AMA reactivity.
- PDC-E2-directed ELISA selectively detects the defined target antigen.
- Higher sensitivity and specificity for its ELISA approach.

Indirect immunofluorescence

PDC-E2-specific ELISA

Differential comparison

IgM elevation is a supportive—not defining—finding

- Many patients have increased circulating IgM.
- The biological basis of this elevation is not established in the source text.
- IgM is not one of the three specified Robbins diagnostic criteria.

May be elevated

Mechanism uncertain

Not a core criterion

Robbins diagnosis uses a two-of-three framework

- Persistently elevated alkaline phosphatase for more than 6 months.
- Positive antimitochondrial antibody test.
- Characteristic liver histology showing bile duct injury.
- Any two of these three support the textbook diagnosis.

Any two of three source criteria

ALP elevated >6 months

AMA positive

Characteristic histology

Robbins 11th-edition diagnostic framework

Diagnostic combinations: Serology may obviate histologic proof

- Persistent ALP elevation plus AMA positivity provides two criteria.
- AMA plus characteristic histology can also reach two criteria.
- Persistent ALP elevation plus characteristic histology supports AMA-negative disease.

Any two of three source criteria

ALP elevated >6 months

AMA positive

Characteristic histology

AMA-negative PBC remains within the disease spectrum

- A minority of typical patients lack detectable AMA.
- The textbook labels some of these cases autoimmune cholangiopathy/cholangitis.
- Clinical presentation, histology, and natural history are otherwise similar.

AMA-positive PBC

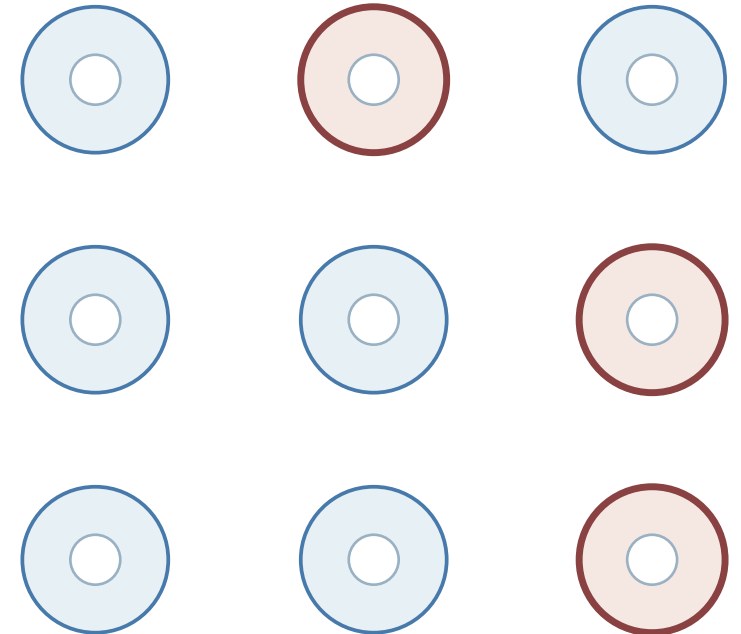
AMA-negative PBC

Differential comparison

Morphology is especially useful when serology is negative

- A characteristic florid duct lesion can support a difficult diagnosis.
- Patchy portal involvement reduces biopsy sensitivity for the most specific lesion.
- Chronic cholestatic injury alone should not be mistaken for diagnostic duct destruction.

