Assessment of some biochemical tests in liver diseases

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- **Significant liver damage may occur in patients who have normal findings on liver function tests.**
- **Biochemical screening of healthy, asymptomatic people has revealed that up to 6% have abnormal liver enzyme levels.**

Liver Function Test

- Interpretation must be performed within the context of the patient's risk factors, symptoms, concomitant conditions, medications, and physical findings
- Rarely provide specific Dx, but rather suggest a general category of liver disease
- Differing laboratories → differing normal values

LFT’s

- Markers of hepatocellular damage
- Cholestasis
- Liver synthetic function

Liver Function Test

Advantages

- sensitive, noninvasive method of screening liver dysfunction
- pattern of laboratory test abnormalities to recognize type of liver disorder
- assess severity of liver dysfunction
- follow cause of liver disease

Disadvantages

- lack sensitivity
  - normal results in serious liver disease
- not specific for liver dysfunction
- seldom lead to specific diagnosis

Liver Function Test

Liver chemistry test	Clinical implication of abnormality
ALT	Hepatocellular damage
AST	Hepatocellular damage
Bilirubin	Cholestasis, impair conjugation, or biliary obstruction
ALP	Cholestasis, infiltrative disease, or biliary obstruction
PT	Synthetic function
Albumin	Synthetic function
GGT	Cholestasis or biliary obstruction

Serum enzyme tests

They indicate type of liver injury :Hepatocellular or cholestatic

They direct the choice of the serological and imaging tests

SGPT & SGOT

Markers of Hepatocellular damage (Transaminases)

- AST- liver, heart skeletal muscle, kidneys, brain, RBCs
- Clearance performed by sinusoidal cells, half-life 17hrs

- ALT – more specific to liver, very low concentrations in kidney and skeletal muscles.
- Half-life 47hrs

SGPT & SGOT

- Causes of abnormality of SGPT & SGOT
  - Viral hepatitis.
  - Nonalcoholic steatohepatitis.
  - Autoimmune hepatitis.
  - Alcohol related liver injury.
  - Drug induced hepatitis.

SGPT & SGOT

- Minor increase (< 2 times)
  - Obesity
  - Fatty liver
  - Drugs
- Mild increase (2 to< 5 times)
  - Alcohol
    - SGOT / SGPT ratio
    - SGOT rarely exceeds 300 i.u./ml
    - SGPT > 500 → not alcoholic
    - Abstinence 6-8 weeks → normal enzymes

SGPT & SGOT

- Mild increase (2 to< 5 times)
  - Drugs
    - Stop and retest
    - Risk benefit analysis may be needed
  - Chronic HCV & HBV
    - SGOT / SGPT < 1
    - < 5 times
  - NASH
    - SGOT / SGPT <1
    - Isolated increase SGPT

SGPT & SGOT

- Moderate increase (5-15 times)
  - Acute viral hepatitis (A & B)
- Severe increase (>15 times)
  - Acute viral hepatitis (A & B)
  - ICU & serious cardiac dysfunction
  - