Basic Science

Gastroenterology and Hepatology

R2 Tanapat / Aj.Nopaorn

Liver function test Interpretation

Outline

Biochemical test

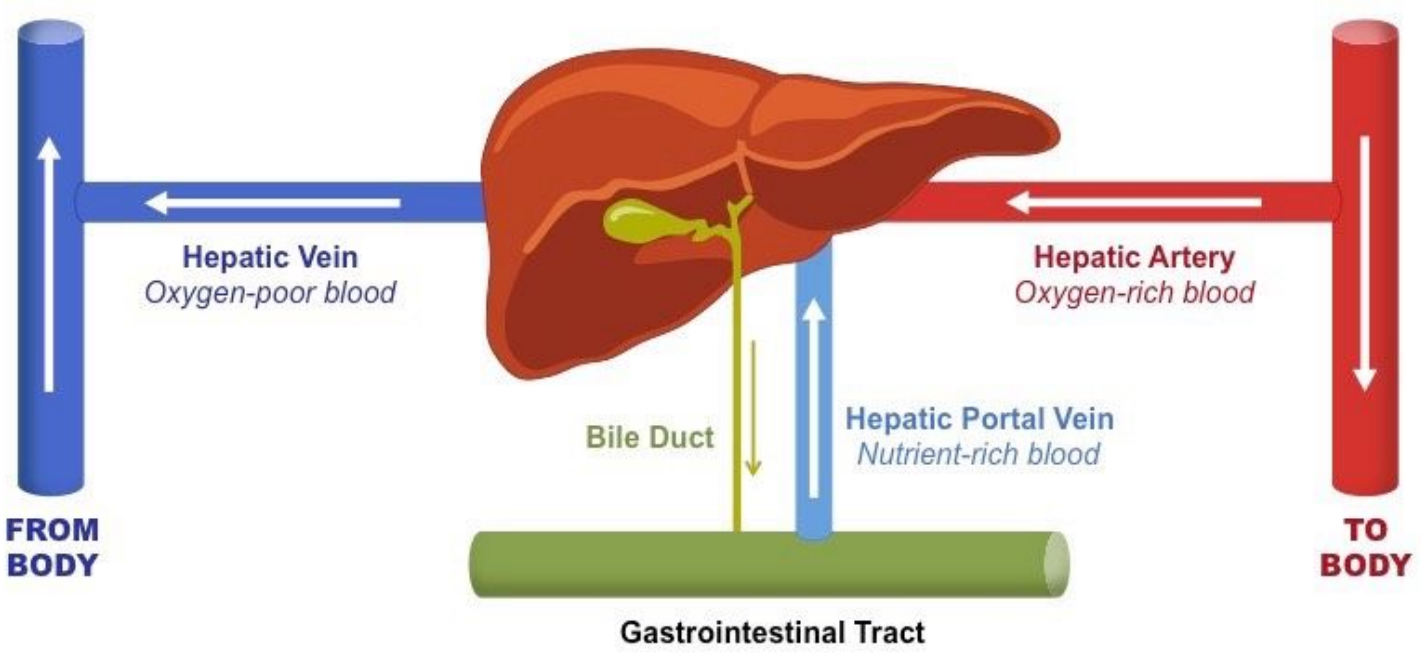
- Liver injury
  AST, ALT, LDH
- Bile flow
  ALP, GGT, 5'NT
- Endogenous metabolite
  Ammonia

Function test

- Synthetic
  Albumin
  Hemostasis
  Lipoprotein
- Excretory
  Bilirubin
- Special test

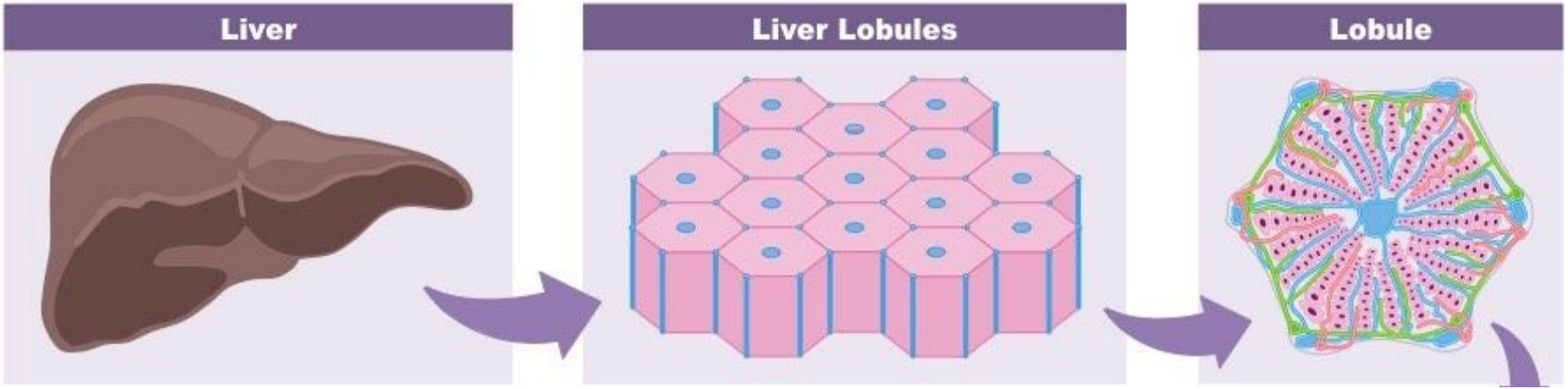
- **Approach to abnormal liver function test**
- **Quiz**

Anatomy



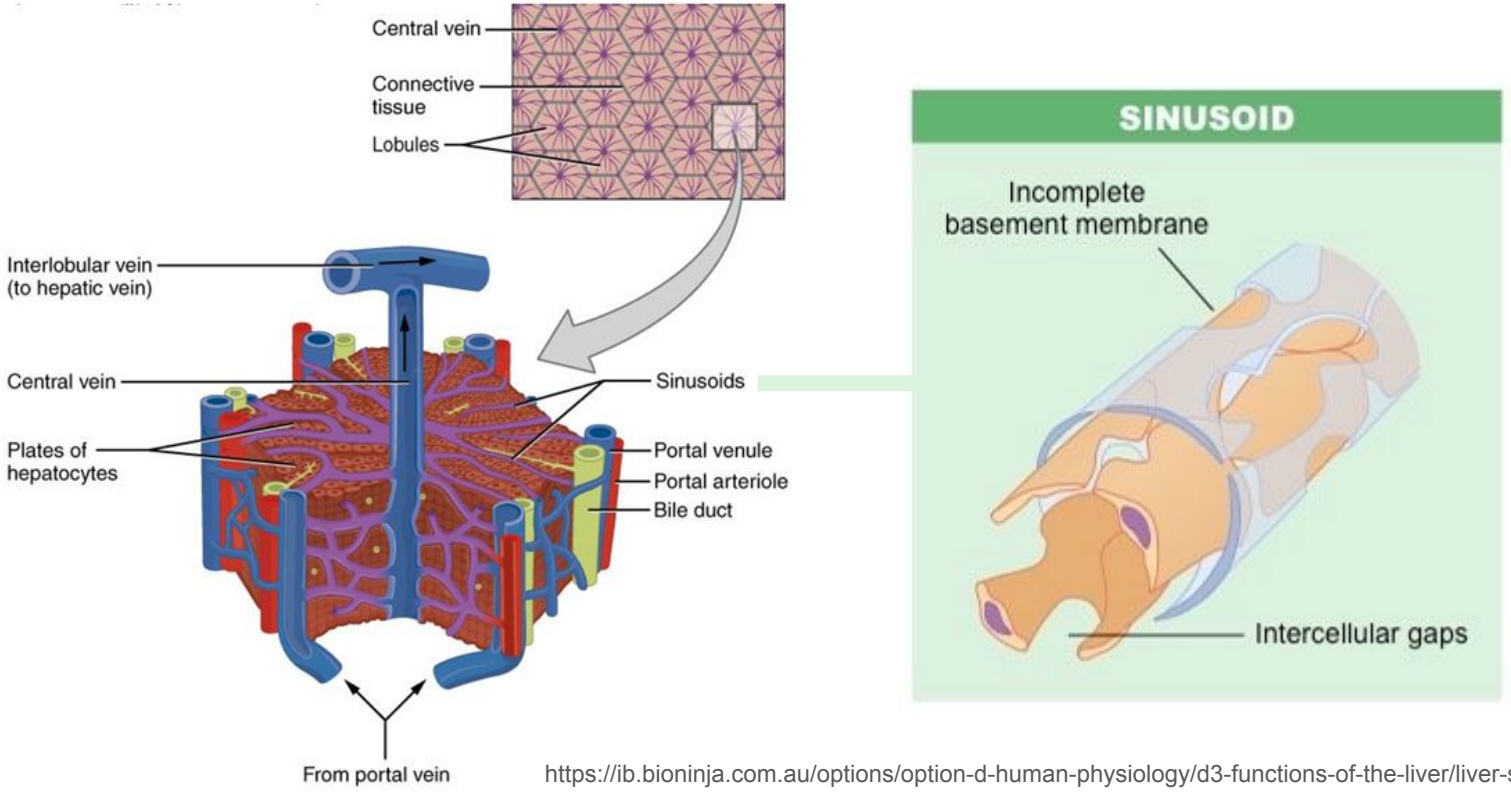
https://ib.bioninja.com.au/options/option-d-human-physiology/d3-functions-of-the-liver/liver-structure.html

Anatomy



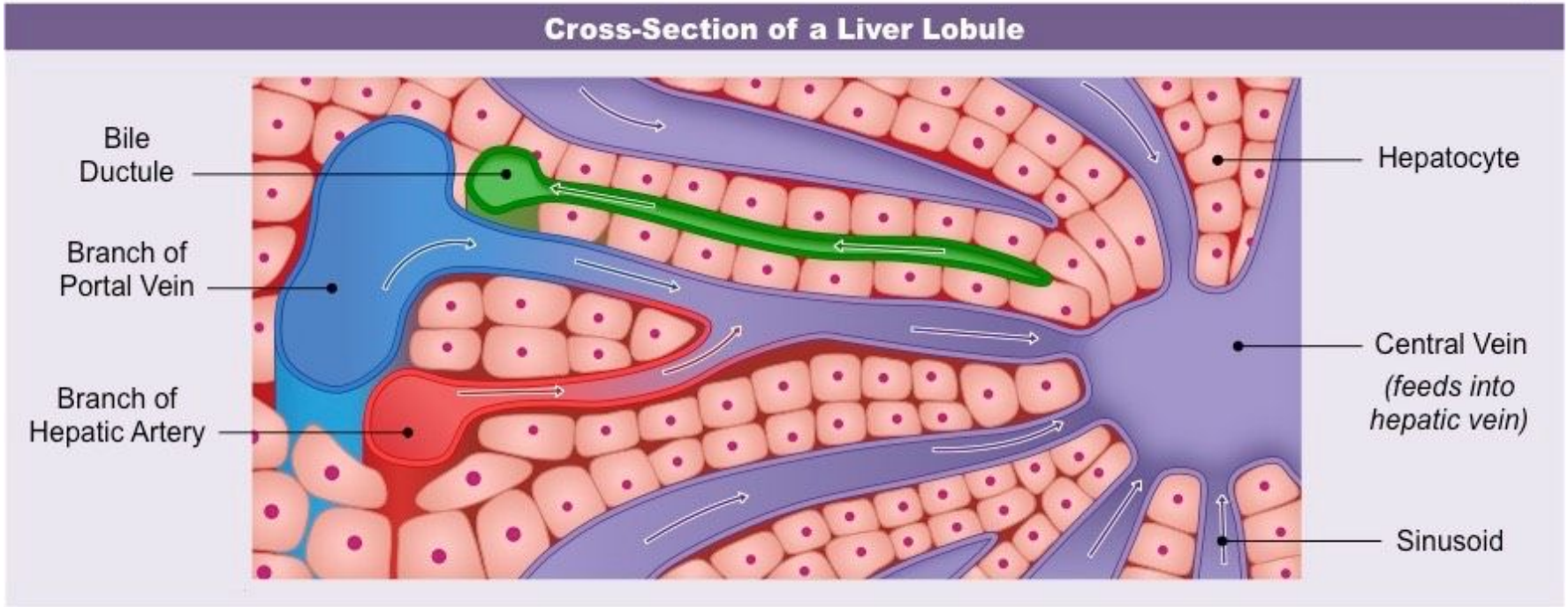
https://ib.bioninja.com.au/options/option-d-human-physiology/d3-functions-of-the-liver/liver-structure.html

Microscopic anatomy



https://ib.bioninja.com.au/options/option-d-human-physiology/d3-functions-of-the-liver/liver-structure.html

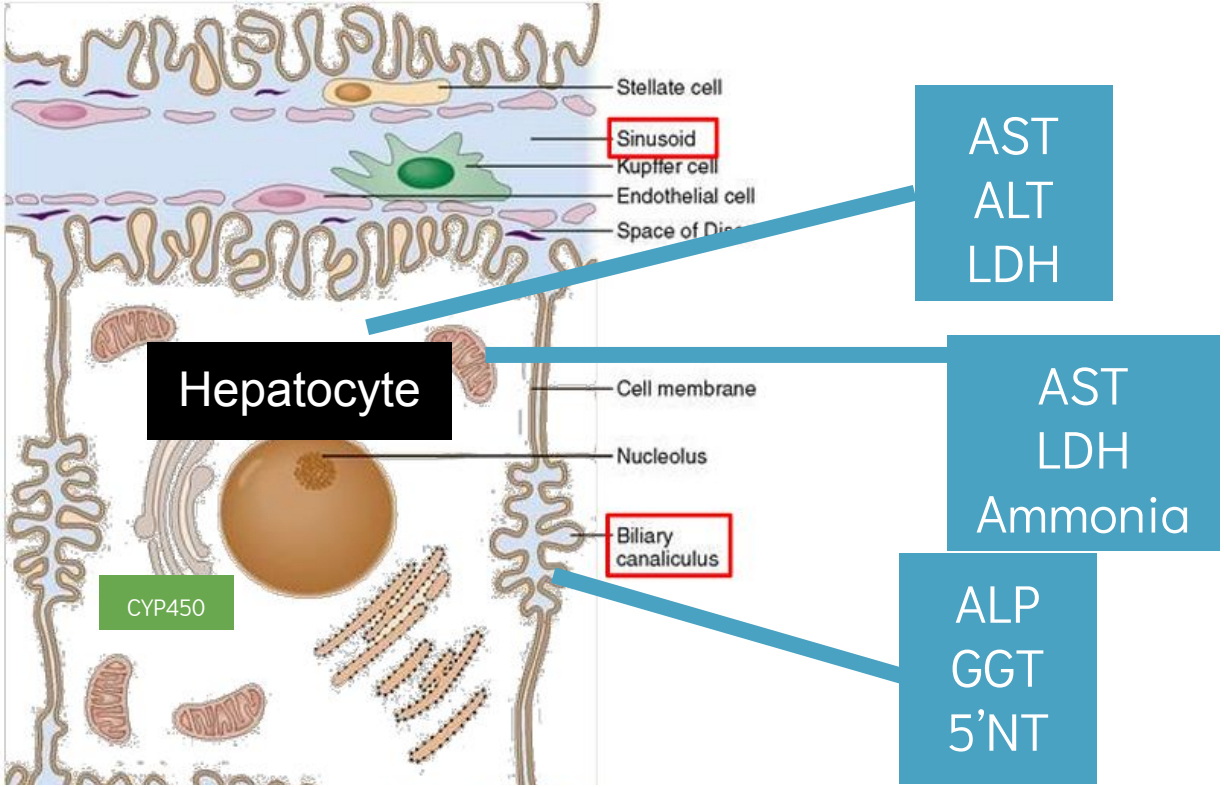
Microscopic anatomy



https://ib.bioninja.com.au/options/option-d-human-physiology/d3-functions-of-the-liver/liver-structure.html

- Liver injury
- Bile flow
- Endogenous metabolite

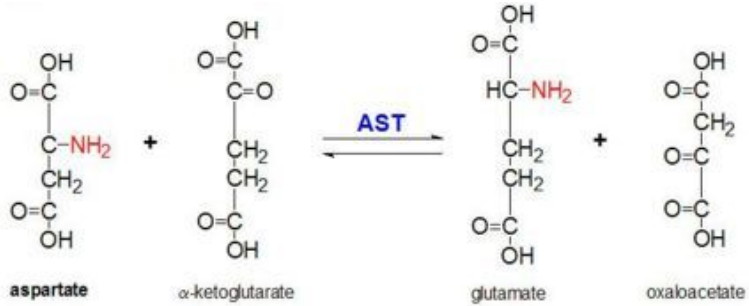
Microscopic anatomy



Evaluate liver injury

1. Aspatate aminotransferase (AST)

- transfer amino group from aspatate to ketoglutaric acid for oxaloacetic forming (substrate of Krebs cycle)
- found in **cytoplasm and mitochondria** of **liver**, skeletal muscle, cardiac muscle, brain, kidney, red blood cell, pancreas
- clearance by reticuloendothelial system ($T_{1/2}$ = 17 hr.)



1. Aspatate aminotransferase (AST)

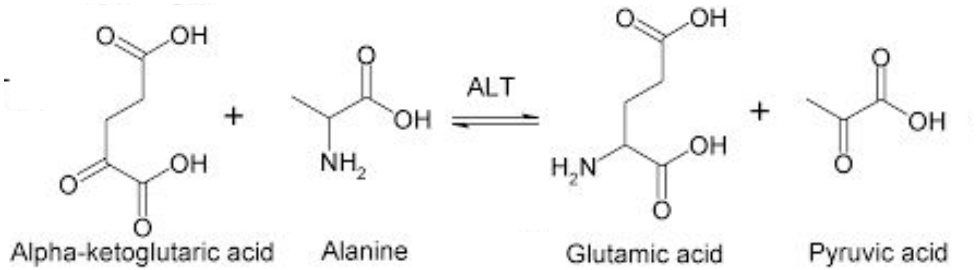
Normal value

Age	U/L
Preterm	29-59
0-14 days	32-162
15 day - 1 year	20-67
1-12 years	21-36
12-18 years - Male - Female	14-35 13-26

level does not correlate with severity of liver disease

2. Alanine aminotransferase (ALT)

- transfer amino group from alanine to ketoglutaric acid for pyruvic forming (substrate of Krebs cycle)
- found in **cytoplasm** of **liver** **more specific than AST
- clearance by reticuloendothelial system ($T_{1/2}$ = 47 hr.)



