
بنام خدا

Icter

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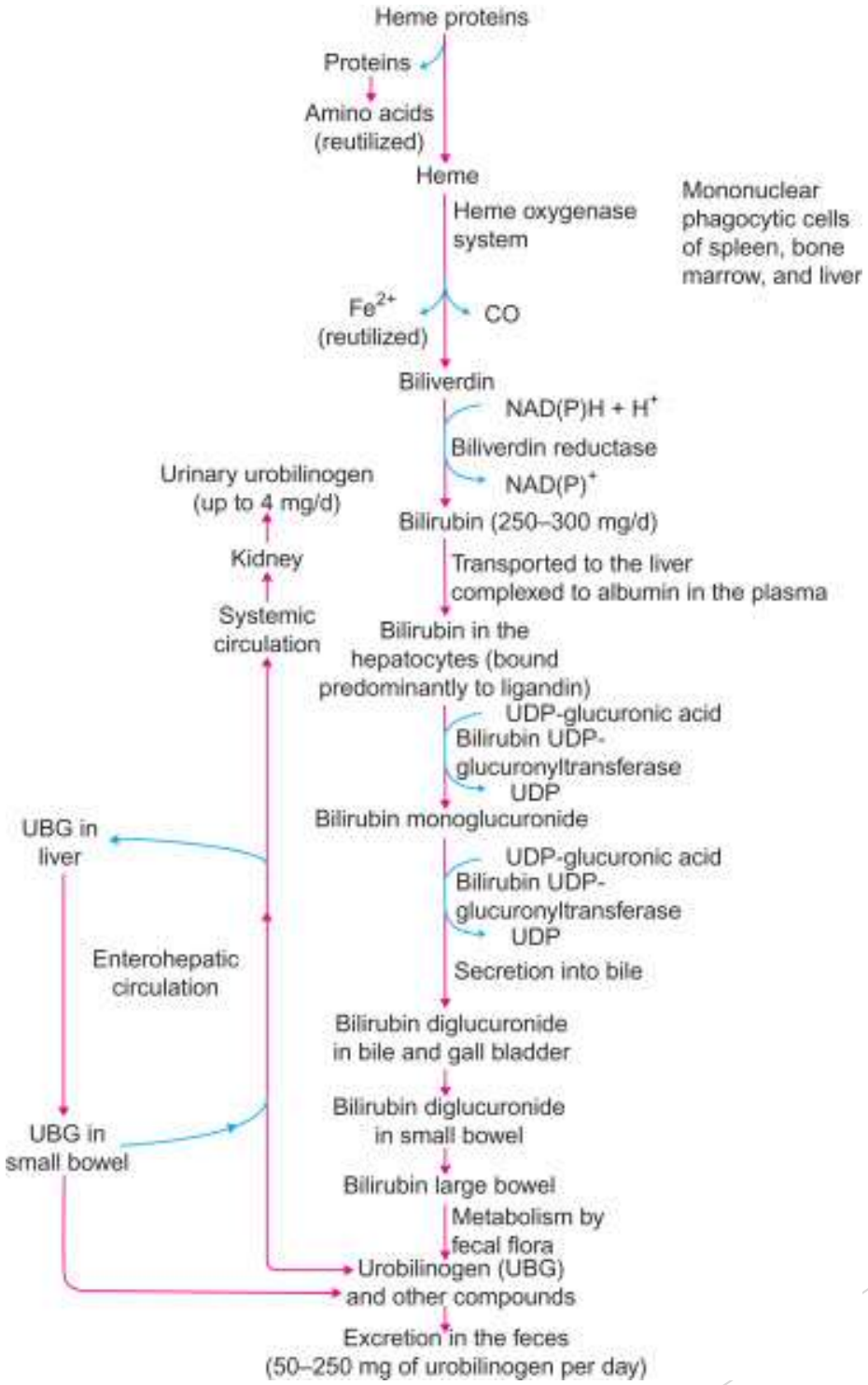
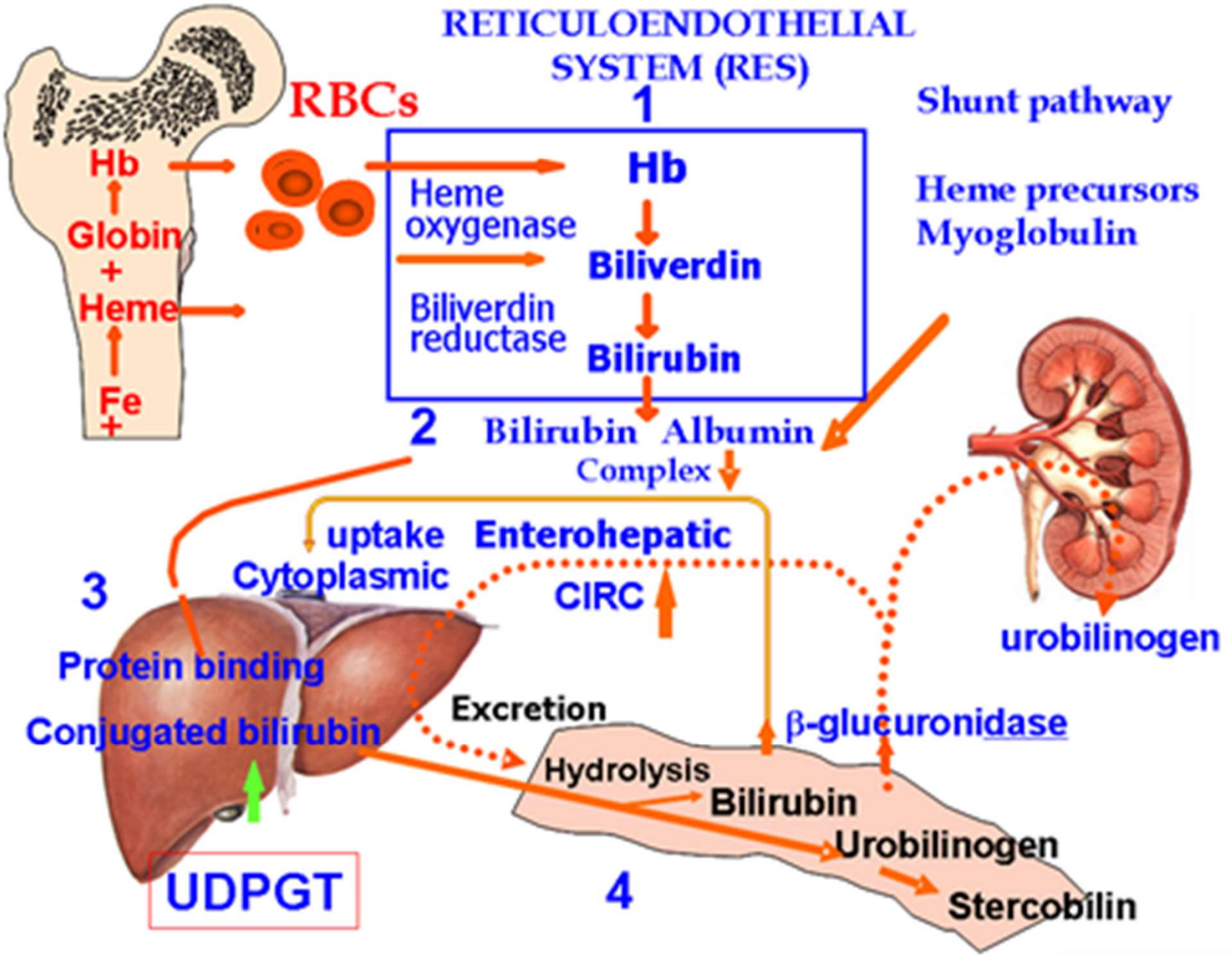
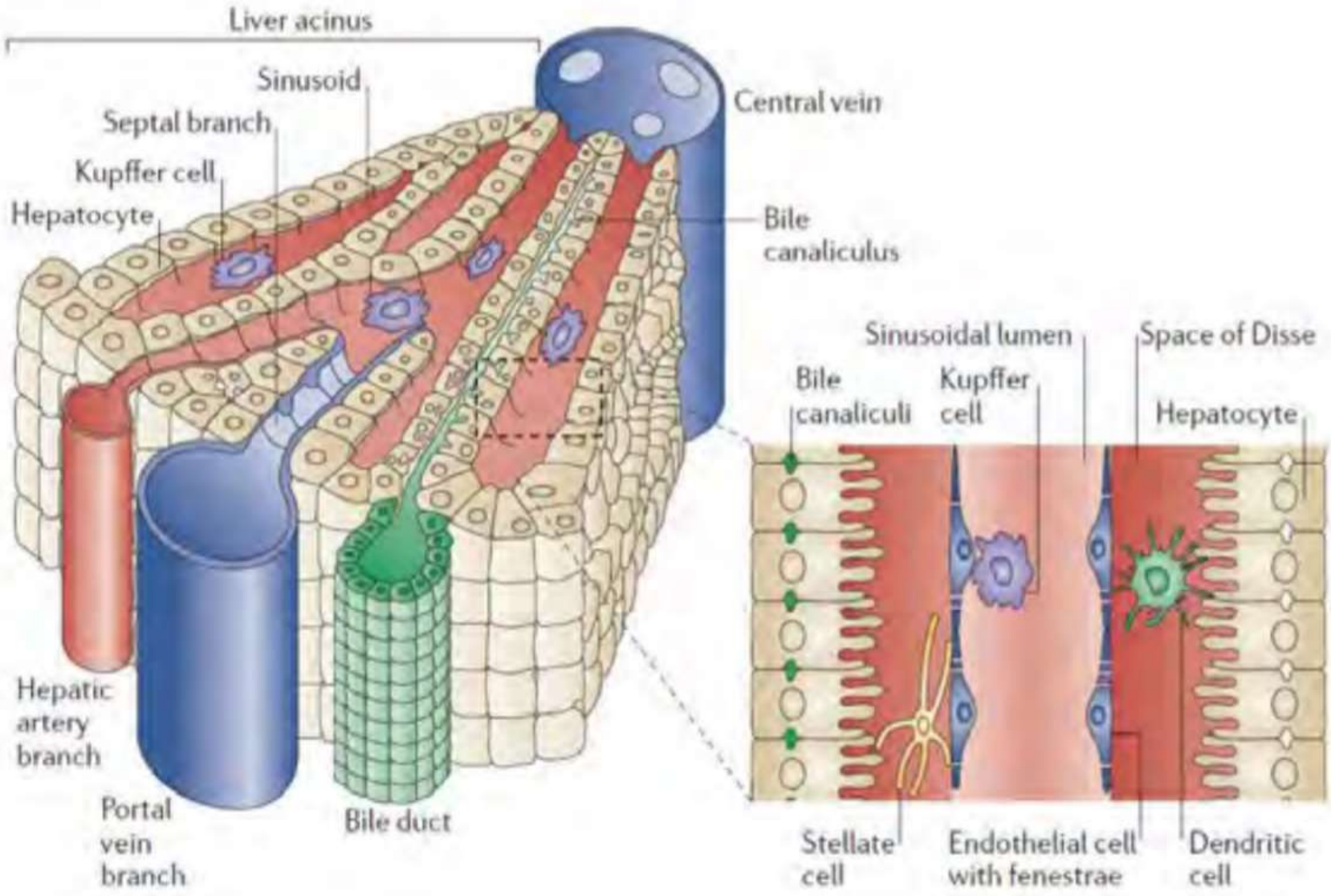
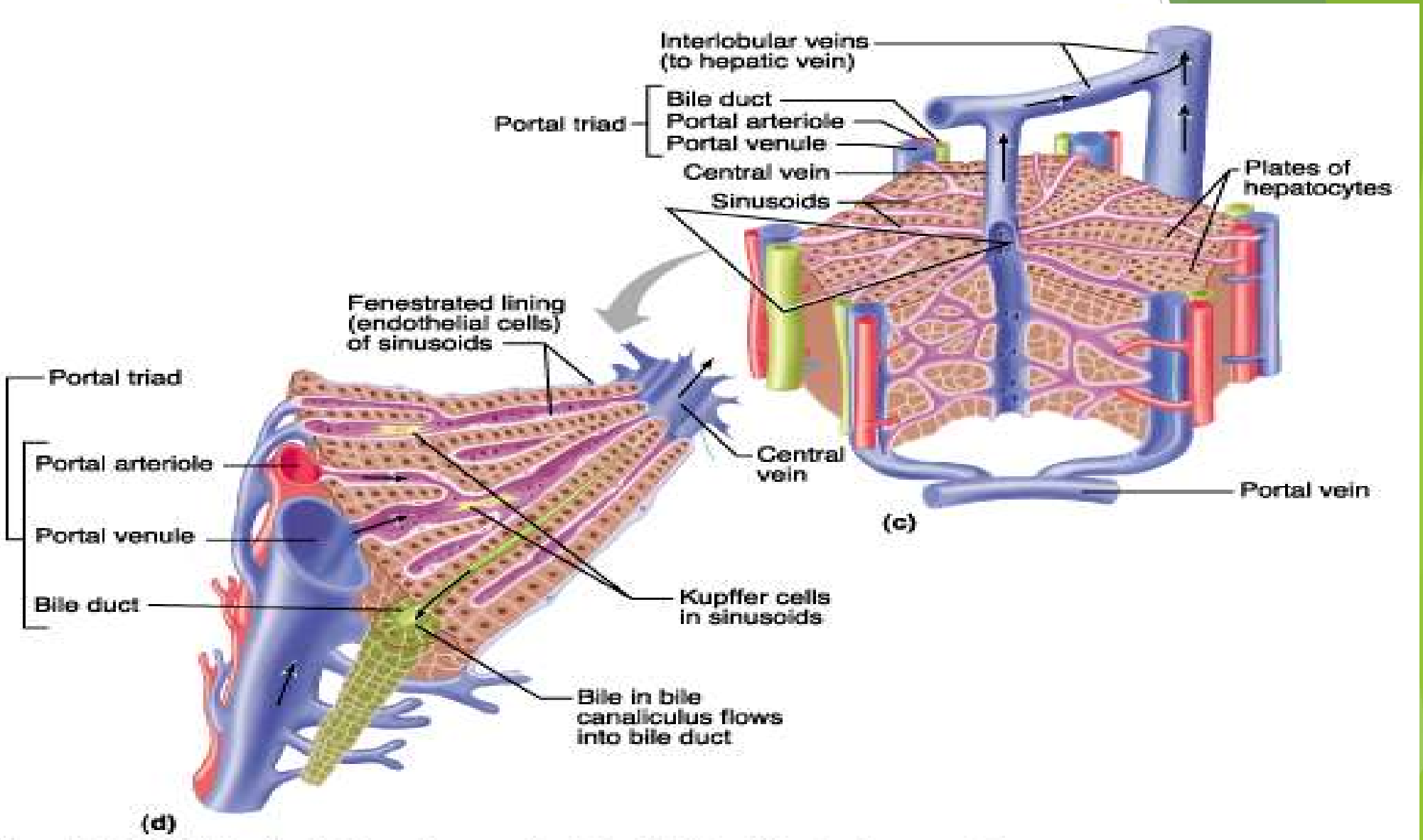
References

