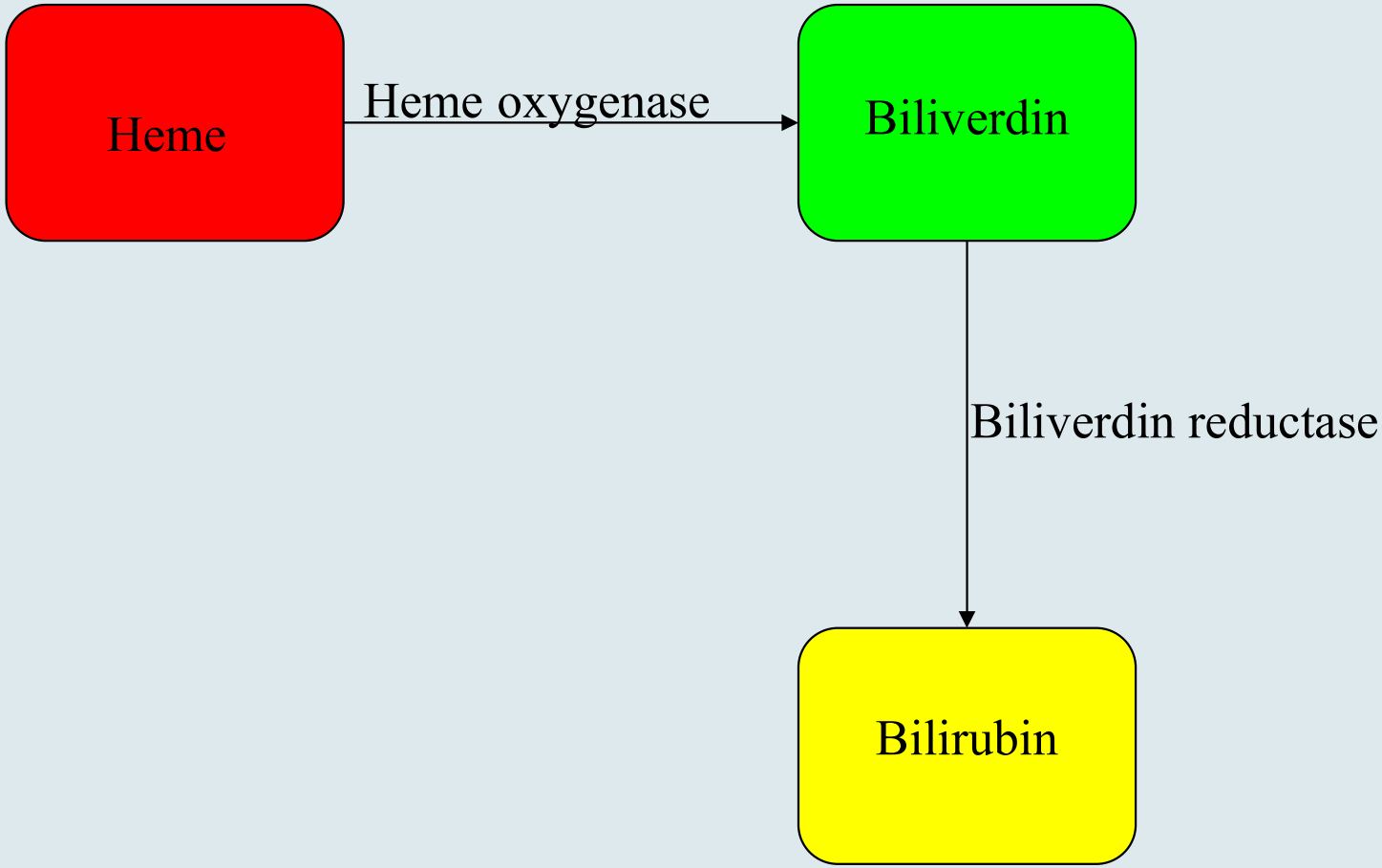
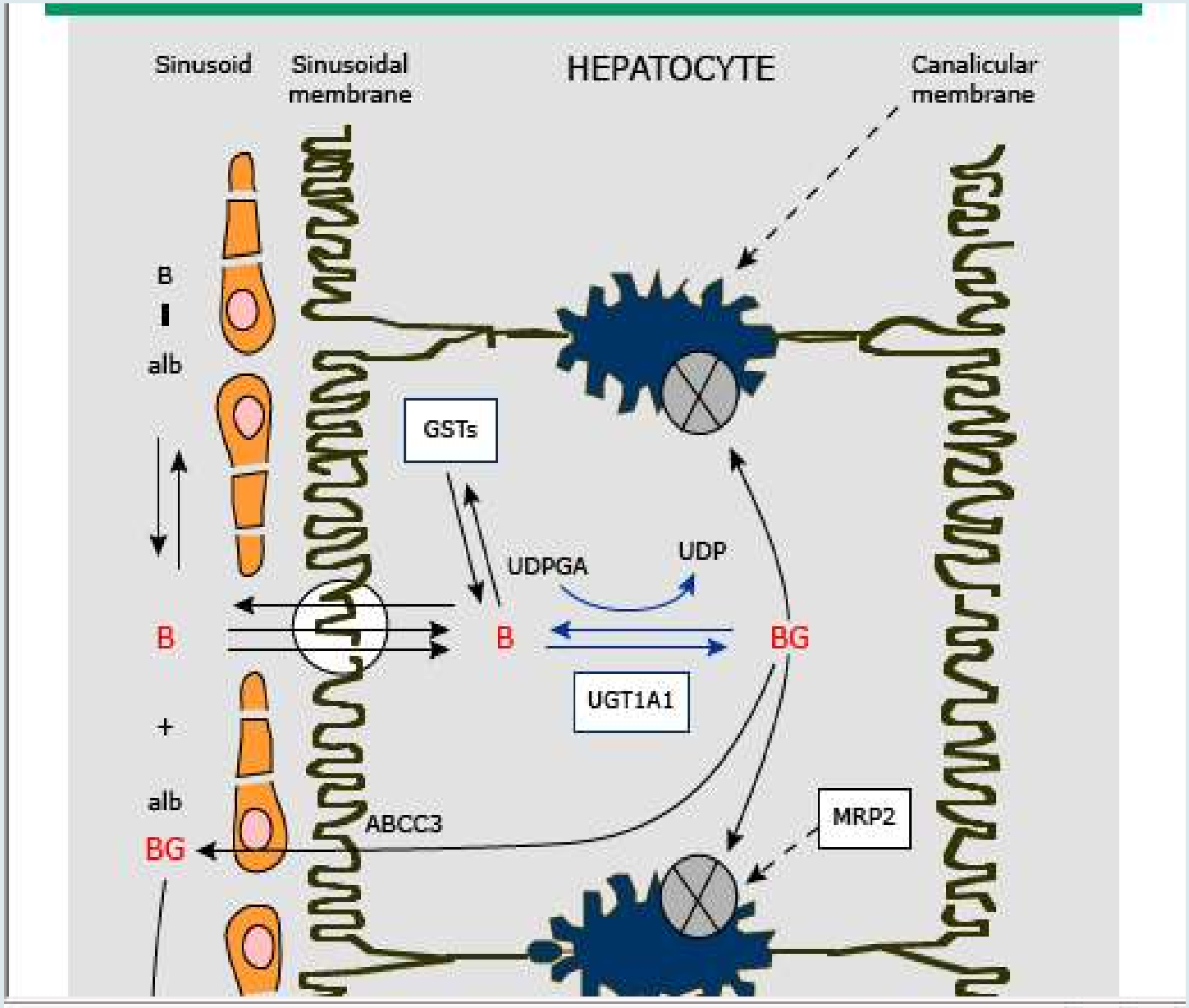
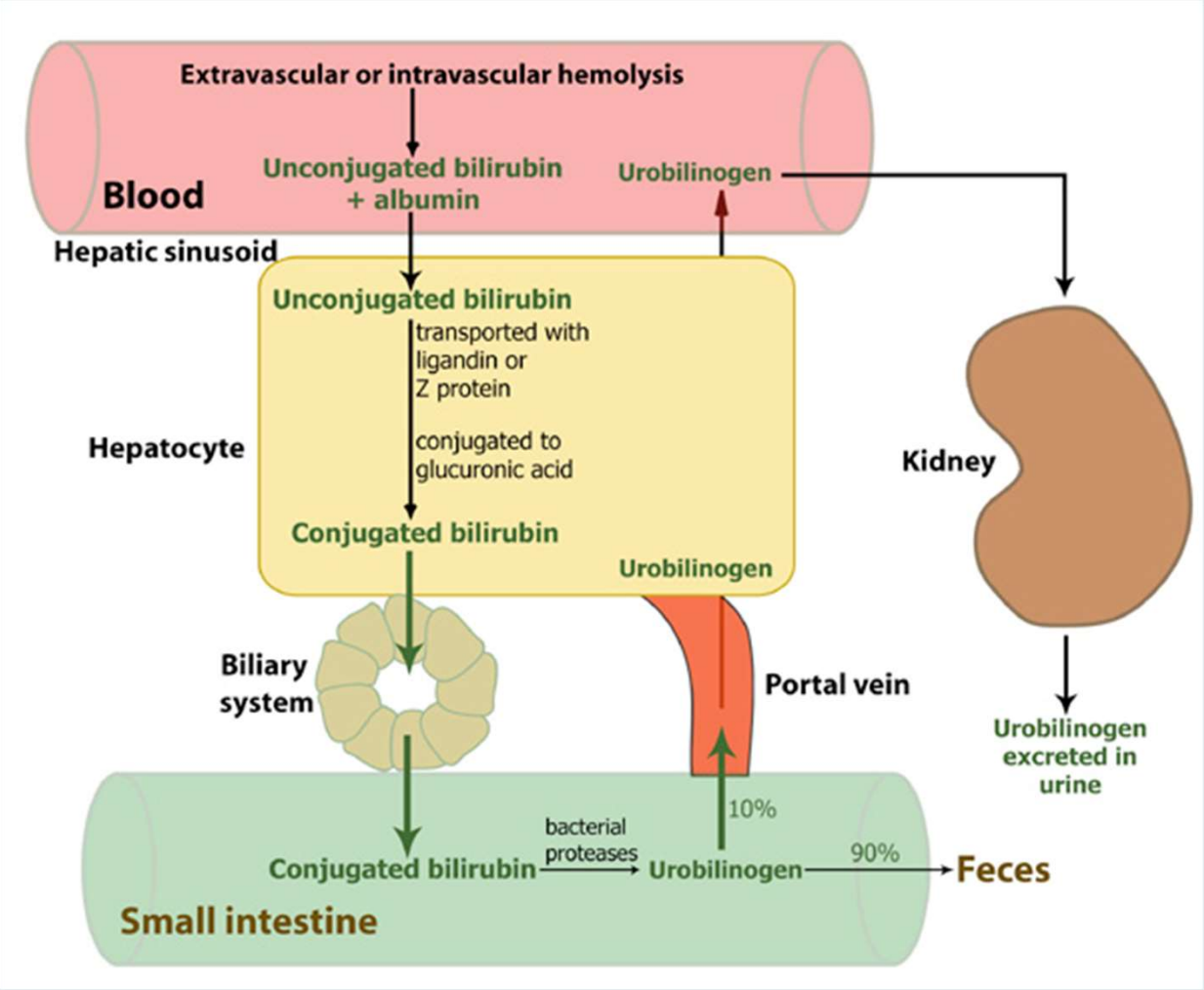