2. Alanine aminotransferase (ALT)

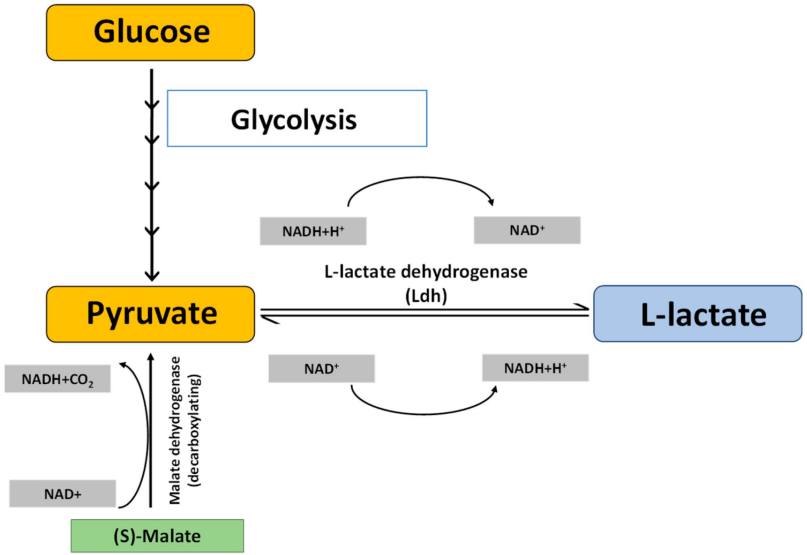
Normal value

Age	U/L
Preterm	11-15
0-1 year	5-33
1-12 years	9-25
12-18 years - Male - Female	9-26 8-22

level does not correlate with severity of liver disease

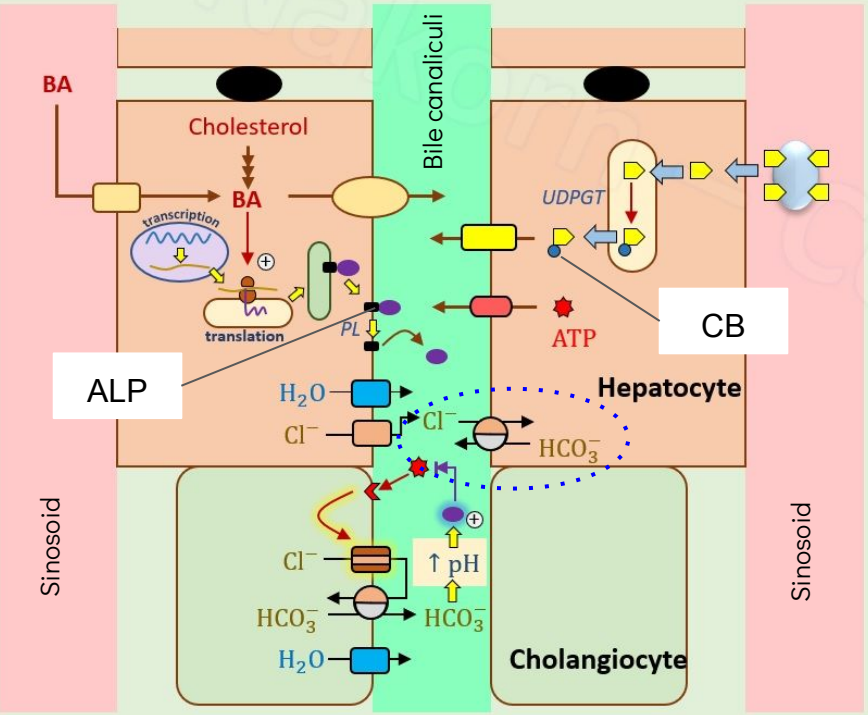
3. Lactate dehydragenase (LDH)

- convert pyruvate to lactate
- found in cytoplasm and mitochondria of several organ
- elevate LDH : rhabdomyolysis, acute kidney injury, hemolysis, ischemic hepatitis, infection, malignancy, fracture



Evaluate bile flow

Normal physiology of bile flow



Function: Negative regulator of bile flow

Content in bile canaliculi

1. Bile acid (BA)
2. Conjugated bilirubin (CB)
3. Fluid and Electrolyte
4. ALP (regulate by BA production)
5. ATP

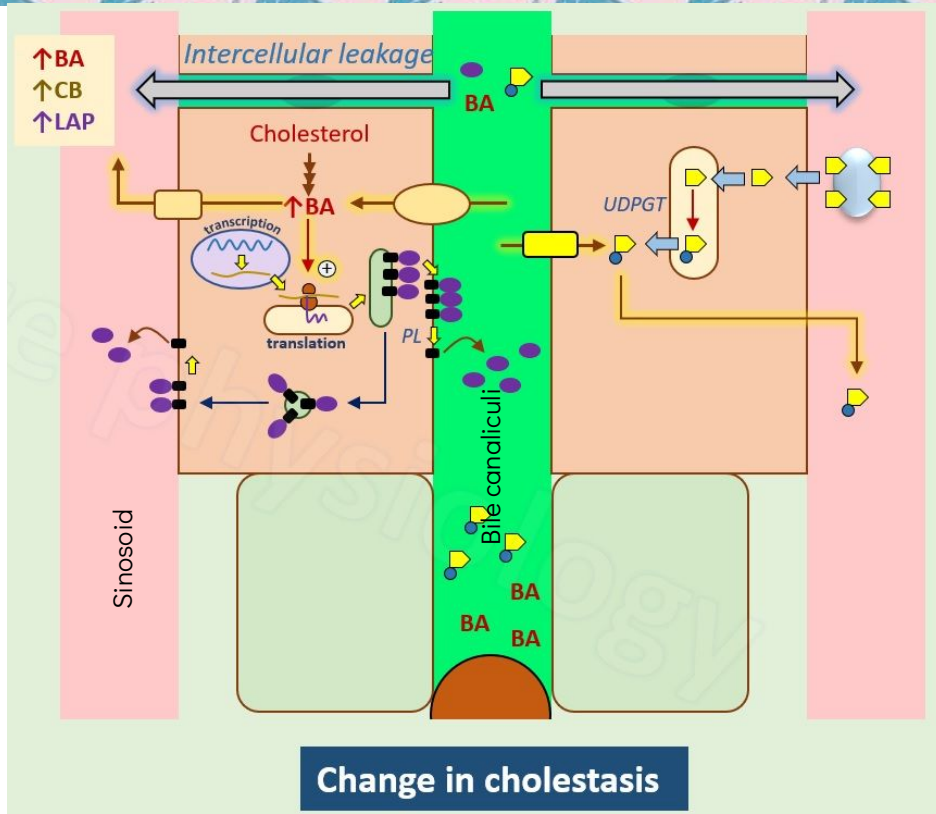
In bile duct

- ATP stimulate Cl transport to lumen
- Cl move to intracellular by Cl-HCO_3 exchange
- pH in bile duct is increased by HCO3 in lumen
- ALP hydrolyse ATP
  → Decrease HCO_3 secretion

Physiology in cholestasis

Obstruction of bile flow

- accumulate of BA,CB in hepatocyte
- increase intracellular BA stimulate ALP production
- BA,CB,ALP reflux to sinusoid due to increased pressure in bile canaliculi



1. Alkaline phosphatase (ALP)

- hydrolyze organic phosphate ester (ATP,ADP,AMP) in bile regulation process
- found in **liver (canalicular membrane), bone**, small intestine, kidney, placenta, WBC
- ALP level in **children is higher than adult** due to bone growth.
  (peak at 10-15 years)
- $T_{1/2}$ = 1 week

1. Alkaline phosphatase (ALP)

Normal value

Age	U/L
Preterm	57-330
0-14 days	90-273
15 day - 1 year	134-518
1-10 years	156-369
10-13 years	141-460
13-15 years	127-517 (M), 92-280 (F)
15-17 years	89-365 (M), 54-128 (F)
17-19 years	59-164 (M), 48-95 (F)

Elevation of ALP

Physiologic	Pathologic
• Pregnancy • Adolescent • Transient hyperphosphatemia of infancy • Benign familial hyperphosphatasemia of intestinal origin • Blood group O • Macro-ALP	• Biliary tract obstruction • Primary biliary cirrhosis • Primary sclerosing cholangitis • Medication: steroid • Bile ductopenia • Liver metastatic malignancy • Bone disease eg. Rickets • Chronic kidney disease

2. Gamma glutamyltransferase (GGT)

- transfer gamma glutamyl group between peptide
- found in cell membrane of **hepatocyte, cholangiocyte**
- found in other organ: kidney, pancreas, spleen, small intestine, heart, brain and seminal vesicles
- GGT level was peak in neonatal period.