- Nelson ٢٠١٩
- Liver Disease In Children (Suchy) ٥th edition
- Uptodate

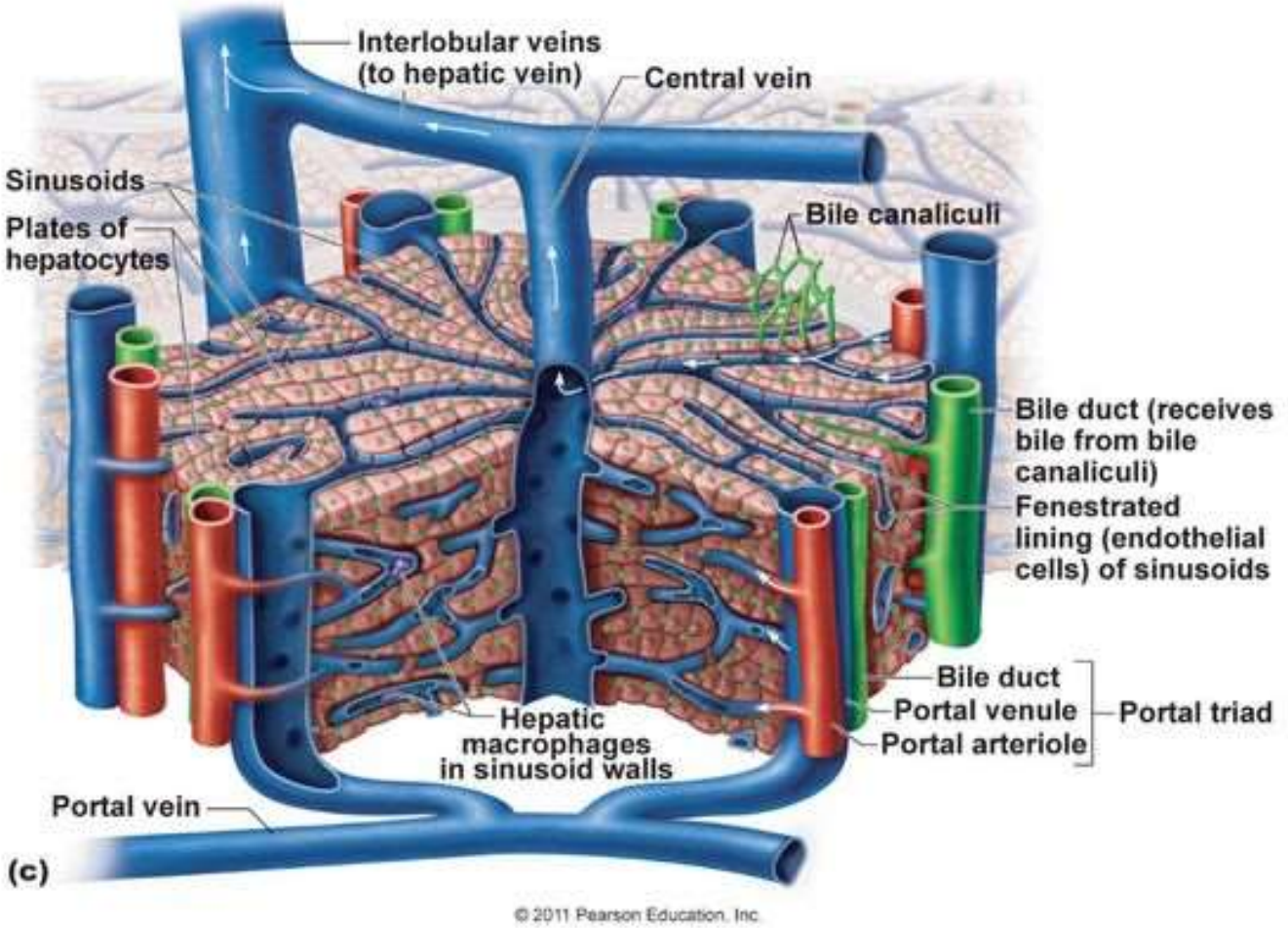

Heme proteins
Proteins
Amino acids
(reutilized)
Heme
Heme oxygenase
system
Mononuclear
phagocytic cells
of spleen, bone
marrow, and liver
Fe2+
(reutilized)
CO
Biliverdin
NAD(P)H + H+
Biliverdin reductase
NAD(P)+
Urinary urobilinogen
(up to 4 mg/d)
Bilirubin (250–300 mg/d)
Kidney
Transported to the liver
complexed to albumin in the plasma
Systemic
circulation
Bilirubin in the
hepatocytes (bound
predominantly to ligandin)
UDP-glucuronic acid
Bilirubin UDP-
glucuronyltransferase
UDP
Bilirubin monoglucuronide
UBG in
liver
UDP-glucuronic acid
Bilirubin UDP-
glucuronyltransferase
UDP
Enterohepatic
circulation
Secretion into bile
Bilirubin diglucuronide
in bile and gall bladder
Bilirubin diglucuronide
in small bowel
UBG in
small bowel
Bilirubin large bowel
Metabolism by
fecal flora
Urobilinogen (UBG)
and other compounds
Excretion in the feces
(50–250 mg of urobilinogen per day)


RETICULOENDOTHELIAL SYSTEM (RES)
RBCs
1
Shunt pathway
Hb
Globin
+
Heme
Fe
+
Heme oxygenase
Hb
Biliverdin
Biliverdin reductase
Bilirubin
Heme precursors
Myoglobulin
2
Bilirubin Albumin Complex
uptake
Cytoplasmic
Enterohepatic CIRC
3
Protein binding
Conjugated bilirubin
Excretion
β-glucuronidase
Hydrolysis
Bilirubin
Urobilinogen
Stercobilin
urobilinogen
UDPGT
4

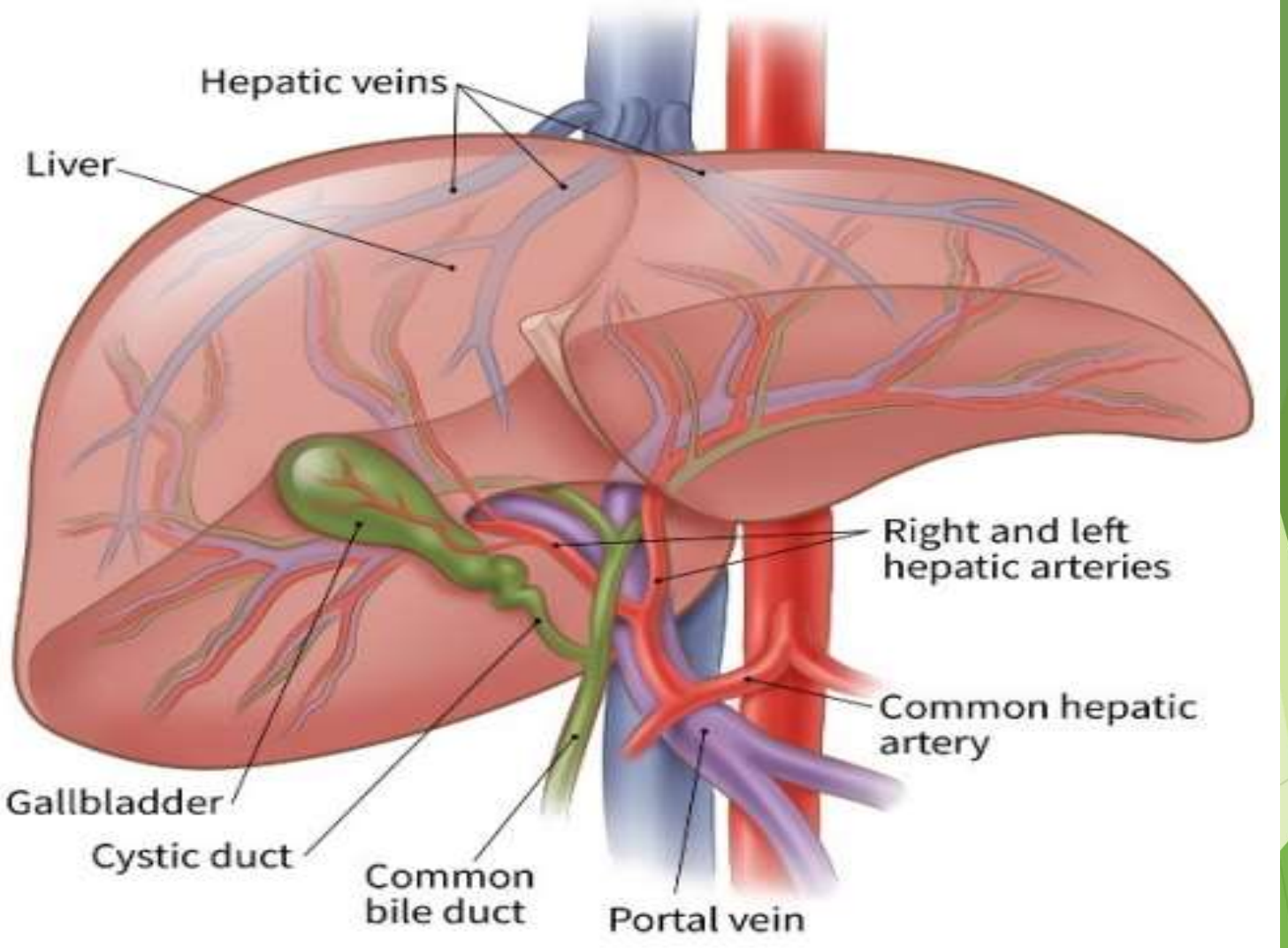

Liver acinus
Sinusoid
Septal branch
Kupffer cell
Hepatocyte
Central vein
Bile canaliculus
Hepatic artery branch
Portal vein branch
Bile duct
Sinusoidal lumen
Space of Disse
Bile canaliculi
Kupffer cell
Hepatocyte
Stellate cell
Endothelial cell with fenestrae
Dendritic cell