In the name of God
Jaundice or icter
HOSEIN SANEIAN
Ped. Gastroenterologist
۱۴۰۳

BILIRUBIN PHYSIOLOGY




Sinusoid
Sinusoidal membrane
HEPATOCYTE
Canalicular membrane
B
alb
GSTs
UDPGA
UDP
B
B
BG
UGT1A1
+
alb
BG
ABCC3
MRP2

Bilirubin Metabolism:



* Unconjugated bilirubin is bound to albumin in plasma (hydrophobic)

- Beyond neonatal period, **NL bili <١ mg/dL** (# **٩٩% in unconjugated form**).
- Jaundice usually **becomes clinically** apparent when the serum bilirubin concentration is **>٢ mg/dL** which is **٢xUNL(Neonate>٥mg/dL**)

Differential Dx of Indirect Hyperbilirubinemia:

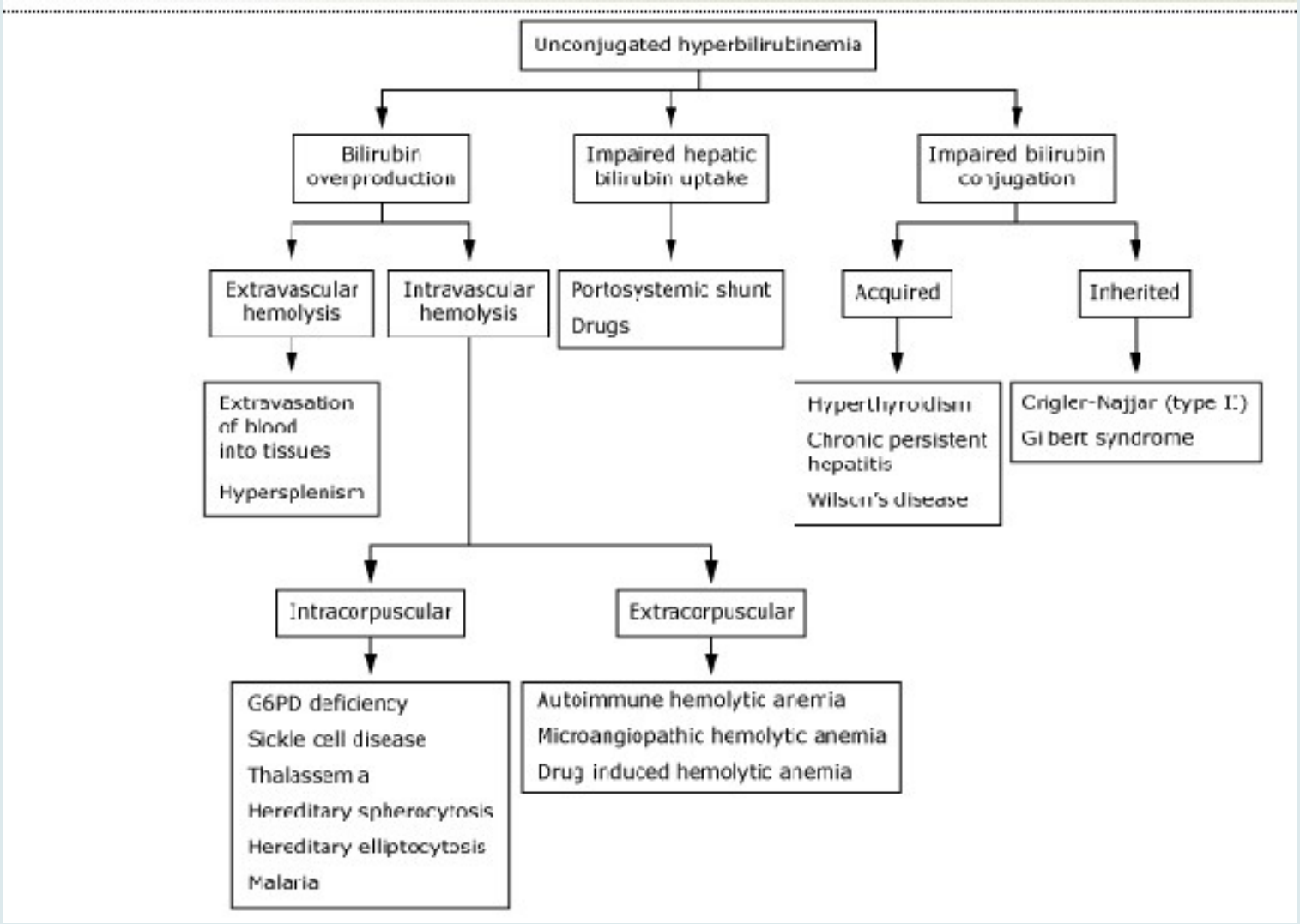
- Disorders of Production: Increased RBC destruction
  - Isoimmunization:
    - Rh, ABO, other component incompatibilities
  - RBC Biochemical defects:
    - G6PD, pyruvate kinase deficiency
  - RBC Structural Abnormalities:
    - Spherocytosis, elliptocytosis, infantile pyknocytosis
  - Infection:
    - Bacterial, viral, protozoal
  - Sequestration:
    - Bruising, cephalohematomas, hemangiomas
  - Polycythemia:
    - IDM, delayed cord clamping
  - Hemoglobinopathy

