

CASE 1

- 30 y/o female
- 3 วัน อ่อนเพลีย มีไข้ต่ำๆ เหนื่อยมากขึ้น
สังเกตว่าตา/ตัวเหลือง
- PH : no known underlying dis.
- PE : T 37.8°C, moderate pale and jaundice,
lung – clear, liver 1 cm below RCM,
spleen 3 cm below LCM

| AST (0-40) | ALT (0-40) | TB (0.3-1.2) | DB (0.1-1.0) | ALP (40-120) | GGT (0-50) | ALB/GLOB (3.5-5.5/1.5-3.5) |
|---------------|---------------|-----------------|-----------------|-----------------|---------------|-------------------------------|
| 46 | 25 | 4.6 | 0.6 | 110 | 70 | 4.2/3.1 |

CASE 1

- What is the most likely diagnosis ?

 - 1) Gilbert's disease
 - 2) Hemolysis
 - 3) Congestive heart failure
 - 4) Thyrotoxicosis
 - 5) Acute viral hepatitis

CASE 2

- 26 y/o male
- 10 วัน อ่อนเพลีย, เบื่ออาหาร, N-V, มีไข้ต่ำๆ
4 วัน เริ่มมีตาเหลือง ปัสสาวะสีเข้ม
- PH : ดื่ม alcohol เป็นครั้งคราว
- PE : T 36.4°C, not pale, moderate jaundice,
liver 2 cm below RCM with mild
tenderness, spleen not palpable

| AST (0-40) | ALT (0-40) | TB (0.3-1.2) | DB (0.1-1.0) | ALP (40-120) | GGT (0-50) | ALB/GLOB (3.5-5.5/1.5-3.5) |
|---------------|---------------|-----------------|-----------------|-----------------|---------------|-------------------------------|
| 1040 | 1250 | 10 | 6.8 | 140 | 86 | 3.8/3.4 |

CASE 2

- What is the most likely diagnosis ?

 - 1) Alcoholic hepatitis
 - 2) Acute viral hepatitis
 - 3) Ischemic hepatitis
 - 4) Drug-induced hepatitis
 - 5) Autoimmune hepatitis

CASE 3

- 56 y/o male
- 5 วัน อ่อนเพลีย, เบื่ออาหาร, N-V, มีไข้ต่ำๆ
สังเกตว่าตา/ตัวเหลืองมากขึ้น
- PH : heavy alcohol drinking
- PE : T 37°C, agitated, not pale, moderate
jaundice, liver 2 cm below RCM with mild
tenderness, spleen not palpable

| AST (0-40) | ALT (0-40) | TB (0.3-1.2) | DB (0.1-1.0) | ALP (40-120) | GGT (0-50) | ALB/GLOB (3.5-5.5/1.5-3.5) |
|---------------|---------------|-----------------|-----------------|-----------------|---------------|-------------------------------|
| 3250 | 2000 | 20.4 | 16 | 140 | 250 | 3.5/3.4 |

CASE 3

- What is the most likely diagnosis ?

 - 1) Alcoholic hepatitis
 - 2) Acute viral hepatitis
 - 3) Ischemic hepatitis
 - 4) Drug-induced hepatitis
 - 5) Wilson's disease

CASE 4

- 47 y/o female
- ตรวจสุขภาพประจำปี พบว่าผลเลือดตับผิดปกติ
- PH : 3 yr ตรวจพบไขมันสูง รับประทาน simvastatin 10 mg/day ทานมาตลอด
- PE : BW 75 kg, not pale, no jaundice, 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 (0-50) | ALB/GLOB (3.5-5.5/1.5-3.5) |
|---------------|---------------|-----------------|-----------------|-----------------|---------------|-------------------------------|
| 76 | 90 | 0.8 | 0.2 | 87 | 52 | 4.8/2.5 |

CASE 4

- What is the most likely diagnosis ?
 - 1) Chronic hepatitis B
 - 2) Chronic hepatitis C
 - 3) Statin-induced hepatitis
 - 4) NAFLD/NASH
 - 5) Autoimmune hepatitis

