Approach to Patients with Jaundice For Internists

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Overview: Approach to Jaundice

Prehepatic (indirect bili. >80%)

- Often mild jaundice (TB 3-5) (TB >10 may be seen in a hemolytic crisis)
- Urine color – normal (dark urine may occur from hemoglobinuria)

→ **Hemolysis Gilbert**

+ acute illness

Hepatic (direct bili. >50%)

Hepatocellular

- Prodromal/systemic symptoms
- RUQ discomfort
- No/mild pruritus
- Dark urine
- Stool color – normal

→ **Acute hepatitis e.g. virus, alcohol, drugs, toxin, and AIH**

D/Dx: flare of chronic liver disease

Mixed

Cholestasis

- Prominent pruritus
- Dark urine
- Pale stool (if severe)

Intrahepatic

- Pruritus before jaundice

→ **Drug, toxins, sepsis, genetic, infiltration**

Extrahepatic (obstructive)

- Pain or painless
- Palpable GB

→ **Bile duct obstruction**

Jaundice: Clues from History Taking

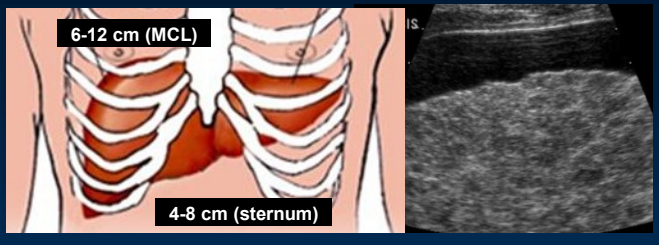
- Travel to the endemic area – HEV, tropical liver disease
- Eat raw/uncooked foods/food handling – HAV (shellfish), HEV (pork)
- MSM, high-risk sexual activities – HBV, HCV, HAV, SY
- Striking fever – biliary tract infection, systemic infection, HAV, liver abscess
- Chronic heavy alcohol drinking – alcoholic hepatitis
- Drugs, herbs, dietary supplements – DILI
- Rash, eosinophilia – DILI
- Epigastric/RUQ pain – CBD stones (biliary pain), malignancy
- Weight loss – malignancy, cirrhosis, hyperthyroid
- Intense pruritus – cholestasis
- Pale stool – obstructive jaundice, esp. from cancer
- Hx of jaundice in the past – HBV, AIH
- Underlying autoimmune diseases esp. thyroiditis – AIH, PBC
- Fatigue, myalgia, arthralgia – AIH
- Recurrent cholangitis – CBD/IHD stones, PSC, biliary ascariasis
- Intermittent jaundice with melena – CA ampulla
- Positive family Hx of liver disease – HBV, Wilson, familial cholestasis

Jaundice: Clues from Physical Exam

- KF rings – Wilson disease
- Xanthelasma – PBC
- Skin hyperpigmentation – hemochromatosis, PBC, prolonged jaundice
- Scratch marks – PBC, cholestasis
- Cutaneous stigmata of chronic liver, white nails – underlying cirrhosis, AIH, HBV, alcohol
- Superficial vein dilatations – portal HT, Budd-Chiari syndrome (on the back)
- Cervical LN – malignancy, IgG4-related disease
- Leg edema – cirrhosis, liver congestion, Budd-Chiari syndrome
- Ascites – cirrhosis, malignancy, liver congestion, Budd-Chiari syndrome
- Liver exam:
  - Left lobe hypertrophy, shrunken, nodular surface – cirrhosis
  - Hepatomegaly (span >12 cm) – fatty infiltration (esp. alcohol), infiltrative dis, congestion
  - Palpable mass – tumor (benign, malignant), abscess
  - Tenderness – hepatitis (generalized tender), abscess/mass (point tenderness)
  - Hepatic bruits – HCC, alcoholic hepatitis, AVM
- Palpable mass – malignancy
- Palpable gallbladder – malignant bile duct obstruction, CA gallbladder