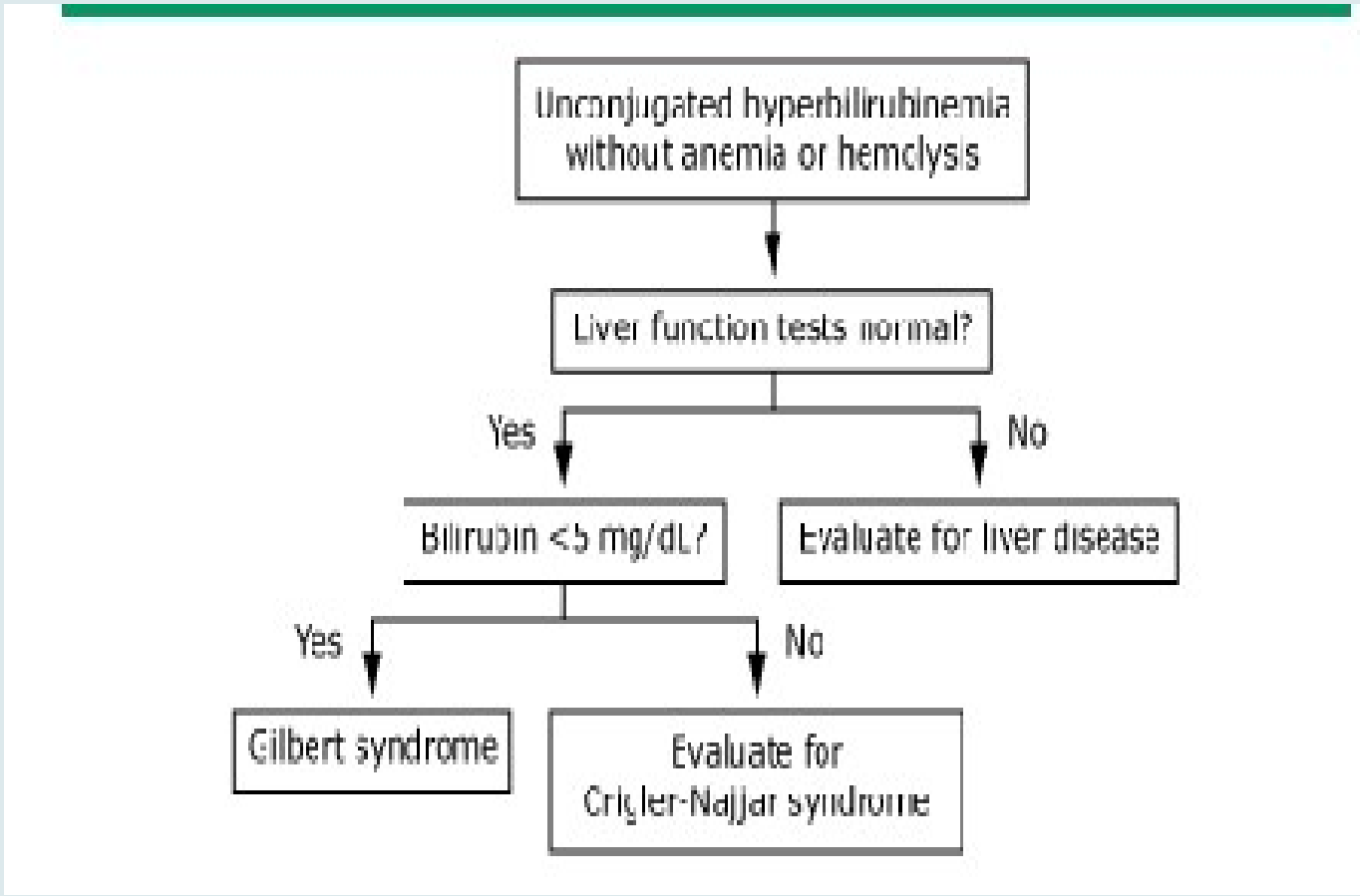
Differential Dx of Indirect Hyperbilirubinemia:

- Disorders of Hepatic Uptake:
  - Gilbert Syndrome

Differential Dx of Indirect Hyperbilirubinemia:

- Disorders of Conjugation:
  - Crigler-Najjar Syndrome Type I
  - Crigler-Najjar Syndrome Type II


Unconjugated hyperbilirubinemia
Bilirubin overproduction
Impaired hepatic bilirubin uptake
Impaired bilirubin conjugation
Extravascular hemolysis
Intravascular hemolysis
Portosystemic shunt
Drugs
Acquired
Inherited
Extravasation of blood into tissues
Hypersplenism
Hyperthyroidism
Chronic persistent hepatitis
Wilson's disease
Crigler-Najjar (type I)
Gilbert syndrome
Intracorpuscular
Extracorpuscular
G6PD deficiency
Sickle cell disease
Thalassemia
Hereditary spherocytosis
Hereditary elliptocytosis
Malaria
Autoimmune hemolytic anemia
Microangiopathic hemolytic anemia
Drug induced hemolytic anemia


Unconjugated hyperbilirubinemia without anemia or hemolysis
Liver function tests normal?
Yes
No
Bilirubin <5 mg/dL?
Evaluate for liver disease
Yes
No
Gilbert syndrome
Evaluate for Crigler-Najjar syndrome

- If the serum bilirubin level is **not elevated**, the jaundiced appearance may represent **carotenemia**,

- usually found in **infants and toddlers** whose diets consist of **large** amounts of **strained yellow vegetables**, particularly carrots.
- Unlike jaundice, the **sclerae are not discolored**.
- In carotenemia, **the skin color** characteristically is more yellow-orange rather than yellow, and more noticeable over **the palms and soles**.

- Although the ***diet*** is a **major cause** of carotenemia in childhood,
- **other causes :**

-- nephrotic syndrome,

-- diabetes mellitus,

-- anorexia nervosa,

-- liver disease,

-- hypothyroidism.

