Practical Approach to Patient with Liver Disease

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Case 1

- An 18 YO student from Addis Ababa presented with malise,anorexia,fatigue,myalgia,jaundice of 2 weeks

- P/E: Mild icterus and RUQ tenderness

Case 1: Investigation

ALT	1700	2031	1215	167
AST	1070	1450	190	69
GGT	219	171	156	145
ALP	200	165	116	95
INR	1.25	1.21	1.08	0.81
T. Bil	2..6	2..15	1.85	1.84
conjugated	1.90	1.83	1.05	0.68
T. protein	6.0	6.41	7.21	7.35
Albumin	3.6	3.7	3.7	3.76

Negative further tests

- HBV markers negative
- HCV Ab-negative
- Abdominal sonography-unremarkable
- What further tests?

Case 2

- A 40 year old farmer from Northern Ethiopia presented with fatigue and progressive abdominal distension of three months.
- He lost 5 family members recently from similar complaints. He noted similar problems among his neighbors.
- He was noted to have pallor, splenomegally, and ascites
- EGD reveled Esophageal varices and PHG
- Lab =ALP &Bil↑,pancytopenia
- Sonography=diffusely echogenic liver and ascites
- DDx?

Liver

- Biggest and busiest
- >1000 complex functions

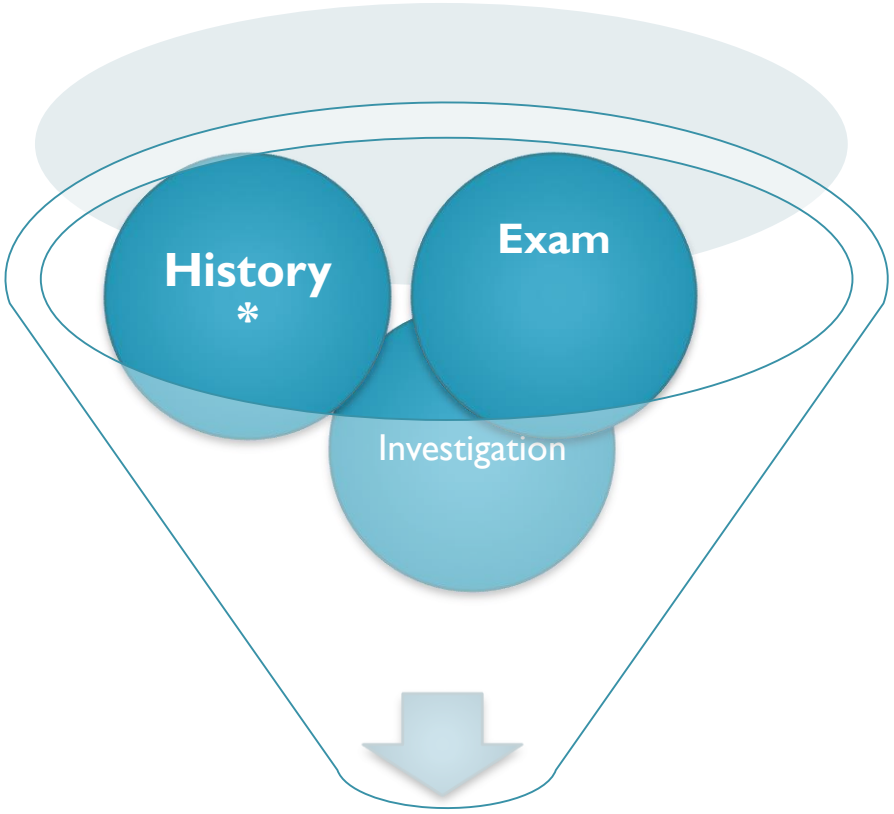
- Too many DDx
- Several tests required for Dx
- Most tests non sensitive/specific

- Hepatocellular, choelstatic, mixed,external

Questions

- Normally abnormal and abnormally normal LBT?
- Methods of localization ?
- How to differentiate so many DDx ?
- How to assess prognosis?
- When to observe/ biopsy liver ?

Diagnose Liver Ds



Diagnosis

Approach to liver Ds

- **History**: Family, travel,tattoo,alchol,blood Tx, contact,drug,toxin,HD,sytemic Ds,Sx,
- Pregnancy(hyperemsis,PE,cholestasis,HELP, fatty

- **P.E:** v/s, icterus, CLD, PHN,Murphy,LAP, systemic,urine,stool,rashes,---

- **LBT**: Hepatocellular, cholest, mixed,10% NI
- **Etiologic** Tests
- **Imaging**: US,EUS, CT, MRCP, ERCP. Fibroscan,venogram,

Challenges---

- But all these are non specific !
- 2.5 % abnormal in population
- Fluctuating values
- Abnormally normal-fulminant/ESLD

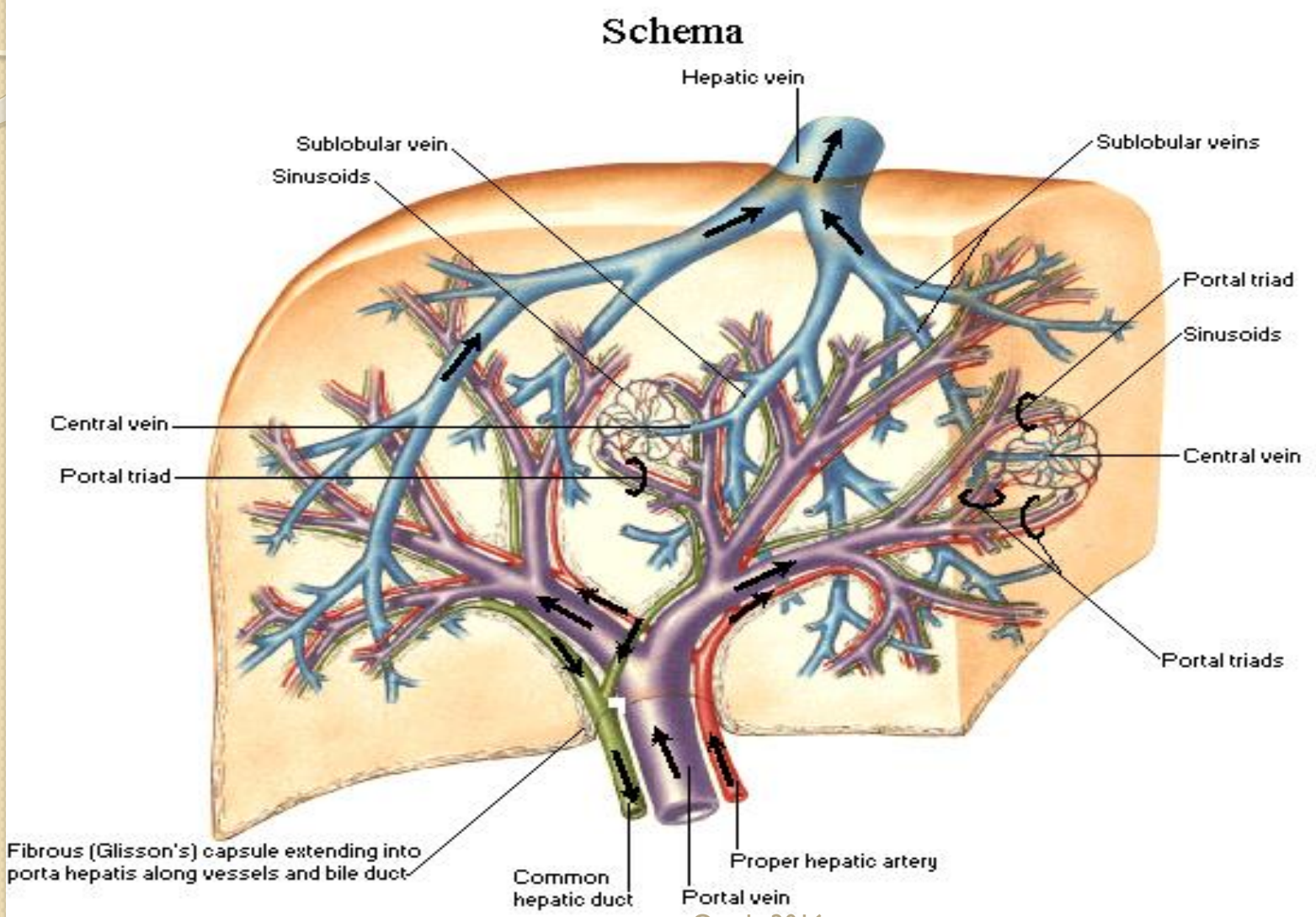
Eg.Abnormal LBT in USA 249 blood donors

- Fatty liver 22-56 %-Obesity↑*
- ALD 11-48 %

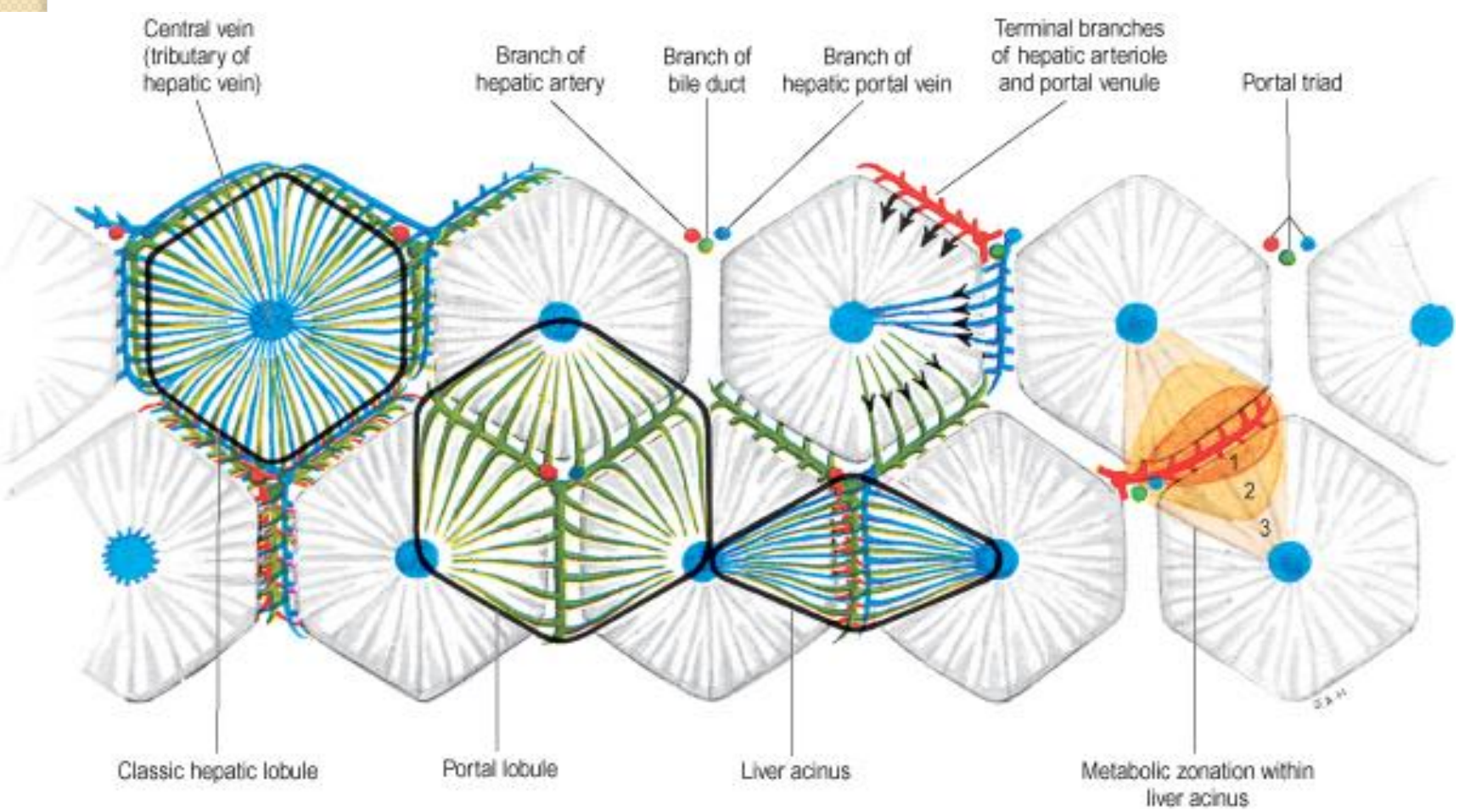
- HCV 17-20%
- Miscellaneous 4-8%
- Unexplained 2-9%