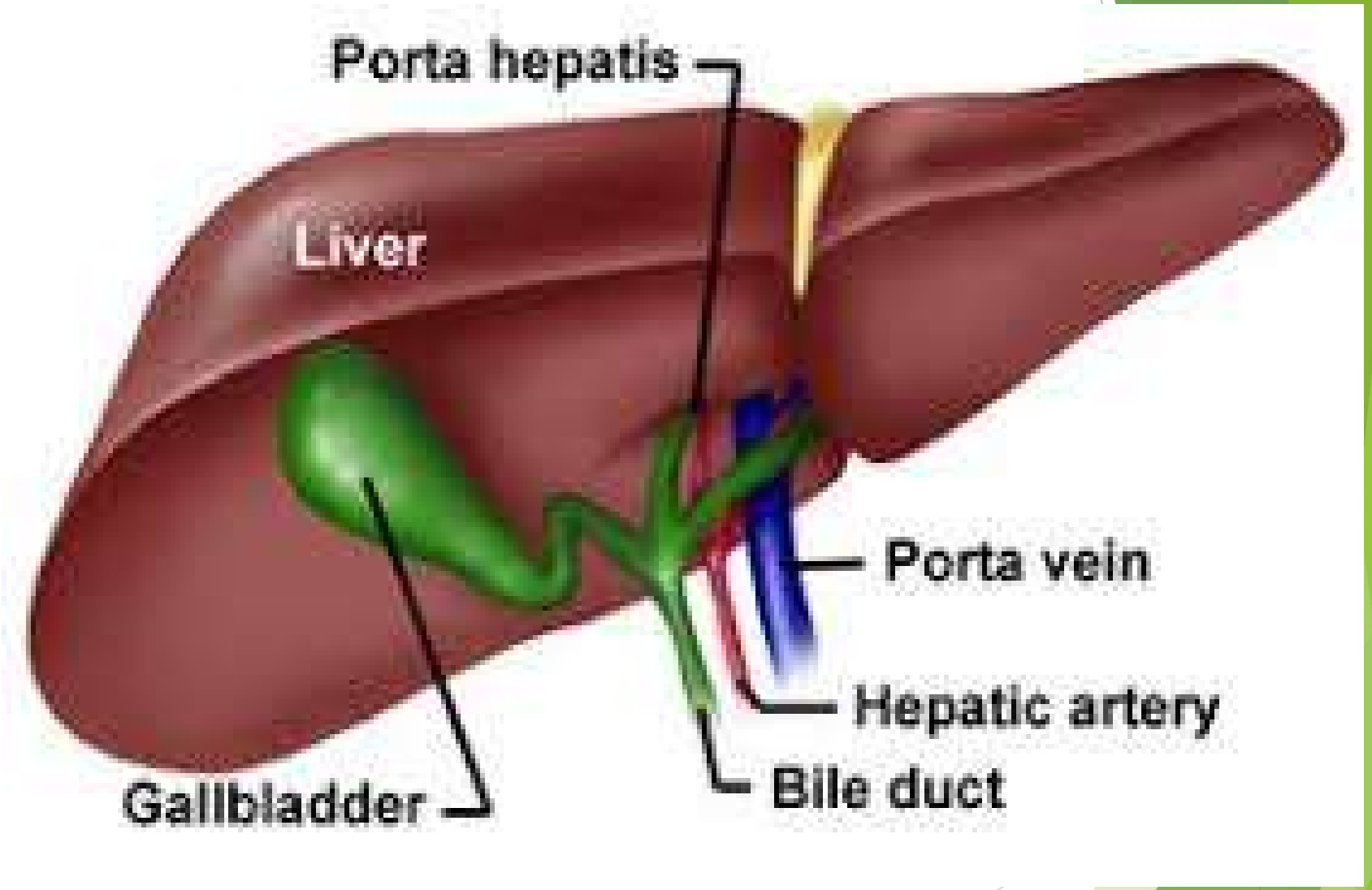
Stracture of a lobule



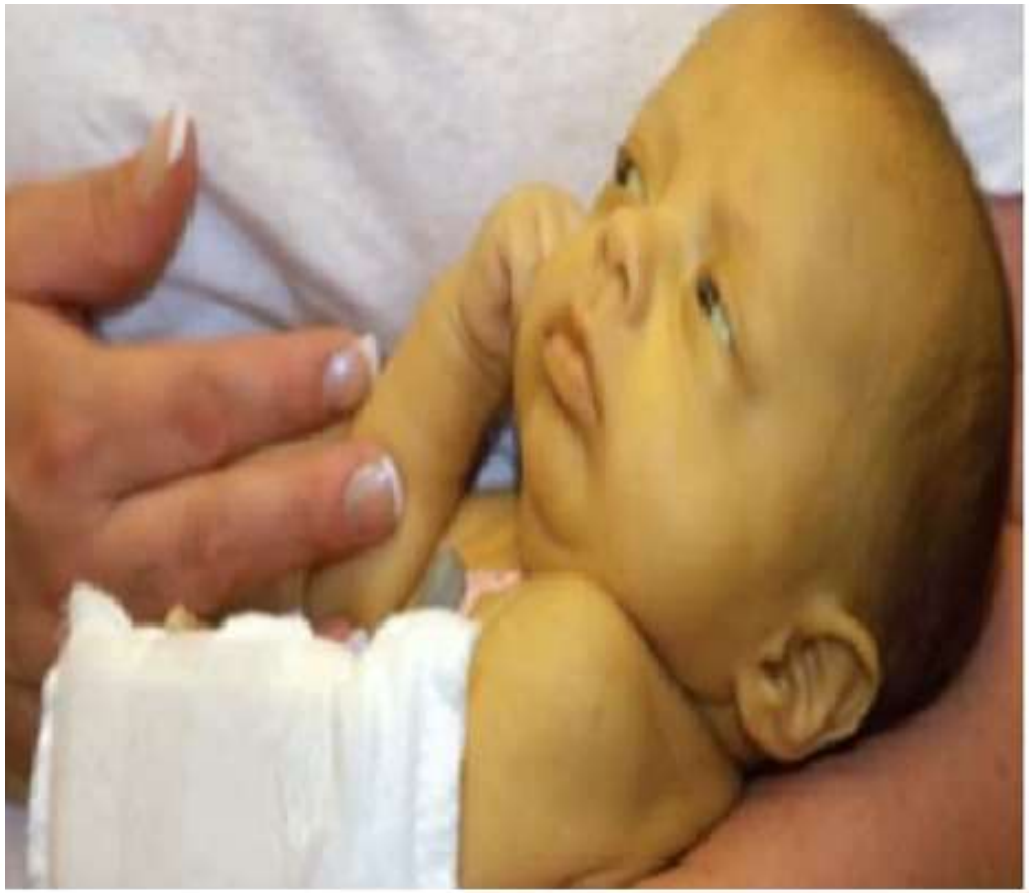
Anatomy of liver



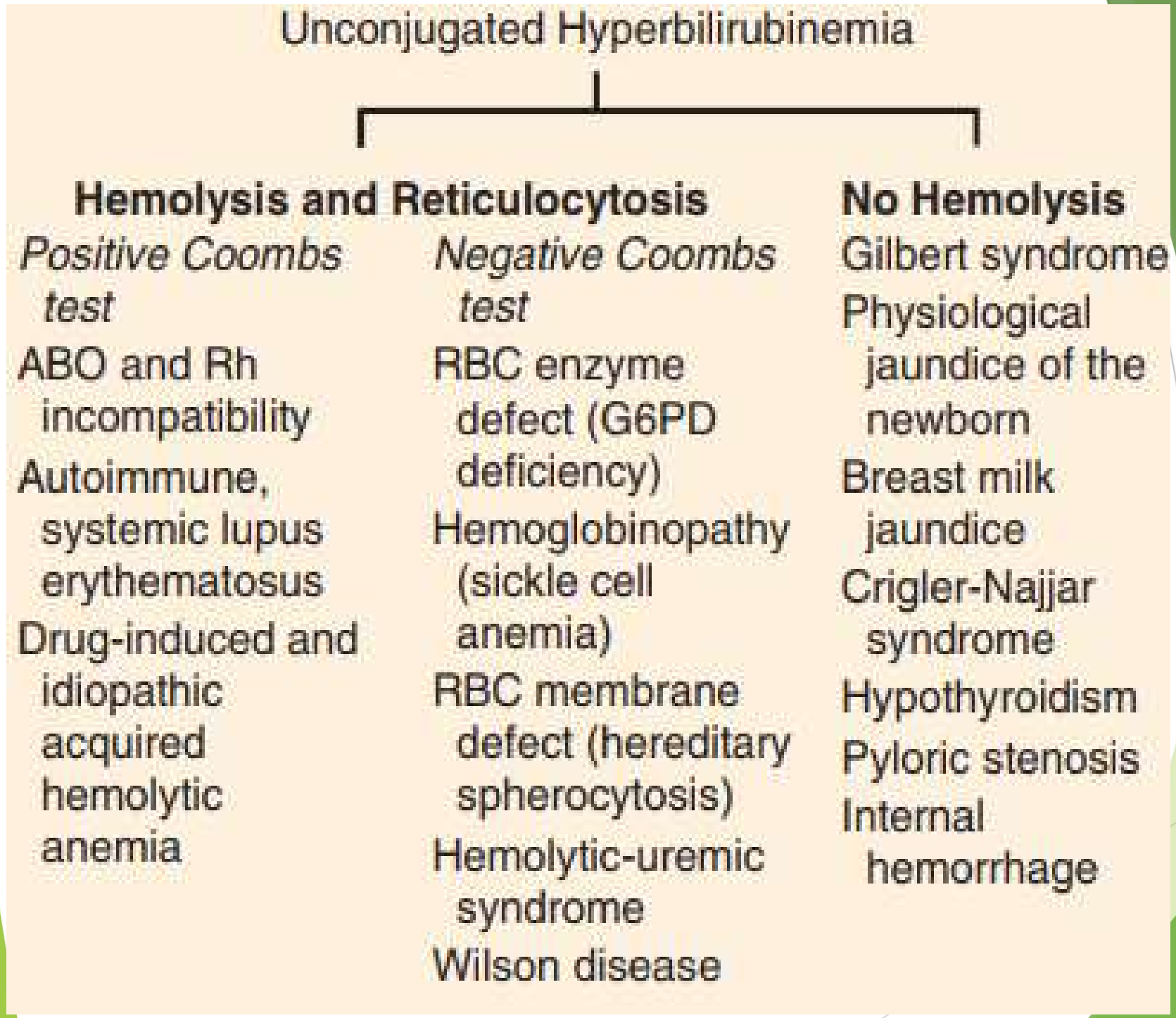
Anatomy of liver



Direct Hyperbilirubinemia



Indirect Hyperbilirubinemia


Unconjugated Hyperbilirubinemia
Hemolysis and Reticulocytosis
Positive Coombs test
ABO and Rh incompatibility
Autoimmune, systemic lupus erythematosus
Drug-induced and idiopathic acquired hemolytic anemia
Negative Coombs test
RBC enzyme defect (G6PD deficiency)
Hemoglobinopathy (sickle cell anemia)
RBC membrane defect (hereditary spherocytosis)
Hemolytic-uremic syndrome
Wilson disease
No Hemolysis
Gilbert syndrome
Physiological jaundice of the newborn
Breast milk jaundice
Crigler-Najjar syndrome
Hypothyroidism
Pyloric stenosis
Internal hemorrhage

Indirect Hyperbilirubinemia

١.DISORDERS OF PRODUCTION

Disorders associated with increased erythrocyte destruction:

ISOIMMUNIZATION

- Rh incompatibility
- ABO incompatibility
- Other blood group incompatibilities

ERYTHROCYTE BIOCHEMICAL DEFECTS

- Glucose-٦-phosphate dehydrogenase deficiency
- Pyruvate kinase deficiency
- Hexokinase deficiency
- Congenital erythropoietic porphyria
- Other biochemical defects

STRUCTURAL ABNORMALITIES OF ERYTHROCYTES

- Hereditary spherocytosis
- Hereditary elliptocytosis
- Infantile pyknocytosis
- Other

INFECTION

- Bacterial
- Viral
- Protozoal

SEQUESTERED BLOOD

- Subdural hematoma and cephalohematoma
- Ecchymoses
- Hemangiomas

٢.DISORDERS OF HEPATIC UPTAKE

Gilbert syndrome

٣.DISORDERS OF CONJUGATION

Crigler-Najjar Syndrome Type I

Crigler-Najjar Syndrome Type ll

Transient Familial Neonatal Hyperbilirubinemia (Lucey-Driscoll Syndrome)

Pyloric Stenosis

Hypothyroidism

۴.DISORDERS OF EXCRETION

- Impaired hepatic excretion of bilirubin from disorders such as hepatocyte injury results in conjugated hyperbilirubinemia

۵.DISORDERS OF ENTEROHEPATIC CIRCULATION

- BREAST-FEEDING FAILURE JAUNDICE
- BREAST MILK JAUNDICE

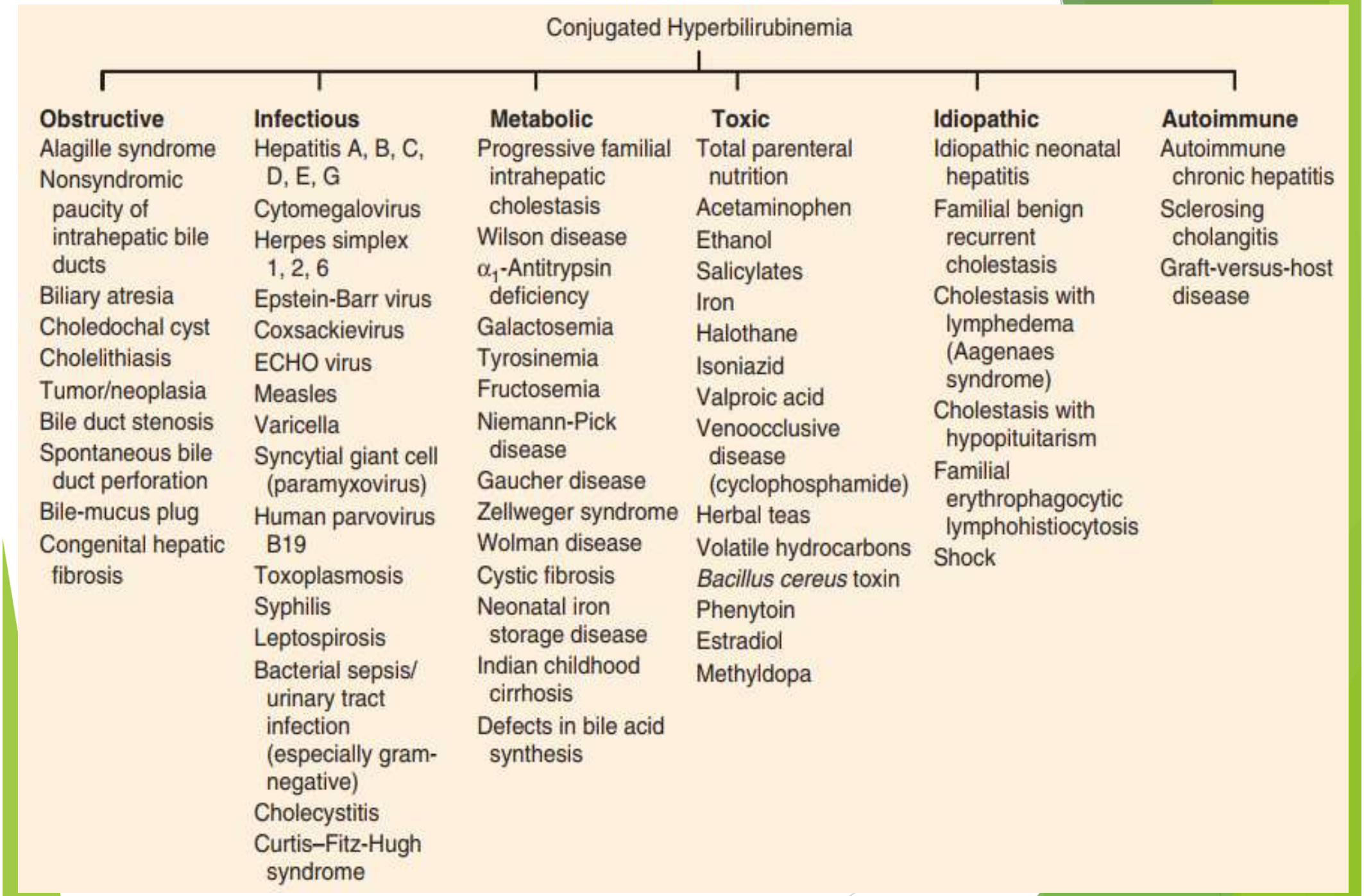
Cholestasis

- Measurable decrease in bile flow
- Accumulation in blood and extrahepatic tissues of substances normally excreted in bile (e.g. bilirubin, bile acids, and cholesterol)

When cholestasis occurs?