2. Gamma glutamyltransferase (GGT)

Normal value

Age	U/L
Preterm	7-807
0-14 days	19-383
15 days - 1 years	8-127
>1-18 years	6-21

2. Gamma glutamyltransferase (GGT)

Elevate of GGT

- Hepatobiliary diseases eg. **Biliary tract obstruction, Alagille syndrome, progressive familial intrahepatic cholestasis type 3**
- Pancreatic diseases
- COPD
- CKD
- Diabetic melitus
- Myocardial infarcton
- Medication; carbamazepine, phenytoin, barbiturates

3. 5'Nucleotidase (5'NT)

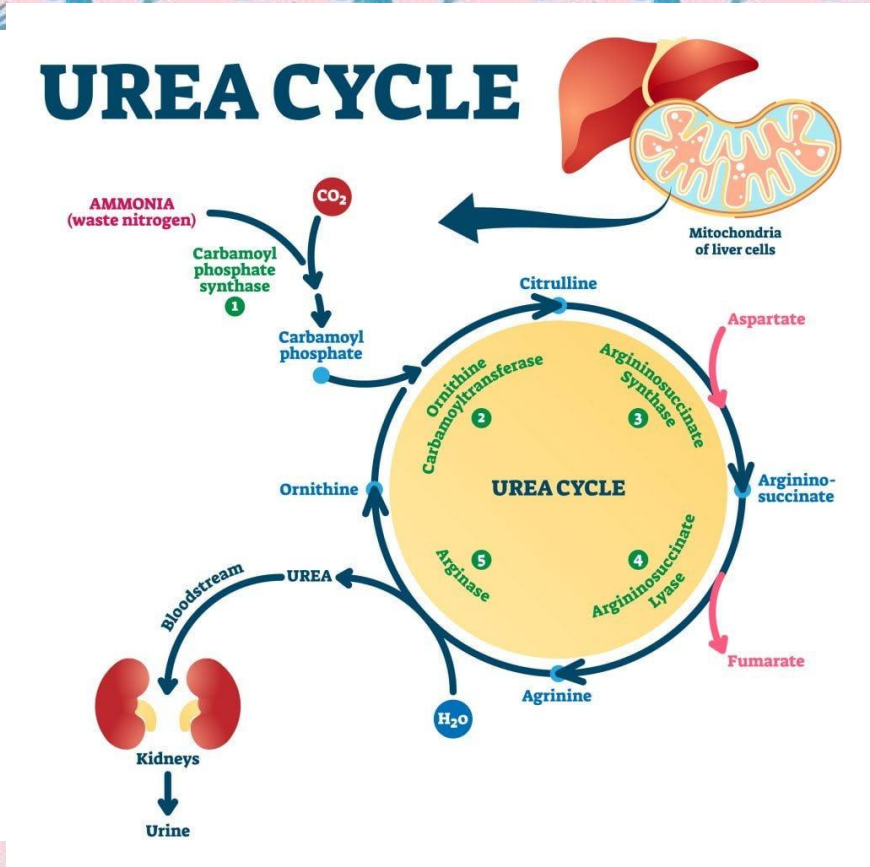
- hydrolysis enzyme of nucleotide eg. Adenosine 5-phosphate, Inosine 5-phosphate
- found in liver, intestine, brain, heart, vessel, pancreas

Origin of enzyme

	Liver	Pancreas	Bone	Intestine	Brain	Heart	Other
ALP	••		••	•			•
GGT	•	•		•	•	•	•
5'-NT	•	•		•	•	•	•

Endogenous metabolite

Ammonia metabolism



Ammonia

- produced by bacteria in intestine
- metabolite to urea by urea cycle in liver
- amonia level **dose not corelate with severity of liver disease** and hepatic encephalopathy

Ammonia

Elevate of ammonia level

- Liver disease; Fullminant hepatitis, Chronic hepatitis, Cirrhosis
- Portosystemic shunts
- Urea cycle defect
- Mitochondrial fatty acid beta oxidation defect
- Reye syndrome
- Chronic kidney disease
- Medication eg. Valproic acid

Ammonia

Normal value

Age	µmol/L
Newborn	64-107
0-14 days	56-92
2 weeks - 18 years	21-50
>18 years	11-32

- Synthetic
- Excretory
- Special test

Synthetic function

1. Albumin

- maintain intravascular oncotic pressure
- produce by liver about 150 mg/kg/day
- $T_{1/2}$ = 14-21 days —> **not found low albumin in acute liver failure**

Low albumin level was found in several cause

- chronic liver disease
- malnutrition
- protein losing enteropathy
- chronic systemic inflammation
- Nephrotic syndrome

Albumin

Normal value

Age	g/dL
Preterm	1.1-3.9
0-14 days	2.6-4.3
15 days - 1 year	2.8-4.7
1-8 years	3.8-4.7
8-15 years	4.1-4.8
>15 years	4.1-5.1 (M) , 4.0-4.0 (F)

2. Coagulopathy

Abnormal hemostasis in liver disease

- Impair synthesis of coagulation factor

  → **fibrinogen, prothrombin, factor V, factor VII, factor IX, factor X, factor XI**

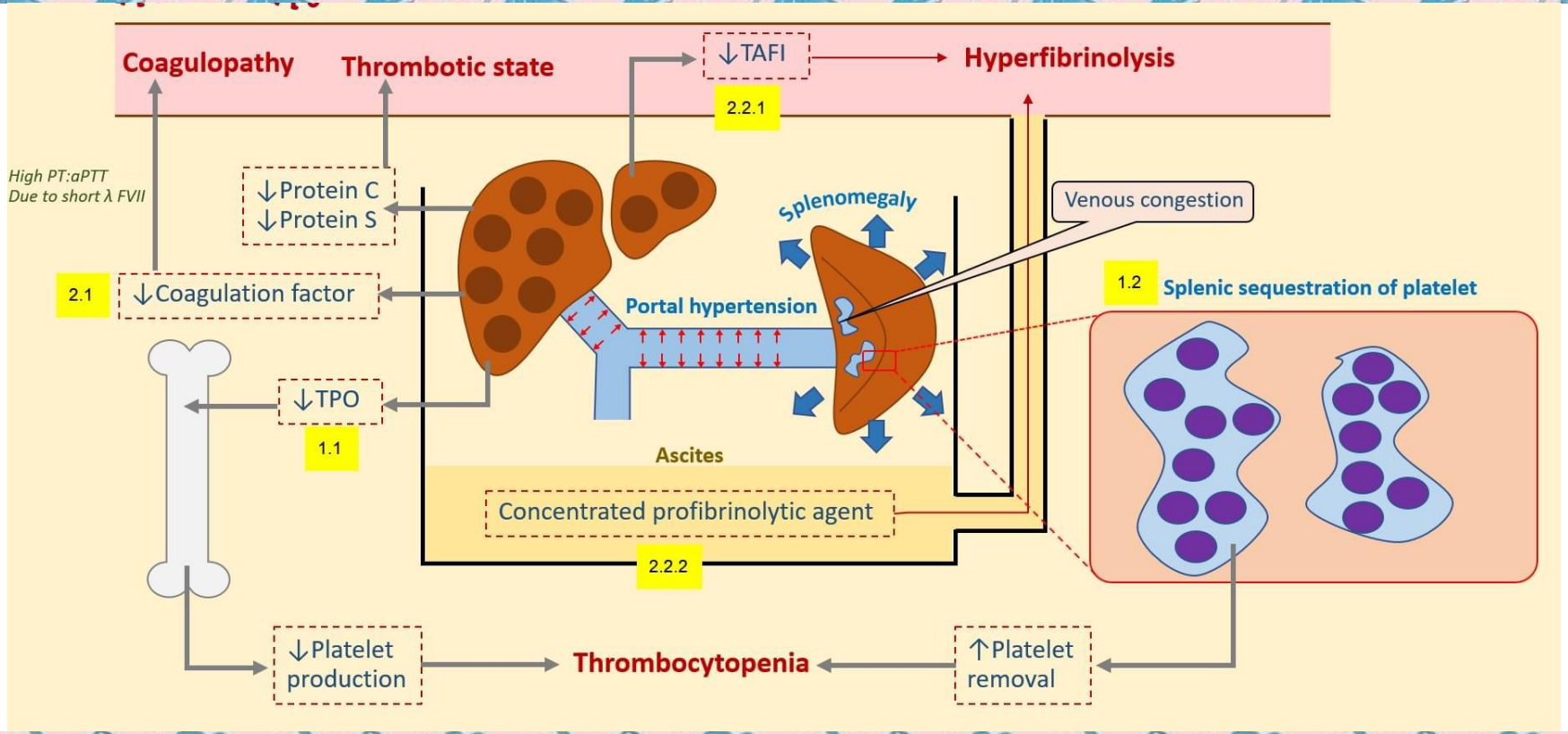
- Vitamin K deficiency due to impair fat soluble vitamin absorption

  → decreased vitlamin K dependent coagulation factor

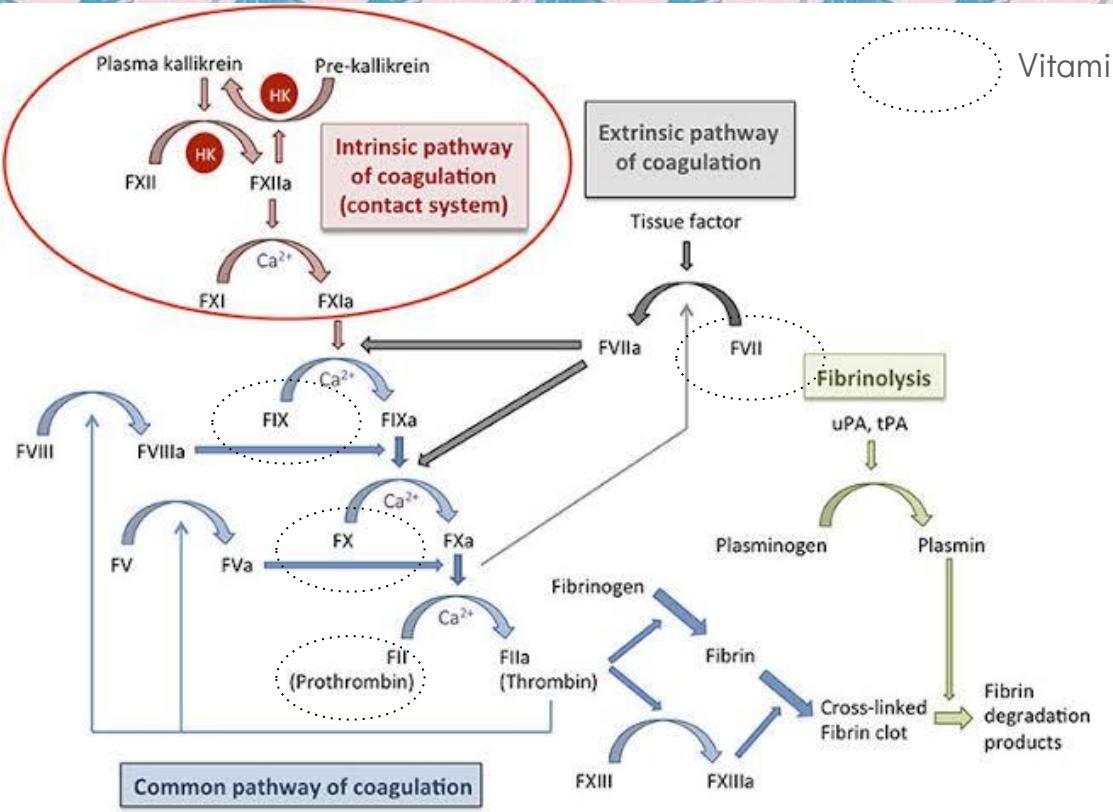
  Factor VII is the shortest half-life ($T_{1/2}$ = 6hr) → **prolong PT/INR**

