Abnormal Liver Function Tests

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Interpretation of Abnormal Liver Enzymes

- **Biochemical Tests**
- **Viral Serologies**
- **Auto-antibodies**
- **History and Physical Exam Findings**

Bilirubin

- 70-80% from destroyed RBC
- Total bilirubin is < 1 mg/dl in 99%; direct ≤0.3 mg/dl (Van den Bergh) or ≤ 0.1 mg/dl (Ektachem)
- Free direct bilirubin (half life = 4 h)
- Delta conjugated bilirubin (T1/2 = 12-14 d)
- Hemolysis gives T. bilirubin ≤ 5 mg/dl, mostly indirect (no bilirubin in urine)

Bilirubin

- Bilirubin ≥ 10 mg/dl, absence of biliary tree dilatation supports non-obstructive jaundice
- Degree of bilirubin elevation do not correlate well with severity of acute disease
- In ESLD, a composite score of Bilirubin, Creatinine & INR, predicts survival. (MELD)
- Bilirubin in urine usually indicates hepatobiliary disease (direct bilirubin)
- Urobilinogen (in urine) is decreased in biliary obstruction (but also with antibiotics)

Isolated Bilirubin Elevation

Case # 1

- 23 y.o. caucasian, female, nurse-student, in usual state of good health found to have mild conjunctival icterus while practicing physical exam skills. Only symptom is anorexia and nausea, that she usually gets during her menstruation.
- Denies dark urine, alcohol abuse, drug abuse, previous hepatitis. Not taking medications other than naproxen for her menstrual cramps.

Case # 1 Labs.

- T. bili= 3.2 mg/dl (nl: 0.1-1); D. bili= 0.1
- ALT, AST, Alk. Phosph., T. protein, albumin, LDH were all normal
- CBC was normal; Retic count= Nl
- Intravenous Nicotinic acid (50 mg) caused 2-3X increase of Indirect Bilirubin.

Case # 1

- **DIAGNOSIS**: Gilbert's Syndrome
  (decreased activity of Uridine-Diphosphate Glucoronosyltransferase)

Causes of Hyperbilirubinemia

Indirect (Isolated)

- Gilbert's Syndrome (< 6 mg/dl)
- Crigler-Najjar I (25-48 mg/dl)
- Crigler-Najjar II (6-25 mg/dl)
- Hemolysis (< 5 mg/dl)
- Ineffective erythropoiesis
- Neonatal jaundice
- Sepsis

Causes of Isolated Hyperbilirubinemia

Indirect (Isolated) *, continued*

- Congestive heart failure
- Portocaval shunt
- Drugs
  - Pregnanediol
  - Chloramphenicol
  - Novobiocin
  - Rifampin/rifamycin
  - Probenecid

Causes of Isolated Hyperbilirubinemia

Direct (60%) + Indirect (Isolated)

- Dubin-Johnson S (2-25 mg/dl)
- Rotor S (< 10 mg/dl)
- Hepatic Storage Disease

Causes of Hyperbilirubinemia

Hyperbilirubinemia + Elevation of Liver Enzymes

- Hepatocellular disease
- Intrahepatic cholestasis
- Extra hepatic cholestasis
- Mixed.

Markers of Hepatocellular Necrosis

ALT *(SGPT) or Alanine Aminotransferase*

- Almost all from liver cytosol; lesser amounts in muscle; injury causes rise
- True normal range is lower than that accepted by most labs
- **Alcohol injury**: usually < 200 IU/L + AST/ALT ≥ 2
- **Hepatocellular injury**: usually > >300 IU/L (peak 350-10000)
- **Obstruction**: usually < 400 IU/L
- **Acute bile duct obstruction or liver ischemia**:
  > 300 IU/L x < 48-72 h

Markers of Hepatocellular Necrosis

ALT *(SGPT) or Alanine Aminotransferase*

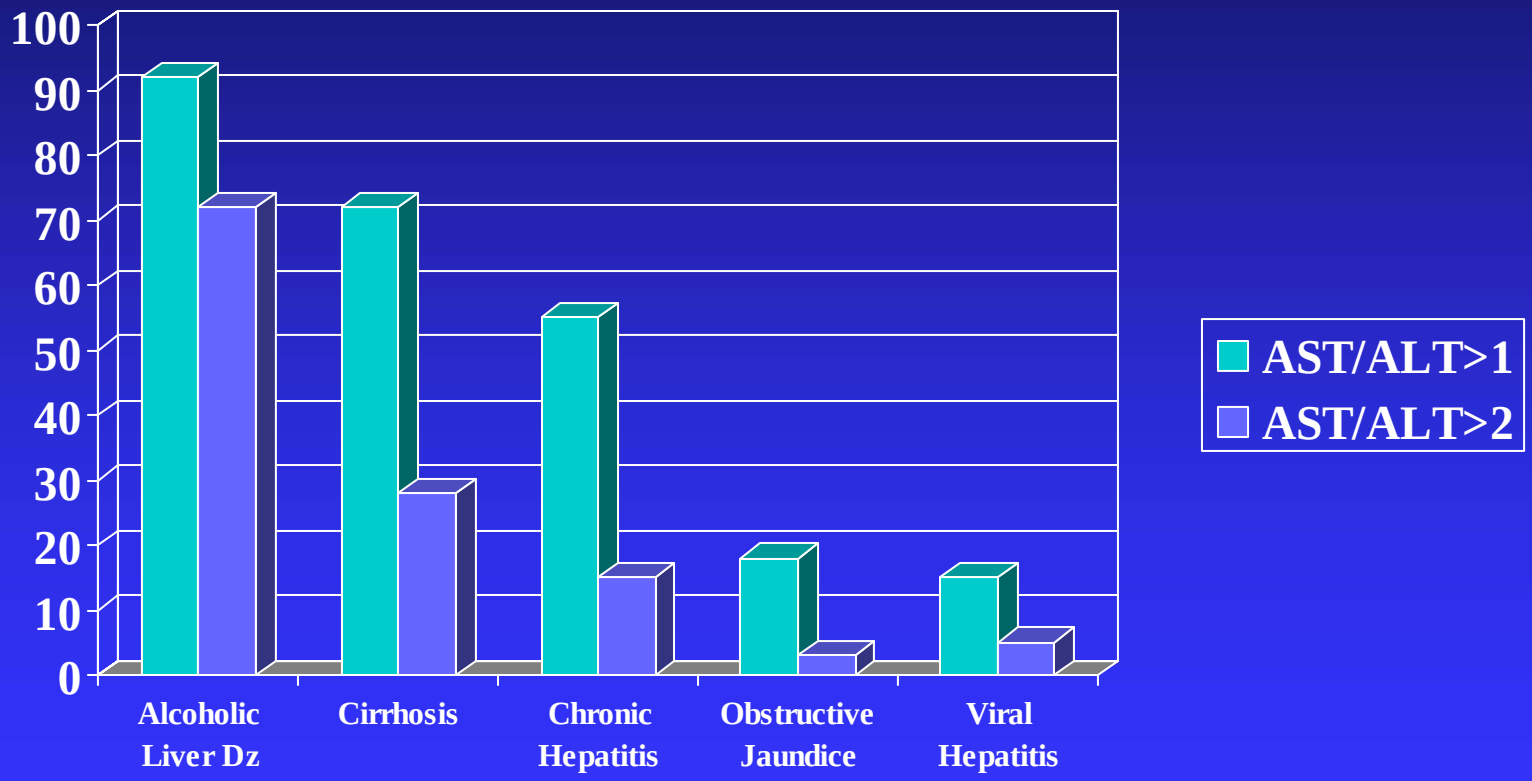
- Half-life of ALT >> AST
- In acute muscular injury, peak AST/ALT > or = 3; after 3-4 days levels are similar; (peak AST 400-10000)
- In chronic muscle injury (polymyositis) AST and ALT levels are similar (50-1000). (Hepatology. 2005 Feb;41(2):380-2)