Clinical Diagnosis of Cirrhosis

- **Physical exams**
  - Cutaneous stigmata of CLD
  - Signs of portal HT
  - Prominent left lobe liver
- **Basic lab**
  - AST > ALT
  - Platelet count <150,000 /mm^3
  - ↑ globulin, reverse A/G ratio
  - ↑ TB, ↑ PT/PTT
- **Non-invasive tests for fibrosis**
  - FIB-4 >2.67, APRI >2.0
  - Transient elastography >12-14 kPa



- **U/S findings**
  - Liver: coarse liver echo, nodular surface, ↑ LL/RL ratio
  - PV diameter >13 mm
  - Splenomegaly

- 40 y/o male
- 10 วัน อ่อนเพลีย, เบื่ออาหาร, N-V, มีไข้ต่ำๆ
  4 วัน เริ่มมีตาเหลือง ปัสสาวะสีเข้ม
- PH: No known underlying disease
- ดื่ม alcohol เป็นครั้งคราว, ซื้อยาแก้ปวดทานเองบ่อยๆ
- PE: T 36.4°c, not pale, moderate jaundice, liver 2 cm below RCM with mild tenderness, spleen not palpable

Acute hepatitis

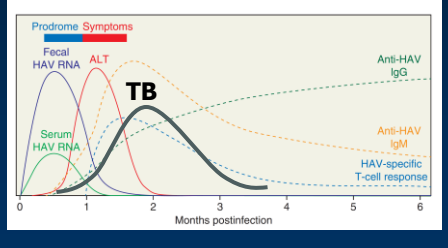
AST (0-40)	ALT (0-40)	TB (0.3-1.2)	DB (0.1-1.0)	ALP (40-120)	INR (0.8-1.1)	ALB/GLOB (3.5-5.5/1.5-3.5)
1040	1250	10	6.8	140	1.2	3.8/3.4

Common Etiologies of Acute Hepatitis

Etiologies	Key lab investigations
Common causes	
Viral hepatitis A	• Anti-HAV IgM
Viral hepatitis B	• HBsAg, anti-HBc IgM
Drugs and toxins	• Timeline, hypersensitivity features, drug/toxin level
Alcoholic hepatitis	• Heavy drinking, AST/ALT>2:1, AST <400 U/L
Less common causes	•
Viral hepatitis E	• Anti HEV IgM, HEV-RNA (immunocompromised)
Viral hepatitis C	• HCV-RNA, anti-HCV (late presentation)
Autoimmune hepatitis	• ANA, SMA, IgG
Wilson disease	• Copper studies, KF rings (by slit lamp), ALP/TB <4
Systemic infections	• Serologies, Ag, PCR, specific exposure/risks
Ischemic hepatitis	• Hypotension/CHF, AST >1,000 U/L, peak AST>ALT

Acute Viral Hepatitis A (HAV)

- **Risk factors:** MSM, exposure to contaminated water/uncooked foods
- **Clinical clues:**
  - Prodromal symptoms (fever, malaise, N-V) → subside, followed by jaundice
  - Atypical features (age >50 yr): cholestatic jaundice, relapsing hepatitis
- **LFT clues:**
  - ↑↑ ALT > AST (often 500-2,500 U/L)
  - ↑ TB (peak after ALT)
  - ALP normal/mild ↑
- **Diagnosis:** anti-HAV IgM
- **Management:** supportive (ALF 3/1,000)
  - Higher risk of ALF in older pt. (>50 yr) and pt. with chronic liver dis.
  - Close observation for ALF if INR >1.5, rapid rise in bilirubin, persistent N-V



ALF, acute liver failure

Acute Viral Hepatitis B (HBV)

- **Risk factors:** sexual/parenteral exposure, FHx of HBV, non-immunized
- **Clinical clues:**
  - Prodromal symptoms (may not be obvious) before the onset of jaundice
  - Hx of complete vaccination – often protective
  - Positive FHx or stigmata of chronic liver dis. – suggest HBV flare
- **LFT clues:**
  - ↑↑ ALT > AST (often 500-2,000 U/L)
- **Diagnosis:** HBsAg, anti-HBc IgM
  - Patients with severe HBV flare may have anti-HBc IgM+ (low titer)
- **Management:** supportive (acute liver failure: 2/100)
  - Start antiviral (TAF) if severe (INR>1.5, TB >3-10, protracted jaundice)
  - Higher risk of ALF in older pt. (>50 yr) and pt. with chronic liver dis.