Impaired bile formation by the hepatocyte ⇨ intrahepatic

Obstruction to the flow of bile through the biliary tree ⇨ extrahepatic


Conjugated Hyperbilirubinemia
Obstructive
Alagille syndrome
Nonsyndromic paucity of intrahepatic bile ducts
Biliary atresia
Choledochal cyst
Cholelithiasis
Tumor/neoplasia
Bile duct stenosis
Spontaneous bile duct perforation
Bile-mucus plug
Congenital hepatic fibrosis
Infectious
Hepatitis A, B, C, D, E, G
Cytomegalovirus
Herpes simplex 1, 2, 6
Epstein-Barr virus
Coxsackievirus
ECHO virus
Measles
Varicella
Syncytial giant cell (paramyxovirus)
Human parvovirus B19
Toxoplasmosis
Syphilis
Leptospirosis
Bacterial sepsis/ urinary tract infection (especially gram-negative)
Cholecystitis
Curtis–Fitz-Hugh syndrome
Metabolic
Progressive familial intrahepatic cholestasis
Wilson disease
α_1-Antitrypsin deficiency
Galactosemia
Tyrosinemia
Fructosemia
Niemann-Pick disease
Gaucher disease
Zellweger syndrome
Wolman disease
Cystic fibrosis
Neonatal iron storage disease
Indian childhood cirrhosis
Defects in bile acid synthesis
Toxic
Total parenteral nutrition
Acetaminophen
Ethanol
Salicylates
Iron
Halothane
Isoniazid
Valproic acid
Venoocclusive disease (cyclophosphamide)
Herbal teas
Volatile hydrocarbons
Bacillus cereus toxin
Phenytoin
Estradiol
Methyldopa
Idiopathic
Idiopathic neonatal hepatitis
Familial benign recurrent cholestasis
Cholestasis with lymphedema (Aagenaes syndrome)
Cholestasis with hypopituitarism
Familial erythrophagocytic lymphohistiocytosis
Shock
Autoimmune
Autoimmune chronic hepatitis
Sclerosing cholangitis
Graft-versus-host disease

Classification of Cholestatic Disorders

- ***Infectious***: CMV, HSV, HBV, Adenovirus, Toxoplasmosis, rubella, UTI, SEPSIS, TB, …
- ***Toxins:*** Drugs (including ceftriaxone), TPN, aluminum, prenatal alcohol and methamphetamine exposure, herbal products
- ***Endocrine:*** Hypothyroidism, panhypopituitarism
- ***Immune:*** Gestational alloimmune liver disease
- ***Cardiovascular:*** Shock and hypoperfusion (heart failure, asphyxia,…), Budd-Chiari syndrome, Veno-occlusive disease
- ***Anatomic obstruction:*** Biliary atresia, Choledochal cyst, Cholelithiasis, Biliary sludge, inspissated bile, mucus plug, perforation of choleduct, Tumor or mass, Bile duct stenosis
- Genetic and metabolic
- Other: Idiopathic neonatal hepatitis/transient neonatal cholestasis, Malignancy (leukemia, neuroblastoma, hepatoblastoma),HLH, GVHD, Histiocytosis X

Genetic and metabolic:

- Aagenaes syndrome/hereditary cholestasis with lymphedema
- (LSC١)
- α-١-antitrypsin deficiency (SERPINA١)
- Alagille syndrome (JAGGED١, NOTCH٢)
- Arthrogryposis-renal dysfunction-cholestasis syndrome
- (VPS٣٣BVPS٣٣BVPS٣٣BVPS٣٣B, VIPAR)
- Caroli disease and congenital hepatic fibrosis (PKHD١)
- Chromosomal abnormalities (Trisomy ٢١, Turner syndrome)
- Citrin deficiency (SLC٢٥A١٣)
- COACH syndrome (TMEM٦٧)
- Congenital disorders of glycosylation

Genetic and metabolic:

- Cystic fibrosis (CFTR)
- Disorders of bile acid synthesis (AKR١D١, AMACR, CYP٧B١, HSD٣B٧,
- CYP٧A١, CYP٢٧A١)
- Disorders of bile acid conjugation (BAAT, SLC٢٧A٥)
- Dubin Johnson (MRP٢)
- Farber disease type IV (ASAH١)
- Fatty acid oxidation defects (SCAD, LCAD)
- Galactosemia (GALT)
- Gaucher disease type ٢ (GBA)
- Glycogen storage disease type IV (GBE١)

Genetic and metabolic:

- Hereditary fructose intolerance (ALDOB)
- Jeune syndrome (IFT٨٠, DYNC٢H١, WDR١٩, IFT١٤٠, TTC٢١B)
- Mitochondrial respiratory chain disorders (DGUOK, MPV١٧, POLG)
- Mucolipidosis type II/ I cell disease (GNPTAB)
- Mucopolysaccharidosis type VII (GUSB)
- Neonatal ichthyosis–sclerosing cholangitis syndrome (CLDN١)
- Neonatal sclerosing cholangitis (DCDC٢)
- Nielsen syndrome of Greenland Eskimos
- Niemann–Pick disease type C (NPC١, NPC٢)

Genetic and metabolic:

- North American Indian childhood cirrhosis (NAIC)
- Peroxisomal disorders
- Progressive familial intrahepatic cholestasis types ١-٢
- Lipid storage diseases (SCP٢)
- Tyrosinaemia (FAH)
- Urea cycle defects
- Wolman disease/cholesterol ester storage disease (LIPA)

When to Evaluate

- A serum conjugated (direct) bilirubin concentration of >١ mg/dL with a total bilirubin of <٥ mg/dL

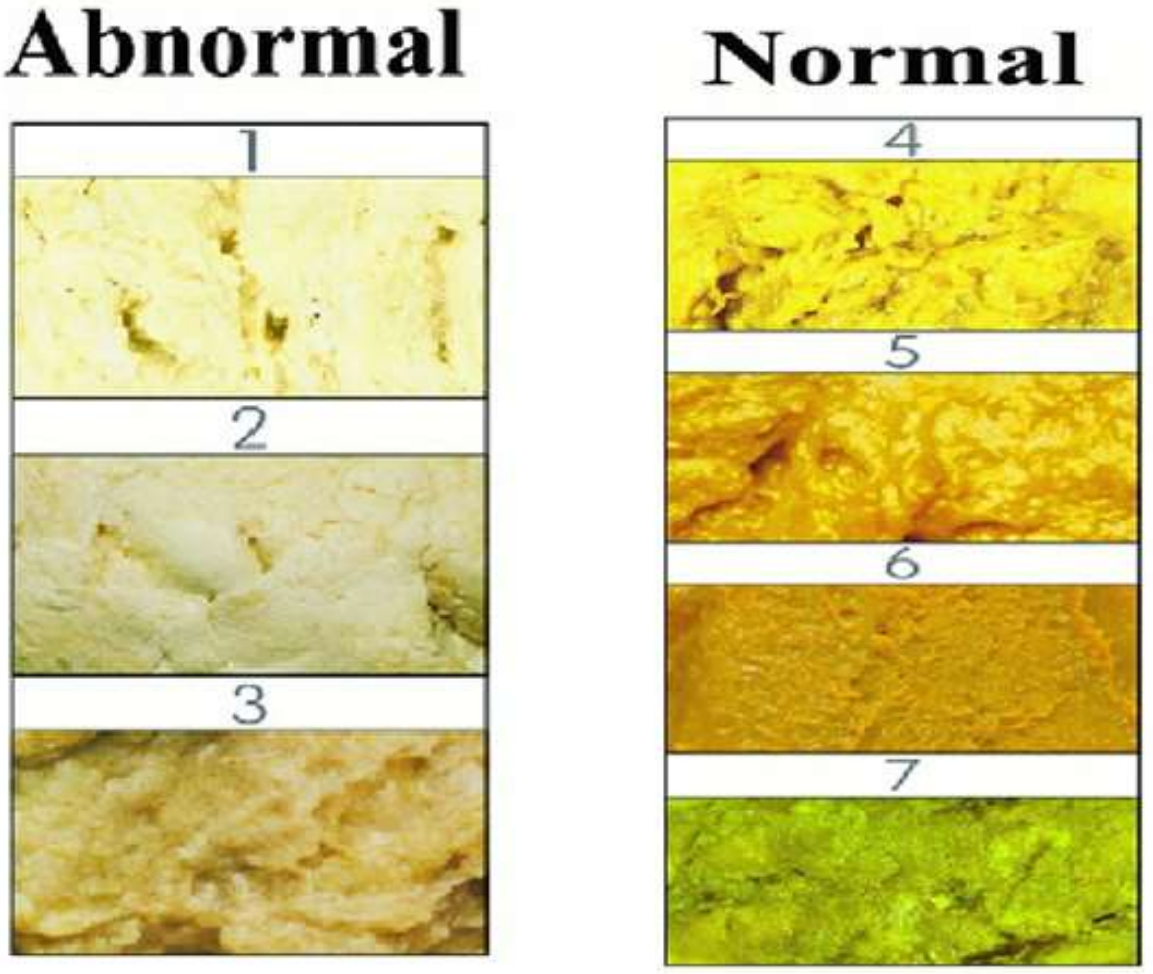
or

- over ٢٠% of the total bilirubin concentration if the total is >٥ mg/dL

Clinical manifestations of cholestatic liver disease

- Jaundice
- Acholic Stool
- Decreased fat stores
- FTT
- Hepatosplenomegaly
- Hemorrhagic disease
- Irritability, poor feeding, vomiting, and lethargy
- Pruritus, xanthoma
- Ascite, edema
- LBW, microcephaly, purpura
- Dysmorphic facies
- Neurologic abnormalities

Stool color



Evaluation

- The initial goal of the physician must be to exclude rapidly life-threatening but potentially treatable disorders such as gram-negative infection, endocrinopathies (such as panhypopituitarism), galactosemia, and inborn errors of bile acid metabolism
- Prompt identification of cholestatic infants is also required to minimize the risk of hemorrhage from vitamin K deficiency.
- Between ۲/۴% and ۱۵% of newborns will still be jaundiced at two weeks of age; the majority are breast-fed. These infants should be evaluated for cholestasis by measurement of total and conjugated serum bilirubin. However, with reliable follow-up, this testing may be deferred until three weeks of age in jaundiced breast-fed infants if stool color, urine color, and physical examination are normal.

Initial investigations to establish the presence of cholestasis, define the severity of the liver disease, and detect readily treatable disorders

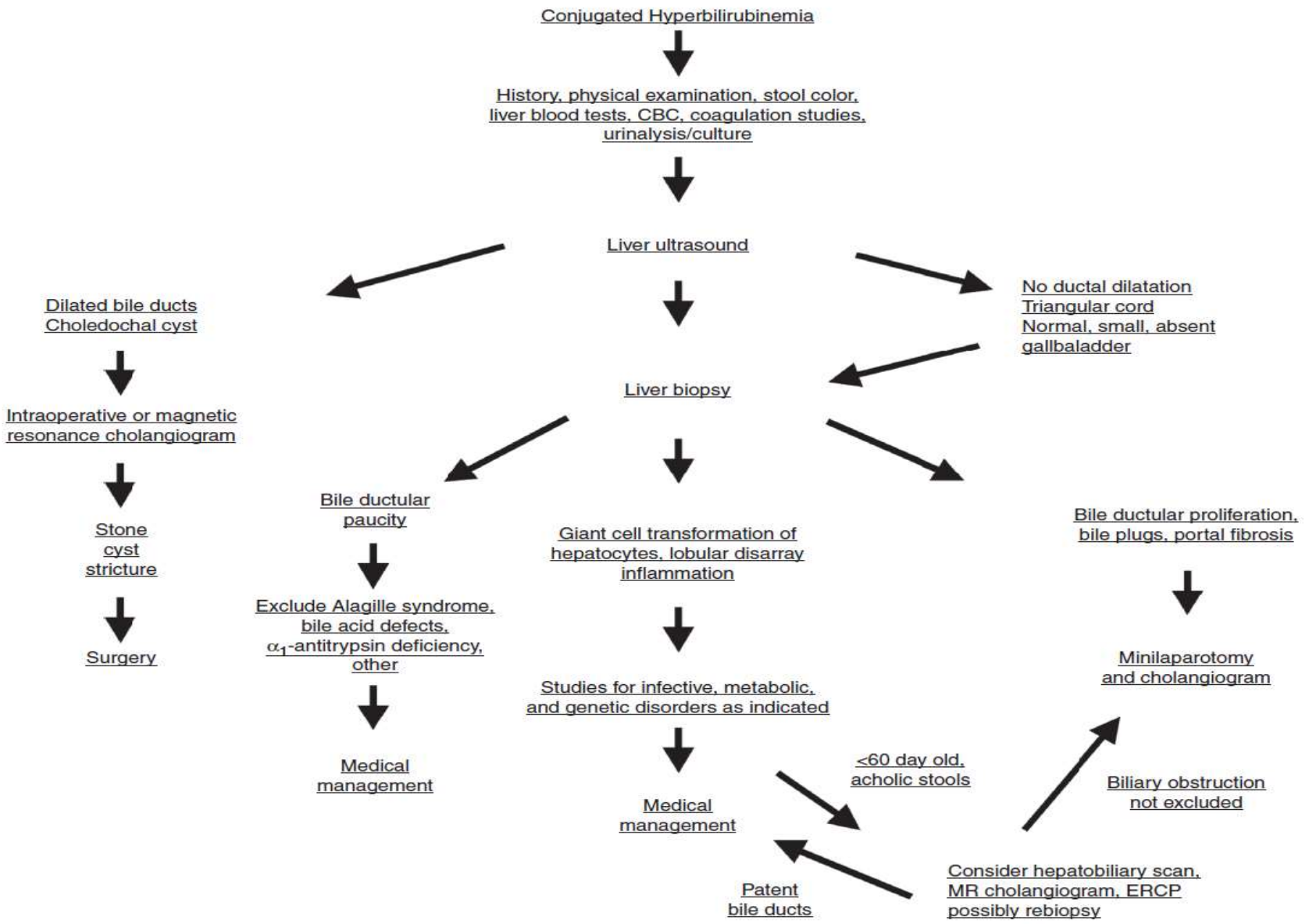
EVALUATION	RATIONALE
INITIAL TESTS	
Total and direct bilirubin	Elevated direct fraction confirms cholestasis
AST, ALT	Hepatocellular injury
GGT	Biliary obstruction/injury
RBC galactose-1-phosphate uridyltransferase	Galactosemia
α_1-Antitrypsin level	α_1-Antitrypsin deficiency
Urinalysis and urine culture	Urinary tract infection can cause cholestasis in neonates
Blood culture	Sepsis can cause cholestasis
Serum amino acids	Aminoacidopathies
Urine organic acids	Organic acidurias
Very-long-chain fatty acids	Zellweger syndrome, peroxisomal disorders
Carnitine profile	Mitochondrial and fatty acid oxidation disorders
Sweat chloride or CF mutation analysis	Cystic fibrosis
Urine culture for cytomegalovirus	Congenital cytomegalovirus infection
INITIAL IMAGING STUDY	

- History (including pregnancy, early neonatal course);
- Presence of extrahepatic anomalies or extrahepatic disease;
- Stool color;
- Bili (Total & Direct)
- Serum tests for liver injury and liver function: AST, ALT, GGT, BS, Albumin, PT, CBC
- If concerns for infection: blood and urine cultures.