CASE 5

- 60 y/o male
- 5 wk สังเกตว่าตาเหลืองขึ้นเรื่อยๆ เบื่ออาหาร, นอนลด, คัด, มีสภาวะซีเซิม/อุจจาระสีซีด
- PH : no known underlying dis.
- PE : cachexic, not pale, marked jaundice, no stigmata of CLD, liver just palpable, no splenomegaly

| AST (0-40) | ALT (0-40) | TB (0.3-1.2) | DB (0.1-1.0) | ALP (40-120) | GGT (0-50) | ALB/GLOB (3.5-5.5/1.5-3.5) |
|---------------|---------------|-----------------|-----------------|-----------------|---------------|-------------------------------|
| 38 | 26 | 18 | 15.4 | 720 | 590 | 2.8/2.8 |

CASE 5

- What is the most likely diagnosis ?
 - 1) Primary biliary cirrhosis (PBC)
 - 2) Disseminated TB
 - 3) CBD stone
 - 4) Hepatocellular carcinoma (HCC)
 - 5) Cholangiocarcinoma

CASE 6

- 53 y/o female
- 2 วัน ปวดจุกท้อง RUQ ต่อมาเริ่มมีไข้สูง, ตา/ตัวเหลือง, N-V
- PH : no known underlying dis.
- PE : T 39.5°C, not pale, moderate jaundice, tenderness at epigastrium

| AST (0-40) | ALT (0-40) | TB (0.3-1.2) | DB (0.1-1.0) | ALP (40-120) | GGT (0-50) | ALB/GLOB (3.5-5.5/1.5-3.5) |
|---------------|---------------|-----------------|-----------------|-----------------|---------------|-------------------------------|
| 650 | 720 | 7.2 | 5.5 | 160 | 110 | 3.9/3.2 |

CASE 6

- What is the most likely diagnosis ?
 - 1) Acute viral hepatitis
 - 2) Systemic infection
 - 3) Acute cholecystitis
 - 4) CBD stone with asc. cholangitis
 - 5) Pyogenic liver abscess(es)

Interpretation of Liver Function Tests

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14th January 2010

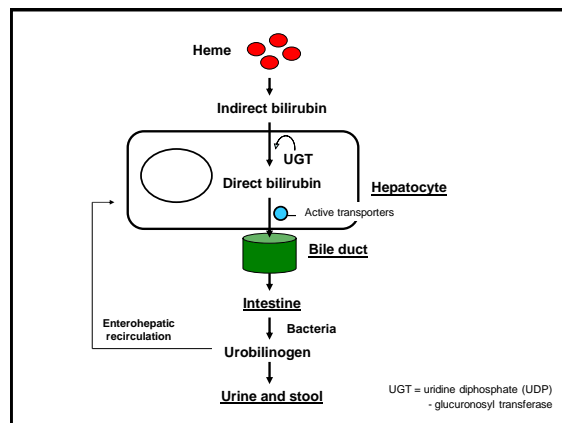
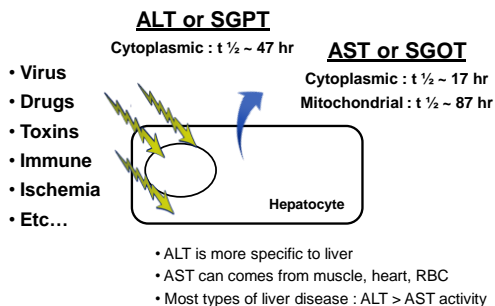
ประชุมราชวิทยาลัยอายุรแพทย์แห่งประเทศไทย จังหวัดสุรินทร์

Liver Function Tests

| Chemistry | Interpretation |
|-----------|--|
| ALT, AST | Hepatocellular damage |
| Bilirubin | Overproduction, impaired conjugation Hepatocellular damage Cholestasis (both intra- and extra-hepatic) |
| ALP | Cholestasis (infiltration, SOL) |
| GGT | Cholestasis (infiltration, SOL) |
| Albumin | Synthetic function |
| PT | Synthetic function |