- Africa-HBV,HCV,toxin /DILI

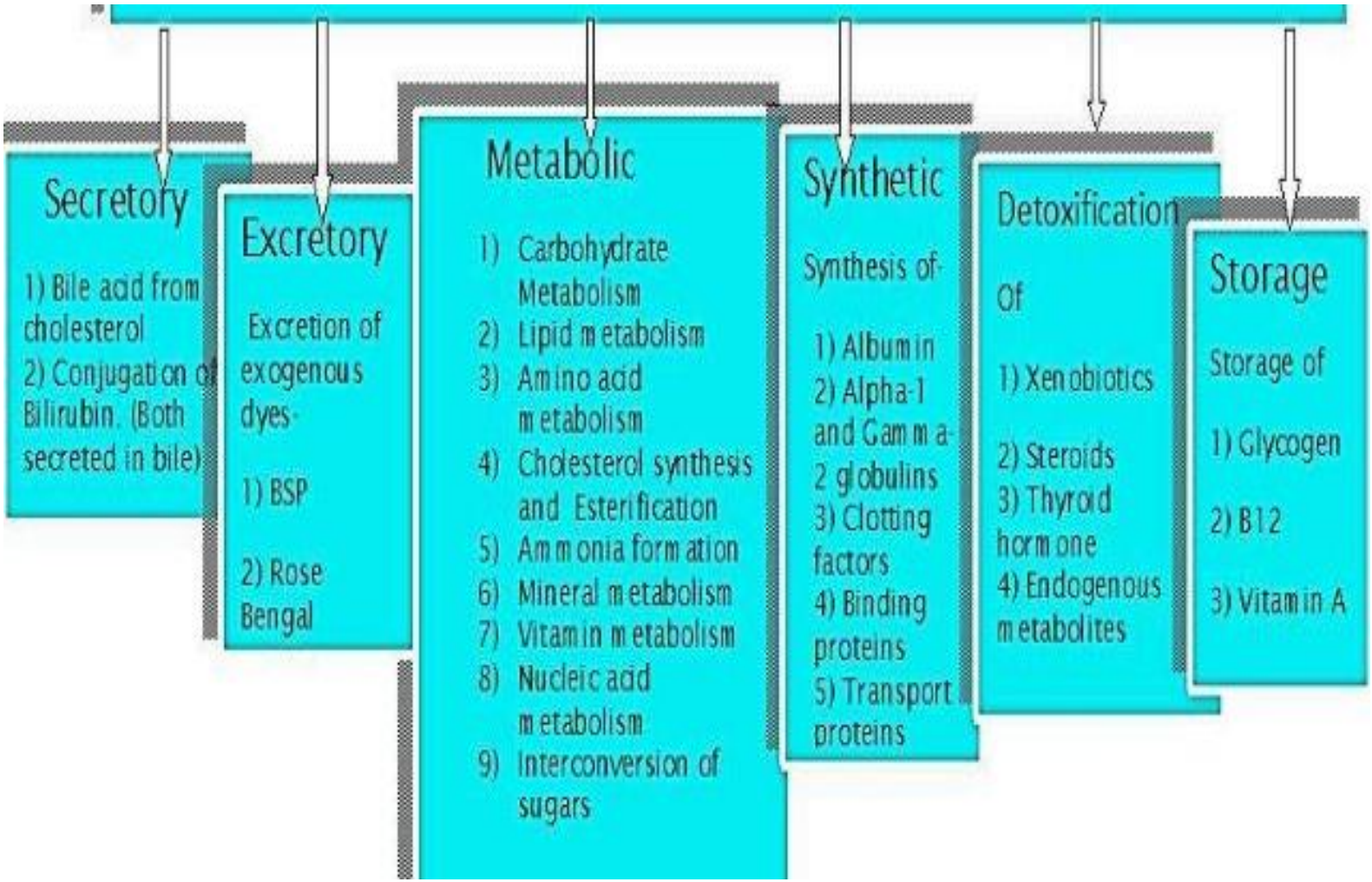
Hepatic Circulation



Functional Organizations Lobules,Acini, Cords/ plates



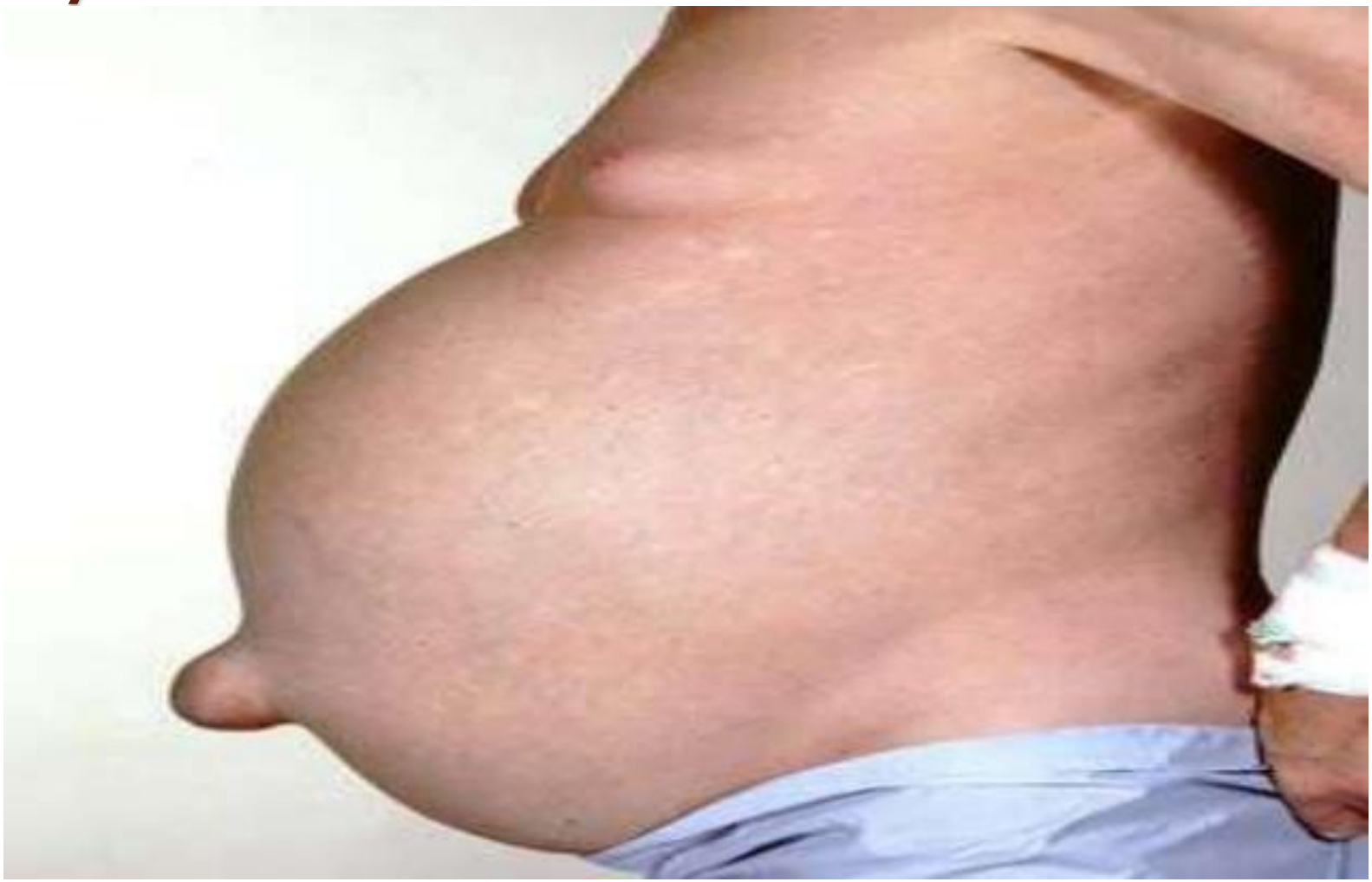
Hepatic functions---



Functions of the Liver

- Metabolic activities
- Homeostasis,
- Nutrition& immune defense
- Synthesis
- Fetus-haemopoiesis.
- Detoxification/excretion
- Secretion
- Storage:

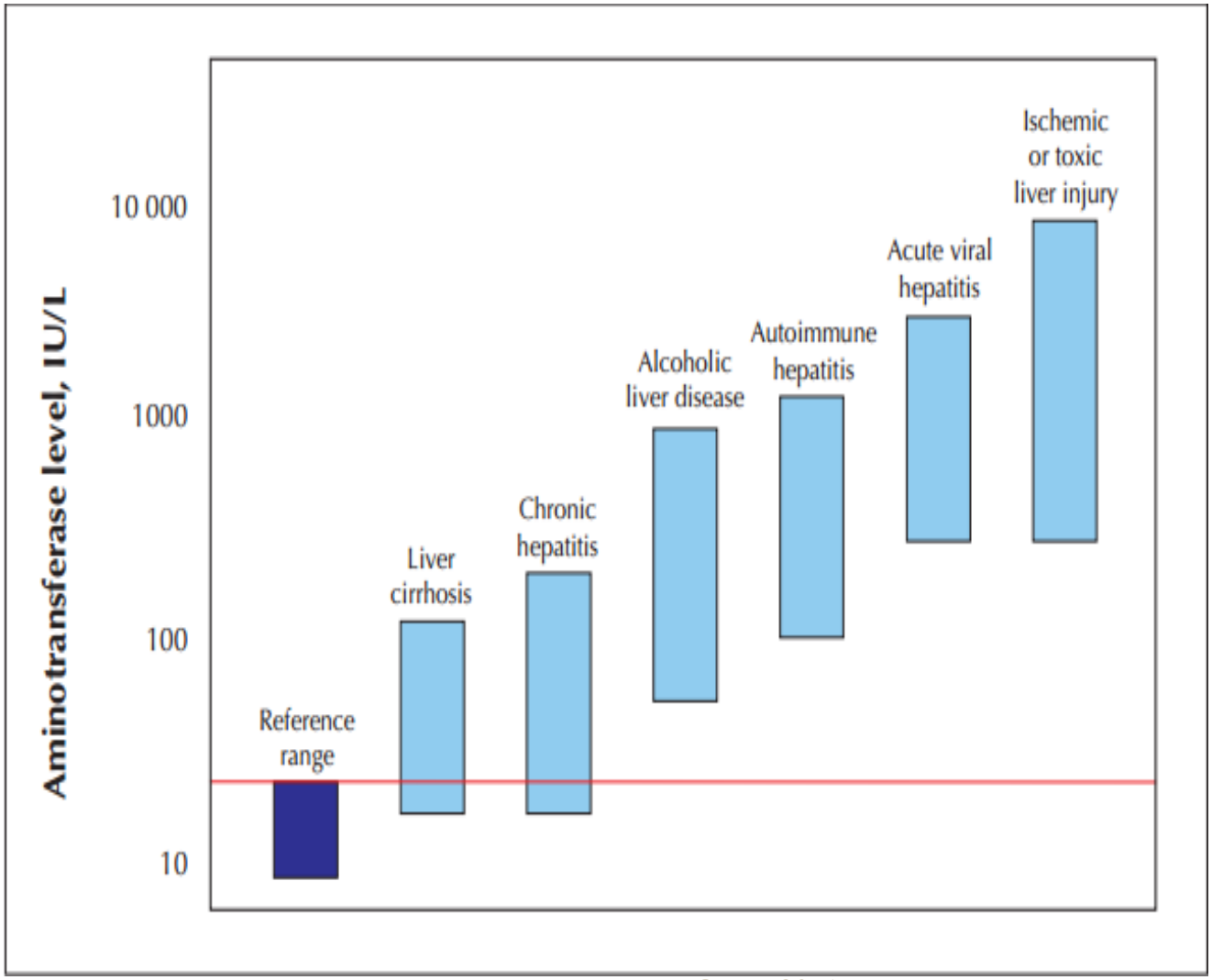
Transaminases could be Nl but dysfn



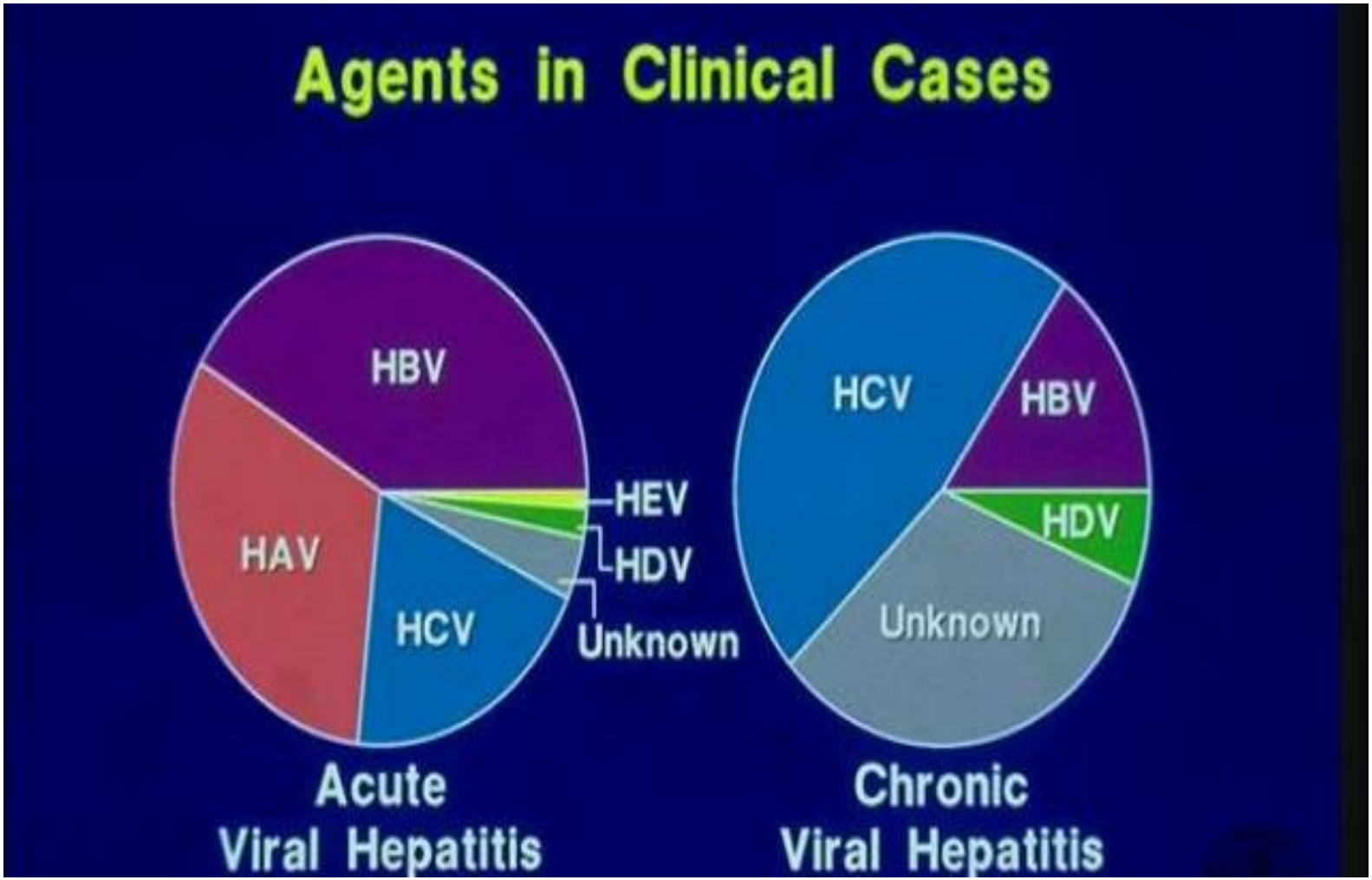
DDx broad

- **Viral hep*--Acute/ALF**>chronic/ESLD
- Metabolic: NAFLD, Wilson, Hemom, **DILI***
- Immunologic: AIH, PBC, PSC
- Infiltrative: Amyl/sarcoid, granuloma
- Vascular: VOD, BCS
- Neoplasm: HCC, Cholangio, Mest
- Non-hepatic: CHF, **shock***, myopathy, Thyroid, celiac, adrenal Ds
- *>AMT>10UNL—others <5UNL

Aminotransferase level



Transaminitis



LBT categories

- **Detoxification & Excretory function**
  - Serum Bilirubin
  - Urine Bilirubin
  - Blood Ammonia
- **Biosynthetic function**
  - Serum Albumin
  - Serum Globulin
  - Coagulation factors
- **Hepatocye injury**
  - ALT
  - AST
- **Cholestasis**
  - Alk. Phosphatase
  - 5'-nucleotidase,
  - γ-glutamyl transpeptidase (GGT)

Liver Enzymes

- thousands in liver.