HBsAg may be negative in 10-20% of acute hepatitis B at presentation (early clearance)

D/Dx: Acute vs Flare of Hepatitis B

	Acute Hepatitis B	Flare of Chronic HBV
Age	Any age	Any age
History	Unvaccinated Risk of HBV acquisition (incubation period 1-4 months)	Known for HBsAg+ Positive family history of HBV Recent immunosuppression
PE	No evidence of CLD	Evidences of CLD and/or PHT
Anti-HBc IgM	Positive high titer (>1:10,000 or >10 S/CO)	Negative or positive low titer
HBV-DNA	Varies: often relatively low (< 10^5) with fluctuation	Often high
HBeAg	Positive low levels (<30 S/CO)	Higher levels or negative
HBsAg	Positive (may be negative in 10-20% at presentation from early clearance)	Positive
FU HBsAg at 3-6 mo	>90% become negative (resolved)	Often continue to be positive
Antiviral therapy	Recommends only for severe cases	Recommends for most cases

Adapted from Puri P. J Clin Exp Hepatol 2013

Alcoholic Hepatitis (AH)

- **Risk factors:** Chronic drinking (F >20-50 g/d; M >30-60 g/d)
- **Clinical clues:**
  - Fever, jaundice, anorexia, RUQ pain, agitation
  - Up to 50% already cirrhosis, malnutrition
  - Tender hepatomegaly, ascites (~30%)
- **LFT clues:**
  - ↑ AST > ALT (AST/ALT ratio >2); maximum AST <400 U/L
  - Chronic heavy alcohol drinking: ↑ GGT, ↑ MCV
- **Management:** abstinence and supportive
  - Nutrition: oral/EN, energy: 35-40 kcal/kg/d, protein: 1.2-1.5 g/kg/d
  - If mDF ≥32 (severe AH: mortality 20-40%): start prednisolone 40 mg/d
  - Search for and manage other alcohol-related complications

If AST >400 → exclude other concomitant cause e.g. drugs esp. APAP, and virus

*mDF, Maddrey discrimination function = [4.6 x PT above normal (s)] + TB (mg/dl)

Alcohol Contents of Various Beverages

1 standard drink ~10-14 grams of alcohol

Common serving size (1 standard drink)

Beer 4-6% alc.	330 ml 12 oz.
Wine 10-15% alc.	150 ml 5 oz.
Whiskey Vodka, Brandy 36-40% alc.	45 ml 1.5 oz.

เหล้าขาว 30-40% alc.

1 กั๊ง (50 ml)	~2 drinks
1 กั๊ก (187 ml)	~6 drinks
1 แบน (375 ml)	~12 drinks
1 กลม (750 ml)	~24 drinks

Drug-Induced Liver Injury (DILI)

- **Mechanisms:**
  - Intrinsic DILI e.g. acetaminophen (APAP), amiodarone
  - Idiosyncratic DILI: metabolic or immunoallergic (most drugs)
- **Clinical clues:**
  - Receiving commonly implicated drugs and herb/dietary supplements
  - Latent period: 4 days to 8 wk (can be longer)
  - Hypersensitivity features e.g. fever, rash, eosinophilia, arthralgia
  - Previous reports: Pubmed, LiverTox.nih.gov, ChatGPT
- **LFT clues:**
  - Vary: Hepatocellular (R ratio >5), mixed (R 2-5) or cholestasis (R <2)
- **Management: drug withdrawal**
  - NAC for APAP hepatotoxicity and early non-APAP drug-induced ALF
  - Corticosteroids for drug-induced AIH, DILI with hypersensitivity features