AST = aspartate aminotransferase ; ALT = alanine aminotransferase ; ALP = alkaline phosphatase ;
GGT = gamma-glutamyl transpeptidase ; PT = prothrombin time ; SOL = space-occupying lesion(s)

Aminotransferases

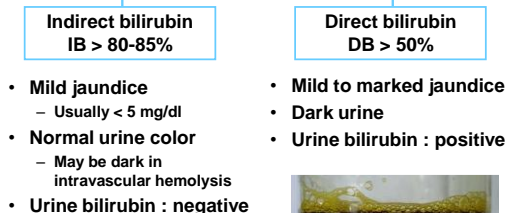


Alkaline Phosphatase (ALP)

- Activity in serum is primarily derived from 3 sources : liver, bone & intestine (10-20%)
 - ↑ GGT with ↑ ALP is useful to confirm liver origin
- Increased ALP : mechanisms
 - Present in canalicular membrane of hepatocyte
 - Cholestasis → retained bile acid
 - induced synthesis and altered solubilization
 - leakage of ALP into serum
- Half-life 7 days

Hyperbilirubinemia

(TB > 2-3 mg/dl → Jaundice)

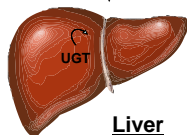


Causes of Indirect Hyperbilirubinemia

RBC



Hepatic delivery
(hepatic blood flow)

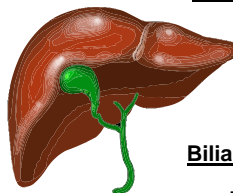


Liver

- **Increased production**
 - Hemolysis
 - Ineffective erythropoiesis
- **Impaired hepatic uptake and/or conjugation**
 - Gilbert's syndrome
 - CHF
 - Thyrotoxicosis
 - Drugs
 - Portosystemic shunt

Causes of Direct Hyperbilirubinemia

Liver



Biliary tract

- **Hepatocellular jaundice**
- **Intrahepatic cholestasis (medical cholestasis)**
- **Extrahepatic cholestasis (obstructive jaundice)**

Different Features Between Hepatocellular and Cholestatic Jaundice

Hepatocellular

- **S&S**
 - Malaise, weakness, anorexia, N-V
 - Jaundice
 - Dark urine
 - Normal-colored stool
- **LFT**
 - \uparrow DB > 50% of TB
 - \uparrow ALT, AST > 5x
 - ALP : N or \uparrow < 3x

Cholestasis

- **S&S**
 - Jaundice
 - Pruritis
 - Dark urine
 - Pale stool
- **LFT**
 - \uparrow DB > 50% of TB
 - \uparrow ALP > 5x
 - ALT, AST : N or \uparrow < 3x

Hepatocellular Injury (Hepatitis)

Acute Hepatitis

- Acute – subacute onset
- \pm Symptoms & jaundice
- ALT, AST $\uparrow\uparrow$ 3x to > 40x
- TB : varies
- Liver failure ?
 - Encephalopathy
 - TB $\uparrow\uparrow\uparrow$
 - PT prolongation

Chronic Hepatitis

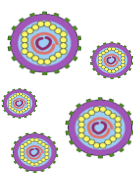
- Duration > 6 months
- Usually asymptomatic
- PE usually normal
- ALT, AST \uparrow < 5x
- TB usually normal
- Cirrhosis ?
 - Cutaneous stigmata
 - \uparrow AST > ALT
 - Reverse A/G ratio

Common Causes of Hepatocellular Jaundice

Drugs



Virus



Alcohol



Less Common Causes of Hepatocellular Jaundice

- **Systemic infection**
 - DHF, typhus, typhoid, leptospirosis
- **Ischemic hepatitis**
- **Autoimmune hepatitis (AIH)**
- **Wilson's disease**
- **HSV, CMV, EBV**
- **Reye's syndrome**
- **Acute Budd-Chiari syndrome (BCS)**
- **Acute CBD obstruction**