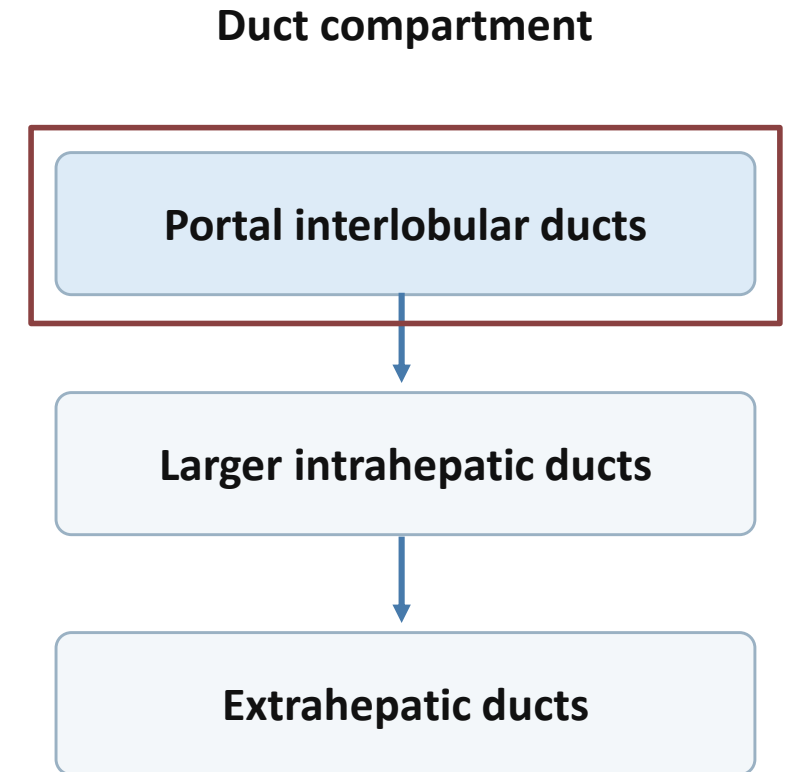
Patchy portal tract involvement



Schematic: Selected ducts injured; Sampling matters

Large-duct imaging is usually unremarkable in PBC

- The primary injury is in small intrahepatic ducts rather than the major biliary tree.
- Typically normal PBC radiology with PSC beading and strictures.
- A normal large-duct study does not rule out PBC.



PBC target: Upper compartment

Anatomical differential: PBC versus PSC

- PBC: Small interlobular intrahepatic ducts, with florid inflammatory duct lesions.
- PSC: Extrahepatic and large intrahepatic ducts, with fibrosis and strictures.
- The anatomical difference explains why cholangiographic appearances diverge.

PBC: Small ducts

PSC: Large ducts

Differential comparison

Epidemiology and associations help separate PBC from PSC

- PBC: Approximately 90% female; Median age near 50 years table.
- PSC: Approximately 70% male; Median age near 30 years in the table.
- Sjögren/thyroid disease suggests PBC; Inflammatory bowel disease suggests PSC.

**PBC: Female / autoimmune
associations**

**PSC: Male / inflammatory
bowel disease**

Differential comparison

Serology differentiates—but does not perfectly classify

- PBC is typically AMA positive, whereas PSC is usually AMA negative.
- PBC can show ANA; PSC may show antineutrophil cytoplasmic antibodies.
- Interpret panels in the context of duct anatomy and imaging.

PBC: Characteristic AMA

PSC: ANCA association

Differential comparison

Histologic contrast: Florid lesion versus onion-skin scar

- PBC: Lymphocytic or granulomatous destruction of small interlobular ducts.
- PSC: Dense concentric fibrosis may entrap or obliterate a duct.
- Neither single lesion should be used without clinicopathologic correlation.

PBC: Florid duct lesion

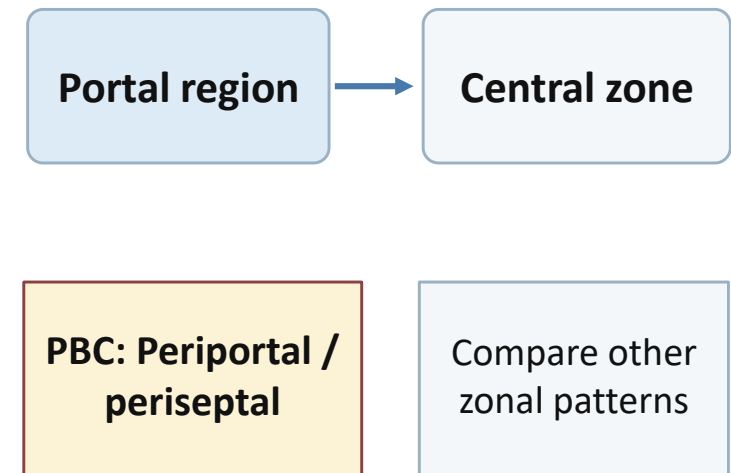
**PSC: Concentric periductal
fibrosis**

Differential comparison

Other cholestatic diseases can mimic individual findings

- Large-duct obstruction alters bile flow through a mechanical process.
- Drug-associated and sepsis-associated cholestasis may show different zonal patterns.
- The combination of duct-centered inflammation, AMA, and clinical context is more discriminating.