- Drawbacks: sensitivity/Specifity

  - <5x mild; Metabolic Ds
  - 5-10 Moderate : CVH,ALD
  - >Severity: toxic, Acute VH,shock
  - Fluctuating/progressive course

Aminotransferases

- AST
  - cytosol and mitochondria
  - liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lung, leukocytes, RBC.
- ALT: Mainly liver cytosol

>Rise 1000x:
-VH,Toxins,DILI, Ischemic(hospitalized*),
-AIH,BCS,Fulminanat Wilson, OBJ

ALP GGT; Biliary membrane +:=cholestasis,infitrative

.

A) Hepatocellular necrosis

- Hepatocyte damage…CM injury… plasma
- ALT/ SGPT

- Degree of elevation in disease states:
  - Minimal: chronic hep
  - Moderate < 3oo U/L ALD
  - Striking elevations—>1000 U/L—

  (viral hep, AIH, Wilson, ischemic hep, or toxin- or DILI)

AST:ALT De Rittis ratio>2

- Depln of vit B6 in alcoholics-↓ ALT synthesis
- Damage to mitochondria releasing mAST
- High ratio in recent binge & advanced ALD
- Could be normal in chronic alcoholics

Diagnostic Clues…

- Relative pattern of elevation of AST>ALT
  - Duration of disease CLD >1:1
  - Alcoholic liver disease >1:2-3
- Pattern of jaundice
  - Cholestatic Vs hepatocellular feature
- Enzymes not prognostic-normal in ESLD
- Follow disease activity-serially.

ALT predominant---pyrodoxine*

- <5-15 xUNL
- Acute/Chronic viral hep
- Ischemic Hep
- DILI, acute BCS, VOD

- NAFLD
- Hemochromatosis
- AIH
- AATD, Wilson, Celiac

AST predominant

- ALD—pyrodoxine def for ALT
- Cirrhosis—thrombocytopenia/spleen
- Myopathy, exercise

- Hemolysis
- Thyroid Ds
- Pancreas, bowel,Bone,placenta,---

B) Enzymes for Cholestasis

- Clinical utility/ specificity
  - ALP
  - 5'- neucleotidase
  - GGT--Liver

- ALP
  - 4 different isozymes
  - Physiologic elevations: children/adolesent,pregnant

  - > 4x : cholestatic , infiltrative: cancer , amyloidosis---.

ALKALINE PHOSPHATASE

- **liver, bone,** placenta,small intestine &kidney. >4x Infiltrative cholestasis with GGTP & 5'NT-HB specific (Bone if without GGT/5NT)
  - 4 different isozymes-bound hep canalicular membrane
  - Physiologic milder elevations

- **Physiological**

1. age > 60 can have ALP (1–1.5 X normal)
2. Blood types O and B.
3. children and adolescents-bone growth
4. late in normal pregnancies

ALT:ALP ratio

- >5=Hepatocellular
- <2=Cholestasis
- 2-5 mixed

Isolated ALP↑

Hepatobiliary Disease

- Early cholestasis
- AIDS cholangiopathy
- Hepatic infiltration by tumor or granulomata. bone mets

- ***Jaundice may be absent***

Others

- Hodgkin's disease
- Diabetes
- Hyperthyroidism
- CHF
- Amyloidosis
- IBD

Low ALP

- Reduced ALP activity due to displacement of the co-factor zinc by copper
- Eg.
  - Hypothyroidism,
  - Pernicious anemia,
  - Zinc deficiency,
  - Congenital hypophosphatemia
  - fulminant hepatitis and hemolysis

Gamma Glutamyl Transpeptidase, GGTP

- liver (**hepatocytes & cholangiocytes**), kidney, pancreas, spleen, heart, brain, and seminal vesicles. T 1/2 =26 days

  - NOT in bone & pregnancy
  - Localizes ALP to HB sources-R/o HB ds if N(90% NPV)

  - High sensitivity but specif for hepatobiliary Ds
  - HCC, CBD stones , CLD, phenytoin, alcohol, barbiturate, DILI, fever, CHF, pancreas, DM, IHD,

Disproportionate ALP GGT↑

- Ca , TB
- Amyloidosis
- Sarcoidosis
- Others

5′-Nucleotidase

- Hep canalicular and sinusoidal membranes
- intestine, brain, heart, B/vessels, pancreas.
- 2nd & 3rd trimesters of pregnancy
- Primarily in hepatobiliary Ds but NOT bone

LDH rise

- Hepatocellular necrosis
- Shock liver
- Cancer
- Hemolysis
- DILI

AIH

- 20% negative Ab
- ASMA, AMA, ANA,
- Electrophoresis: gamaglobulins↑
- Rarely acute

ALD

- Mild-moderate transaminitis
- AST>ALT 2-3:1
- ALT normal or low
- GGT:ALP >2.5

Wilson Ds

- Genetic biliary Cu excretion
- Ceruloplasmin ↓ in 80%
- Kayer-Fleisher ring
- Urin cu >100 microgm/day Dx
- Liver Bx> 250 microgm/day

Cholestasis Ds

- **A. Intrahepatic**
- Viral hepatitis
- ALD
- DILI, VOD
- PBC
- Familial
- Pregnancy
- TPN
- Post Op, LTx
- Sepsis
- Paraneop syndrome
- Infiltrative: TB, NHL, Amyl/sarcoid---

Cholestasis---

- B. Extra hepatic:
- HBP cancers
- Choledocholithiasis
- Biliary stricture
- Chronic pancreatitis
- AIDS cholangiopathy
- Mirizzi's syndrome-GB/cystic D stone compress CBD
- Ascariasis