Investigations to establish a specific diagnosis

- Abdominal ultrasound
- Alpha-١ antitrypsin level and phenotype
- Infectious work-up as indicated from history and physical examination (blood cultures, viral cultures, serologies)
- Metabolic testing: serum amino acids, urine organic acids, acylcarnitine, newborn screen
- T٤, TSH (if low GGT and concern for hypopituitarism or hypothyroidism)
- Urine and serum analysis for bile acid and bile acid precursors (especially if low GGT)

- Urine reducing substances and/or red blood cell galactose-1-phosphate uridyltransferase for galactosemia
- Echocardiogram, eye exam for posterior embyrotoxon, spine films if concerned for Alagille syndrome
- Liver biopsy for histology, immunohistochemistry, electron microscopy and snap freeze for enzymatic testing if indicated
- Exploratory laparotomy and intraoperative cholangiogram
- Genetic testing (targeted gene panels, whole exome sequencing, whole genome sequencing based on clinical suspicion and clinical availability of testing)


Conjugated Hyperbilirubinemia
History, physical examination, stool color, liver blood tests, CBC, coagulation studies, urinalysis/culture
Liver ultrasound
Dilated bile ducts
Choledochal cyst
Intraoperative or magnetic resonance cholangiogram
Stone
cyst
stricture
Surgery
No ductal dilatation
Triangular cord
Normal, small, absent gallbaladder
Liver biopsy
Bile ductular paucity
Exclude Alagille syndrome, bile acid defects, α_1-antitrypsin deficiency, other
Medical management
Giant cell transformation of hepatocytes, lobular disarray inflammation
Studies for infective, metabolic, and genetic disorders as indicated
Medical management
Bile ductular proliferation, bile plugs, portal fibrosis
Minilaparotomy and cholangiogram
<60 day old, acholic stools
Biliary obstruction not excluded
Consider hepatobiliary scan, MR cholangiogram, ERCP possibly rebiopsy
Patent bile ducts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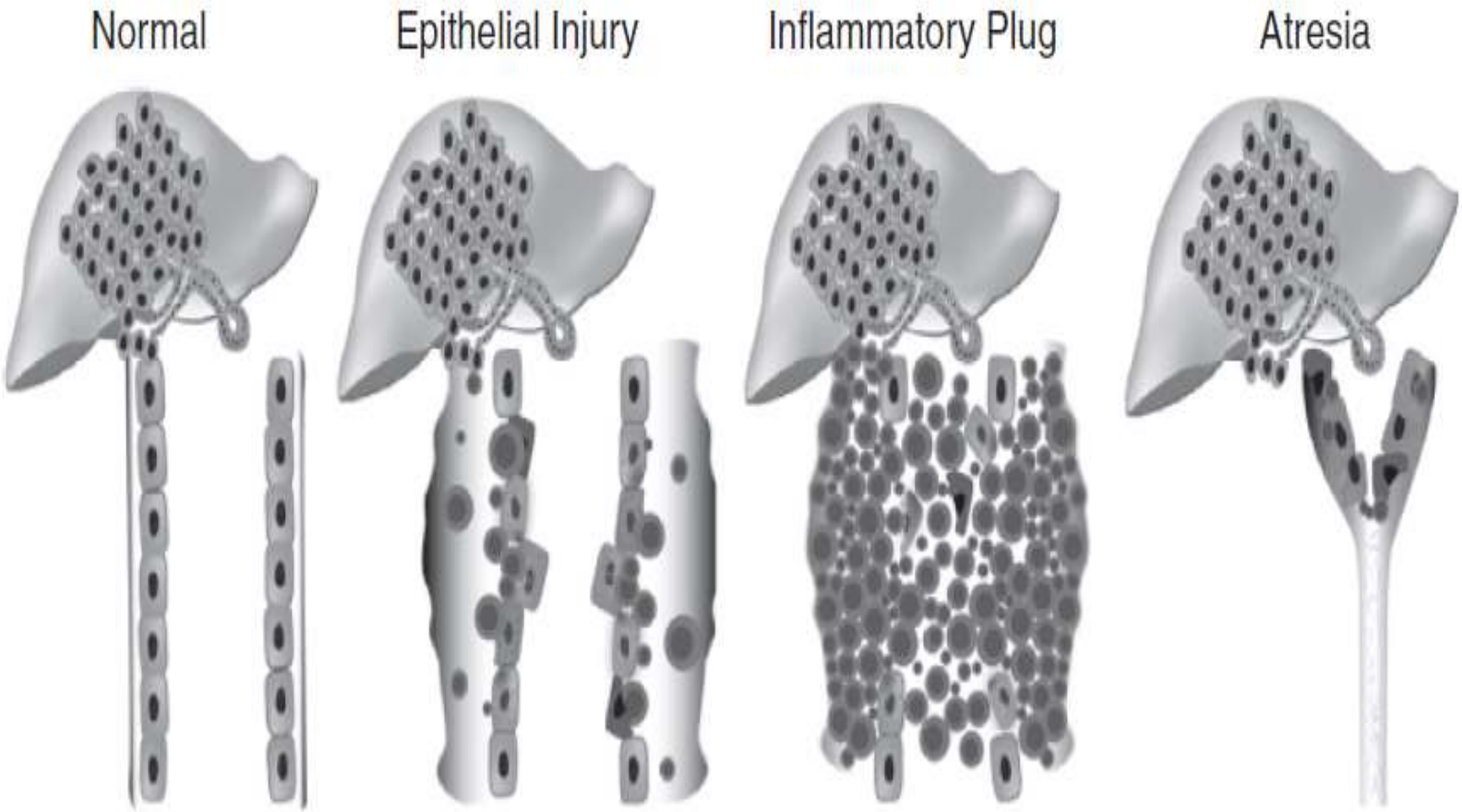
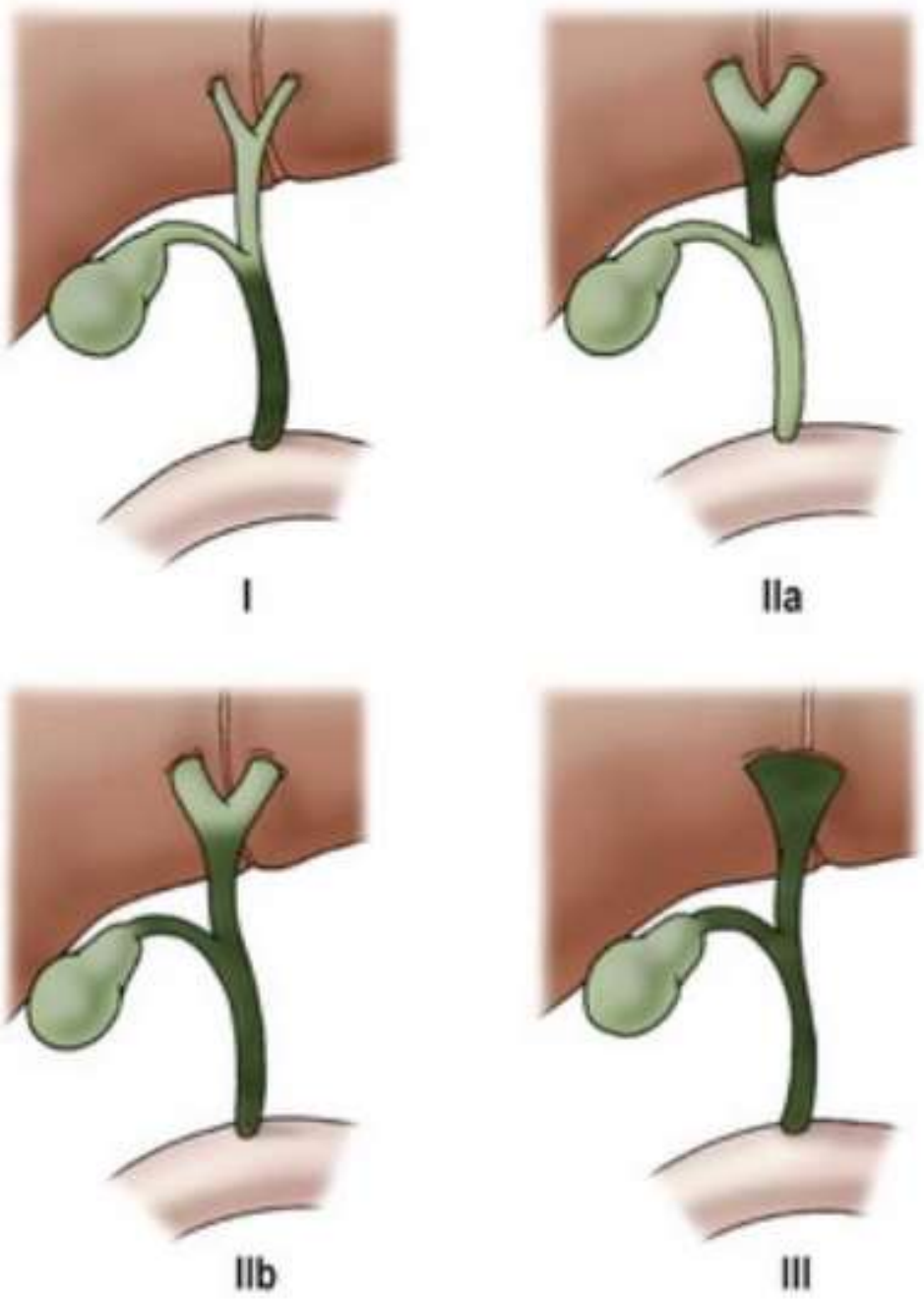
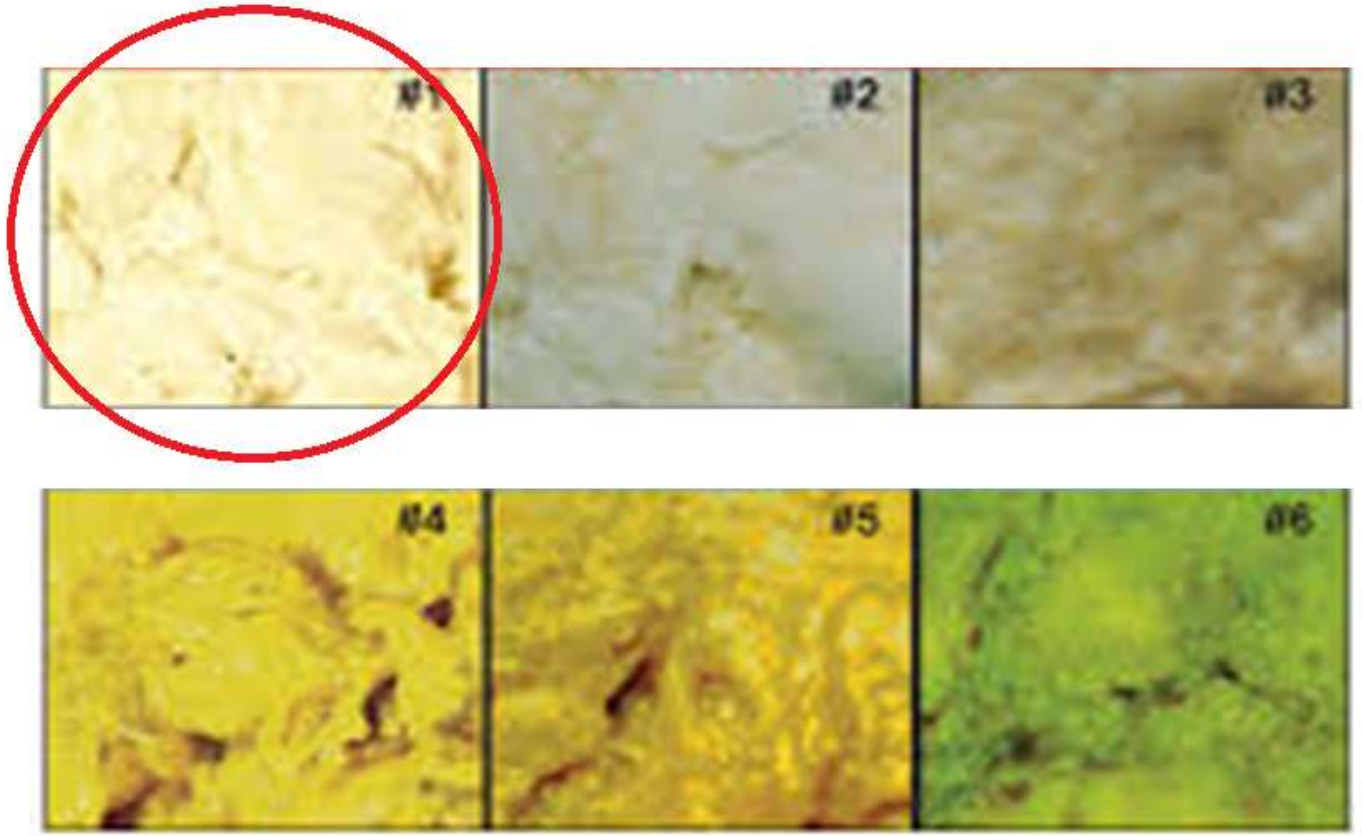
Biliary Atresia