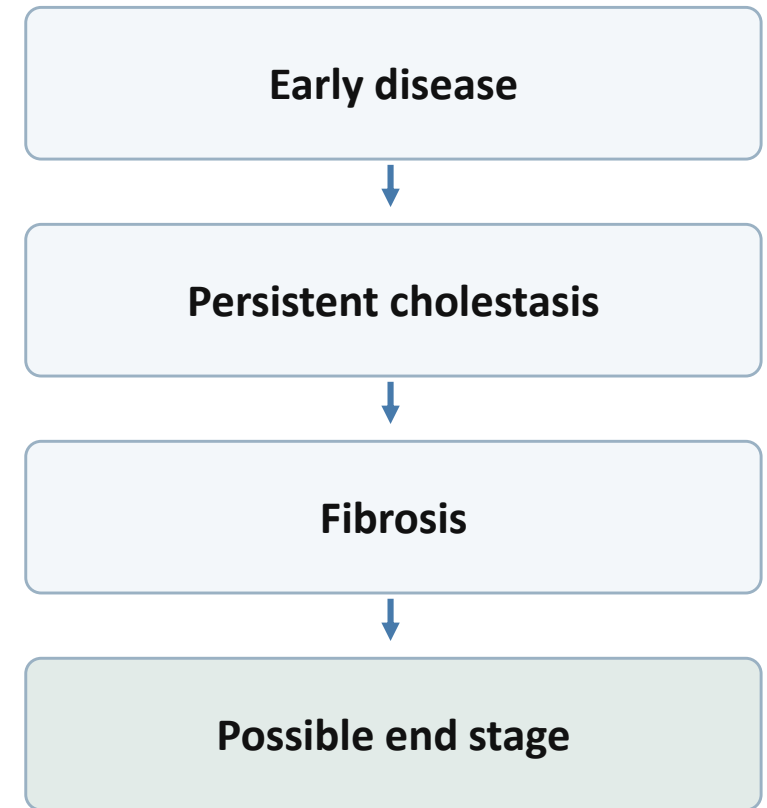
Schematic hepatic acinar axis



Conceptual distribution; Not tissue scale

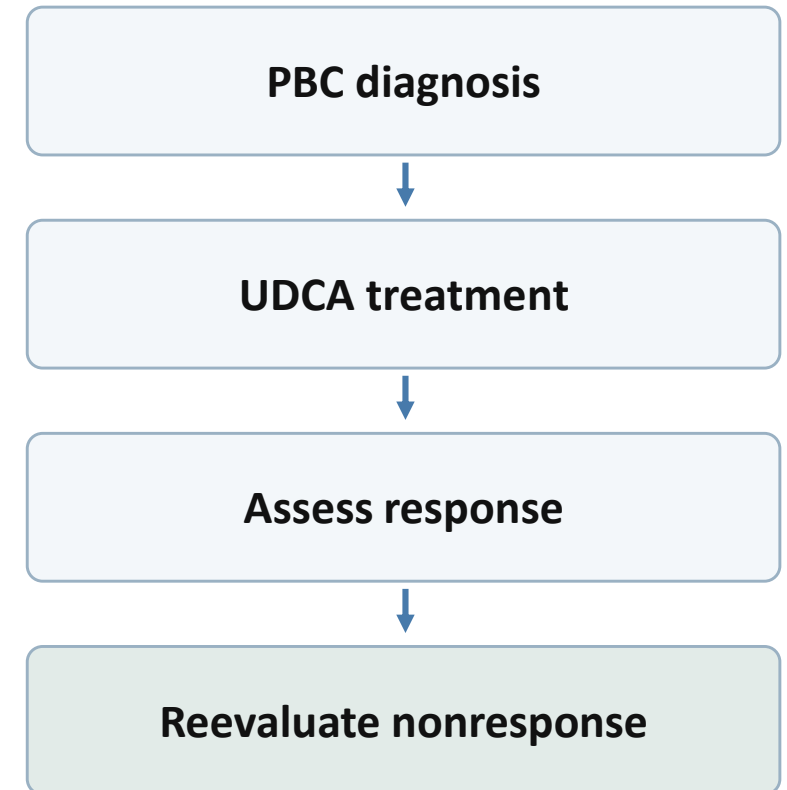
Long-term course: Slow but potentially progressive