Markers of Hepatocellular Necrosis

***AST** (SGOT) or Aspartate Aminotransferase*

- Higher in: liver, heart, skeletal muscle, kidney, brain, pancreas, lungs, WBC and RBC; injury causes rise
- In liver: 80% mitochondrial/20% cytosol
- In serum: mostly from cytosol
- **Alcohol injury**: usually < 300 IU/L and AST/ALT ≥ 2
- **Hepatocellular injury**: usually >> 300 IU/L
- **Obstruction**: usually < 400 IU/L

AST/ALT ratio in different disorders



Markers of Hepatocellular Necrosis

Classic Patterns of Elevation

- **Rapid and high** (>> 300 IU/L) up and down: acute biliary obstruction or liver ischemia
- **Sustained and high** (>> 300 IU/L x >> 1 week): viral or toxic hepatitis
- **Prolonged** (months) **with peaks and troughs**: chronic HCV
- **Prolonged** (months) **mild/moderate elevation**: chronic viral hepatitis, metabolic, immune or toxic liver disease

Case # 2

- 55 y/o female with 3 months history of fatigue and progressive weakness and muscular achines. Over the last month has difficulty climbing the stairs to her third floor apartment. Has mild dysphonia and dysphagia. Denies jaundice. Does not take medications, OTC drugs, nor "natural therapies". Denies alcohol abuse, or other drug abuse.
- **LABS**: **-CBC**=nl; **-U/A**= nl; **-TSH**= nl;
  -CMP: electrolytes, glucose, creat, protein, albumin, alk. phosphatase & bilirubin are nl.
  ALT= 320 U/L (nl: 10-40), AST= 350 U/L (nl: 10-40)

Case # 2 Additional studies

- LABS:
  - Creatine kinase (CK)= 520 U/L (normal: 26-140 U/L)
  - Aldolase= 30 U/L (normal:1-8 U/L)
- Electromyogram and muscle Bx: consistent with polymyositis.
- Work up for occult malignancy was negative.
- **DIAGNOSIS**: PRIMARY POLYMYOSITIS

Markers of Cholestasis

Alkaline Phosphatase

- Liver, bone, intestine (all heat labile) and placenta (heat stable)
- Concomitant elevation of GGT in person older than 4 years old excludes bone origin
- Concomitant elevation of ALT or Direct Bilirubin supports liver origin
- Normal GGT makes liver origin very unlikely

Markers of Cholestasis

Alkaline Phosphatase*, continued*

- Elevation ≥ 4-fold suggests intra-hepatic or extra-hepatic cholestasis
- Elevation < 3-fold is less specific
- ***"Isolated" elevation*** : partial bile duct obstruction, infiltration (eg: granulomas, Primary Biliary Cirrhosis), or focal liver mass (eg: metastasis).
- ***Elevated "liver type" alkaline phosphatase without liver involvement***: Hodgkin's disease, myeloid metaplasia, congestive heart failure, renal cell carcinoma, intra-abdominal infections

Markers of Cholestasis

GGT (γ-Glutamyl Transpeptidase)

- Not in bone
- Normal range reached in children > 4 y.o. and persists during pregnancy.
- Elevation: alcohol, Dilantin, COPD, diabetes, renal failure
- Elevated alkaline phosphatase with:
  - Elevated GGT suggest liver origin
  - Normal GGT, unlikely liver origin

Markers of Cholestasis

5' Nucleotidase

- In elevated alkaline phosphatase:
  - Elevated 5' nucleotidase in absence of pregnancy indicates liver origin
  - Normal 5' nucleotidase does not exclude liver origin (less sensitive than GGT)

Case # 3

- 45 y.o. female with 1 year hx. itching. Investigation by her dermatologist shows abnormal liver enzymes.
- Past hx.: Hypothyroidism, controlled on thyroid replacement, and of breast Ca treated by lumpectomy & radiation 2 years ago. Last oncology check 3 months ago was “free of disease”.
- Has some fatigue and persistent itching.

Case # 3 Labs

- CBC = normal, PT= normal
- AST, ALT, T. Bilirubin, T. Protein, Albumin = Normal
- Alkaline Phosphatase = 580 (nl < 98), GGTP= 1080 (nl < 50)
- AMA = 1/640; TSH & T4 = nl
- CT scan of abdomen = normal; no metastasis/focal lesions

Case # 3

- Liver Bx: Primary Biliary Cirrhosis, stage 2; no evidence of tumor metastasis.

- **DIAGNOSIS:** Primary Biliary Cirrhosis
  -No evidence of cirrhosis (Stage 2)

Markers of Synthetic Function

Prothrombin Time

- Activity of Factors VII (shortest half life), V, X and II
- Prolonged when Factor VII < 40%
- PT longer than 4 seconds over control, not corrected by parenteral Vitamin K, indicates severe hepatocellular disease
- In jaundice, normalization of PT with parenteral Vitamin K indicates cholestasis or warfarin use.

Markers of Altered Immunoregulation: Gammaglobulins

- Suggest reticuloendothelial cell dysfunction or portocaval shunting. GI tract antigens not cleared by the liver cause systemic inflammatory response
- Severe hypergammaglobulinemia (> 3 gm) seen in autoimmune hepatitis; mostly polyclonal IgG .
- Moderate hypergammaglobulinemia in cirrhosis and chronic hepatitis
- Very high polyclonal IgM in primary biliary cirrhosis
- Very high IgA often in alcoholic liver disease

Serologic Markers of Viral Hepatitis A, B, and C

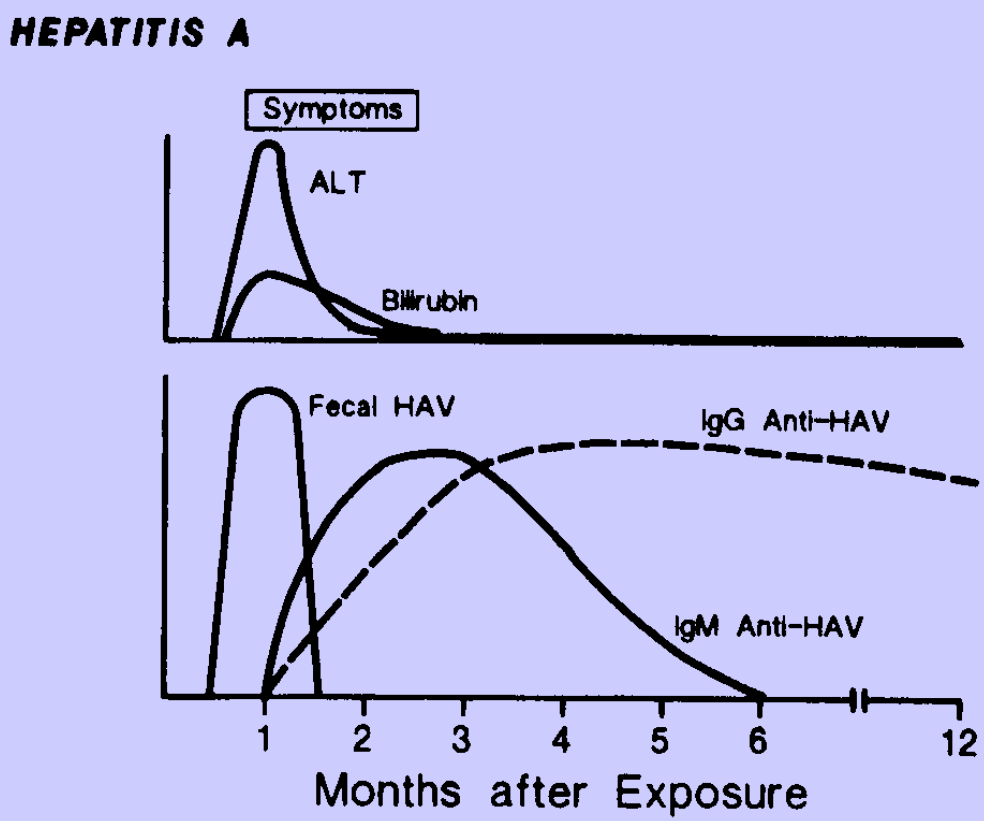
Markers of Viral Hepatitis A: *Anti-HAV*

- Total antibody (IgA + IgG + IgM)
- Remains (+) for decades
- **Indicates immunity**