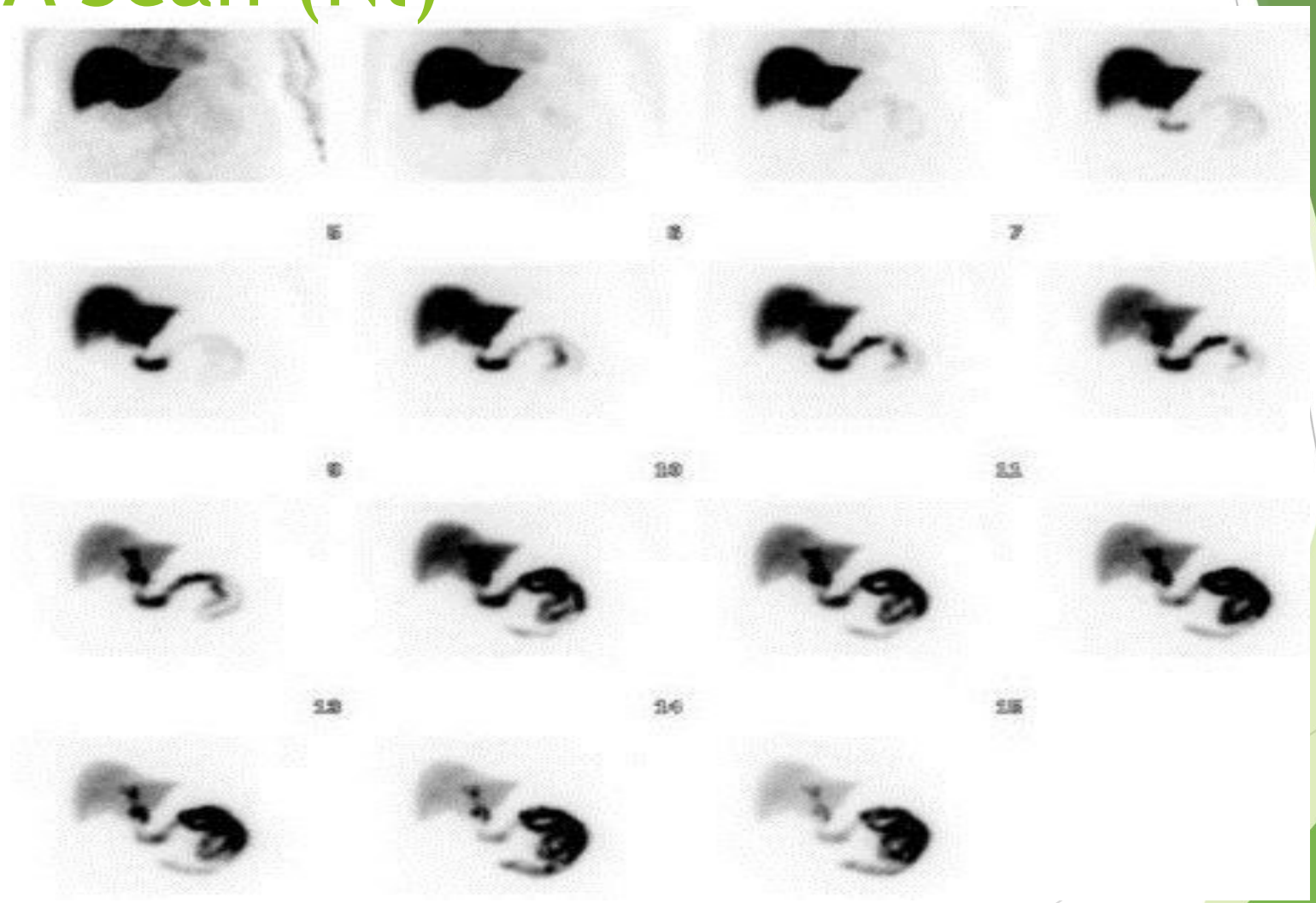

Normal
Epithelial Injury
Inflammatory Plug
Atresia


I
IIa
IIb
III

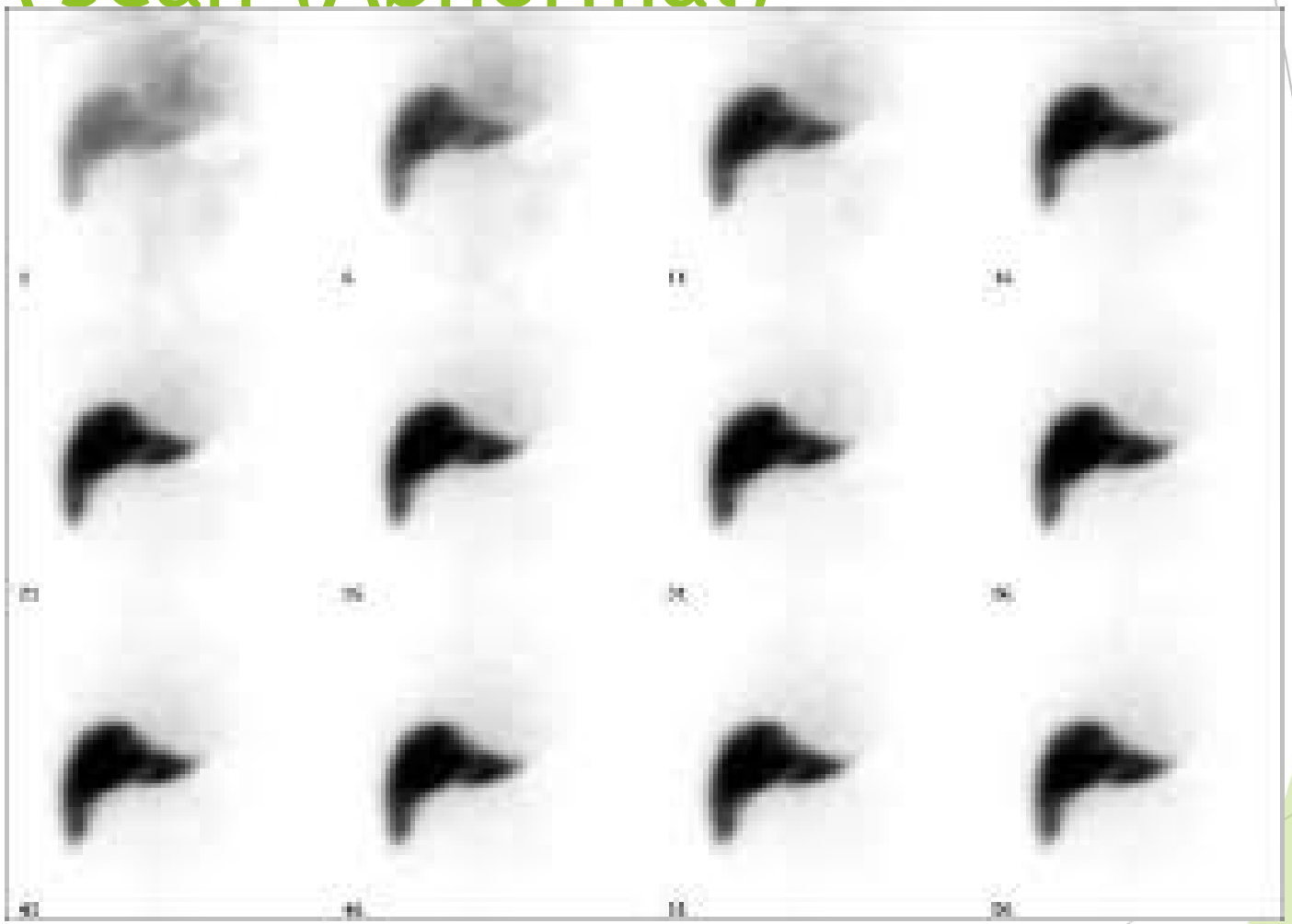
Stool color

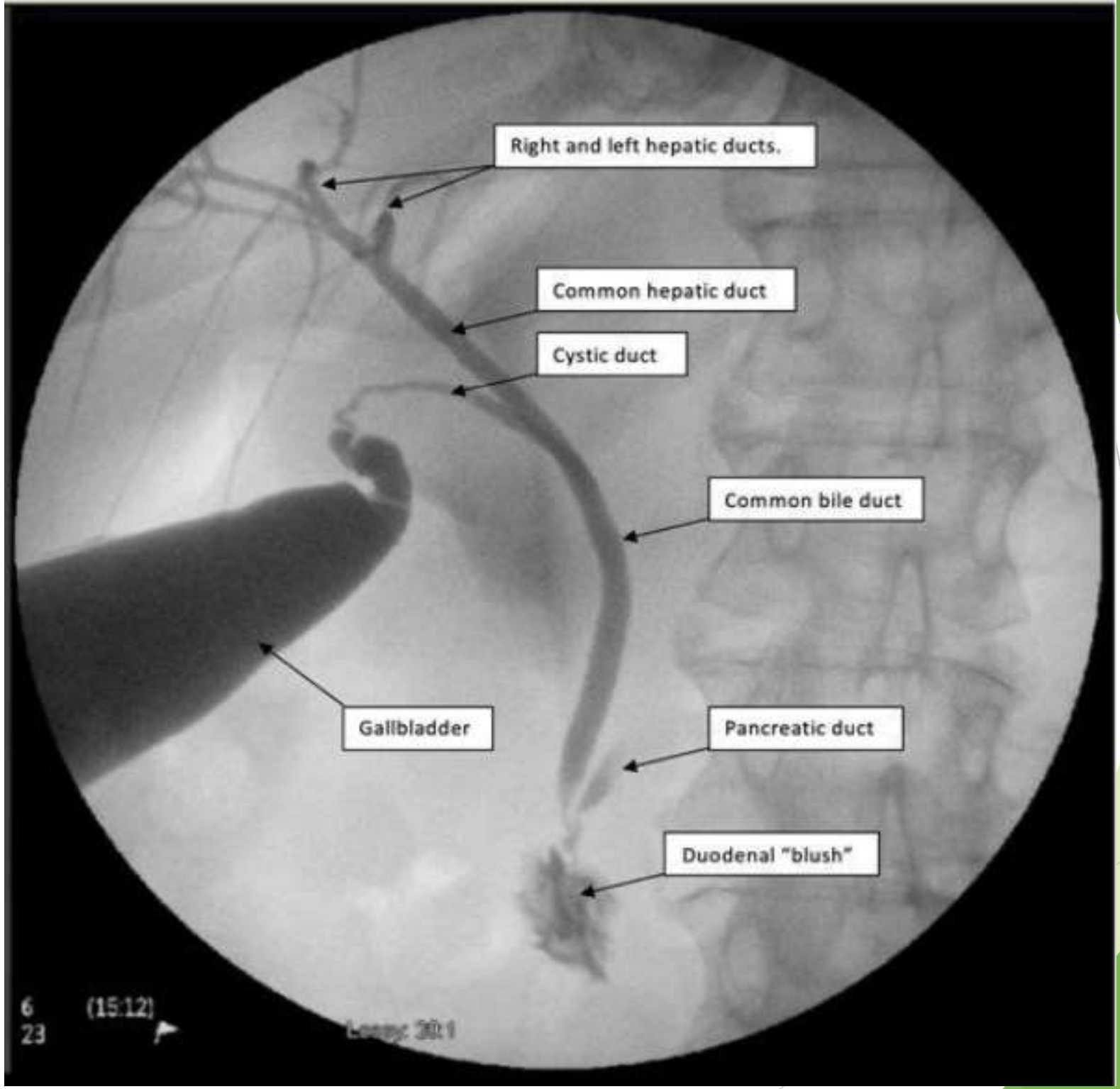


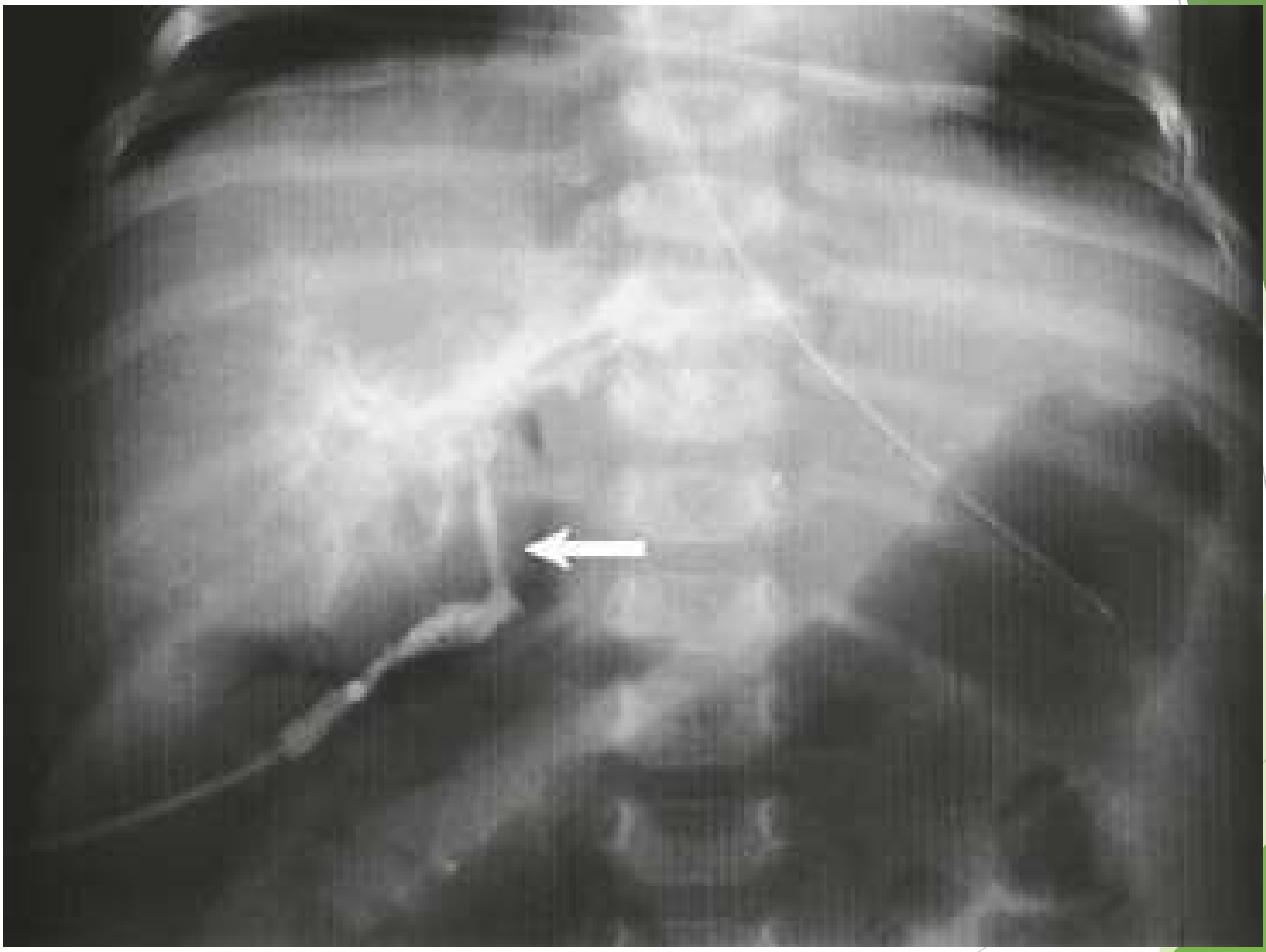
HIDA Scan (Nl)