- PBC as generally slowly progressive.
- End-stage liver disease occurs in approximately 20%–25% over 15–20 years description.
- These population estimates are not individualized predictions.



Ursodeoxycholic acid modifies progression

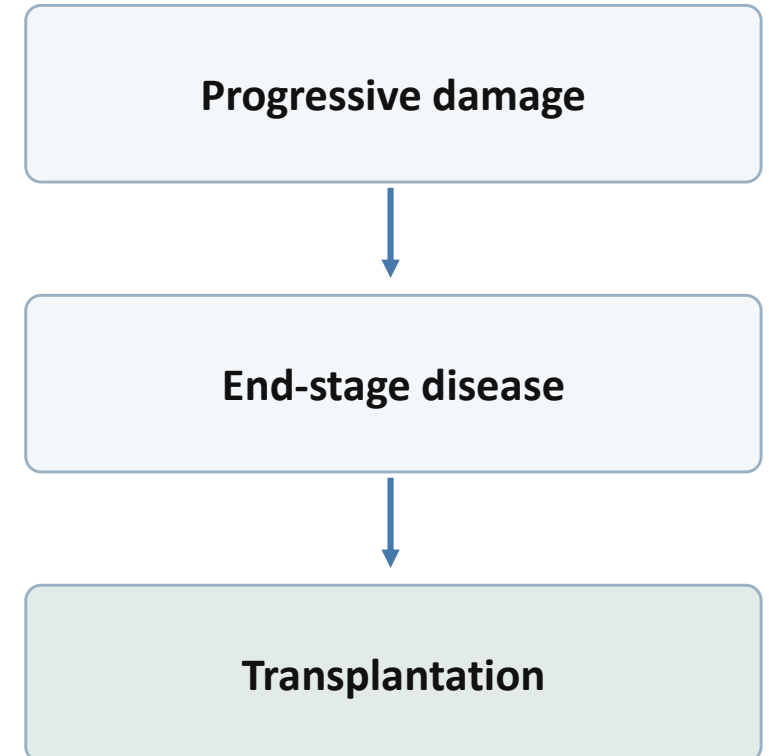
- Oral ursodeoxycholic acid is described as the principal disease-modifying therapy.
- It slows disease progression in most affected patients.
- Inadequate response in up to 40%, requiring specialist reassessment.



Conceptual mechanism

Advanced disease may require liver transplantation

- Transplantation is an established option for end-stage disease.
- Survival exceeding 70% at 7 years after transplantation.
- This historical source estimate should not be substituted for current center-specific outcomes.



Hepatocellular carcinoma remains a relevant long-term risk

- As with other chronic hepatic injury, PBC increases the risk of hepatocellular carcinoma.
- Risk assessment should consider the extent and chronicity of liver disease.
- Clinical surveillance policy is beyond the source-based pathology teaching scope.

Clinical and pathological context

Integrate history, serology, laboratory profile, and morphology.

Case A: Biochemical presentation without symptoms

- A middle-aged woman is asymptomatic but has persistently increased alkaline phosphatase.
- AMA testing is positive; Large-duct imaging is unrevealing.
- Which disease mechanism explains this pattern, and which criteria are met?