Markers of Viral Hepatitis A: ***Anti-HAV IgM***

- (+) at onset of symptoms of Hepatitis A
- Remains (+) up to 7 months
- **Best test to diagnose acute hepatitis A**

Hepatitis A


HEPATITIS A
Symptoms
ALT
Bilirubin
Fecal HAV
IgG Anti-HAV
IgM Anti-HAV
1
2
3
4
5
6
12
Months after Exposure

Markers of Viral Hepatitis B: *HBsAg*

- Very sensitive; no false (-)
- False (+) 1/10,000 to 1/1,000
- Turns (+) during incubation and declines; 10% (-) at onset of symptoms
- **Always (+) in chronic hepatitis B (best marker)**

Markers of Viral Hepatitis B: *Anti-HBs*

- Titer ≥ 1 IU/L is (+);

  Titer ≥ 10 IU/L is protective
- False (+) in 1%
- Post-acute HBV: 20% never have anti-HBs and 20% lose anti-HBs in a few years
- Titer ≥ 10 IU/L indicates response to vaccine

Markers of Viral Hepatitis B: *Anti-HBc*

- False (+) in 3%
- No false (-)
- Not present post-vaccination
- **Best & most lasting marker of previous (or current) HBV infection**

Markers of Viral Hepatitis B:
Anti-HBc IgM

- Strongly (+) before symptoms of acute HBV
- Remains (+) for months
- May be weakly (+) in chronic HBV
- **Best Diagnostic test for acute HBV**

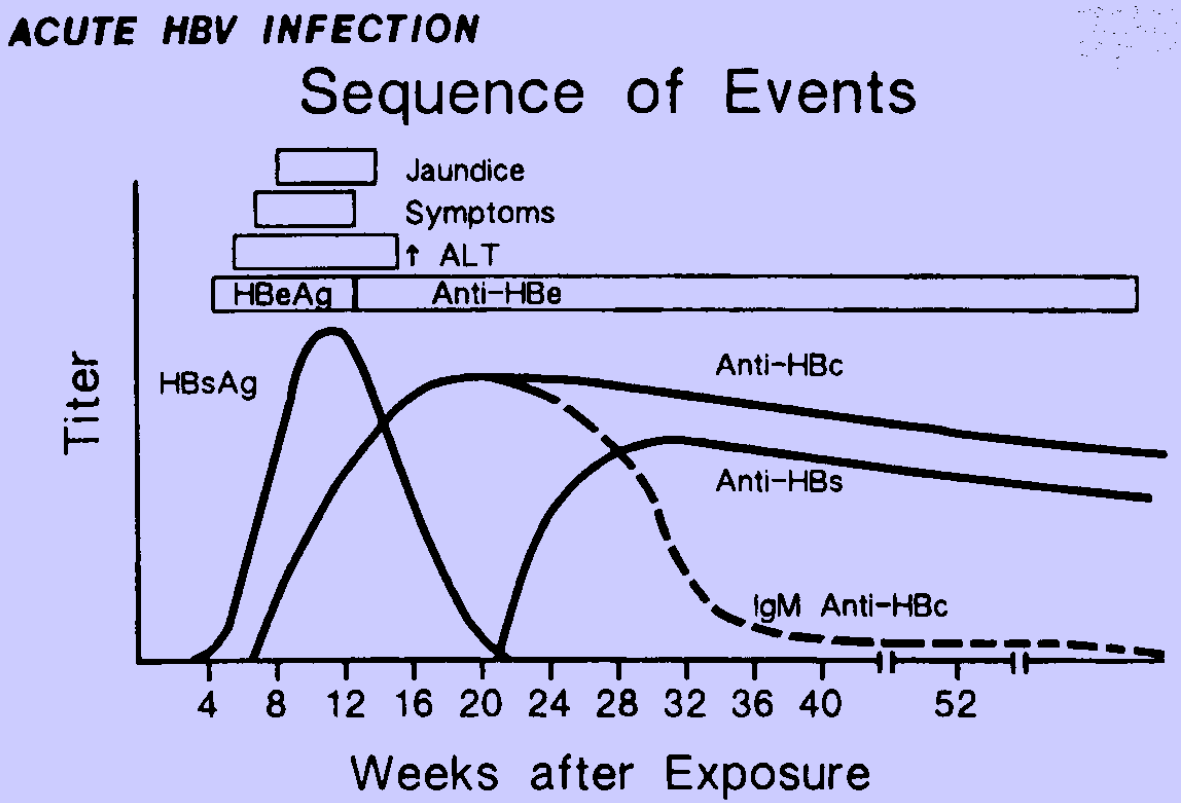
Markers of Viral Hepatitis B:
HBeAg

- Active viral replication
- 90% have HBV-DNA > 10^5 g.e./ml
  (10^5 g.e. = 0.35 pg)
- Negative in pre-core mutant virus infection, even when replicating rapidly.

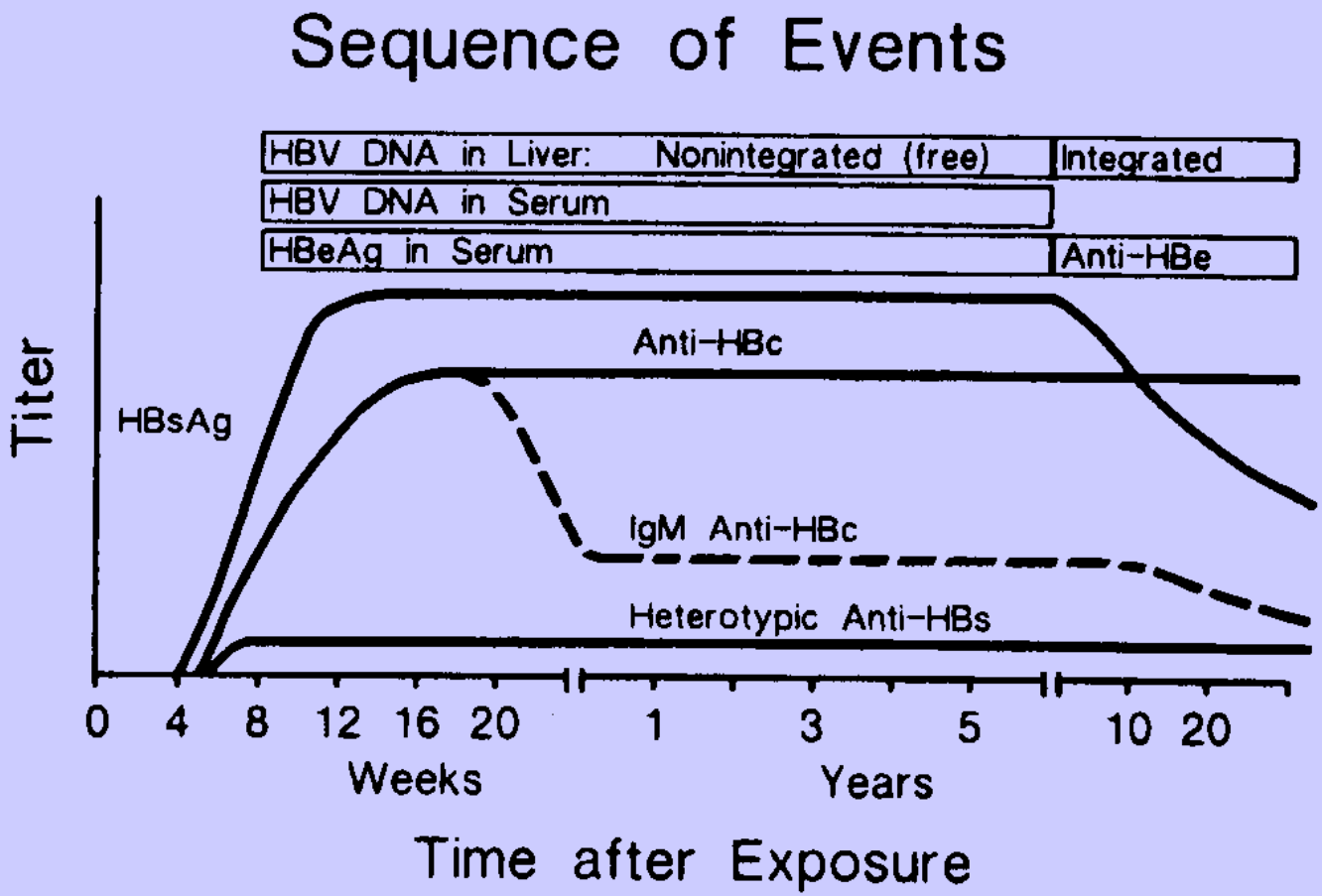
Markers of Viral Hepatitis B:
HBV-DNA by Hybridization or PCR