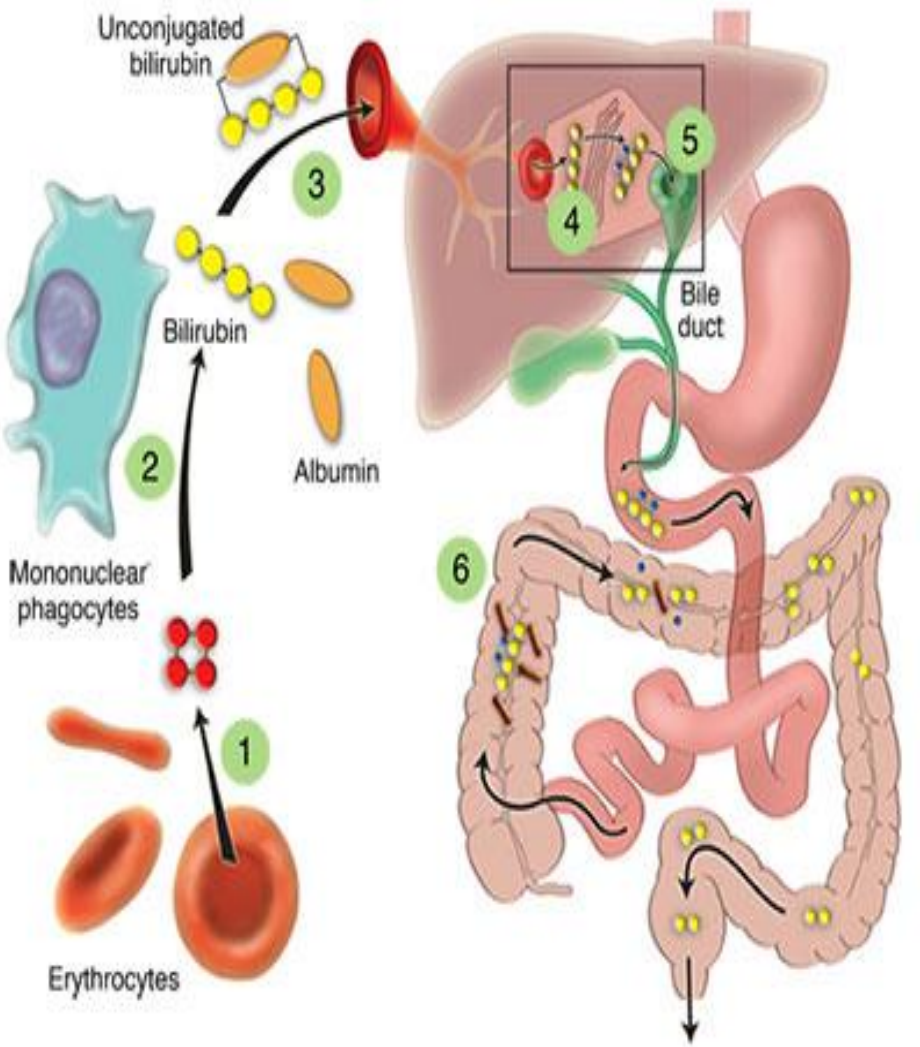
C) Mixed : HC& Cholestasis

- Viral Hepatitis
  - HAV,HBV, HCV---fibrosing
  - Others: EBV, CMV
- Alcoholic hepatitis
- DILI
- Solid organ transplantation

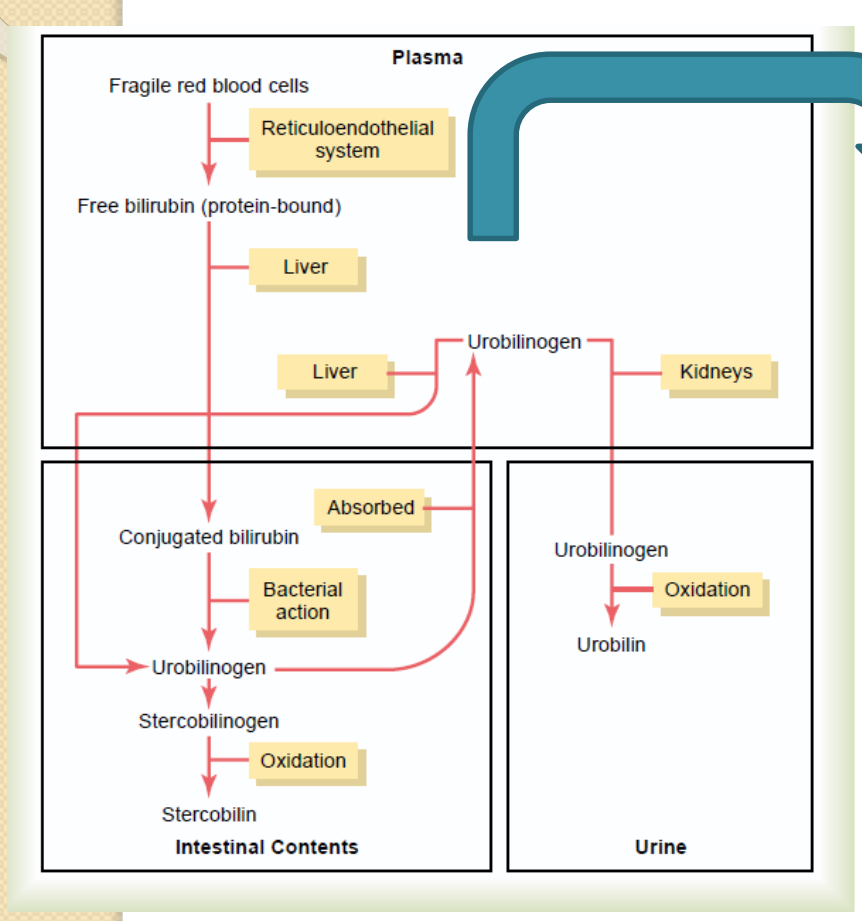
2) Bilirubin

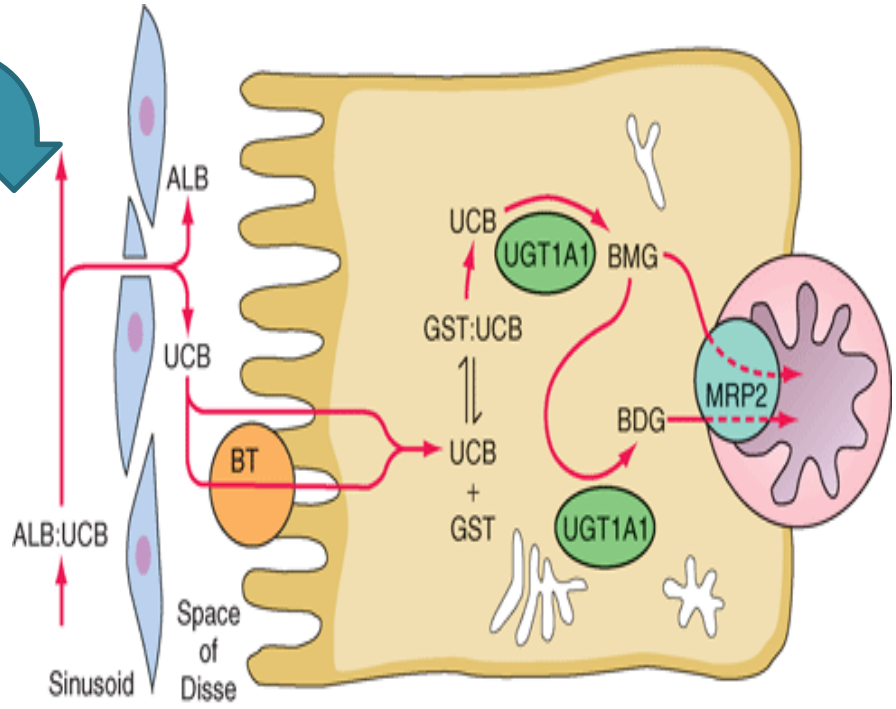
- breakdown product- porphyrin ring of heme- proteins.
- Daily synthesis = 250 – 300mg (95% RES Hb)
- Exists in 2 forms
  - Indirect/ Unconjugated
  - Direct/ conjugated –dizo reactant
  - Delta Bil-albumin t1/2=14-21days(vs 4hrs-lagging jaundice)
  - Bilirubinuria-Dx Liver Ds early=direct Bil
- Normal serum T.Bilirubin-van den Bergh Rxn
  - Total =0.2 - 0.9 mg/dl - in 95% population (15% conjugated.