HIDA Scan (Abnormal)



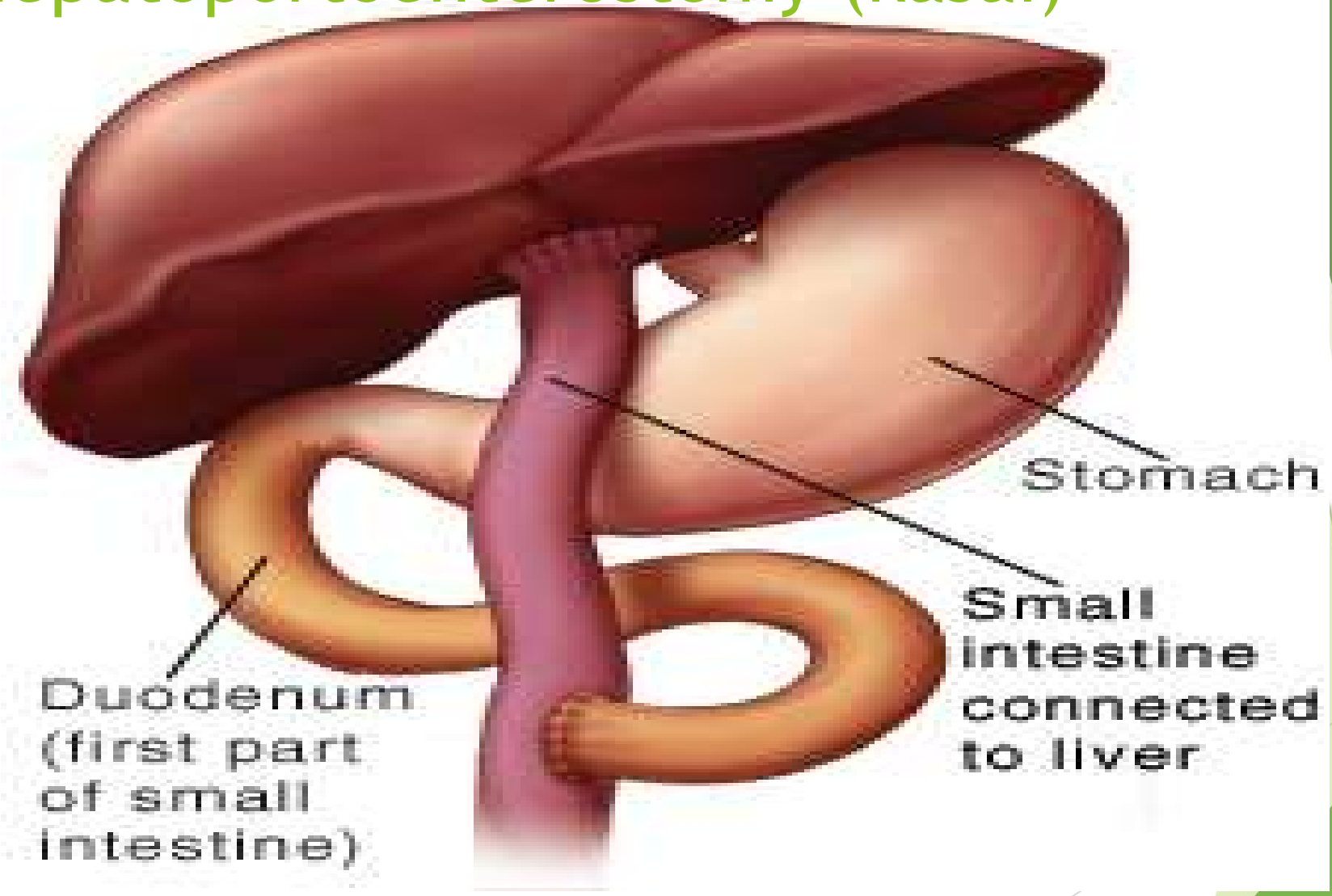

Right and left hepatic ducts.
Common hepatic duct
Cystic duct
Common bile duct
Gallbladder
Pancreatic duct
Duodenal "blush"
6
23
(15:12)



Treatment

- Kasai
- Liver transplantation

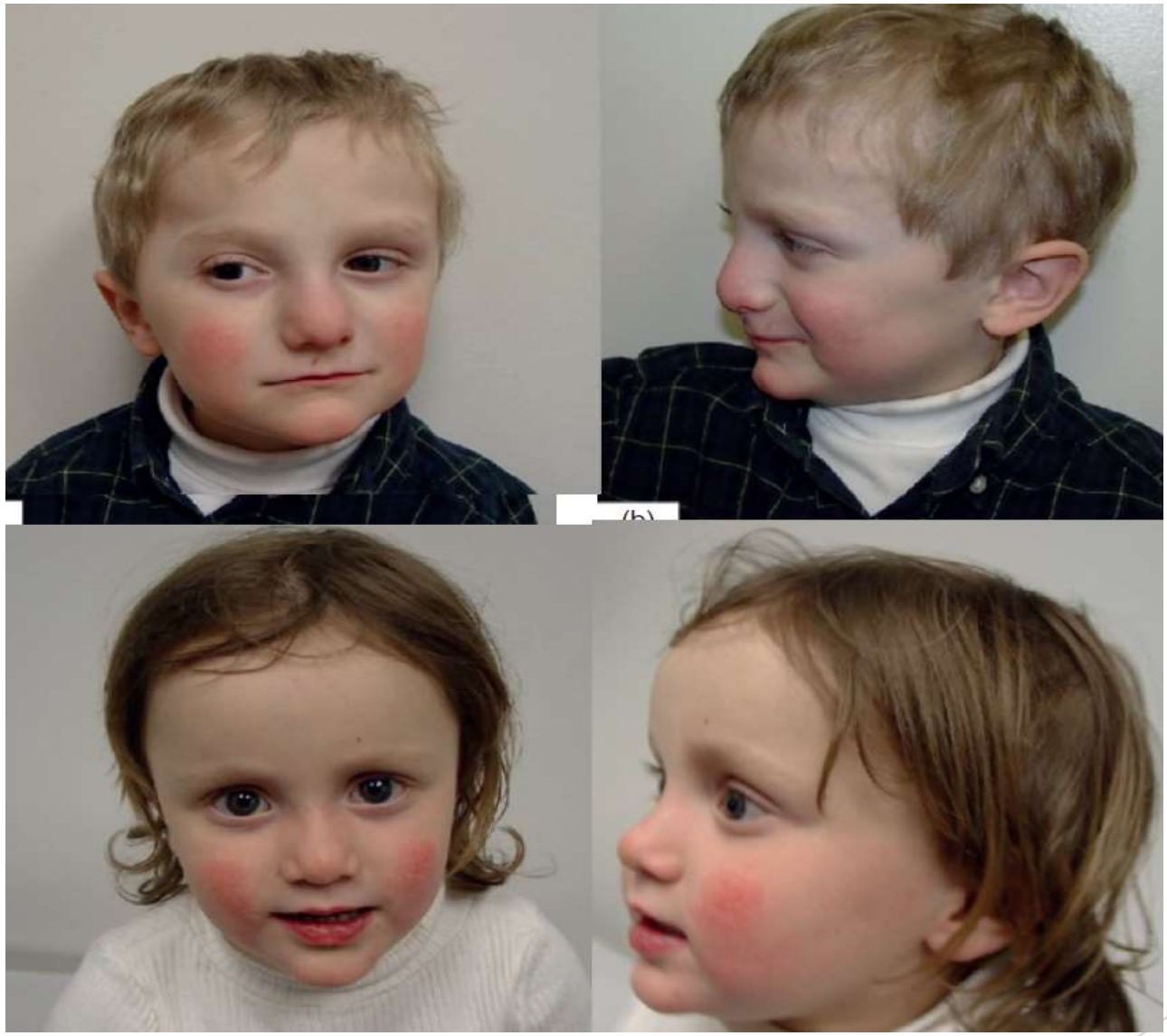
Hepatoportoenterostomy (kasai)



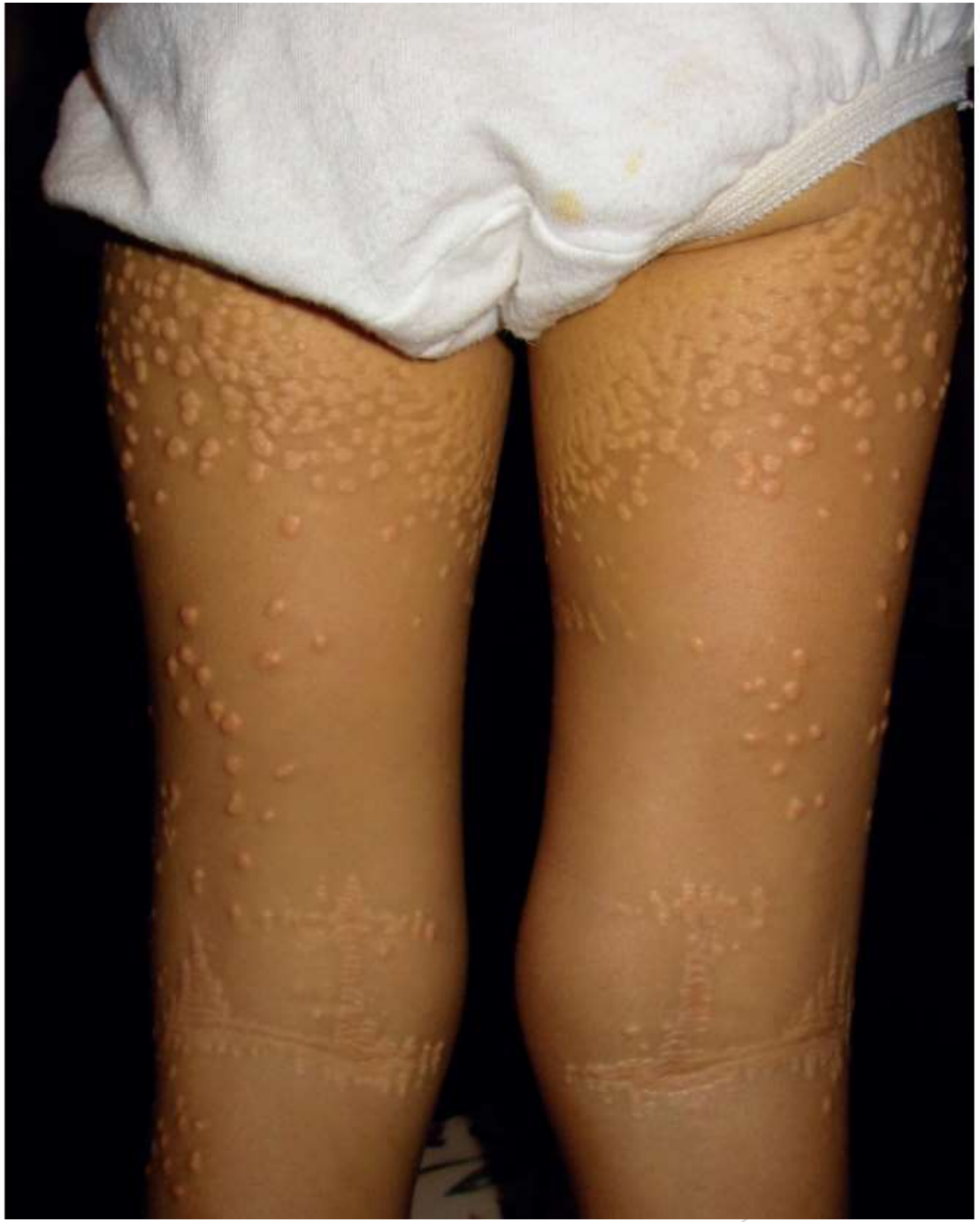
Alagille Syndrom (Arteriohepatic Dysplasia)