- Hybridization detects > 10^5 g.e./ml (20000 IU/mL) (1 pg = 2.86 x 10^5 g.e./ml)
- PCR detects > 100 g.e./ml (20-40 IU/mL)
- HBV-DNA < 200 pg/ml (6 x 10^7 g.e./ml) respond better to interferon
- **With "wild" HBe(+) infection: elevated ALT *plus* values of 10^5 g.e./ml (20000 IU/mL) indicate active chronic hepatitis.**
- **With "pre-core" or "core-promoter" HBe(-) mutant virus: elevated ALT *plus* values > 10^4 g.e./ml (2000 IU/mL) indicate chronic active disease.**

Acute HBV Infection



Chronic HBV Infection



Case # 4

- 23 y/o female, who did not have pre-natal care, comes in labor and gives birth to a "healthy boy". Her admission labs shows she is HBsAg(+), has mild microcytic anemia, U/A was normal, and has ALT= 95 U/L (nl: 10-40), AST= 80 U/L (nl: 10-40), alk. Phosph. = 210 U/L (nl: 40-100); bilirubin, protein, and albumin were normal.
- Denies alcohol or other drug abuse. No sexual promiscuity. Her parents came from Italy 3 years before her birth.

Case # 4

- Newborn received immediately “Hepatitis B immune globulin” and HBV vaccination.
- Mother labs: anti-HBcIgM(-), HBeAg(-), anti-HBe(-), HBV-DNA = 60,000 ge/mL (12000 IU/mL)
- Liver Bx: Portal activity: 3, Lobular: 2, Stage 3 fibrosis.
- Plan: treat patient (likely pre-core mutant).

Markers of Viral Hepatitis C: *Anti-HCV*

- Usually ELISA-3
- False (+) in low prevalence population without risk factors (40%) and hypergammaglobulinemia
- Rare false (-)
- Acute HCV turns (+) at week 4 in 74%; 98% are (+) by week 20

Markers of Viral Hepatitis C: *Anti-HCV, continued*

- Not a protective antibody
- May remain (+) up to 10 years post-acute infection
- Almost all patients with chronic HCV are anti-HCV (+)
- **Indicates past or current infection**

Markers of Viral Hepatitis C:
HCV-RNA
(Target Amplification Quantitation)

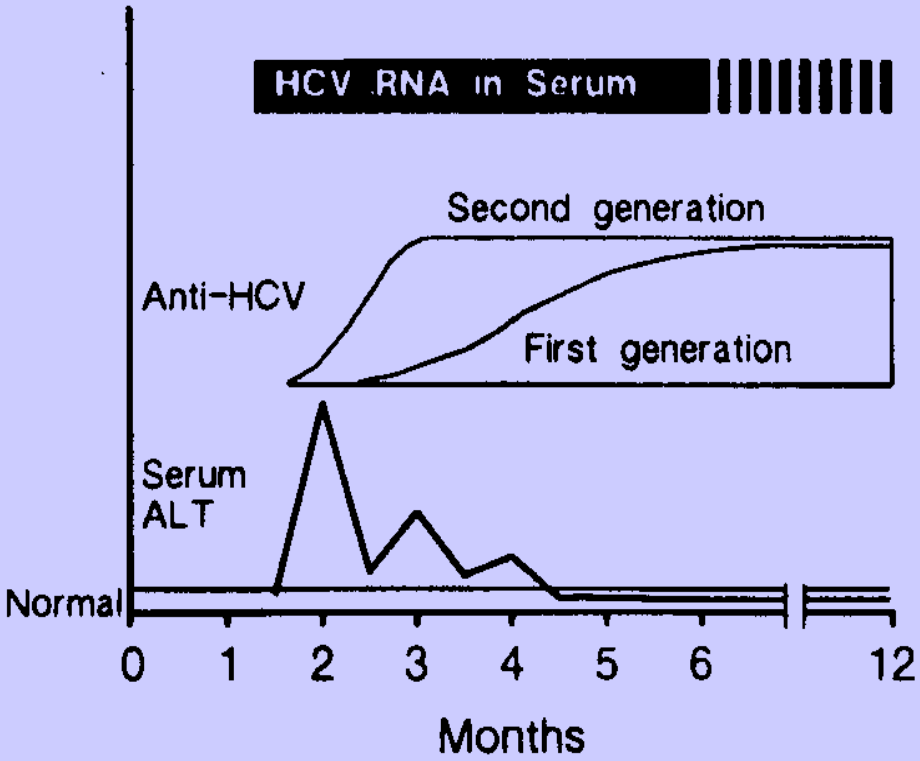
- Detects more than 600 IU/mL (more than 10 IU/mL with "Real Time" techniques)
- Low viral load (≤ 400,000 IU/mL) respond better to therapy
- Infrequently false (+) or false (-)

Prediction of SVR (Naïve)

PEG-Interferons + Ribavirin

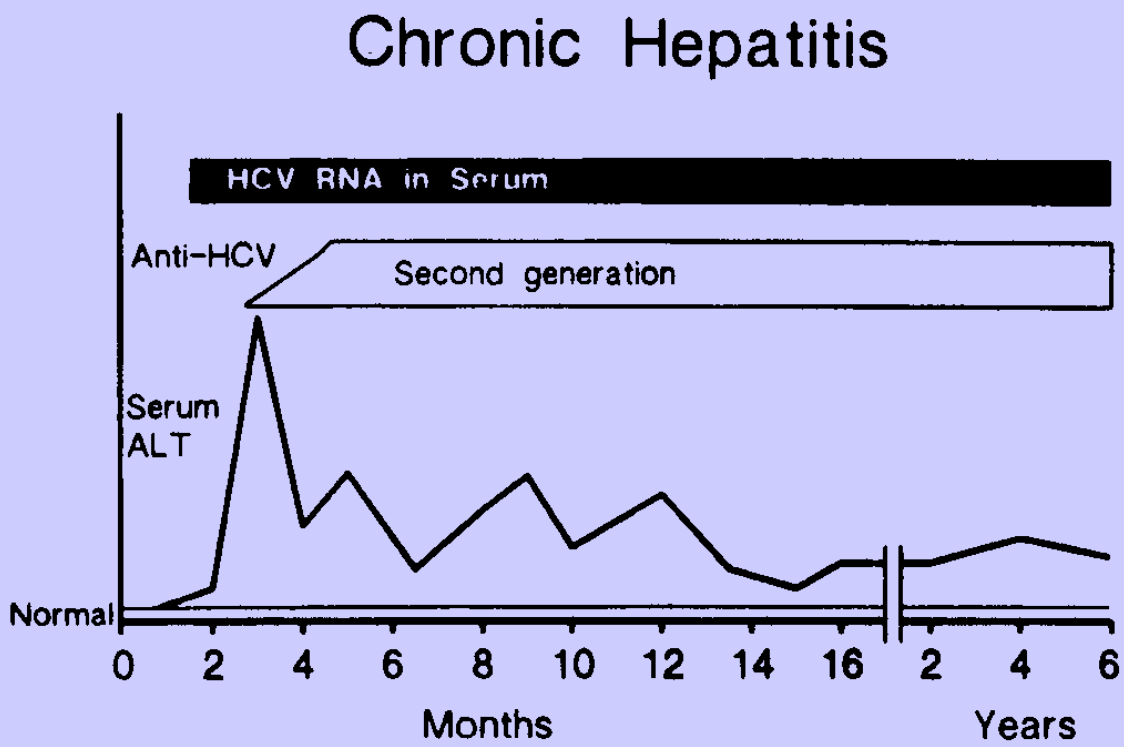
HCV-RNA Status @ 12 wk	***% Non-Responders***	***% SVR***
HCV-RNA (-) (less than 50 IU/ml)	20	**80**
HCV-RNA (+) & drop > 2 log	60	**40**
HCV-RNA (+) & drop < 2 log	**98.4**	1.6

Acute Hepatitis C Virus



Chronic Hepatitis C Virus

HEPATITIS C VIRUS



Case # 5

- 52 y.o. war veteran with intermittently elevated ALT & AST over 2 years. Hx. EtOH abuse x 15 y; quit 3 y ago. Hx tattoos, IV drugs and sexual promiscuity from age 18 to 25. No medications nor “natural therapies”. Fam Hx (-). Has some fatigue.
- Examination: Small, hard liver. Splenomegaly. Spider angiomas.