Autoimmune Hepatitis (AIH)

- All age groups; peak 30-50 yr (F:M ~4:1)
- **Clinical clues:**
  - Extrahepatic symptoms e.g. fatigue, arthralgia, oligomenorrhea
  - Concurrent autoimmune disease (10-40%) e.g. thyroiditis, synovitis, UC
  - Acute hepatitis with signs of chronic liver dis. (25-40%)
  - History of jaundice (20-40%)
- **LFT and serology clues:**
  - ↑ ALT > ALT (often 300-1,200 U/L; AST >ALT if cirrhosis)
  - ↑ Serum globulins (>1.5 xULN)
  - Positive (>1:80) ANA and/or SMA (anti-smooth muscle antibody)

10-30% of AIH are seronegative

- **Diagnosis:** Liver biopsy – interface hepatitis (lymphoplasmacytic infil.)
- **Management:** Corticosteroids + azathioprine (long-term)

Acute Viral Hepatitis E (HEV)

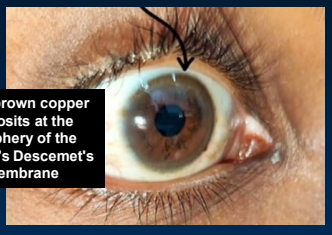
- **Risk factors:**
  - Traveled to highly endemic area, contact with pigs/pork, organ transplant
- **Clinical clues:**
  - Often seen in men (>women), age >40 y, and with comorbidities
  - Clinical similar to acute hepatitis A: but with less fever and GI symptoms
  - May precipitate acute-on-chronic liver failure
- **LFT clues:**
  - ↑↑ ALT > AST (often 300-1,500 U/L)
  - ALP normal/mild ↑
- **Diagnosis:** anti-HEV IgM ±IgG (HCV-RNA for immunosuppressed pt.)
- **Management:** supportive
  - Ribavirin 600-1,000 mg/d for severe acute hepatitis E, ACLF, and persistent hepatitis in immunocompromised hosts

Acute Viral Hepatitis C (HCV)

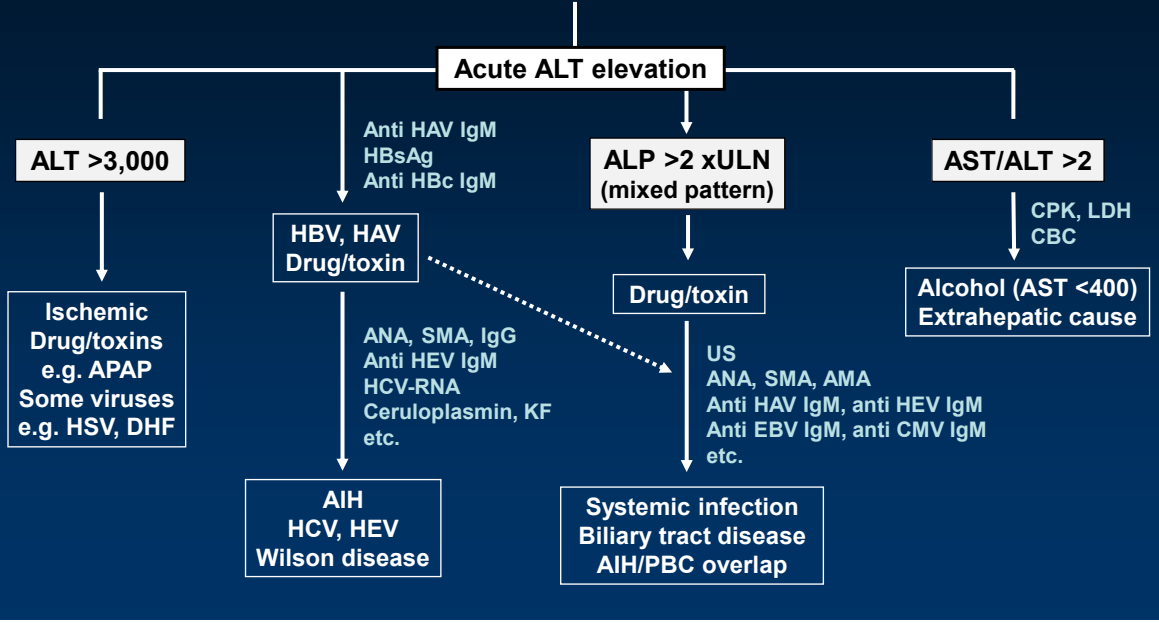
- **Risk factors:**
  - MSM (esp. with HIV and/or STDs), high-risk sexual activities
  - IV and intranasal illicit drug users
  - Prisoners, healthcare personnels
  - Recent piercing, tattoo, on hemodialysis or recent hospitalization
- **Clinical clues:**
  - Non-specific, similar to other viral hepatitis
- **LFT clues:**
  - ↑↑ ALT > AST
- **Diagnosis:** HCV-RNA or HCV Ag (anti-HCV+ after 4-12 wk of infection)
- **Management:** Sofosbuvir-velpatasvir 12 wk (as chronic hepatitis C)
  - Advice: about drug interaction e.g. with PPI, avoid re-infection

