PRIMARY BILIARY CHOLANGITIS

DEFINITION:
Chronic Cholestatic Liver Disease
due to destruction of small intrahepatic bile ducts
Previously known as Primary Biliary Cirrhosis

DIAGNOSIS
Two of the following…
- Alkaline phosphatase (ALP) >1.5 times the upper limit of normal
- Antimitochondrial Antibodies (AMA) at a titre of 1:40 or higher
- Histologic evidence of PBC (non-suppurative inflammation and destruction of intrahepatic bile ducts)

EPIDEMIOLOGY
- Australian Prevalence = 5 in 100,000

RISK FACTORS
- GENDER: **90-95% WOMEN**
- AGE: 30 – 65 years old (**Middle Aged**)
- GENETICS: First Degree Relative 100x increase in risk

Associated With…
- **SJOGREN'S SYNDROME** (65-80% of people with PBC)
- **Thyroid Disease** (10-15%)
- **Limited Cutaneous Scleroderma** (5-15%)
- **Classic Rheumatoid Arthritis** (5-10%)

PATHOPHYSIOLOGY *(exact cause unknown)*

T-cell AUTOIMMUNE DISEASE of the SMALL Intralobular Bile Ducts

INFLAMMATORY process of portal tracts → Small bile ducts (epithelial cells) are destroyed by rogue T cells
→ Fibrosis and bile stasis (signs & symptoms of cholestasis)
→ Progresses to destruction of bile ducts → CIRRHOSIS (signs & symptoms of liver failure)

CLINICAL PRESENTATION

INITIALLY: Asymptomatic (50-60% diagnosed incidentally by abnormal exam or LFTs)

OR signs & symptoms of cholestasis…
- FATIGUE: excessive daytime somnolence affecting quality of life
- PRURITIS (+ excoriations): worse on limbs and at night, precedes jaundice by years
- HYPERPIGMENTATION (darkening skin) and dry skin ~ commonly trunk & arms
- Xanthelasma & xanthomata (due to altered cholesterol metabolism)
- Right upper quadrant discomfort

LATER: signs chronic liver disease/ cirrhosis leading to chronic liver failure
- Jaundice (present at diagnosis for some)
- Hepatomegaly
- Portal Hypertension
  - Splenomegaly
  - Ascites
  - Oesophageal varices

EXAM MCQ: SJOGREN'S + FATIGUE + ITCH + HYPERPIGMENTATION = Primary Biliary Cholangitis
Especially if a middle aged woman with raised ALP!!!

INVESTIGATIONS: Typical Results

BLOODS	**Full Blood Exam (FBE)**	▪ Normal +/- Eosinophilia (early PBC) ▪ +/- Microcytic Anaemia (Iron Deficiency) if portal hypertension GI loss	
	Fasting Lipids	▪ Elevated Cholesterol ▪ Mild increase in LDL and VLDL, larger increase in HDL	
	Liver Function Tests (LFTs)	**ALP**	▪ **Twice upper limit of normal**
		Transaminases (AST, ALT)	▪ Normal or slightly elevated
		GGT	▪ Increased
		Bilirubin	▪ Normal (increases with progression of disease)
	Immunoglobulin	**IgM**	▪ Often elevated
	AUTOIMMUNE Markers	**Anti-Mitochondrial Antibodies (AMA)**	▪ **98% SPECIFIC** (i.e. it's virtually diagnostic) ▪ Elevated in 95% ▪ NOT pathogenic ~ just a good marker
		ANA	▪ Positive in 70%
IMAGING	**LIVER ULTRASOUND**	▪ May show diffuse alteration in liver architecture ▪ No evidence of extrahepatic biliary obstruction	
	MRCP or ERCP	▪ **Absence of narrowing** rules out bile duct obstruction which can mimic PBC	
LIVER BIOPSY	Confirms Diagnosis & Stages Severity ▪ Portal Tract Infiltrate (initially ZONE 1) = lymphocytes, plasma cells +/- hepatic granulomas (40%; not specific). ▪ As disease progresses: loss of **small** bile ducts with ductular proliferation → Portal tract fibrosis → CIRRHOSIS		

DIFFERENTIAL DIAGOSIS
- Drug Induced Cholangitis
- Bile Duct Obstruction (Gallstone, Cancer)
- Primary Sclerosing Cholangitis and Autoimmune Hepatitis (OVERLAP SYNDROMES)
- Viral Hepatitis