Case # 5 Labs

- CBC normal except for ***plat=85K***; PT= normal
- **ALT: 45-88; AST: 34-74;** Alk Phos, T. bili & T. protein = nl. ***Alb= 3.1***
- anti-HA IgM(-), ***anti-HA(+)*** = **past HAV**
- HBsAg(-), ***anti-HBc (+),*** anti-HBcIgM(-), ***anti-HBs(+)*** **= past HBV**
- ***anti-HCV(+)*** **= past or current HCV**

Case # 5

- HCV-RNA = 650,000 IU/ml
- Liver Bx: Chronic hepatitis with cirrhosis.

Case # 5

- **DIAGNOSIS:** Chronic hepatitis C with cirrhosis

Markers of Autoimmune Liver disease

ANA (anti-nuclear antibody)

- Granulocyte specific (anti-centromere, -ribonucleoprotein, or, -ribonucleoprotein complex)
- Pattern: homogeneous or speckled
- Titer ≥ 1:40 in adults, ≥ 1:20 in children
- ANA (+) in 67% of AIH-1 and 24% of PBC
- **Auto-Immune Hepatitis type 1 (AIH-1) defined by ANA (+) and/or ASMA (+)**

ASMA (anti-smooth muscle antibody)

- Can be: anti-actin, -tubulin, -vimentin, -desmin, or -skeletin
- Sometimes (+) in hepatitis C
- Titer ≥ 1:40 in adults, ≥ 1:20 in children
- **ASMA (+) found in 87% of AIH;**
  54% ANA(+) & ASMA (+)

Anti LKM-1 (anti-liver/kidney microsomal)

- Anti-cytochrome P450 2D6
- **Defines Type 2 AIH** (4% of adult AIH in USA)
- Titer ≥ 1:40 in adults, ≥ 1:20 in children
- 2-10% of Hepatitis C

AMA (anti-mitochondrial antibody)

- Anti-pyruvate dehydrogenase – E_2/anti-M_2 AMA
- 95% of PBC are AMA (+)
- Titer ≥ 1:160

Evaluation of a Patient With Jaundice

Patient With Jaundice: *History*

- Family History
  - Wilson's (Cu)
  - Hemochromatosis
  - A_1 Antitrypsin Deficiency
  - Benign recurrent intrahepatic cholestasis
- Travel History
  - HAV
  - Hydatid cyst
  - HEV
  - Amoebic liver abscess

Patient With Jaundice: *History*

- Sexual Promiscuity & Male Homosexuality
  - HBV
  - Amoeba
  - HDV
  - HCV
  - Syphilis
  - HIV + mycobacteria or fungus
- IV Drugs
  - HBV
  - HDV
  - HCV
  - HIV + mycobacteria or fungus

Patient With Jaundice: *History*

- Skin Rash
  - HBV
  - Drugs
- Work
  - Health Care: viral hepatitis
  - Plastics: Vinyl Chloride - angiosarcoma
  - Insecticides: Arsenic – angiosarcoma, hepatoma
  - Ceramics: Beryllium - granulomas

Patient With Jaundice: *History*

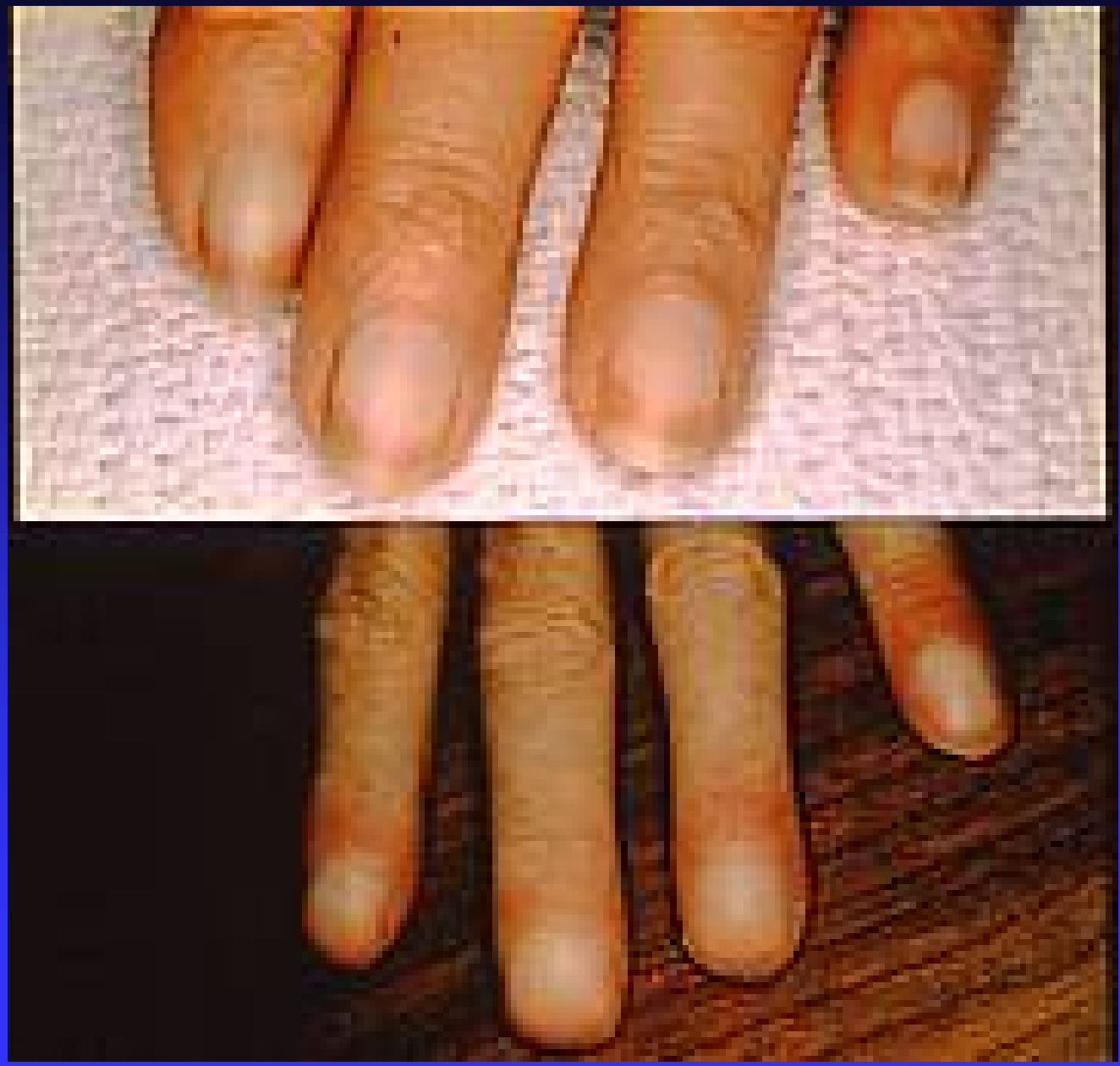
- Blood Products
  - HBV
  - HDV
  - HCV (before 1986)
  - HIV + other pathogens
- Pain in RUQ
  - Gallstones
  - Liver Abscess
  - Hepatitis

Patient With Jaundice: *History*

- Pruritus:
  - Chronic extrahepatic obstruction
  - Primary Biliary Cirrhosis (PBC)
- High Fever:
  - Cholangitis
  - Liver abscess
  - Alcoholic hepatitis
- Symptoms of CHF or Hx of Hypotension:
  - Ischemic hepatitis