Acute Viral Hepatitis

- **Most common** : HBV, HAV
 - Pt. with specific risk : HEV, HCV ?
- **Prodromal symptoms** (flu-like, malaise, N-V) before the onset of jaundice
- **Fever disappears** after jaundice begins
- **↑↑ ALT > AST**, often < 2,000 U/L
- **Serology**
 - Anti-HAV IgM
 - HBsAg, anti-HBc IgM

Alcoholic Hepatitis

- **Heavy, continued drinking**
- **Fever, jaundice, anorexia, RUQ pain**
- **Up to 50% already cirrhosis**
- **Hepatomegaly ± tenderness, ascites (~30%)**
- **Clues**
 - **↑ AST > ALT (< 300 U/L, AST/ALT ratio > 2)**
 - Alcohol induces release of mitochondrial AST ⁽¹⁾
 - Pyridoxine deficiency decreases ALT activity ⁽²⁾
 - **Elevated GGT**

(1) Zhou SL, et al. Hepatology 1998
(2) Diehl AM, et al. Gastroenterology 1984

Drug-Induced Hepatitis

- **Both modern and herbal medicine**
- **Mechanisms**
 - Direct toxic : Paracetamol
 - Idiosyncrasy : Sulfa, phenytoin, CBZ, PTU, anti-TB
- **Onset of exposure usually 4 days – 8 weeks**
- **Patterns of LFT : varies**
- **Diagnosis by careful Hx, exclusion of other causes and improvement after withdrawal**

Ischemic Hepatitis

- **Hx of shock or hypotension (30-50%)**
- **Old age, heart disease, ICU**
- **Acute hepatitis during hospitalization**
- **Clues**
 - **Marked ALT ↑↑↑ (up to 10,000 U/L)**
 - **AST > ALT (early)**
 - **Marked ALT ↓↓↓ within 72 hr**
 - **Bilirubin : normal or mild ↑**
 - **Transient PT prolongation**
 - **Elevated LDH**



Autoimmune Hepatitis (AIH)

- **Middle-age or teenage female**
- **Acute or chronic hepatitis, or cirrhosis**
- **Hx of fatigue, arthralgia, myalgia, jaundice**
- **Clues**
 - Concurrent autoimmune dis. (up to 40%)
 - Acute hepatitis with signs of chronic liver dis.
 - Increased serum globulin
- **Autoantibodies**
 - ANA (anti-nuclear antibody)
 - SMA (smooth muscle antibody)

Wilson's Disease

- **Age 20-40 yr**
- **Acute or chronic hepatitis, or cirrhosis**
- **Clues**
 - **KF-ring (~50%)**
 - **CNS : EPS or neuropsychiatric**
 - **ALF with intravascular hemolysis, ↑ AST > ALT**
 - **low ALP, ALP/TB ratio < 2**
- **Laboratory**
 - Serum ceruloplasmin < 20 mg/dl
 - 24-hr urine copper > 40 mcg



LFT Clues in Acute Hepatocellular injury

- Level of aminotransferase elevation
- Predominant AST or ALT
- Rate of aminotransferase declination

Level of Aminotransferase

- Mild ALT elevation (1-2 xULN) is non-specific and usually normal when repeated
- Alcoholic hepatitis : < 300 U/L
- Viral hepatitis : Rarely > 2,000 U/L
- Marked ALT elevation (> 15-20 xULN)
 - Ischemic hepatitis
 - Acute BCS
 - Drug & toxins : particularly PCM & mushroom
- ALT level poorly correlated with the extent of hepatocellular injury

Predominant AST (AST/ALT ratio >1)

- Alcoholic hepatitis
 - AST/ALT ratio usually > 2
- Wilson's disease
- Any hepatitis flare in cirrhosis
- Ischemic hepatitis
- Some drugs

Rate of Aminotransferase Declination

- Rapid ALT declination
 - Ischemic hepatitis
 - Acute CBD obstruction
 - Acute BCS
 - Slow ALT declination
 - Viral hepatitis : 10% /day or 50% /week
 - Drug-induced (varies)
 - Autoimmune and metabolic disease
- } ~ Normal in 3 days