Acute Wilsonian (WD) Hepatitis

- Young adults (<40 yr), positive FHx (AR)
- Clinical and LFT clues:
  - KF rings (50-90%), neuropsychiatric symptoms
  - Coombs-negative hemolytic anemia
  - Rapid progression to renal failure
  - ↑ ALT (AST/ALT ratio >1, AST <1,000 U/L), ↑↑ TB
  - Normal or subnormal ALP (typically <40 U/L)
  - ALP (U/L) / TB (mg/dL) ratio <2-4)
- Copper studies: unreliable to diagnose WD in an acute setting
  - For those with chronic presentation – serum ceruloplasmin <20 mg/dL, serum free copper >25 µg/dL, 24-hr urine copper >40 µg/day
- Management: D-penicillamine, liver transplant if severe (curative)


Gold/brown copper deposits at the periphery of the cornea's Descemet's membrane

Lab Investigations for Acute Hepatitis



Cholestasis

- 60 y/o male
- 1 wk สังเกตว่าตาเหลืองขึ้นเรื่อยๆ, อ่อนเพลีย, คันตามตัว, ปัสสาวะสีเข้ม/อุจจาระสีปกติ, ไม่ปวดท้อง
- PH : no known underlying dis.
- PE : not pale, moderate jaundice, no stigmata of CLD, liver and spleen – not palpable

AST (0-40)	ALT (0-40)	TB (0.3-1.2)	DB (0.1-1.0)	ALP (40-120)	GGT (5-40)	ALB/GLOB (3.5-5.5/1.5-3.5)
91	108	5.8	3.8	670	420	4.0/3.4

Common Causes of Intrahepatic Cholestasis

- Genetic disorders e.g. BRIC, PFIC, ICP
- Drugs, herbal medicine, TPN
- Sepsis (endotoxemia-induced cholestasis)
- Thyrotoxicosis
- Benign and malignant infiltrative liver diseases
- Paraneoplastic syndrome
  - Vanishing bile duct syndrome (Hodgkin lymphoma)
  - Stauffer syndrome (RCC)
- Primary biliary cholangitis (PBC)
- Hepatocellular diseases e.g. viral/alcoholic hepatitis, cirrhosis
- Vascular disorders e.g. BCS, SOS, congestive hepatopathy