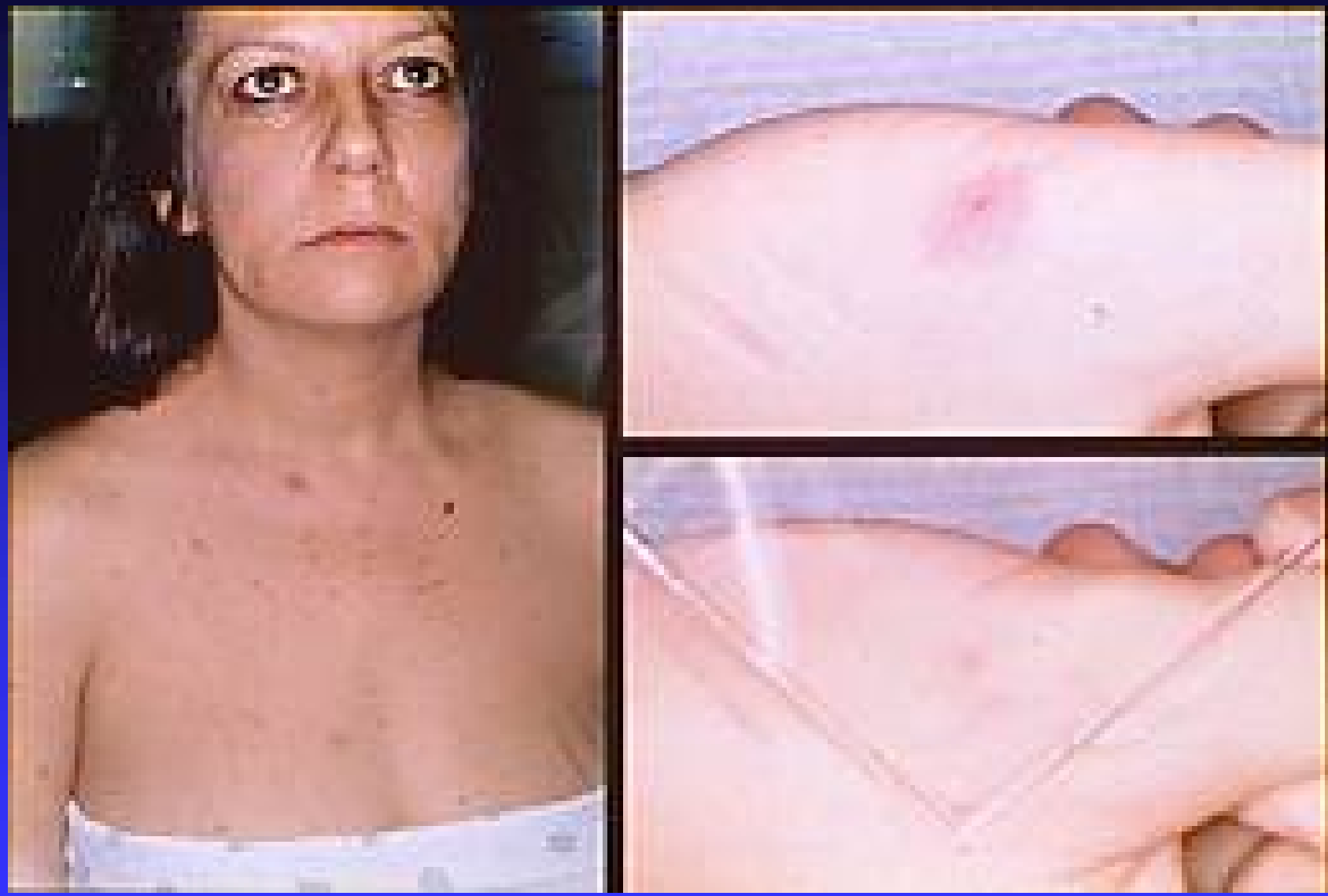
Patient With Jaundice: *Physical Exam - General*

- Parotid enlargement: Alcohol
- Clubbing: Cirrhosis
- Dupuytren's contracture: Alcohol
- Gynecomastia: Alcohol, cirrhosis; Aldactone
- Testicular atrophy: Alcoholic cirrhosis



Patient With Jaundice: *Physical Exam - Skin*

- Spider Angiomata: Cirrhosis
- Palmar erythema: Cirrhosis
- Xanthelasma: PBC, chronic biliary obstruction
- Bronze color: Hemochromatosis
- Excoriations: Cholestasis (itching), PBC
- Photosensitivity blisters: Porphyria
- Azure nail beds: Wilson's
- Urticaria: HBV

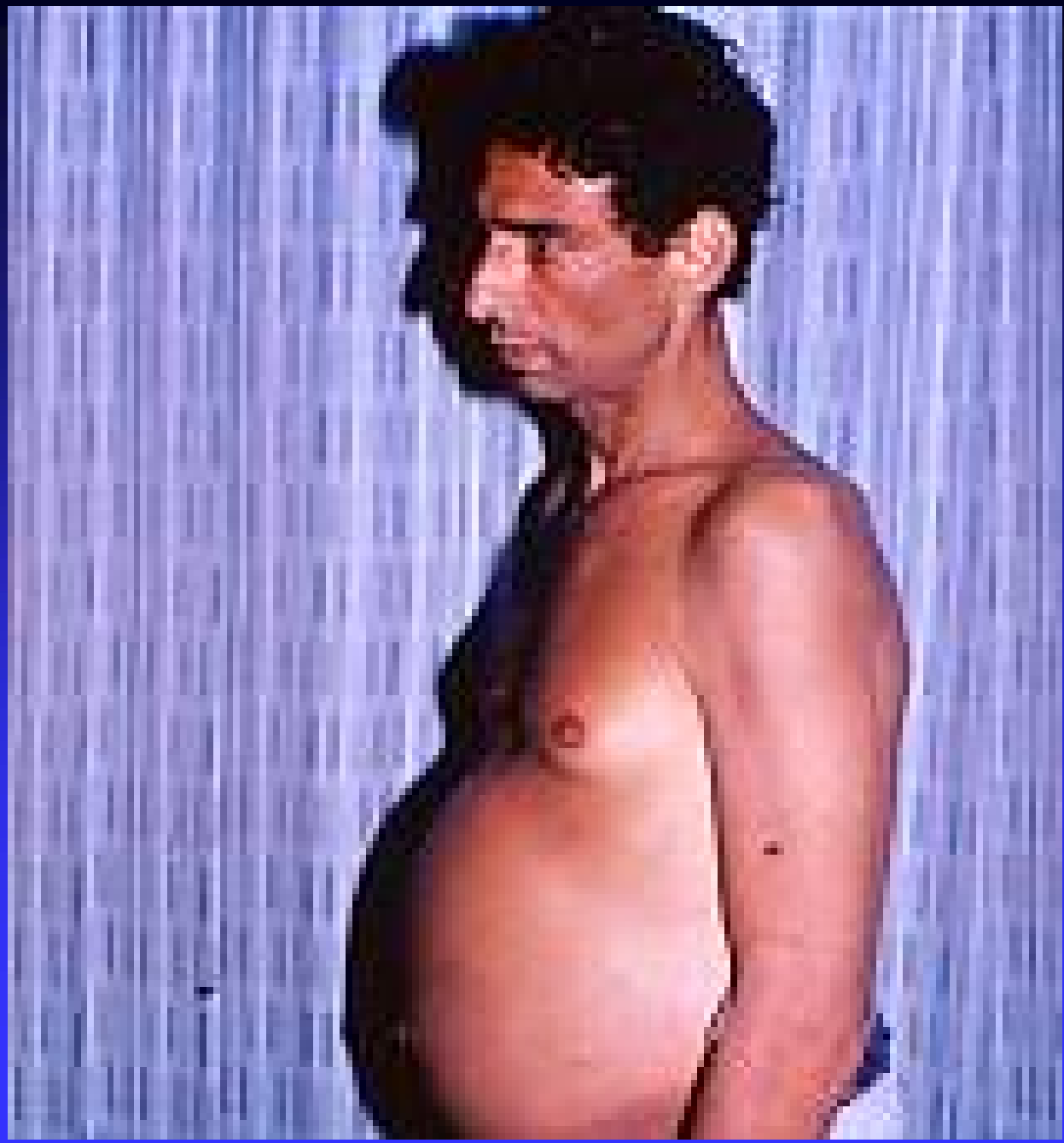


Patient With Jaundice: *Physical Exam - Eye*

- Kayser-Fleischer ring: Wilson's, PBC
- Lacrimegaly: Alcohol

Patient With Jaundice: *Physical Exam - Abdomen*

- Splenomegaly: Portal hypertension
- Ascites: Portal hypertension; ⇓ albumin
- Collateral circulation: Portal hypertension
- Hepatic rub: Tumor



Patient with Jaundice: *Physical Exam*

- GI Tract:
  - Inflammatory Bowel Disease: Primary sclerosing cholangitis (PSC)
  - Esophageal or rectal varices: Portal hypertension
  - Colitis: PSC, amoebic abscess
- Neurologic
  - Asterixis: Encephalopathy
  - Hyperreflexia: Encephalopathy

Questions ?