LESS LIKELY
- IgG4-Related Disease
- Sarcoidosis
- Bacterial, Fungal, & Viral Infections
- Hepatic Amyloidosis
- Lymphoma And Solid Organ Malignancies
- Endocrine Dysfunction
- Cardiac Diseases

MANAGEMENT		
PREVENT FURTHER INSULTS	▪ Avoid Hepatotoxins ▪ Hepatitis A and B Vaccinations	
SOOTHE ITCH	▪ **+/- EMOLLIANT CREAM** ▪ **+/- CHOLESTYRAMINE** (also treats hypercholesterolaemia)	
IMPROVE PROGNOSIS	**URSODEOXYCHOLIC ACID** (Hydrophilic Bile Acid) 13-15mg/kg per day Improves bile flow, replaces toxic hydrophobic bile acids and reduces biliary epithelium apoptosis → Improved LFTs, reduced disease progression and longer transplant-free survival **Cholestyramine and ursodeoxycholic acid should NOT be taken at the same time of day because they bind together in the intestine, significantly reducing the absorption of ursodeoxycholic acid.**	
COMPLICATIONS	**IMPORTANT SCREENING TESTS**	**MANAGEMENT**
CIRRHOSIS	▪ LFTs (every 3 – 6 months)	▪ TRANSPLANT *(serum bilirubin persistently >100 µmol/L or intolerable symptoms)*
HYPOTHYROIDISM (20%)	▪ TSH (annual)	▪ Thyroxine
METABOLIC BONE DISEASE	▪ DEXA Scan (every 6 months)	▪ Calcium & Vitamin D for low bone density ▪ Bisphosphonates if osteoporosis is severe
MALABSORPTION	Bile salt unable to enter duodenum → body is unable to emulsify and absorb dietary fat = **STEATORRHOEA** + **Loss of fat-soluble vitamins (A,D, E, K)** ▪ Vitamin D (annually) ▪ Vitamin A and K if Bilirubin > 20umol/L ▪ *Vitamin E deficiency occurs in very advanced disease (i.e. requiring transplant)*	▪ Dietary Fat Restriction ▪ +/- Vitamin A ▪ +/- Vitamin D ▪ +/- Vitamin E ▪ +/- Vitamin K
HYPERLIPIDAEMIA *Especially hypercholesterolemia*	▪ Fasting Lipids ▪ Screen for Metabolic Syndrome ***Not at an increased risk of death from atherosclerosis (unclear why ~ ?high HDL/ good cholesterol)***	▪ Dietary Changes ▪ Lipid Lowering Agents: Ursodeoxycholic Acid, Statins (avoid in patients with significant cholestasis), Fibrates

DON'T GET CONFUSED…

	PRIMARY BILIARY CHOLANGITIS (PBC)	PRIMARY SCLEROSING CHOLANGITIS (PSC)
Patient Population	Middle Aged Women	Young Males
Bile Ducts Affected	SMALL Bile Ducts *INTRAHEPATIC*	LARGE Bile Ducts +/- Small *INTRAHEPATIC & EXTRAHEPATIC Biliary Tree*
Classic Associations	Sjogren's Syndrme	Ulcerative Colitis
Autoimmune Antibodies	AMA (95%)	pANCA (60%)
ERCP Bile Duct Findings	Absence of duct narrowing	Strictures & Dilatation
PROGNOSIS	Normal life expectancy with Ursodeoxycholic Acid	Median transplant-free survival = 12 years

It is important to note that while PBC and PSC are distinct diseases, 'overlap syndromes' which present with characteristics of PBC, PSC and autoimmune hepatitis should also be considered.

REFERENCES:
- Gershwin, ME. Pathogenesis of primary biliary cholangitis (primary biliary cirrhosis). In: UpToDate, Curhan, GC (Ed), Waltham, MA, 2017.
- Kumar P, Clark M. Kumar & Clark's clinical medicine. 8th ed. Edinburgh: Saunders/Elsevier; 2012.
- Poupon, R. Overview of the treatment of primary biliary cholangitis (primary biliary cirrhosis). In: UpToDate, Curhan, GC (Ed), Waltham, MA, 2017.
- Poupon, R. Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis (primary biliary cirrhosis). In: UpToDate, Curhan, GC (Ed), Waltham, MA, 2017.
- Vojvodic M, Young A, Tyrrell A, Wang V. Toronto Notes 2014. 30th ed. Toronto, Ont.: Toronto Notes for Medical Students; 2014.
- Walker B, Colledge N, Ralston S. Davidson's principles and practice of medicine. 21st ed. Edinburgh: Saunders/Elsevier; 2010.