- Impair Alpha 2-plasmin inhibitor production → **Increase fibrinolysis**
- Hypersplenism → **Thrombocytopenia**

Abnormal hemostasis in liver disease



Coagulation cascade



3. Lipoprotein

Abnormal lipoprotein metabolism in liver disease

- Cholestasis → phospholipid reflux to circulation and form Lipoprotein X

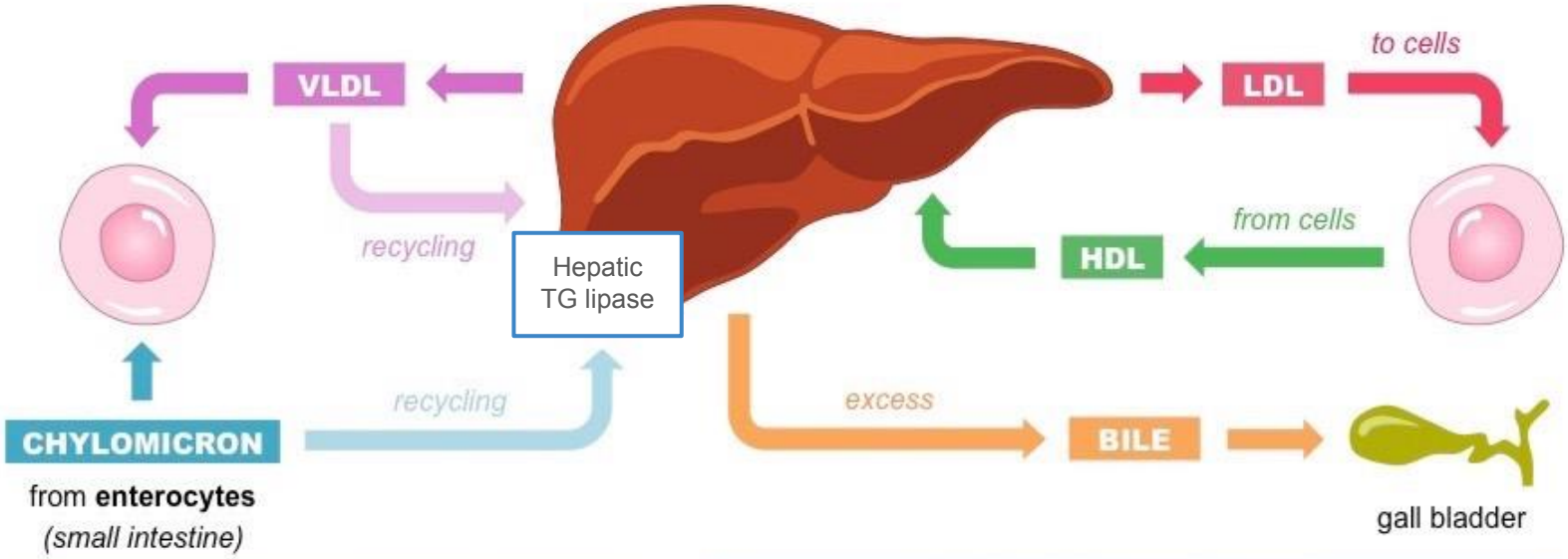
  → increase serum cholesterol

- Acute liver injury → decrease lecithin cholesterol acyltransferase and TG lipase

  → high serum LDL, TG

- Chronic liver disease → low serum cholesterol

Physiology of lipid transport



TRIGLYCERIDE PATHWAY

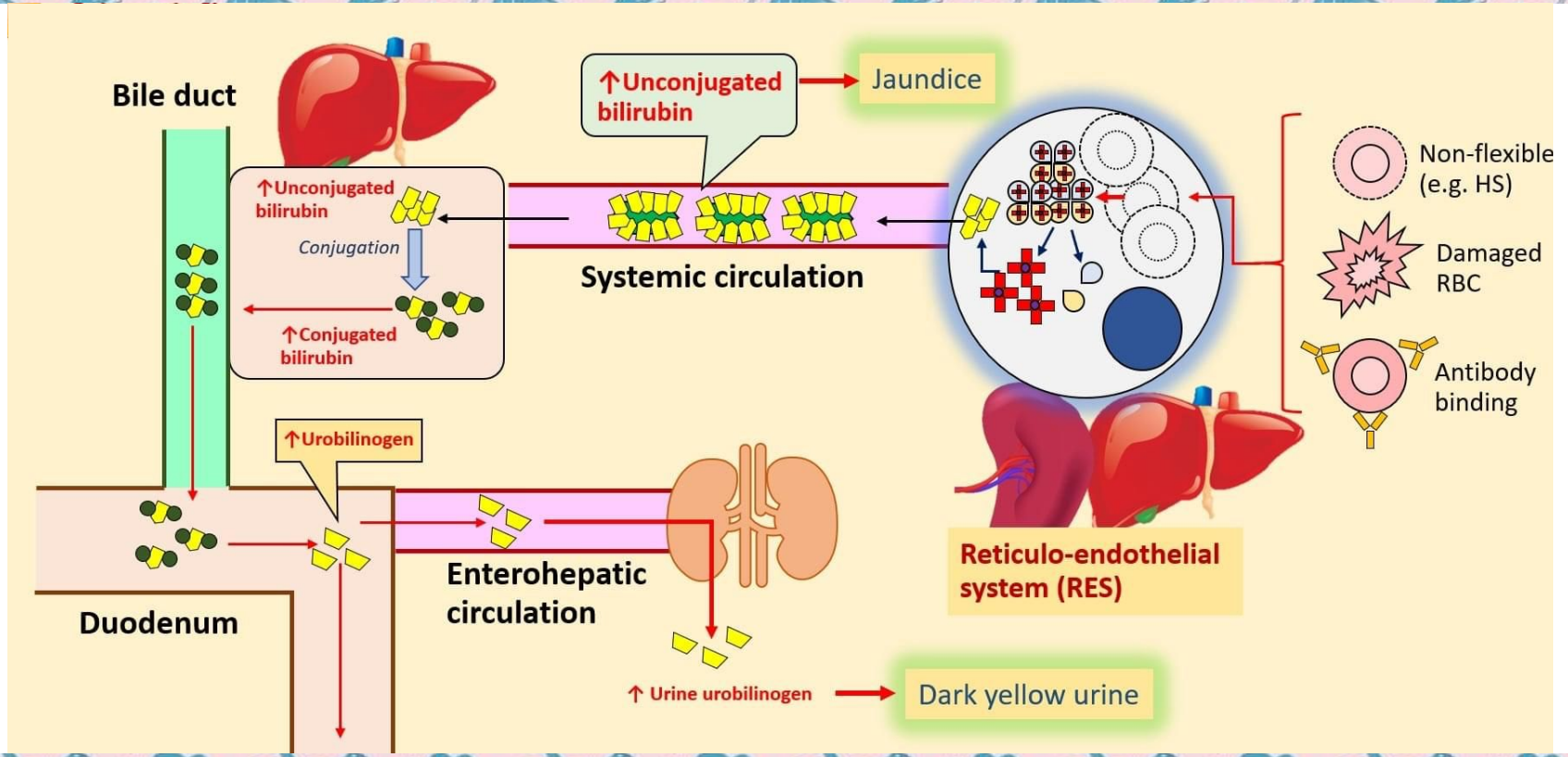
Triglycerides are transported to cells by **VLDL** (from liver) or **chylomicrons** (from intestine) for *energy use or storage* (i.e. adipose tissue)

CHOLESTEROL PATHWAY

Cholesterol is transported to cells by **LDL** for use in *plasma membranes and steroid synthesis*, while excess cholesterol is moved from cells by **HDL** to be converted by liver into bile

Excretory function

Excretory function



Bilirubin

- Produced from heme in reticuloendothelial cells about 4 mg/kg/day
- Heme → Biliverdin →Unconjugate bilirubin → transport to liver
- Unconjugate bilirubin is conjugated by **UDP glucuronosyltransferase** then. excrete to bile canaliculi
- Conjugated bilirubin is hydrolyzed by intestinal bacteria
  1. Urobilinogen
  2. Stercobilinogen