Causes of Chronic Hepatitis

Common

- Hepatitis B
- Hepatitis C
- Alcohol
- Drug-related
- NAFLD/NASH

Less Common

- Autoimmune hepatitis (AIH)
- Wilson's disease
- Hemochromatosis

Non-Alcoholic Fatty liver Disease (NAFLD) Non-Alcoholic Steatohepatitis (NASH)

- 15-30% Prevalence in general population ⁽¹⁾
- Risk factors
 - Metabolic syndrome
 - DM type 2
 - Obesity
- In NASH with fibrosis ⁽²⁾
 - 10-yr Progression to cirrhosis ~ 30%
 - 10-yr Liver-related mortality ~ 10%
- US liver : diffusely increased in echogenicity



⁽¹⁾ Chitturi S, et al. J Gastroenterol Hepatol 2007
⁽²⁾ Matteoni CA, et al. Gastroenterology 1999

Approach to Chronic Hepatitis

Elevated ALT ≥ 6 mo and/or histology suggest chronic

Hx of drugs, alcohol, family Hx, co-morbid conditions and PE

- HBsAg, anti-HCV
- US (FBS, TG)
- ANA, SMA
- Serum ceruloplasmin
- Iron study (SI/TIBC, ferritin) } In selected cases

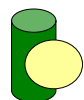
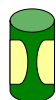
Elevated > 6 mo. without cause → Liver biopsy

US = ultrasound, ANA = anti-nuclear antibody, SMA = smooth muscle antibody, SI = serum iron, TIBC = total iron binding capacity

Common Causes of Intrahepatic Cholestasis

- **Drugs and herbal medicine**
 - Estrogens, anabolic steroids, phenothiazines, amoxy-clavulanate, erythromycin, quinidine, ticlopidine, flucloxacillin, diltiazem, azathioprine, gold, etc.
- Sepsis
- TPN
- Primary biliary cirrhosis (PBC)
- Thyrotoxicosis
- Benign post-operative jaundice
- ICU jaundice

Common Causes of Extrahepatic Cholestasis



Intramural

- Cholangio CA
- Sclerosing - cholangitis
- Benign stricture

Intraluminal

- Stone
- Parasites
- Hemobilia

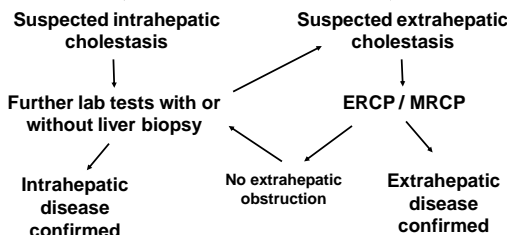
Extraluminal

- Periapillary CA
- Pancreatitis
- Gallbladder CA
- Merizzi's syn.
- Lymphadenopathy

Approach to Patient with Cholestasis

Clinical evaluations | Hx, PE and LFTs

Radiological evaluation (US/CT/MRI)



Differential Causes of Elevated ALP

| | Bile duct obstruction | Intrahepatic cholestasis | Infiltrative liver dis. | SOL |
|-----------------------------|---|-------------------------------------|-------------------------------------|-------------------------------------|
| Pruritis, pale stool | • Complete : yes (may absent in 1 st few wks) • Incomplete : no | Yes or no | Rare | Rare |
| TB level (mg/dl) | • Complete : ↑ < 25-30 • Incomplete : often N | ↑ Up to 50-60 | Often N | Often N |
| ALP level (U/L) | Almost always ↑ • Stone < 500 • Malignancy varies from 3x to >10x | Usually ↑ Varies from 3x to >10x | Usually ↑ Varies from 3x to >10x | Usually ↑ Varies from 3x to >10x |
| US | Dilated IHD ± CBD (may normal in early or partial obstr. & sclerosing duct) | N | Often N | Mass(es) |

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