Interpret the pattern

Anatomy → laboratory
profile → serology →
morphology

Case A: Apply the source-based criteria

- The phenotype suggests autoimmune injury of small intrahepatic bile ducts.
- Persistent ALP elevation and AMA positivity fulfill two textbook criteria.
- A florid duct lesion would be characteristic but is not necessary to form the two-item combination.

Any two of three source criteria

ALP elevated >6 months

AMA positive

Characteristic histology

Case B: Cholestasis with negative AMA

- A patient has persistent cholestatic enzymes but AMA is not detected.
- A biopsy shows patchy destructive lymphocytic inflammation centered on small bile ducts.
- What diagnosis remains possible, and what is the role of sampling?

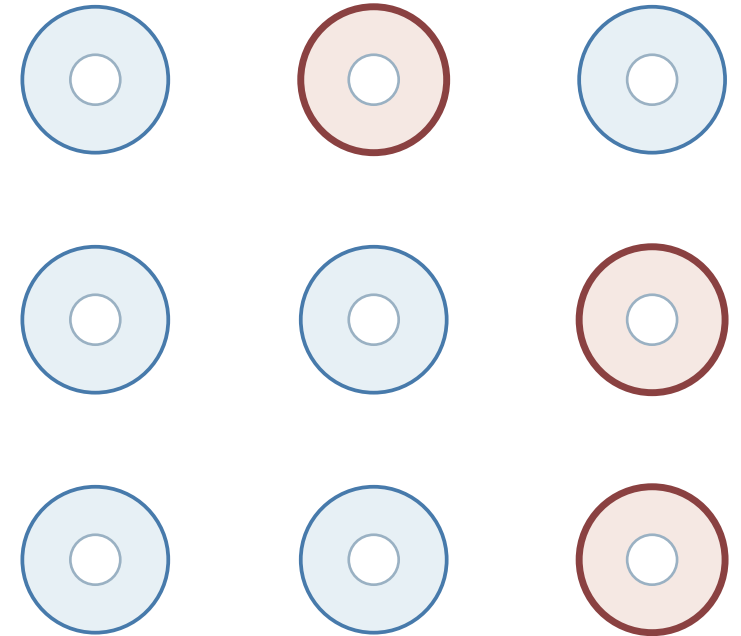
Interpret the pattern

Anatomy → laboratory
profile → serology →
morphology

Case B: Interpret seronegative destructive cholangitis

- AMA-negative PBC remains possible because typical cases can lack AMA.
- Biochemical persistence plus characteristic bile duct histology fulfill the textbook framework.
- Patchiness means a negative core result would require cautious interpretation.

Patchy portal tract involvement



Schematic: Selected ducts injured; Sampling matters

Case C: When PBC is unlikely to explain the image

- A patient with inflammatory bowel disease has cholestasis and biliary strictures.
- Imaging shows alternating strictures and dilatations of large bile ducts.
- Which alternative cholangiopathy better explains the duct distribution?

Interpret the pattern

Anatomy → laboratory
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Case C: Recognize a PSC-pattern process

- Large-duct beading and strictures favor PSC over the typical small-duct pattern of PBC.
- Inflammatory bowel disease is a strong clinical association of PSC.
- Concentric ductal scarring contrasts with the florid duct lesion of PBC.

PBC: Small ducts / normal imaging

PSC: Strictures / beading

Differential comparison

Integrated diagnostic and morphologic synthesis

- Clinical context: Middle-aged patient, often female, with fatigue/pruritus or incidental ALP elevation.
- Serology: AMA, especially PDC-E2-directed, is strongly characteristic but not universal.
- Histology: Patchy destructive small-duct inflammation with possible granulomas; Later ductopenia and cholate stasis.
- Outcome: Fibrosis, cirrhosis or noncirrhotic portal hypertension may develop.

Small-duct attack

Florid duct lesion

AMA / PDC-E2

Chronic cholestasis

Core references and source boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026), Chapter 18, pp. 775–782.
- PBC source section: pp. 780–781; companion sections: Cholestatic Disease and Primary Sclerosing Cholangitis.
- All histologic depictions in this lecture are original editable schematics—not patient photomicrographs.
- Treatment descriptions reproduce the textbook-level framework; current regulatory details were not independently verified.