Classic Criteria, Based on 5 Body Systems for a Diagnosis of Alagille Syndrome

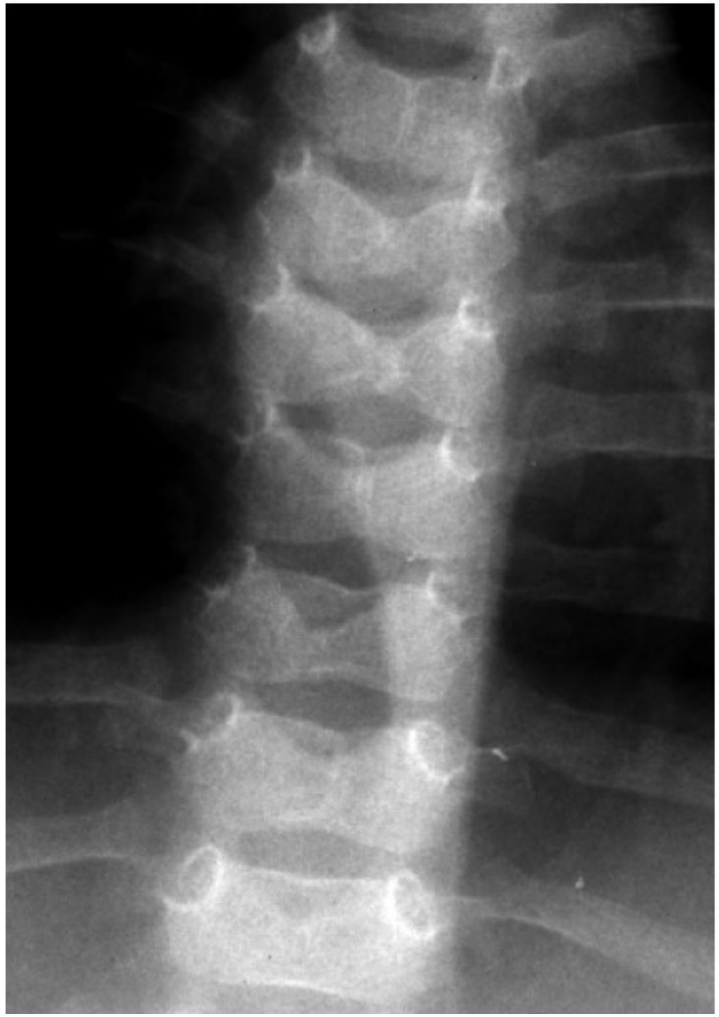
SYSTEM/PROBLEM	DESCRIPTION
Liver/cholestasis	Usually presenting as jaundice with conjugated hyperbilirubinemia in the neonatal period, often with pale stools
Dysmorphic facies	Broad forehead, deep-set eyes, sometimes with upslanting palpebral fissures, prominent ears, straight nose with bulbous tip, and pointed chin giving the face a somewhat triangular appearance
Congenital heart disease	Most frequently peripheral pulmonary artery stenosis, but also pulmonary atresia, atrial septal defect, ventricular septal defect, and tetralogy of Fallot
Axial skeleton/vertebral anomalies	"Butterfly" vertebrae may be seen on an antero-posterior radiograph, and occasionally hemivertebrae, fusion of adjacent vertebrae, and spina bifida occulta
Eye/posterior embryotoxon	Anterior chamber defects, most commonly posterior embryotoxon, which is prominence of Schwalbe's ring at the junction of the iris and cornea



Xanthom



Butterfly vertebrae



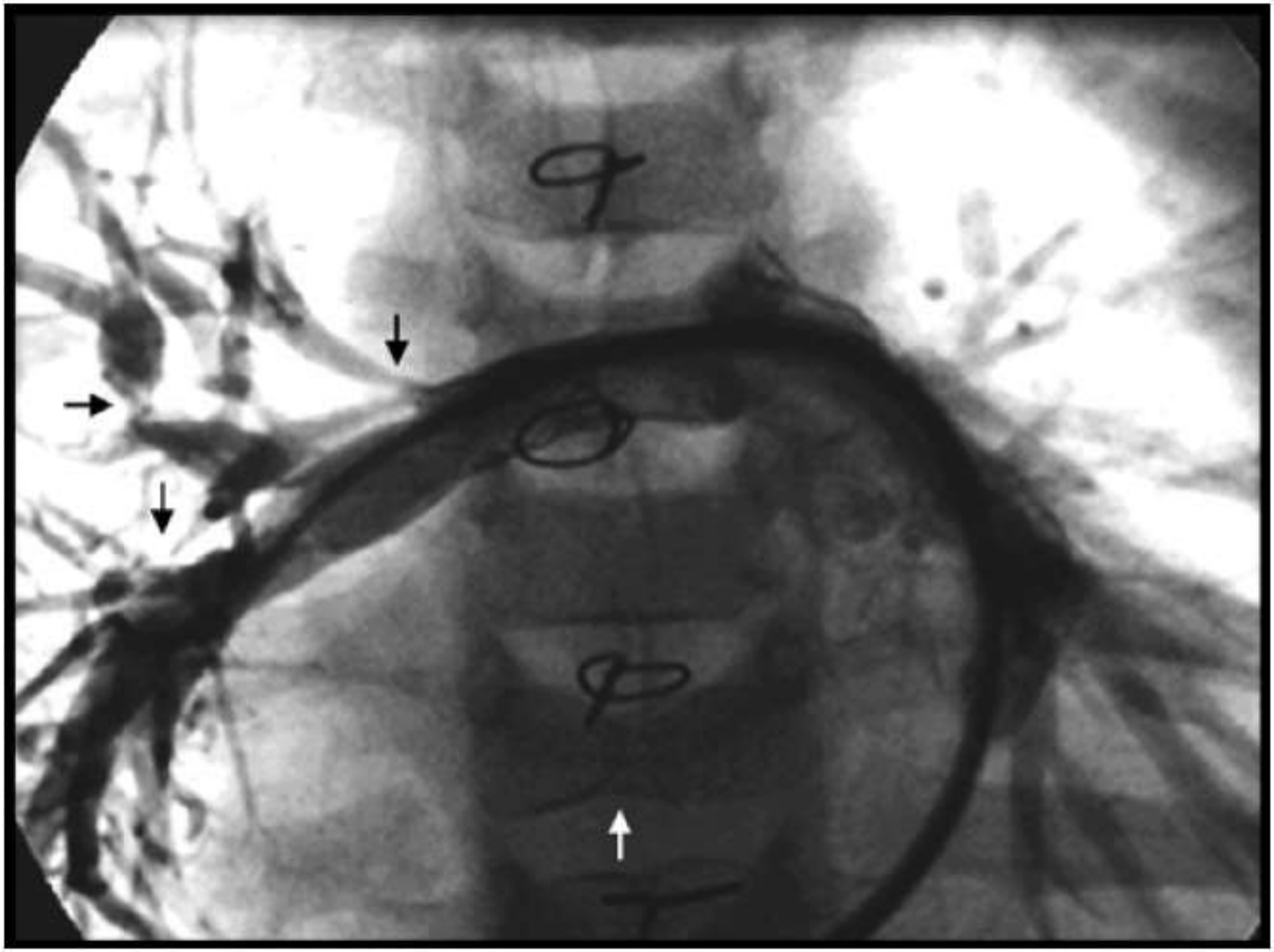
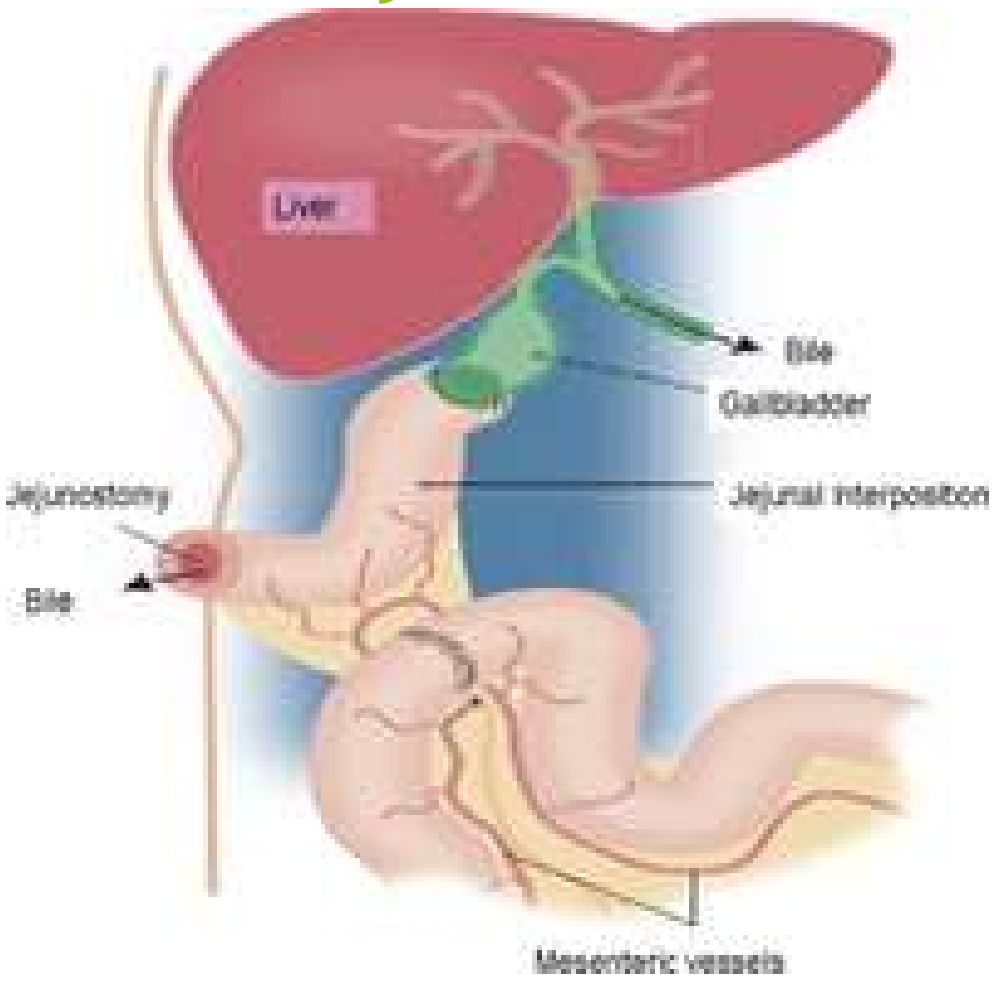


Figure 14.5 Right pulmonary arteriogram demonstrating multiple stenoses (black arrows) in a patient with prior surgery for tetralogy of Fallot, peripheral pulmonic stenoses, a butterfly vertebrae (white arrow), and a deletion of

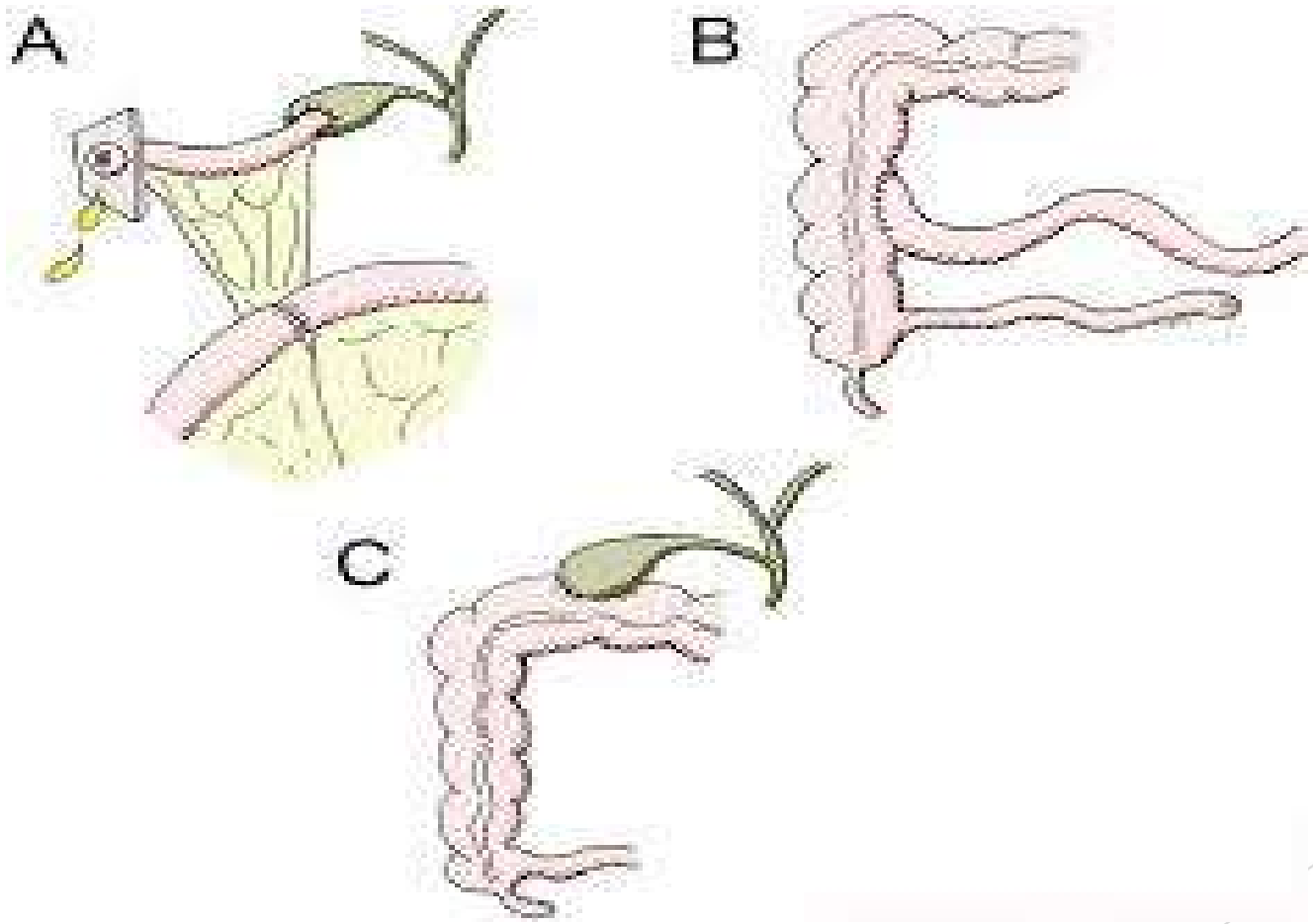
Treatment

- UDCA
- Skin hydration and emollients
- Antihistamins, rifampin, cholestyramine,naltrexone
- EDKA
- Diversion surgery
- Liver Transplantation

external biliary diversion



Internal partial ileal exclusion




شاد وتندرست
باشید