Common Features of Drug-Induced Cholestasis

Phenotype	Features	Typical agents
Cholestatic hepatitis	Marked and prolonged jaundice, pruritus; Mild-moderate ↑ALT and moderate-marked ↑ALP	Amoxy-clav, dicloxacillin, cephalosporins, macrolides, tetracyclines, sulfonamides, quinolones, psychotropes, NSAIDs, AZA, PTU, Kratom, some anticonvulsants
Vanishing bile duct syndrome	Persistent pruritus and jaundice with prolonged ↑ALP and bilirubin; May progress to cirrhosis/liver failure	Same as cholestatic hepatitis
Bland cholestasis	Marked pruritus and jaundice with marked ↑ALP, mild ↑ALT	Anabolic steroids, estrogens
Granulomatous hepatitis	Presence on liver biopsy of granulomas (focal accumulation of modified macrophages); Moderate-marked ↑ALP ± jaundice	Allopurinol, INH, carbamazepine, methyldopa, phenytoin, quinidine, sulphonamides
Sclerosing cholangitis	Acute DILI with histological and/or MRCP evidences similar to PSC	Ketamine, amiodarone, gabapentin, 6-MP amoxy-clav, infliximab, venlafaxine

Common Causes of Extrahepatic Cholestasis

Intramural

- Cholangiocarcinoma
- Primary sclerosing cholangitis (PSC)
- IgG4 related disease
- Secondary SC e.g. ischemic, infection, immunologic, drugs (ketamine, CMT)
- Benign strictures

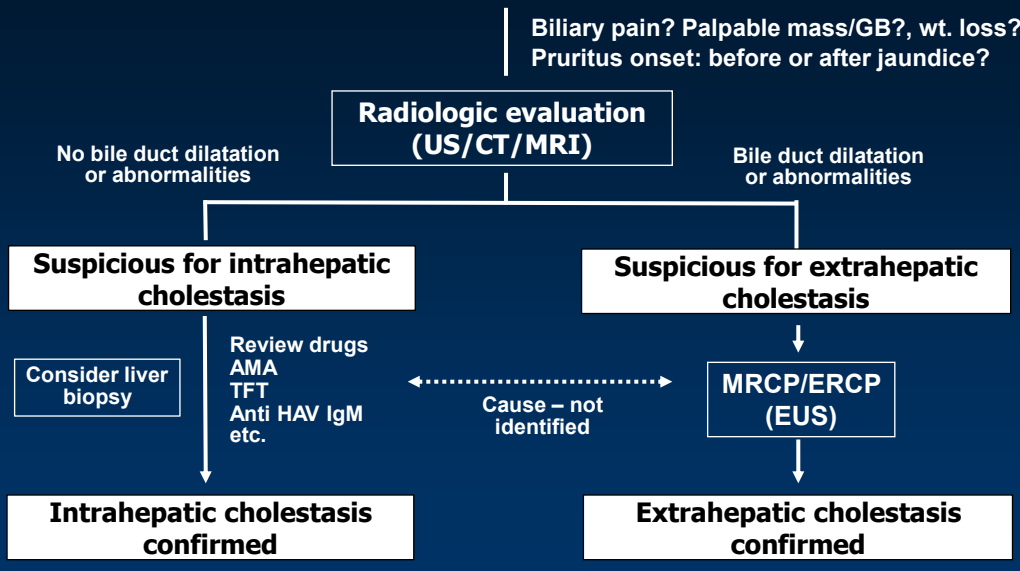
Intraluminal

- Stone
- Parasites (e.g. ascaris, fasciolar spp.)
- Hemobilia
- Mucin (BD-IPMN)

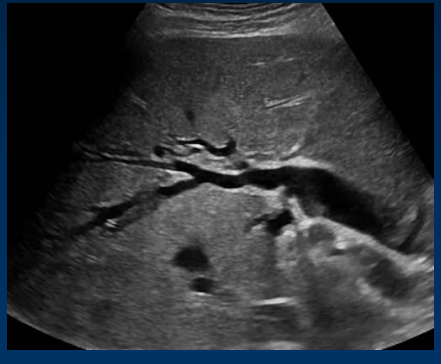
Extraluminal

- Periampullary CA
- Pancreatitis
- Inflammatory pseudotumor
- Gallbladder CA
- Mirizzi syndrome
- Lymphadenopathy
- Portal HT bilopathy