- In patients with **normal liver function**, the serum bilirubin concentration caused by **hemolysis** will ***rarely exceed ۴ mg/dL*** .

- However, hemolysis can lead **to severe hyperbilirubinemia** in patients with **concurrent liver disease, even if mild**.

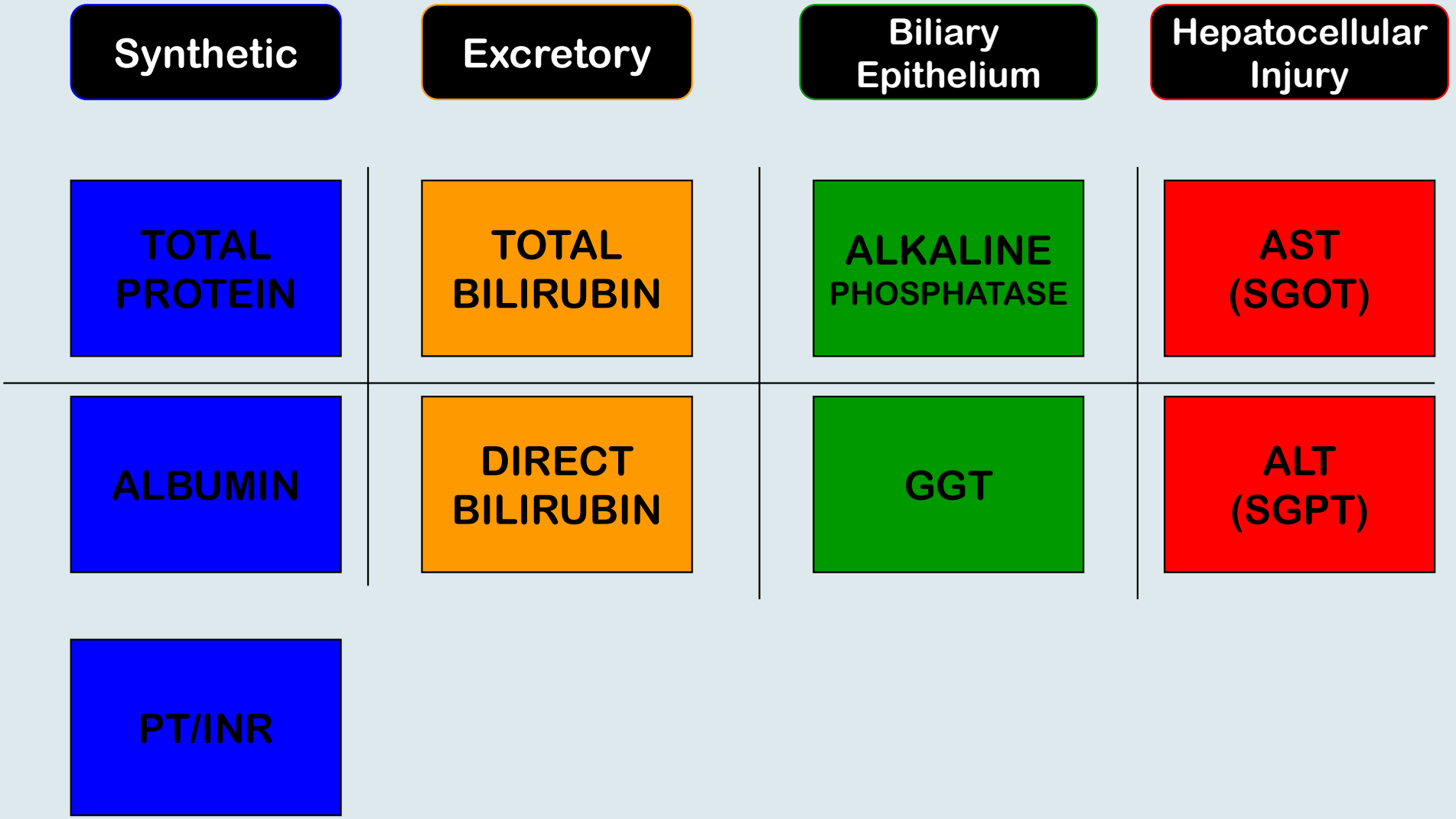
DEFINITION:

- ***Neonatal cholestasis*** is defined as conjugated hyperbilirubinemia developing within the **first ٩٠ days** of extrauterine life.
- Conjugated bilirubin exceeds **١٫٥ to ٢٫٠ mg/dl.**
- a serum direct/conjugated bilirubin **> than ١٫٠** mg/dL if the total serum bilirubin (TSB) is <٥٫٠ mg/dL.

or

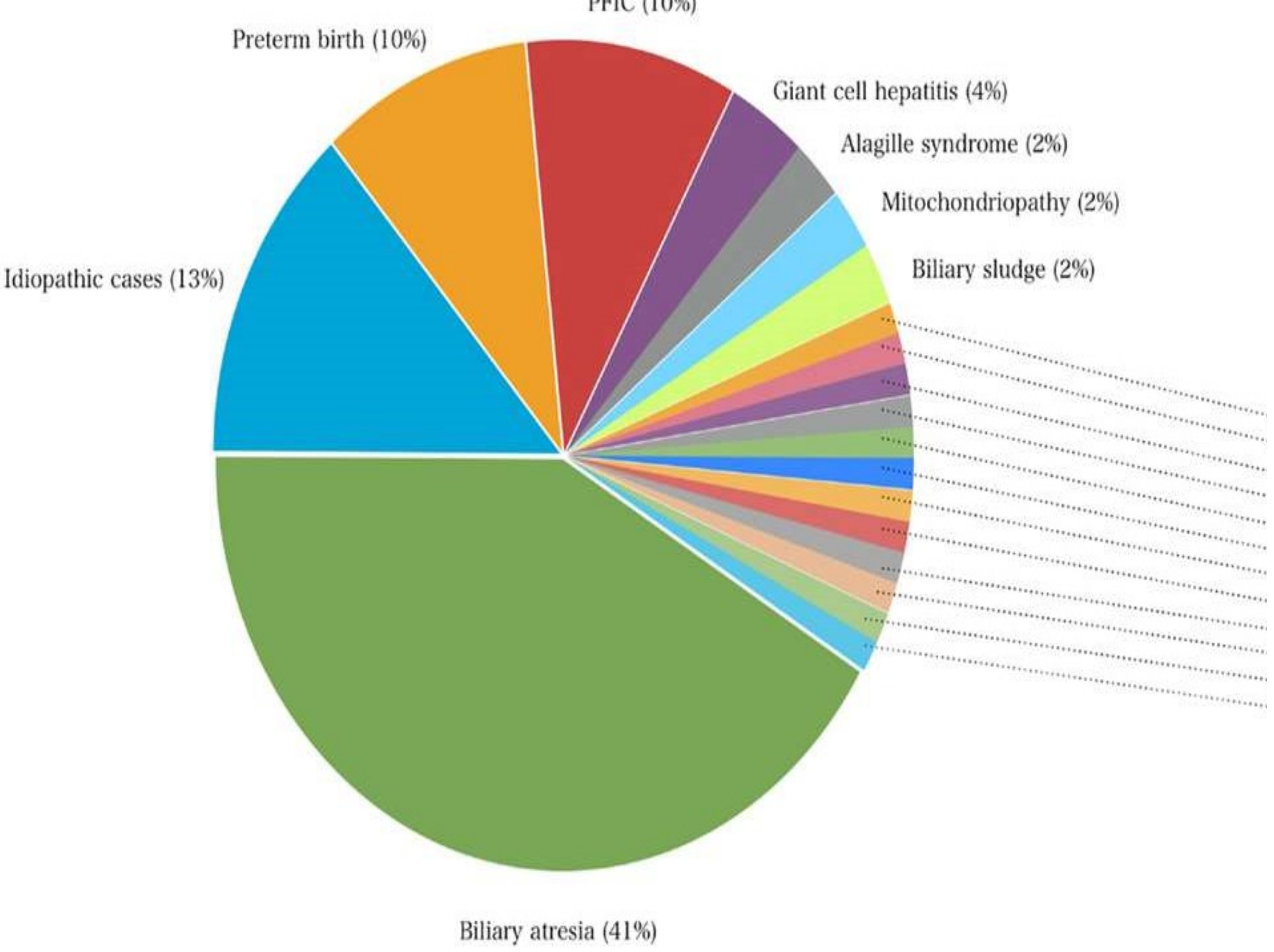
greater than ٢٠ percent of TSB if the TSB is >٥٫٠ mg/dL