Acute Hepatocellular Disease

- **Acute HAV**: anti-HAV IgM (+)
- **Acute HBV**: anti-HBc IgM (+) high titer
- **Acute HBV/HDV coinfection**: anti-HBc IgM (+), and anti-HD IgM (+), or HDAg(+)
- **Acute HDV on chronic HBV**: HBsAg(+) + HBc IgM(-) plus anti-HD IgM or HDAg(+)
- **Acute HCV**: HCV-RNA(+), and sero-conversion to anti-HCV.

Acute Hepatocellular Disease

- **Acute HEV**: anti-HEV IgM(+)
- **Acute CMV**: anti-CMV IgM(+), CMV (+) by culture or PCR in blood or tissue
- **Acute EBV**: acute EBV serology pattern
- **Acute HSV**: anti-HSV I/II IgM(+), HSV(+) by culture or PCR in blood or tissue.
- **Drug or Toxin induced**: history and improvement with removal of drug/toxin.

Acute Hepatocellular Disease

- **Ischemic hepatitis**: history of hypotension, or passive hepatic congestion/heart failure
- **"Acute" Alcoholic Hepatitis**: alcohol abuse > 20 gm/d in females or > 40 gm/d in males, for > 5 years, with AST > ALT, AST & ALT < 300 IU/L, or Liver Bx.
- **"Acute" Auto-immune Hepatitis**: ANA, ASMA, AMA, QIG's, anti-LKM_1, anti-SLA, anti- LP, ANCA, and Liver Biopsy
- **"Acute" Wilson** : ceruloplasmin, free serum Cu, 24 hour urine Cu, eye exam for K-F rings, low uric acid, evidence of hemolysis, Liver Bx with quantitative Cu.

Chronic Hepatocellular Disease

- **Chronic HBV**: HBsAg(+) > 6 months, HBcIgM(-) , HBV-DNA quantitation, HBeAg, anti-HBe; Liver Bx
- **Chronic HBV/HDV**: HBsAg(+), anti-HBc IgM(-) , anti-HD IgG(+) high titer; Liver Bx
- **Chronic HCV**: HCV-RNA quantitation; Liver Bx
- **Hemochromatosis**: high fasting transferrin saturation & ferritin, HFE analysis, Liver Bx with Hepatic Iron Index > 1.9; quantitative therapeutic phlebotomy.
- **Non-Alcoholic Steato-Hepatitis**: (overweight, hyperglycemia, hypertrigliceridemia, hypertension); Liver Bx

Chronic Hepatocellular Disease

- **Alpha$_1$ anti-trypsin**: alpha$_1$ anti-trypsin phenotype and quantitation; Liver Bx
- **Wilson Disease**: ceruloplasmin, free serum Cu, 24 h urine Cu, eye exam for K-F rings, low uric acid, Liver Bx for Cu quantitation.
- **Auto-Immune Hepatitis**: ANA, ASMA, AMA, anti-LKM$_1$, anti-SLA, anti-LP, ANCA, serum QIG's, Liver Bx.
- **Primary Sclerosing Cholangitis**: MRCP. ERCP.
- **Drug or Toxin Induced**: history and improvement with removal of drug/toxin; may need Liver Bx.

Isolated Alkaline Phosphatase

- **Extrahepatic vs. Hepatic**: GGTP, alkaline phosphatase isoenzymes, triple-phase spiral or multi-detector CT scan of abdomen & pelvis (liver, biliary tree, pancreas, kidneys, spleen, lymph nodes).
- **Hepatic without focal lesion**: AMA, serum QIG's, MRCP, Liver Bx with culture (AFB, fungus, virus).
- **Hepatic with solid focal lesion**: AFP, guided Bx, complementary imaging techniques.
- **Hepatic with cystic focal lesion**: CT scan for lesions in other organs, serologies (ameba, echinococcus, cysticercus)

Extrahepatic Cholestasis

- **Pancreas**: Triple-phase spiral or multidetector CT scan, EUS with Bx.; may need therapeutic ERCP.
- **Biliary stone**: Therapeutic ERCP
- **Biliary duct lesion**: MRCP + MRI, CA19-9, CEA, ? PET scan; may need ERCP + Cytology/Bx + stent

Intrahepatic Cholestasis

- **PBC**: AMA, serum QIG's, Liver Bx.
- **PSC**: MRCP or ERCP; ANCA
- **Without focal lesion** (granulomas, infiltration): Liver Bx with culture (AFB, fungus, virus)
- **With focal lesion**: guided Bx
- **Ascending cholangitis**: therapeutic ERCP
- **Alcoholic hepatitis**: history & enzyme pattern; Liver Bx

Intrahepatic Cholestasis

- **Cholestatic HAV**: anti-HAV IgM(+)
- **Graft vs. host disease**: history & Liver Bx
- **Sepsis**: history
- **Drug induced**: history & improvement after discontinuation; may need liver Bx.
- **TPN induced**: history & improvement with enteral nutrition; may need liver Bx.
- **Benign Recurrent Intrahepatic Cholestasis of Pregnancy**: Pregnancy + family history.

Questions ?

Causes of Intrahepatic Cholestasis

1. Drugs (phenothiazines, erythromycin, sulphonylureas, estrogens, etc.)
2. Primary biliary cirrhosis
3. Sclerosing cholangitis
4. Infiltrative diseases (granulomas, tumors, etc.)
5. Ascending cholangitis
6. Septicemia

Causes of Intrahepatic Cholestasis

7. Alcoholic hepatitis
8. Cholestatic HAV
9. Graft vs. host disease
10. Total parenteral nutrition
11. Intrahepatic cholestasis of pregnancy
12. Benign recurrent intrahepatic cholestasis
13. Dubin Johnson

Causes of Extrahepatic Cholestasis

1. Choledocholithiasis (CBD stone)
2. Biliary strictures (benign, malignant, intrinsic or extrinsic)
3. Pancreatic carcinoma
4. Pancreatitis

Causes of Extrahepatic Cholestasis

5. Periampullary carcinoma
6. Cholangiocarcinoma
7. Choledocal cyst
8. Miscellaneous (blood, worms, PSC, etc.)

Anti-SLA (anti-soluble liver antigen)

- Anti-cytokeratin 8 and/or 18
- Defines AIH-3 (100%)

Markers of Viral Hepatitis B: *Anti-HBe*

- Anti-HBe with loss of HBeAg indicates lower or no replication
- 70% of Anti-HBe have

  HBV-DNA $\leq 10^5$g.e./ml

Markers of Viral Hepatitis B: ***HBV-DNA by RT-PCR***

- HBV-DNA $\geq$ 100 g.e./ml
- Too sensitive
- Useful to decide if virus was truly eliminated

Markers of Viral Hepatitis D:
HD Ag

- Transitorily (+) in acute HDV
- Persistently (+) in chronic HDV
- Positive in liver tissue in chronic infections; best test