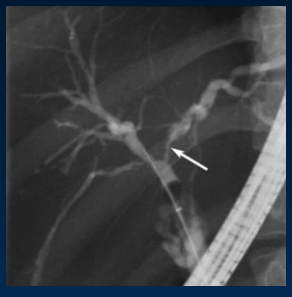
Approach to Cholestatic Jaundice



Situations in which ultrasound may not be able to demonstrate bile duct dilatation (false negative) in patients with bile duct obstruction



- Early BD obstruction
  (less than 1 wk or bilirubin <10 mg/dL)
- Intermittent obstruction
- Incomplete obstruction
- Underlying cirrhosis
- Underlying sclerosing cholangitis



ERCP

Pros

- Better imaging resolution (operator-dependent)
- Therapeutic intervention
- Allows cytologic diagnosis

Cons

- Invasive
- 5% pancreatitis
- 0.5% perforation
- Need expertise
- Limited study in patients with difficult anatomy or complete obstruction
- Radiation exposure

MRCP

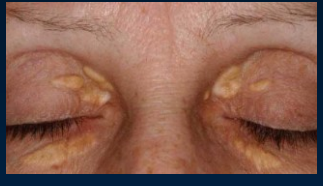
Pros

- Non-invasive
- No radiation exposure
- Can be performed in patients with difficult anatomy
- Allows anatomical evaluation outside the biliary tree

Cons

- Need patient cooperation
- Resolution can be interfered with by stents or surgical clips
- No therapeutic intervention
- Rare, but irreversible instances of nephrogenic systemic fibrosis

Primary Biliary Cholangitis (PBC)

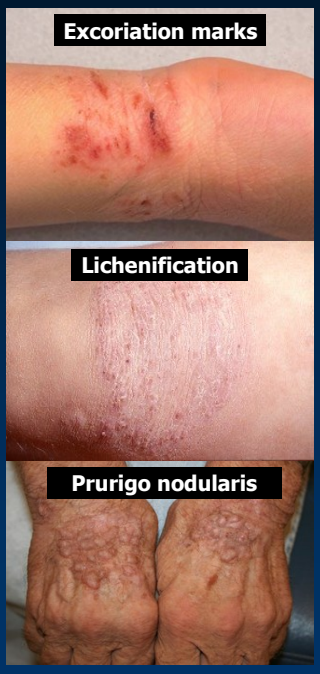


- Middle-aged woman
- Clinical clues:
  - Long Hx of fatigue and pruritus
  - Concurrent autoimmune dis. (80%) e.g. thyroiditis, sicca, arthropathy
  - Skin hyperpigmentation, xanthoma, xanthelasma, excoriation marks
- LFT clues:
  - ↑ ALP, ↑ GGT, normal TB (jaundice occurs late when cirrhosis develops)
  - ↑ Chol, ↑ LDL-C, ↑ HDL
- Diagnosis: AMA (PDC-E2) positive (95% of cases; highly specific)
  - ANA (sp100 or gp210) positive, if AMA negative
- Management: UDCA 13-15 MKD (life-long) – response rate ~80%
  - Vitamin D supplement, cholestyramine 4-12 g for pruritus

*AMA, anti-mitochondrial antibody

Pruritus in Chronic Cholestasis

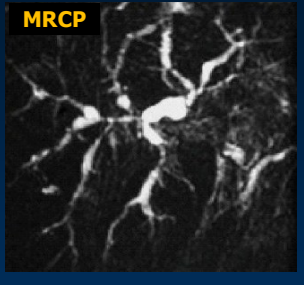
- Common presenting/accompanying symptoms
  - 70-80% of PBC (75% preceding the diagnosis)
  - 20-40% of PSC
- May be generalized or localized, particularly over the palms and soles, and often without any definable primary skin lesion (skin complications from scratching may develop)
- Often worse at night and can be transiently exacerbated by premenstrual state and stress
- Often is relieved by cool temperature
- The severity is variable and may diminish over time (often when cirrhosis develops)