Hepatic Function Panel



Frequency of etiologies

INH	١٥%
EHBA	٢٥-٣٠%
α_1AT	٧-١٠%
Intra hep chol. Syn	٢٠%
Bacterial	٢%
CMV	٣-٥%
Rubella, herpes	١%
Endocrine	١%
Galactosemia	١%
Errors of BA synthesis	٢-٥%


PFIC (10%)
Preterm birth (10%)
Giant cell hepatitis (4%)
Alagille syndrome (2%)
Mitochondriopathy (2%)
Biliary sludge (2%)
Idiopathic cases (13%)
Biliary atresia (41%)

STAGED EVALUATION OF NEONATAL CHOLESTASIS

- Differentiate cholestasis from physiologic breast milk jaundice and determine severity of disease
  - Clinical evaluation (history, physical examination, stool color)
  - Fractionated serum bilirubin (+ serum bile acids)
  - Tests of hepatocellular and biliary disease (ALT, AST, alkaline phosphatase, GGT)
  - Tests of hepatic function (serum albumin, prothrombin time, blood glucose, ammonia)
- Exclude treatable and other specific disorders
  - Bacterial cultures (blood, urine)
  - VDRL test and viral serology as indicated (think HSV)
  - α_1-Antitrypsin phenotype
  - T_4 and TSH (rule out hypothyroidism)
  - Metabolic screen: urine-reducing substances (drugs may cause false positives), urine bile acids, serum amino acids, ferritin, urine organic acids
  - Sweat chloride/mutation analysis
- Differentiate extrahepatic biliary obstruction from intrahepatic disorders
  - Ultrasonography
  - Hepatobiliary scintigraphy (not always essential)
  - Liver biopsy

ALT = alanine transaminase; AST = aspartate transaminase; GGT = γ-glutamyl transpeptidase; HSV = herpes simplex virus; T_4 = thyroxine; TSH = thyroid stimulating hormone; VDRL = Venereal Disease Research Laboratory.

IDIOPATHIC NEONATAL HEPATITIS:

- is defined as prolonged conjugated hyperbilirubinemia **without an obvious etiology** after a **complete evaluation** has excluded identifiable **infectious** and **metabolic/genetic** causes.
- Characteristic findings on liver biopsy are **multinucleated giant cells**; **variable inflammation** with infiltration of lymphocytes, neutrophils, and eosinophils; and **little or no bile duct proliferation.**
- However, these findings also are seen in other conditions,
- **diagnosis is exclusion**, will become **increasingly rare**.

- Generally normal stools or acholic stools with onset at one month-old
- Low birth weight
- Normal liver on exam or hepatomegaly with normal to firm consistency
- Male predominance
- Familial cases (١٥-٢٠%)

- Impaired uptake on radionucleotide scan with normal excretion
- Biopsy shows intralobular inflammation with focal hepatocellular necrosis and disruption of the hepatic architecture.
- No alteration of the bile ducts.
- Giant cell transformation occurs but is non-specific.

EXTRAHEPATIC BILIARY ATRESIA

- a progressive idiopathic disease of the extrahepatic biliary tree
- Generally acholic stools with onset at about ٢ weeks-old
- Average birth weight
- Hepatomegaly with firm to hard consistency
- splenomegaly
- Female predominance
- No well-documented familial cases

Biliary Atresia

- Progressive fibro-obliterative disease
- Healthy at birth and early neonatal period
- Initially mild jaundice

B.A

- Liver biopsy

  -bile duct proliferation
  -portal tract edema,fibrosis,inflammation
  -bile plug
- Early histologic changes may be nonspecific.
- Cannot help to distinguish from other causes of obstruction

B.A

- Intraoperative cholangiogram

  -gold standard in the diagnosis of B.A

  -patency be investigated proximally and distally
- Alternative approach

  -percutaneous gallbladder cholangiogram

  -ERCP

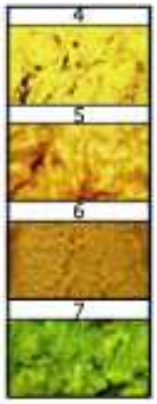
Stool color card used to screen infants for biliary atresia

Infant stool color card

No. of booklet: _____

Abnormal

Normal



It is essential to observe your baby's stool color continuously after discharge from a nursery. If the stool color resembles the numbers 1-3 (white, clay-colored, or light yellowish), the possibility on your baby suffering from biliary atresia is higher. Please take this card and your baby to consult a doctor as quickly as possible. Regardless of what the stool color is, please bring this card to your doctor at 30 days of age for health check. If the baby cannot go back for health check, please fill in the number of the color resembling your baby's stool, along with the following blanks, and mail this card to our registry center.

The baby's stool color is most like No. _____

Date of this kind of stool _____

Name of the baby _____ Birthday_____

Name of the mother _____ Phone _____

Address _____

The hospital or clinic where the baby was born

_____

If the number is No. 1-3, please inform us by fax immediately. We will provide the related infromation

Biliary cysts:

- a rare but treatable cause of conjugated hyperbilirubinemia.
- jaundice,
- abdominal pain,
- abdominal mass,
- vomiting.
- asymptomatic (in sonography seen).
- fibrotic liver disease is likely to develop even in asymptomatic infants
- ascending cholangitis
- biliary adenocarcinoma

- Other extrahepatic causes of biliary obstruction include:
- ●Inspissated bile/plug syndrome (eg, patients with cystic fibrosis)
- ●Gallstones or biliary sludge
- ●Tumors

INFECTIONS :

• Bacterial, protozoal, and viral infections can result in cholestasis.

•Common congenitally acquired pathogens include toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis.

•Less frequent causes are echovirus, adenovirus, and parvovirus B١٩.

•

•**Bacterial infections**, jaundice may be the only presenting sign in patients with a **UTI.**

•**Bacterial infection** also contributes to cholestasis in infants who receive **parenteral nutrition** .

ALPHA-١-ANTITRYPSIN DEFICIENCY

- Alpha-١-antitrypsin makes **up ٩٠% of alpha-١-globulin fraction**
- Associated with **PiZZ** (about **١٠-٢٠%** will have liver disease) and **rarely** with **PiSZ** and **PiZ-null** phenotypes
- Biopsy shows **hepatocellular edema**, **giant cell** transformation, **necrosis**, and **pseudoacinar transformation.**

- Biopsy also shows accumulation **of PAS-positive, diastase-resistant globules** in the **cytoplasm** of **periportal hepatocytes**.
- Varying degrees of **fibrosis** correlate with disease **prognosis.**

INTRAHEPATIC CHOLESTASIS SYNDROMES

- **Includes several** diagnostic entities.