Bilirubin

Normal value

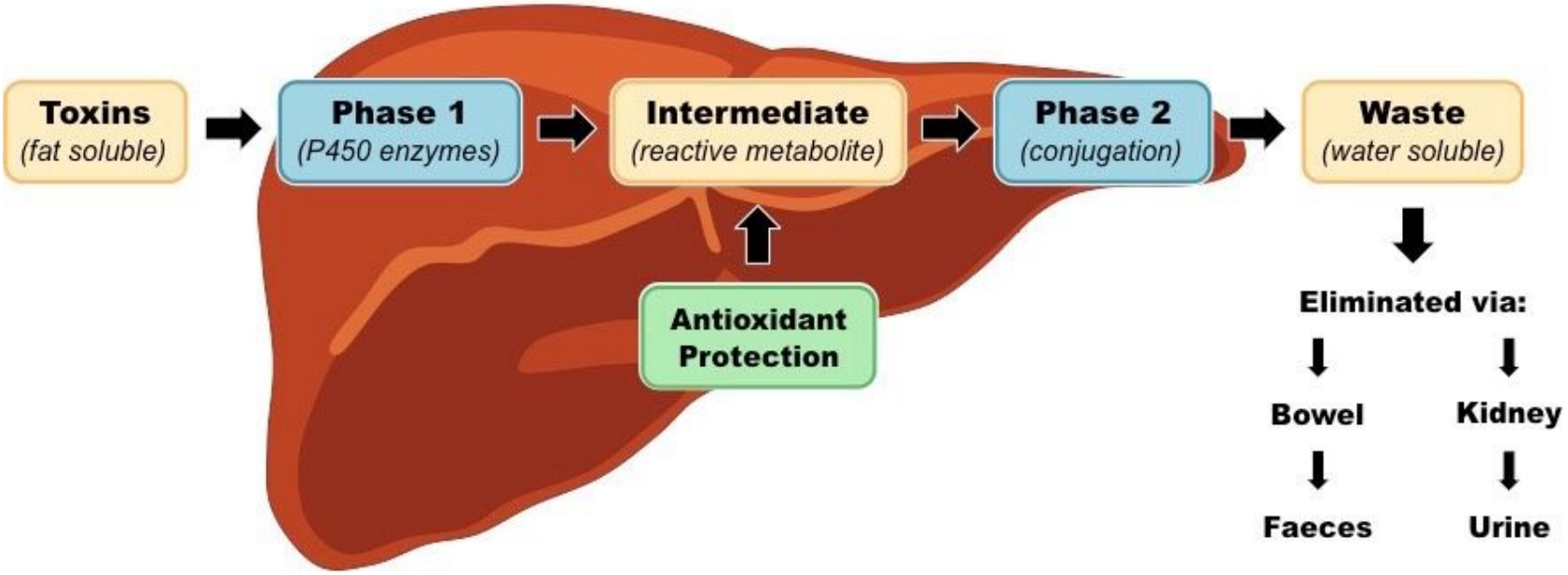
Age	Total (mg/dL)	Conjugated (mg/dL)
0-14 days	0.2-16.6	0.3-1.0
15 days - 1 years	0.3-1.2	0.1-0.4

Direct Hyperbilirubinemia

- DB > 20% of TB
- DB > 1 mg/dL if TB < 5 mg/dL


Special test

Liver detoxification



https://old-ib.bioninja.com.au/options/option-d-human-physiology/d3-functions-of-the-liver/detoxification.html

Special test

1. **Caffeine clearance**

- Evaluate CYP 1A2 function **(Phase I)**
- Measure blood caffeine level after cafferine consuption 200 mg

Special test

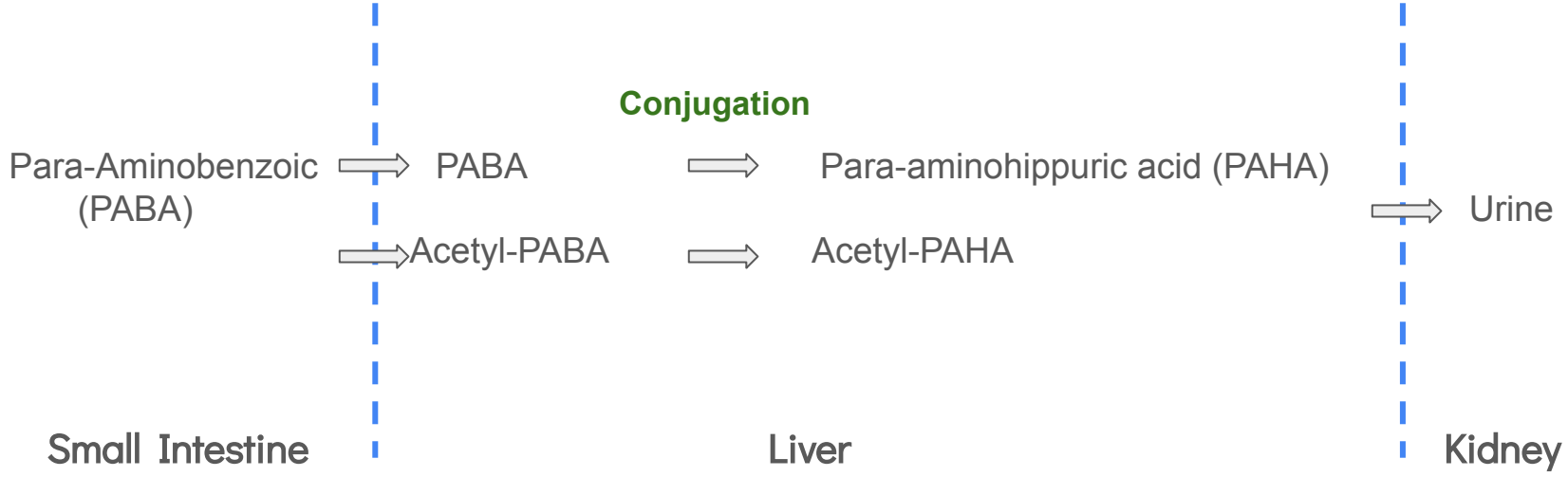
2. Lidocaine metabolite formation (MEGX test)

- Evaluate CYP 3A4 function **(Phase I)**
- Use to evaluate function for liver transplantation
- Lidocaine 1 mg/kg IV then measure monoethylglycinexylidide at 15, 30, 60 min