Metabolism

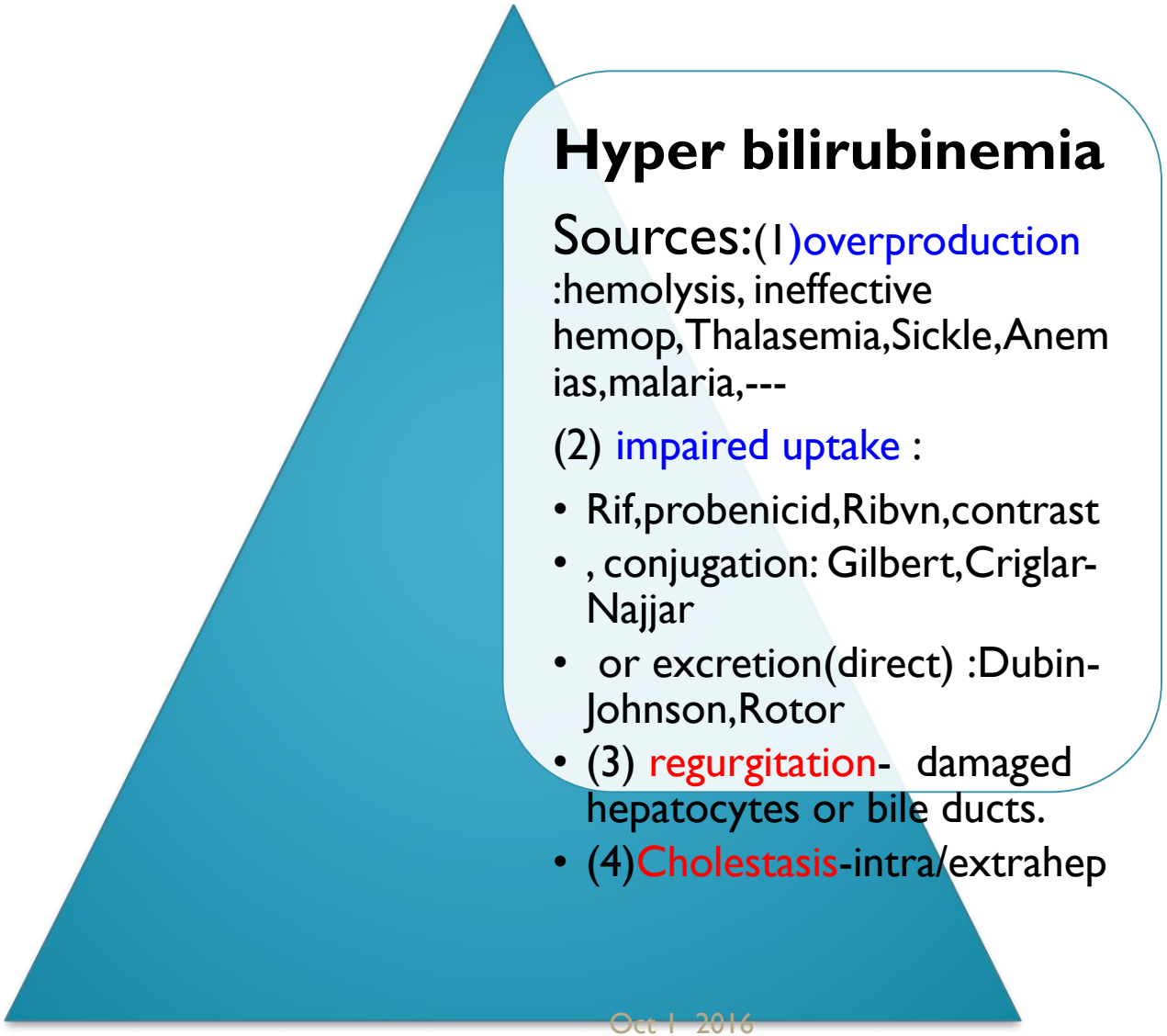

Unconjugated bilirubin
3
Bilirubin
Albumin
2
Mononuclear phagocytes
1
Erythrocytes
4
5
Bile duct
6

Bilirubin Metabolism and Excretion





Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com



Hyper bilirubinemia

Sources:(1)overproduction :hemolysis, ineffective hemop,Thalasemia,Sickle,Anemias,malaria,---

(2) impaired uptake :

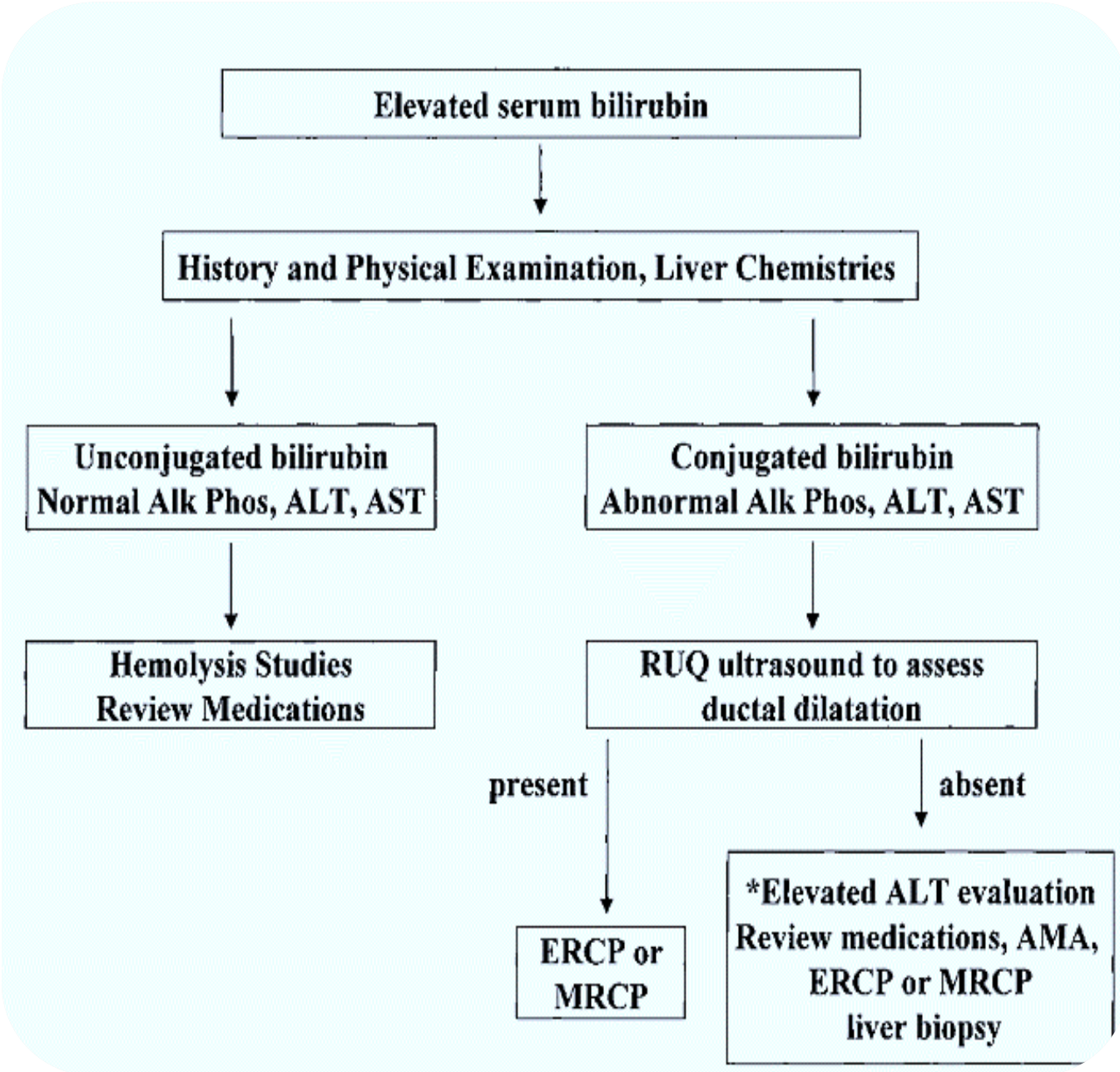
- Rif,probenicid,Ribvn,contrast
- , conjugation: Gilbert,Criglar-Najjar
- or excretion(direct) :Dubin-Johnson,Rotor
- (3) regurgitation- damaged hepatocytes or bile ducts.
- (4)Cholestasis-intra/extrahep