Bunchorntavakul C, Reddy KR. Clin Liver Dis 2012;16(2):331-46

Primary Sclerosing Cholangitis (PSC)

- Young to middle-aged man (rare in Thailand)
- 80% underlying IBD involving the colon (UC>CD)
- Clinical clues:
  - RUQ discomfort, fatigue, and pruritus
  - Recurrent bacterial cholangitis
- LFT clues:
  - ↑ ALP, ↑ GGT (↑ TB if dominant stricture/cholangitis)
  - Positive autoantibodies e.g. p-ANCA, ANA (not specific)
- Diagnosis: Cholangiography – multifocal intrahepatic ± extrahepatic duct strictures (beaded or pruned tree appearance)
- Management: UDCA 15-20 MKD (variable response)
  - Cholestyramine for pruritus, endoscopic Rx for dominant strictures



Secondary Causes of Sclerosing Cholangitis

Infections	• AIDS cholangiopathy (cryptosporidiosis, microsporidiosis, CMV) • Parasitic infection (liver flukes, biliary ascariasis) • Recurrent pyogenic cholangitis (oriental cholangiopathy)
Chronic obstruction and/or external compression	• Choledocholithiasis • Cholangiocarcinoma (CCA) • Portal hypertensive biliopathy • Biliary strictures (e.g. surgical trauma or chronic pancreatitis)
Immunologic	• IgG4-associated cholangiopathy • Immune checkpoint inhibitors • Mast cell cholangiopathy, histiocytosis X, eosinophillic cholangitis • Hepatic allograft rejection (acute and chronic)
Ischemic	• Secondary sclerosing cholangitis in critically-ill patient (SSC-CIP) and COVID-19 • Intra-arterial chemotherapy • Systemic vasculitis • Radiation injury • Post-transplant setting (prolonged ischemic time, HA thrombosis)
Drugs and toxins	• Recreational/illicit drugs e.g. ketamine, cocaine, amphetamine • Chemotherapy e.g. floxuridine, oxaliplatin, 5-FU, irinotecan, cisplatin

Hilar Cholangiocarcinoma

- **Risk factors:** age >50 yr, raw freshwater fish, Northeasterners
- **Clinical clues:**
  - Progressive painless jaundice, weight loss
  - Dark urine, pale stools, pruritus, cholangitis
- **LFT clues:**
  - ↑ ALP, ↑ TB
  - ↑ CA19-9 (not specific)


MRI/MRCP

- **Diagnosis:** MRI/MRCP – irregular stricture of the hilar area with upstream BD dilatation ± periductal infiltration
  - Positive biopsy or brush cytology from BD
- **Management:** surgical resection (5-yr survival after R0: ~30-50%)
  - Unresectable (survival ~12 mo): palliative BD drainage (stent or PTBD), systemic therapy (gemcitabine + cisplatin; IO in selected cases)

IgG4-related Cholangiopathy

- Elderly man (M:F 4:1; age 50-70 yr)
- Clinical clues:
  - Presents as obstructive jaundice
  - Other organ involvement
    e.g. autoimmune pancreatitis (80%), sialadenitis, dacryoadenitis, thyroiditis, lymphadenopathy, retroperitoneal fibrosis
- LFT clues:
  - ↑ ALP, ↑ TB, ↑ serum globulins

MRCP: single or multiple long, segmental strictures of CBD and IHD

- Diagnosis: ↑ serum IgG4 ≥135 mg/dL (If ≥280 – highly specific)
  - Cholangiography: varies (may mimic CCA, PSC, chronic pancreatitis)
- Management: corticosteroids (good response in 4-8 wk) + AZA

Thank You for Your Kind Attention