Special test

3. Para-aminobenzoic acid (PABA) test

- Evaluate conjugate function in **phase II** of hepatic biotransformation

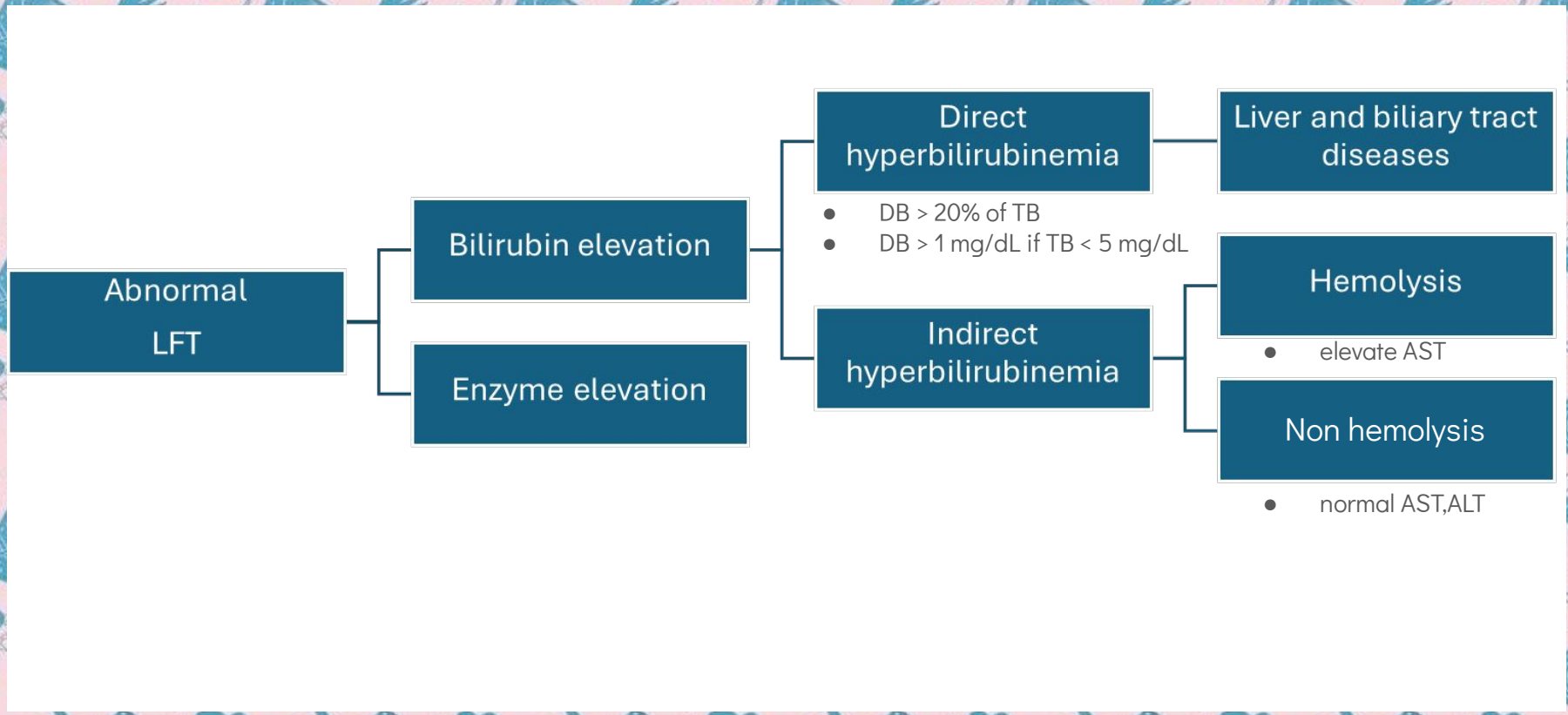


Approach to Abnormal Liver function test

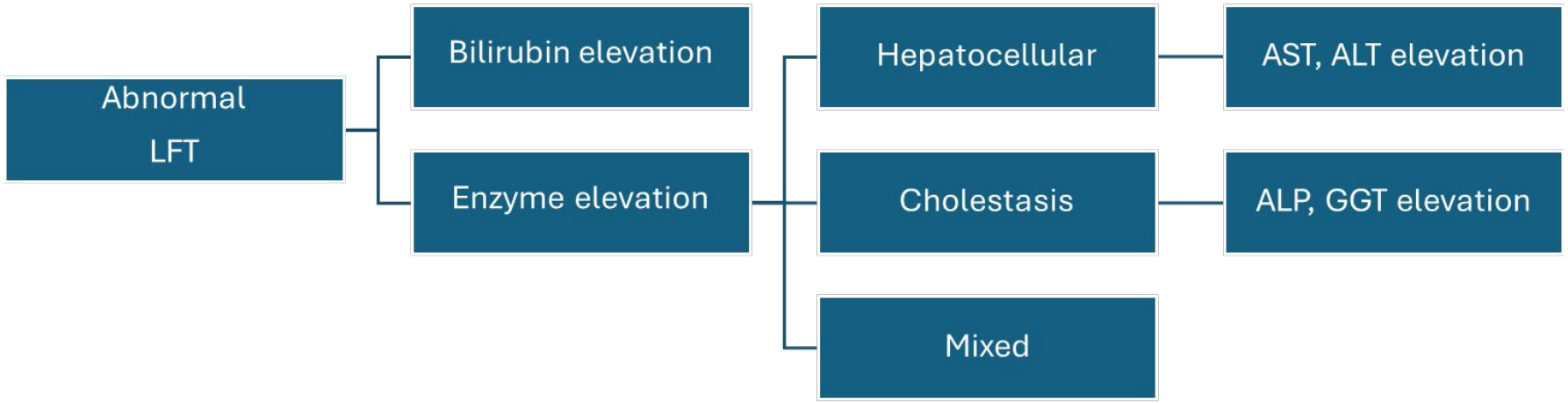
3 steps approach

1. Evaluate pattern of abnormal LFT
   - hepatocellular
   - cholestasis
   - mixed
2. Evaluate cause of abnormal LFT
3. Evaluate prognosis

Evaluate pattern



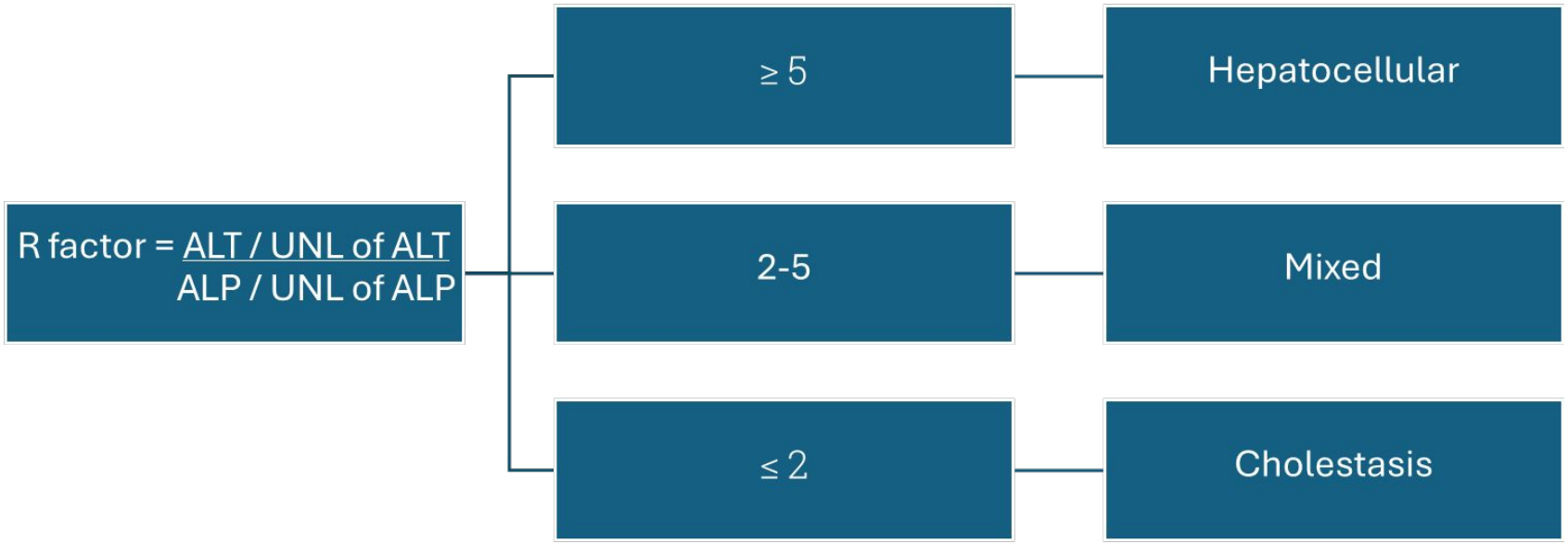
Evaluate pattern



Evaluate pattern

R factor

for evaluate pattern of acute liver injury and drug induced liver injury (DILI)



Hepatocellular cause

INFECTIOUS
Hepatotropic viruses
- HAV
- HBV
- HCV
- HDV
- HEV
- Hepatitis non–A-E viruses

Systemic infection that can include hepatitis
- Adenovirus
- Arbovirus
- Coxsackievirus
- Cytomegalovirus
- Enterovirus
- Epstein-Barr virus
- "Exotic" viruses (e.g., yellow fever)
- Herpes simplex virus
- Human immunodeficiency virus
- Paramyxovirus
- Rubella
- Varicella zoster

Other

NONVIRAL LIVER INFECTIONS
Abscess
Amebiasis
Bacterial sepsis
Brucellosis
Fitz-Hugh-Curtis syndrome
Histoplasmosis
Leptospirosis
Tuberculosis
Other

AUTOIMMUNE
Autoimmune hepatitis
Sclerosing cholangitis
Other (e.g., systemic lupus erythematosus, juvenile rheumatoid arthritis)

METABOLIC
α_1-Antitrypsin deficiency
Tyrosinemia
Wilson disease
Other

TOXIC
Iatrogenic or drug induced (e.g., acetaminophen)
Environmental (e.g., pesticides)

ANATOMIC
Choledochal cyst
Biliary atresia
Other

HEMODYNAMIC
Shock
Congestive heart failure
Budd-Chiari syndrome
Other

NONALCOHOLIC FATTY LIVER DISEASE
Idiopathic
Reye syndrome
Other

Nelson Text book of Pediatrics 21st edition.

Hepatocellular cause

Table 362-1 Disorders Producing Chronic Hepatitis

Chronic viral hepatitis
- Hepatitis B
- Hepatitis C
- Hepatitis D

Autoimmune hepatitis
- Anti-actin antibody positive
- Anti–liver-kidney microsomal antibody positive
- Anti-soluble liver antigen antibody-positive
- Others (includes antibodies to liver-specific lipoproteins or asialoglycoprotein)
- Overlap syndrome with sclerosing cholangitis and autoantibodies
- Systemic lupus erythematosus
- Celiac disease

Drug-induced hepatitis

Metabolic disorders associated with chronic liver disease
- Wilson disease
- Nonalcoholic steatohepatitis
- α_1-Antitrypsin deficiency
- Tyrosinemia
- Niemann-Pick disease type 2
- Glycogen storage disease type iv
- Cystic fibrosis
- Galactosemia
- Bile acid biosynthetic abnormalities

Nelson Text book of Pediatrics 21st edition.