Unconjugated hyperbilirubinemia

- UGTA mutation-Gilbert synd
- UGTA inhibition: Indina/Atazanivir
- Bil uptake inhibition: Rifampin, CAF, genta

Conjugated Hyperbilirubinemia

- 1. Extra hepatic
  - Biliary obstruction: Stone, Ca
  - Pancreatic: Ca, stricture
- 2. Intrahepatic
  - PSC, PBC=AMA
  - Dubin-Jo, Rotor synd=transporter mutation
  - Cholestasis: AIH, Viral: ANA, ASAM, LKM


Elevated serum bilirubin
History and Physical Examination, Liver Chemistries
Unconjugated bilirubin
Normal Alk Phos, ALT, AST
Conjugated bilirubin
Abnormal Alk Phos, ALT, AST
Hemolysis Studies
Review Medications
RUQ ultrasound to assess
ductal dilatation
present
absent
ERCP or
MRCP
*Elevated ALT evaluation
Review medications, AMA,
ERCP or MRCP
liver biopsy

- Synthetic

Hypo albuminemia

- 3.5 to 5.0g/dL t1/2 18-21days-chronic Ds
- hepatocellular dysfunction
- Malnutrition

- protein-losing enteropathy
- nephrotic syndrome

- Chronic inflammatory conditions
- hormonal imbalances

B) Serum Globulins: electropheresis

- 3 types – α,β & γ

- Increased γ- chronic hepatitis and cirrhosis

Eg.

  - IgG = AIH; IgM = PBC; IgA = ALD.

C) Coagulation Factors

- Acute Ds
  - PT
    - vitamin K deficiency
    - obstructive jaundice
    - fat malabsorption of any kind.
    - hepatocellular dysfunction
  - INR
    - Component of MELD score

LDH ↑

- Ischemic hepatitis
- ALT>LDH- acute viral >ischemic hepatitis
- Malignancy

Hyper amonemia

- ALF
- Hepatic encephalopathy
- Decompensated cirrhosis

Dx Clues

Table 302-1 Liver Test Patterns in Hepatobiliary Disorders

Type of Disorder	Bilirubin	Aminotransferases	Alkaline Phosphatase	Albumin	Prothrombin Time
Hemolysis/Gilbert's syndrome	Normal to 86 µmol/L (5 mg/dL) 85% due to indirect fractions No bilirubinuria	Normal	Normal	Normal	Normal
Acute hepatocellular necrosis (viral and drug hepatitis, hepatotoxins, acute heart failure)	Both fractions may be elevated Peak usually follows aminotransferases Bilirubinuria	Elevated, often >500 IU ALT >AST	Normal to <3 times normal elevation	Normal	Usually normal. If >5X above control and not corrected by parenteral vitamin K, suggests poor prognosis
Chronic hepatocellular disorders	Both fractions may be elevated Bilirubinuria	Elevated, but usually <300 IU	Normal to <3 times normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Alcoholic hepatitis Cirrhosis	Both fractions may be elevated Bilirubinuria	AST:ALT > 2 suggests alcoholic hepatitis or cirrhosis	Normal to <3 times normal elevation	Often decreased	Often prolonged Fails to correct with parenteral vitamin K
Intra- and extra-hepatic cholestasis (Obstructive jaundice)	Both fractions may be elevated Bilirubinuria	Normal to moderate elevation Rarely >500 IU	Elevated, often >4 times normal elevation	Normal, unless chronic	Normal If prolonged, will correct with parenteral vitamin K
Infiltrative diseases (tumor, granulomata); partial bile duct obstruction	Usually normal	Normal to slight elevation	Elevated, often >4 times normal elevation Fractionate, or confirm liver origin with 5' nucleotidase or γ glutamyl transpeptidase	Normal	Normal

PROGNOSIS

MELD score vs CP class for LTx priority

Table 301-4 Child-Pugh Classification of Cirrhosis

Factor	Units	1	2	3
Serum bilirubin	µmol/L mg/dL	<34 <2.0	34-51 2.0-3.0	>51 >3.0
Serum albumin	g/L g/dL	>35 >3.5	30-35 3.0-3.5	<30 <3.0
Prothrombin time	seconds prolonged INR	0-4 <1.7	4-6 1.7-2.3	>6 >2.3
Ascites		None	Easily controlled	Poorly controlled
Hepatic encephalopathy		None	Minimal	Advanced

Note: The Child-Pugh score is calculated by adding the scores of the five factors and can range from 5 to 15. Child-Pugh class can be A (a score of 5-6), B (7-9), or C (10 or above). Decompensation indicates cirrhosis with a Child-Pugh score of >7 (class B). This level has been the accepted criterion for listing liver transplantation.

MELD provides a more objective means of assessing disease severity and has less center-to-center variation than the Child-Pugh score and has a wider range of values. MELD is currently used to establish priority listing for liver transplantation in the United States. A similar system using bilirubin, INR, serum albumin, age, and nutritional status is used for children below the age of 12 years [pediatric end-stage liver disease (PELD)].

Further Ix

- LBT--
- Etiologi tests: Viral, Wilson, AIH, Toxin
- Sonography/EUS/Fibroscan
- CT, MRCP/ERCP
- Liver biopsy
- EGD
- FNA-cytology
- Ascites analysis

Tests to detect hepatic fibrosis

- Biological
  - Scores : APRI, FIB4
- Physical
  - Transient Elastography

Liver Bx Indications

- (A) Diagnostic
  - (1) Unspecified Hepatocellular disease
  - (2) Unexplained hepatomegaly
  - (3) Unexplained splenomegaly
  - (4) Hepatic filling defects
  - (5) FUO
- (B) Staging & grading of CLD/malignant.

When to observe?

- LBT<2x UNL
- No CLD s/s
- Normal imaging
- Young/pregnant-ALP
- Non rising LBT
- Seroius DDx excluded

When to biopsy Liver?

- Rising LBT>2x
- CLD s/s
- Focal lesion
- Aging
- Obesity/comorbidity
- Recurrent/flactuating

Local experiences: Cases

- HAV children and young- late exposure1
- VOD-PA epidemic -PA-pyrole 2
- Epidemic dropsy-alkaloid outbreak≈case 2

- Cholestatic/Portal HTN
- HBV-Young family **e** neg& carrier/ tolerant
- HCV-Chronic hepatitis-adults and old

Summary

- Clinical triad approach: HIP
- Normally abnormal vice versa
- Transient abnormal LBT
- Serial LBT—Dx prognosis
- Localization for DDx:HC,cholestat-i/entra
- Imaging
- Etiologic tests
- CIN VIM TTA DDx---Clinic senario/epidm

THANK YOU !