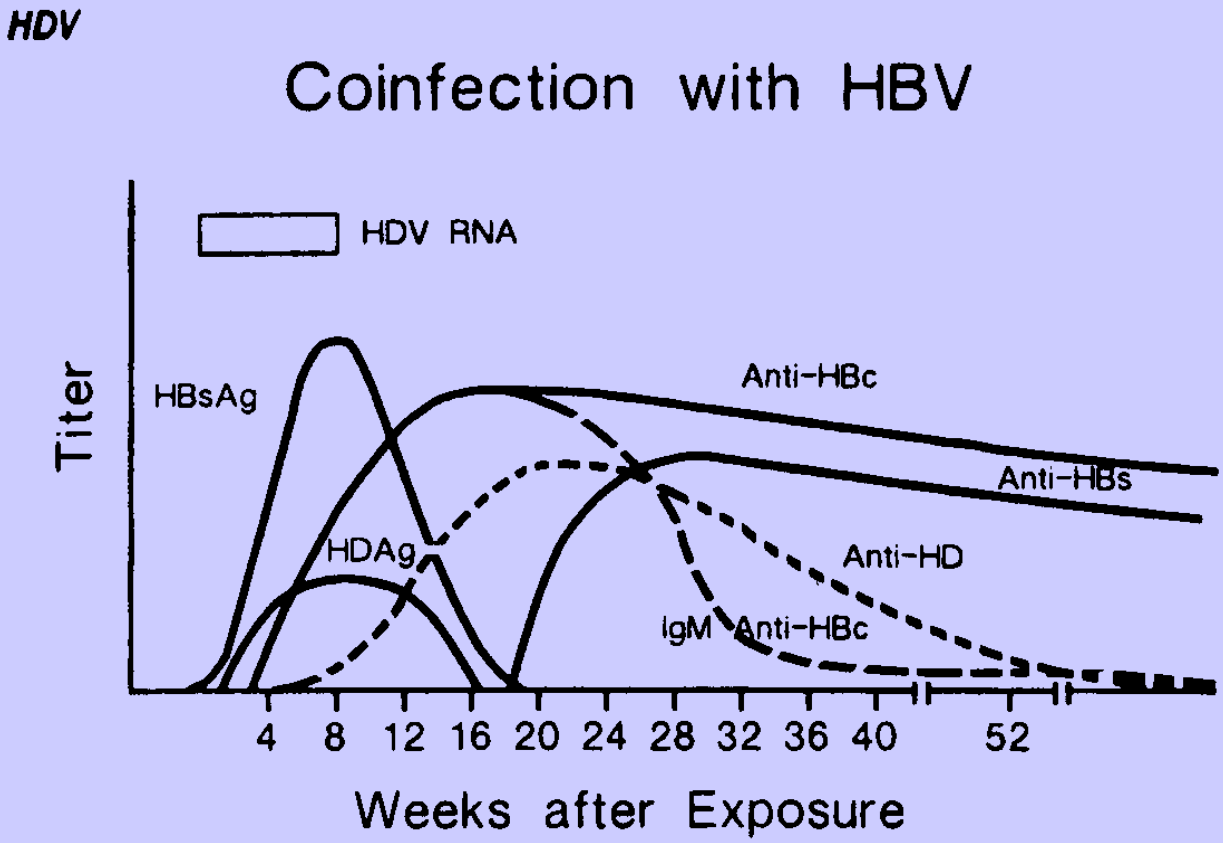
Markers of Viral Hepatitis D: ***Anti-HDV***

- Acute coinfection: (-) or weak (+) [1:10 to 1:100]
- Superinfection: strong (+) $\geq$ 1:1,000
- Chronic HDV: strong and persistent (+)

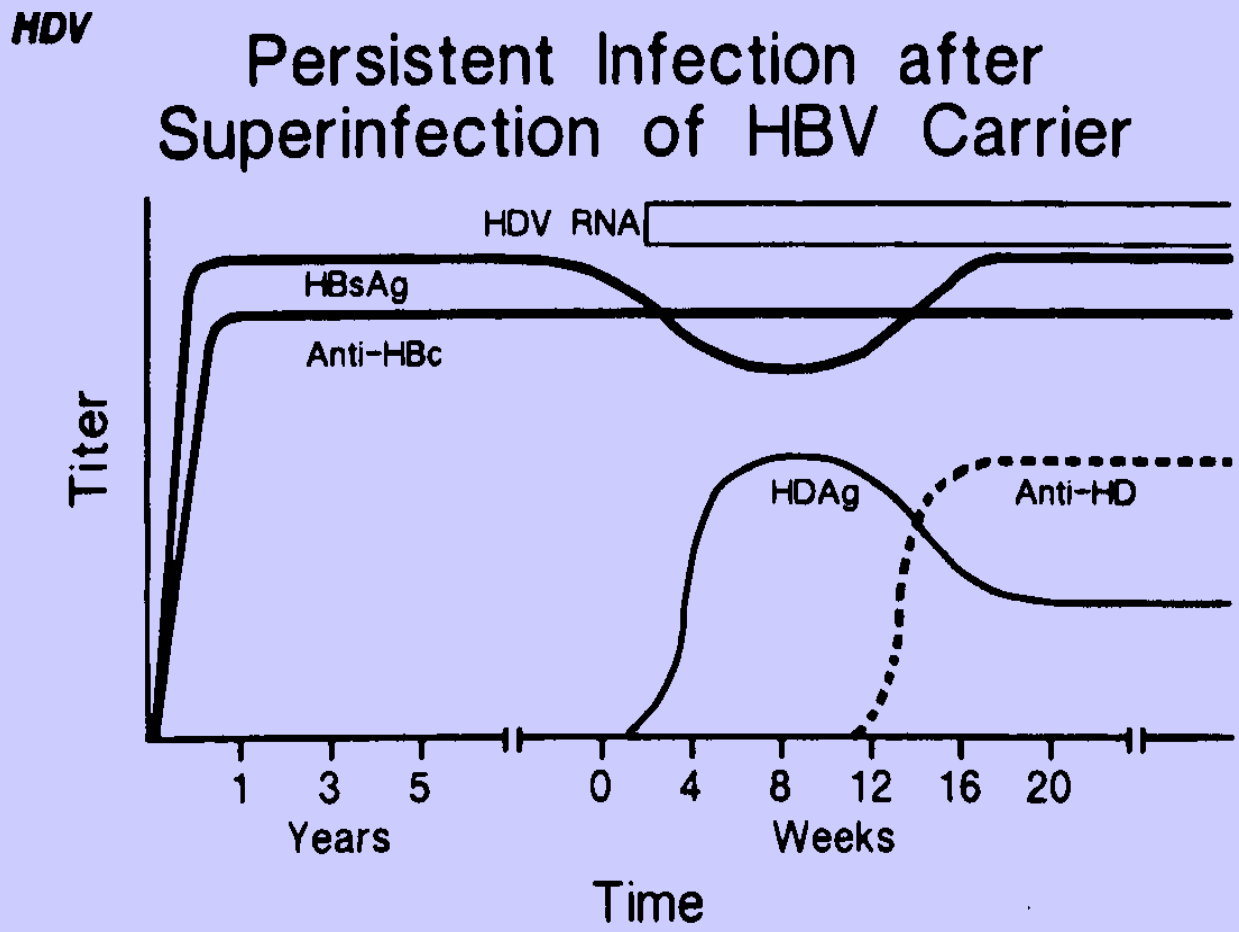
Markers of Viral Hepatitis D: ***Anti-HDV IgM***

- Indicates active infection
- Acute coinfection or superinfection = transitorily (+)
- Chronic infection: Persistently at high titer

HDV Coinfection with HBV



Chronic Hepatitis D



Markers of Viral Hepatitis C:
HCV-RNA by RT-PCR

- Detects ≥ 100 IU/mL
- Best test to assess true response to therapy
- More false (+) and false (-) than the qualitative test

Markers of Viral Hepatitis E: *Anti-HEV*

- 1-8 weeks from onset of clinical illness
- Persists for a few years

Markers of Viral Hepatitis E: *Anti-HEV IgM*

- 1 week earlier than IgG antibody
- Persists 4-5 months
- Best test for acute infection

HEV Infection