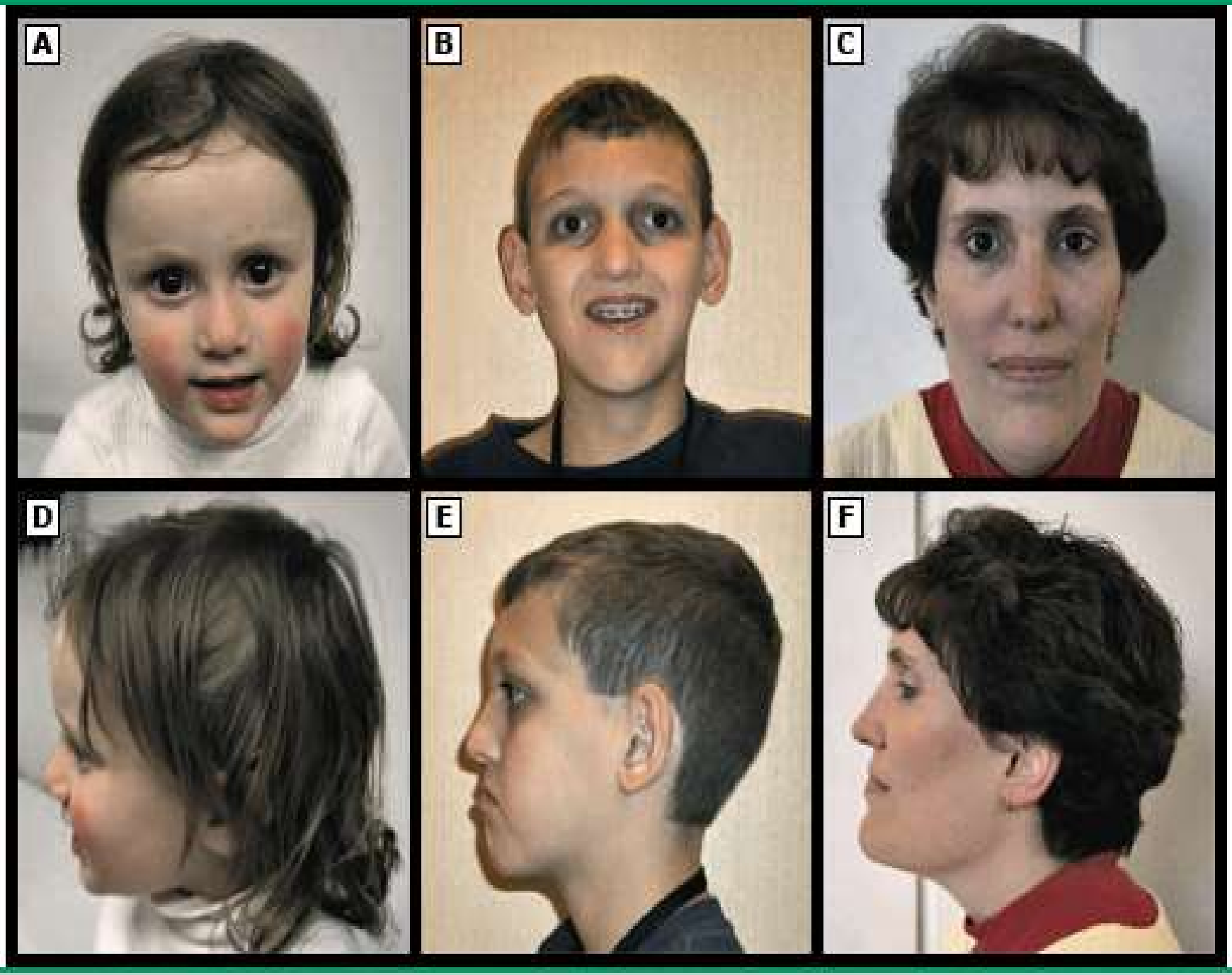
- Biopsies show cholestasis , May show **paucity** of intrahepatic bile ducts, **giant cell** transformation, and/or **fibrosis.**

Alagille syndrome :

- is characterized by the paucity of interlobular bile ducts and the following associated features:
- ●Chronic cholestasis (٩١ percent)
- ●Cardiac anomalies, most commonly peripheral pulmonic stenosis (٨٥ percent)
- ●Butterfly vertebrae (٨٧ percent)
- ●Posterior embryotoxon (prominent Schwalbe line) of the eye (٨٨ percent)
- ●Dysmorphic facies,consisting of broad nasal bridge,triangular facies, and deep set eyes (٩٥%)

- The typical facial features of Alagille syndrome are triangular, with a prominent forehead, deep-set eyes, a pointed chin, and a straight nose with a bulbous tip.
- The facial features change over time, with a more triangular shape during childhood and prominence of the jaw as patients reach adulthood.

Typical facies in Alagille syndrome



- Whether these dysmorphic facies are **specific** to Alagille syndrome is **controversial** .
- Although these features are seen in a **high percentage of patients with Alagille** syndrome, a study found that facial features were **not helpful in distinguishing** Alagille syndrome from other forms of intrahepatic cholestasis .
- authors concluded that these facial features are **characteristic of congenital intrahepatic cholestasis** rather than Alagille syndrome itself.

Galactosemia:

- mixed (conjugated and unconjugated) **hyperbilirubinemia**
- **sepsis** is also common at presentation.
- **Associated features** include **vomiting,** **diarrhea,** **failure to thrive**, **renal tubular acidosis**, **cataracts,** and **coagulopathy.**

Hepatorenal tyrosinemia (also known as hereditary tyrosinemia type ١) is characterized by:

- progressive liver disease,
- renal tubular acidosis,
- neurologic impairment.

- Young infants present with cholestasis and **coagulopathy,** which ***is often disproportionate*** to the apparent degree of liver disease.

Disorders of bile acid metabolism

- Infants with inherited disorders of bile acid synthesis typically develop **severe cholestatic jaundice** from **birth** and **progressive liver failure**.
- Examples of such disorders are ٣-beta-hydroxysteroid **dehydrogenase**/isomerase deficiencies and ٤-oxosteroid ٥-beta **reductase** deficiency.
- inadequate production of primary bile acids , and increased production of aberrant bile acids, which are hepatotoxic…..cholestasis
- Pruritus may or may not be present.

CYSTIC FIBROSIS:

- Neonatal cholestasis is an **uncommon** presentation of CF , occurring in **<٥ %** of patients with CF

- In affected infants**, jaundice** and **hepatomegaly slowly resolve**.

- **Hepatitis** is an **inflammation** of the liver and can result in liver cell **damage** and **destruction.**

- Viral **hepatitis** is one of the most common **causes** of liver disease in the **pediatric** population.

Aminotransferases (formerly transaminases), :

- In ***adults***, normal ALT = ٢٩ to ٣٣ units/L for males and ١٩ to ٢٥ units/L for females.

- Levels above these values should be assessed for **underlying liver disease**

- In ***children***, normal ALT = ١٧ to ٢١ units/L in boys and ١٤ to ٢٠ units/L in girls,

- **AST is present in :**

- liver
- other organs (cardiac muscle, skeletal muscle, kidney, and brain).
- In children, levels decline with age, more so in girls than boys after age ١١.