Hepatocellular cause

Elevate of AST and ALT (>10-15 times of upper normal limit)

- Acute viral hepatitis
- Toxin/Drug induced hepatitis
- Ischemic hepatitis
- Autoimmune hepatitis
- Fulminant Wilson's disease
- Acute bile duct obstruction

useful to follow-up, not correlate with severity of disease

Hepatocellular cause

Elevate of AST and ALT (< 10 times of upper normal limit)

1. AST > ALT
   - Toxin/Drug induced hepatitis
   - Ischemic hepatitis
   - Alcoholic hepatitis (AST:ALT ratio usually more than 2)
   - Wilson's disease
2. ALT > AST
   - Chronic viral hepatitis
   - Non alcoholic fatty liver disease (NAFLD)
   - Autoimmune hepatitis
   - Hemochromatosis
   - Alpha 1-Antitripsin deficiency

Isolated elevate AST : hemolysis, myopathy, myocardial disease, rhabdomyolysis

useful to follow-up, not correlate with severity of disease

Cholestatic cause

INFECTIOUS
Generalized bacterial sepsis
Viral hepatitis
- Hepatitides A, B, C, D, E
- Cytomegalovirus
- Rubella virus
- Herpesviruses: herpes simplex, human herpesvirus 6 and 7
- Varicella virus
- Coxsackievirus
- Echovirus
- Reovirus type 3
- Parvovirus B19
- HIV
- Adenovirus

Others
- Toxoplasmosis
- Syphilis
- Tuberculosis
- Listeriosis
- Urinary tract infection

TOXIC
Sepsis
Parenteral nutrition related
Drug, dietary supplement, herbal related

METABOLIC
Disorders of amino acid metabolism
- Tyrosinemia

Disorders of lipid metabolism
- Wolman disease
- Niemann-Pick disease (type C)
- Gaucher disease

Cholesterol ester storage disease
Disorders of carbohydrate metabolism
- Galactosemia
- Fructosemia
- Glycogenosis IV

Disorders of bile acid biosynthesis
Other metabolic defects
- α_1-Antitrypsin deficiency
- Cystic fibrosis
- Hypopituitarism
- Hypothyroidism
- Zellweger (cerebrohepatorenal) syndrome
- Dubin-Johnson syndrome
- Rotor syndrome

- Wilson disease
- Neonatal iron storage disease
- Indian childhood cirrhosis/infantile copper overload
- Congenital disorders of glycosylation
- Mitochondrial hepatopathies
- Citrin deficiency

GENETIC OR CHROMOSOMAL
Trisomies 17, 18, 21

INTRAHEPATIC CHOLESTASIS SYNDROMES
"Idiopathic" neonatal hepatitis
Alagille syndrome
Intrahepatic cholestasis (progressive familial intrahepatic cholestasis [PFIC])
- FIC-1 deficiency
- BSEP (bile salt export pump) deficiency
- MDR3 deficiency

Familial benign recurrent cholestasis associated with lymphedema (Aagenaes syndrome)
ARC (arthrogryposis, renal dysfunction, and cholestasis) syndrome
Caroli disease (cystic dilation of intrahepatic ducts)

Intrahepatic

Nelson Text book of Pediatrics 21st edition.

Cholestatic cause

Extrahepatic

EXTRAHEPATIC DISEASES
Biliary atresia
Sclerosing cholangitis
Bile duct stricture/stenosis
Choledochal–pancreaticoductal junction anomaly
Spontaneous perforation of the bile duct
Choledochal cyst
Mass (neoplasia, stone)
Bile/mucous plug ("inspissated bile")

MISCELLANEOUS
Shock and hypoperfusion
Associated with enteritis
Associated with intestinal obstruction
Neonatal lupus erythematosus
Myeloproliferative disease (trisomy 21)
Hemophagocytic lymphohistiocytosis (HLH)
COACH syndrome (coloboma, oligophrenia, ataxia, cerebellar vermis hypoplasia, hepatic fibrosis)
Cholangiocyte cilia defects

Nelson Text book of Pediatrics 21st edition.

Non hemolytic indirect hyperbilirubinemiaa

DECREASED DELIVERY OF UNCONJUGATED BILIRUBIN (IN PLASMA) TO HEPATOCYTE
Right-sided congestive heart failure
Portacaval shunt

DECREASED BILIRUBIN UPTAKE ACROSS HEPATOCYTE MEMBRANE
Presumed enzyme transporter deficiency
Competitive inhibition
- Breast milk jaundice
- Lucey-Driscoll syndrome
- Drug inhibition (radiocontrast material)

Miscellaneous
- Hypothyroidism
- Hypoxia
- Acidosis

DECREASED STORAGE OF UNCONJUGATED BILIRUBIN IN CYTOSOL (DECREASED Y AND Z PROTEINS)
Competitive inhibition
Fever

DECREASED BIOTRANSFORMATION (CONJUGATION)
Neonatal jaundice (physiologic)
Inhibition (drugs)
Hereditary (Crigler-Najjar)
- Type I (complete enzyme deficiency)
- Type II (partial deficiency)

Gilbert disease
Hepatocellular dysfunction

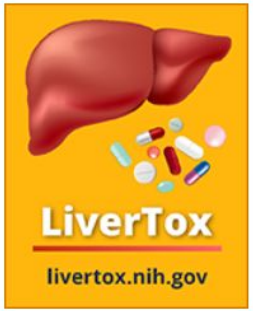
ENTEROHEPATIC RECIRCULATION
Breast milk jaundice
Intestinal obstruction
- Ileal atresia
- Hirschsprung disease
- Cystic fibrosis
- Pyloric stenosis

Antibiotic administration

Nelson Text book of Pediatrics 21st edition.

Drug induce liver injury (DILI)

Drug induce liver injury can elevate enzyme in hepatocellular, cholestasis or mix pattern



LiverTox

Clinical and Research Information on Drug-Induced Liver Injury

Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-.

Copyright and Permissions

Search this book

Scan here

Acute liver failure

Acute liver failure

- Biochemical evidences of liver injury
- INR > 2 or INR > 1.5 with hepatic encephalopathy
- No evidence of chronic liver disease

Acute ontop chronic liver failure

- TB > 5 mg/dL
- INR > 1.5
- Ascites and/or Hepatic encephalopathy
- Onset within 4 weeks
- Evidence of chronic liver disease

Evaluate prognosis

Predict mortality in Cirrhosis

- Child-Turcotte-Pugh prognostic score
- Pediatric end stage liver disease score (PELD) (age < 12 years)
- Model for end stage liver disease score (MELD) (age ≥ 12 years)

Predict mortality in Wilson's disease

- New Wilson index (NWI)

Predict mortality and selection criteria for liver transplantation in acute liver failure

- King's college criteria for paracetamol induce acute liver failure
- King's college criteria for non-paracetamol acute liver failure

Child-Turcotte-Pugh score

Parameters	Point		
	1	2	3
Serum Bilirubin (mg/dL)	2	2-3	>3
Serum Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (s)	1-4	5-6	>6
Hepatic encephalopathy	None	Minimal	Advanced
Ascites	None	Slight	Moderate

Child-Turcotte-Pugh score

Classification	Survival rate	
	1 year	2 years
A (5-6 points)	100%	85%
B (7-9 points)	80%	60%
C (10-15 points)	45%	35%

PELD & MELD

PELD Score (Pediatric End-Stage Liver Disease) (younger than 12)

Calculates the pediatric version of the MELD score for liver cirrhosis severity and transplant planning.

When to Use

Age		years
Bilirubin	Norm: 0.3 - 1.	mg/dL ⇆
Albumin	Norm: 3.5 - 5.5	g/dL ⇆
INR	Norm: 0.8 - 1.2	
History of growth failure UNOS Growth Failure Chart	No 0	Yes +1

MELD Na (UNOS/OPTN)

Quantifies end-stage liver disease for transplant planning with sodium.

Dialysis at least twice in the past week Or CVVHD for ≥24 hours in the past week	No	Yes
Creatinine Cr >4.0 mg/dL is automatically assigned a value of 4.0	Norm: 0.7 - 1.	mg/dL ⇆
Bilirubin	Norm: 0.3 - 1.	mg/dL ⇆
INR	Norm: 0.8 - 1.2	
Sodium	Norm: 136 - 1	mEq/L ⇆

New Wilson index

Parameters	Score				
	0	1	2	3	4
Total bilirubin (mg/dL)	0-5.85	5.86-8.77	8.78-11.69	11.7-17.54	>17.55
AST (U/L)	0-100	101-150	151-300	301-400	>401
INR	0-1.29	1.3-1.6	1.7-1.9	2.0-2.4	>2.5
WBC (10^9/L)	0-6.7	6.8-8.3	8.4-10.3	10.4-15.3	>15.4
Albumin (g/dL)	>4.5	3.4-4.4	2.5-3.3	2.1-2.4	<2.0

Score $\geq$ 11 : high mortality without liver transplant

King's college criteria

Criteria for liver transplant in fulminant liver failure

Paracetamol induced acute liver failure	Non-Paracetamol induced acute liver failure
- ABG pH < 7.3 after resuscitation and > 24 hr since ingestion OR - Blood lactate > 3.5 mmol/L OR - All of below 1. INR > 6.5 2. Cr > 3.4 mg/dL 3. Hepatic encephalopathy gr.III-IV	- INR > 6.5 OR - 3 of 5 following criteria 1. Etiology: indeterminate etiology, DILI 2. Age < 10 or > 40 years 3. Interval of juandice-encephalopathy > 7 days 4. Bilirubin > 17.6 mg/dL 5. INR > 3.5

Take Home messages

- Biochemical test : AST,ALT,ALP
  → Elevation of enzyme was found in hepatobiliary and non hepatobiliary disorder
  → Level dose not correlate with severity
- Function test : Synthetic, Excretion, Detoxification
- 3 steps approach abnormal LFT : pattern, cause, prognosis
  → R-value for evaluate pattern : Hepatocellular, Cholestasis, Mixed
- There are many etiology cause abnormal LFT
  → History taking and physical examination lead to diagnosis
- Drug induce liver injury (DILI) cause abnormal liver enzyme in several pattern

References

- Nelson Text book of Pediatrics 21st edition.
- Ramathibodi Handbook of Pediatrics Diagnostic test 2020.
- Liver diseases in children. วรนุช จงศรีสวัสดิ์. ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย.
- Approach to the patient with abnormal liver function test. พนิดา ทองอุทัยศรี. คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี.
- Interpretation of Liver function tests. World Health Organization (WHO) training-modules
- Nakorn - Core physiology and medical science


Thank you,
Happy Valentine's Day