- ***ALT is present :***

- **primarily** in the liver,
- thus is a **more specific** marker of hepatocellular cell injury.
- correlate with degree of **abdominal adiposity**
- cutoff values should be adjusted for **gender** and **BMI** (**but not age**)

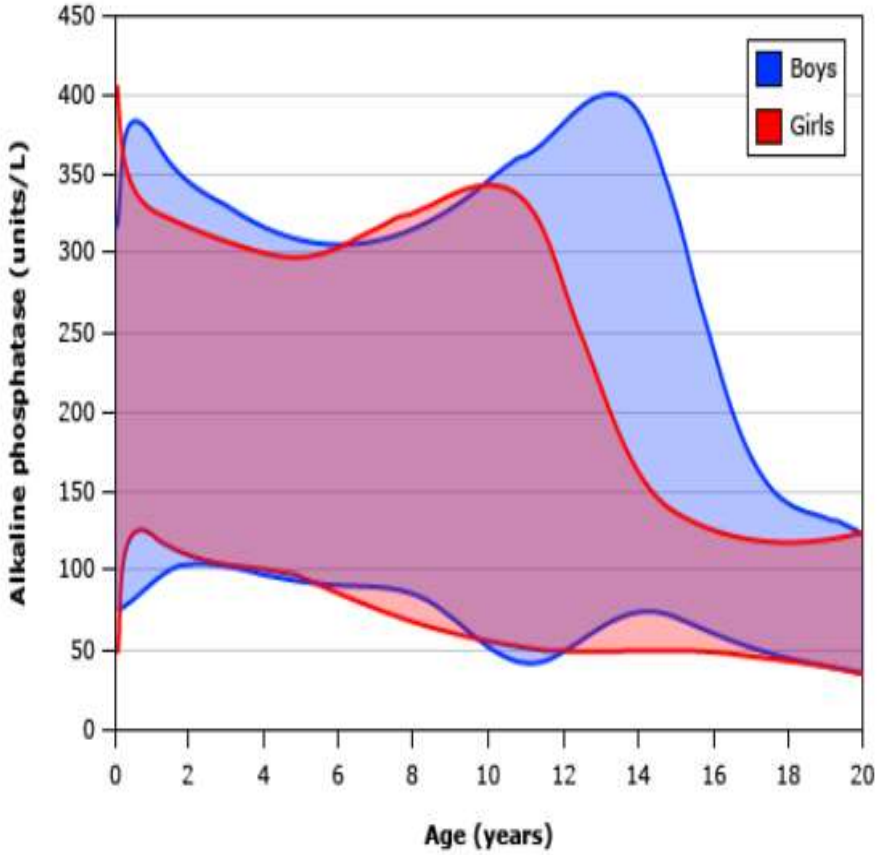
Alkaline phosphatase:

- is derived *predominantly* from the liver and bones.
- An ***elevated Alkp*** can be *fractionated* to determine if it originates from the liver ***or bones***,
- although in practice a liver source is usually confirmed by the simultaneous elevation of other measures of cholestasis (eg, gamma-glutamyl transpeptidase, ٥'-nucleotidase)

Other sources of Alkp :

- Women in the third trimester of pregnancy(influx of **placental** Alkp).
- blood types O and B can have elevated serum Alkp levels after eating a fatty meal (an influx of **intestinal** Alkp).
- **Infants and toddlers** occasionally display transient marked elevations of Alkp in the absence of detectable bone or liver disease.
- In patients with **diabetes mellitus** .

Reference range for serum alkaline phosphatase activity in children and adolescents



Normal ranges for serum alkaline phosphatase activity for boys (blue) and girls (red).

Data from: NIH Clinical reference laboratory, available at: www.cc.nih.gov/ccc/pedweb/pedsstaff/pedlab.html.

Gamma-glutamyl transpeptidase(GGT)

-
- in hepatocytes and biliary epithelial cells,
- in the kidney, seminal vesicles, pancreas, spleen, heart, and brain.
- In normal full-term neonates, serum GGT activity is **six to seven times ULN of the adult** reference range;
- levels then decline and reach low levels by five to seven months of age [١١].
- A gradual increase occurs in girls until age ١٠ and in boys through adolescence

٥'-nucleotidase:

- liver,
- intestine,
- brain,
- heart,
- blood vessels,
- endocrine pancreas,

but it is only released into serum by hepatobiliary tissue.

- its physiologic function is unknown, ٥'-nucleotidase specifically catalyzes hydrolysis of nucleotides such as adenosine ٥'-phosphate, in which the phosphate is attached to the ٥ position of pentose moiety.

Lactate dehydrogenase(LDH)

- a cytoplasmic enzyme present in tissues throughout the body .
- Five isoenzyme forms of LDH are present in serum and can be separated by various electrophoretic techniques.
- The slowest migrating band predominates in the liver .
- This test is not as sensitive as the serum aminotransferases in liver disease and has poor diagnostic specificity, even when isoenzyme analysis is used.
- It is more useful as a marker of hemolysis.
- It can be used in practice to **distinguish ischemic hepatitis** from viral hepatitis
- was used in the past as a marker of **myocardial infarction**

•**Hepatocellular injury** – elevations in ALT and AST. Examples include viral hepatitis, metabolic disorders, and drug toxicity.

•**Cholestatic injury** – elevations of serum ALKP and GGTP, out of proportion to elevation of ALT and AST.

Cholestasis develops due to:

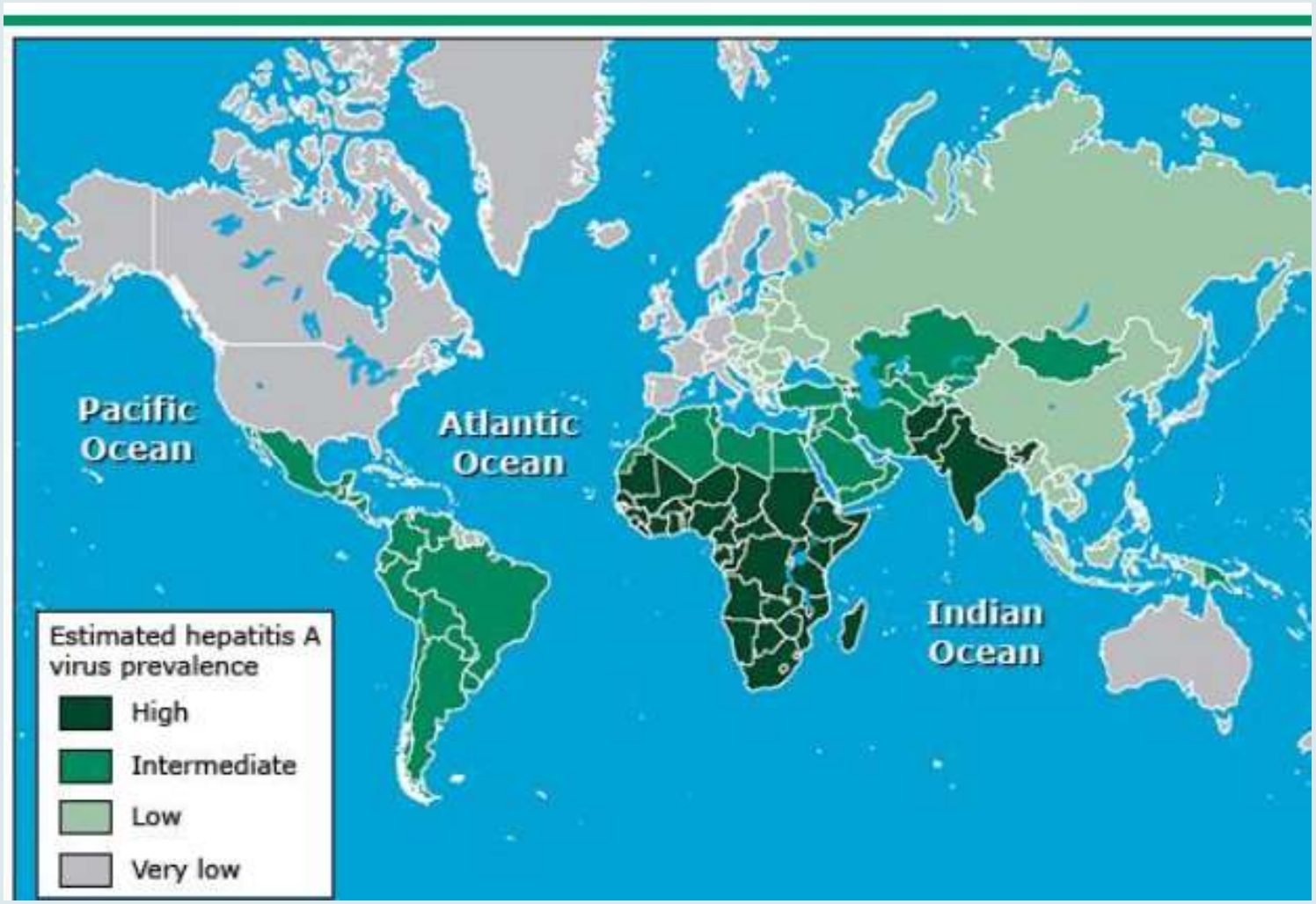
١- diminished bile formation .

٢- diminished excretion

٣-BOTH

• **Both**.

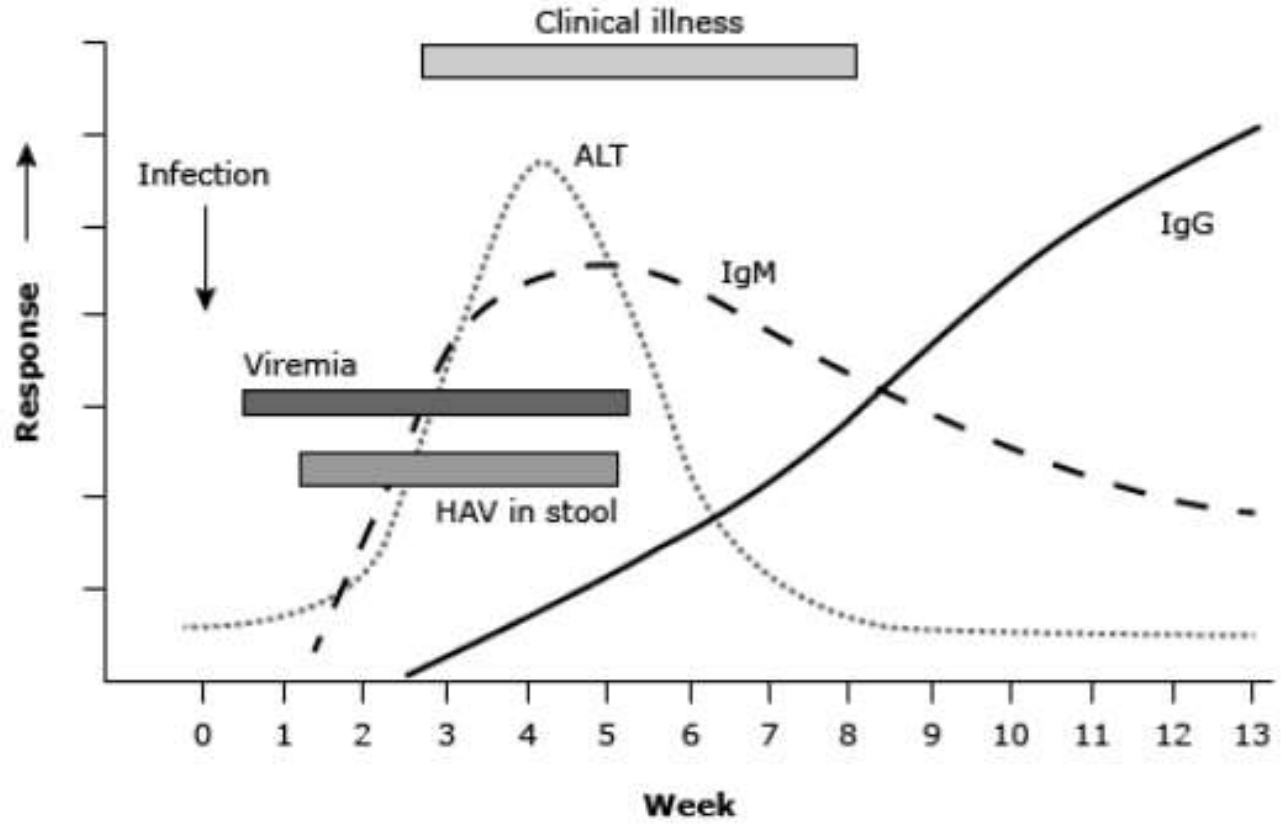
prevalence of antibody to hepatitis A virus (anti-HAV IgG), a marker of previous HAV infection



- one of the most commonly reported **vaccine-preventable** diseases

- incidence in **USA** has **declined** substantially since vaccination was recommended for:
- persons at **increased risk** (in ١٩٩٦),
- children living in states with the **highest incidence** of HAV (in ١٩٩٩),
- **all children** (in ٢٠٠٦) .

- is **still** an important issue in USA.


Clinical illness
Infection
ALT
IgG
IgM
Viremia
HAV in stool
Response
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Week

-

- **HAV RNA** can be detected ***in stools*** **at least** ***one week*** **before** the onset of histological and biochemical evidence of hepatitis, and it can be detected **for at least** ***٣٣ days*** **after** the onset of disease.

- In **neonates and younger** children, HAV RNA can be detected in stools **for several months**.

- HAV disease tends to be **more severe** when acquired at **older ages.**
- under **six** years of age **only one third** develop symptomatic hepatitis, and this often lasts less than **two weeks**.
- **most older children and adults** with HAV infection are jaundiced and have **hepatomegaly**, and they are usually symptomatic for **several weeks**.

- **Acute liver failure** is **rare**,(<١%)

diagnosis

- made by the detection of ***anti-HAV IgM*** in a patient with the ***typical clinical presentation.***
- is the **gold standard** for the detection of acute illness.
- is ***positive*** **at the onset** of **symptoms**,
- ***peaks*** during the **acute or early convalescent phase** of the disease,
- ***remains*** positive for # ***٤-٦ months*** .

PREVENTION AND PROPHYLAXIS:

- **Humans** are the ***only*** known **reservoir** for HAV.
- therefore, virus could be ***eradicated*** with successful prevention strategies.
- hepatitis A vaccine became available in **USA** in ١٩٩٥, HAV infection has declined by **٩٥%**

improved sanitary conditions:

- handwashing
- heating foods appropriately, virus can be inactivated by heating to >٨٥°C for **one minute.**
- avoidance of water and foods from endemic areas.

- **Handwashing** is ***highly effective*** in preventing transmission of virus, since HAV may survive for **up to ٤ hours** on the ***fingertips.***
- ***Chlorination*** and certain **disinfecting** solutions (household bleach ١:١٠٠ dilution) are sufficient to inactivate the virus

pre-vaccination serologic test

- is **no** indication FOR **children** .
- IN **adults** should be based on:
- the expected **prevalence** of immunity,
- **cost** of vaccination compared with the cost of testing .

- Children should not return to school or daycare until:

١- **one week** **after** onset of the illness,

٢- the prophylaxis program for contacts is completed, or directed by the responsible health department .


با تشکر فراوان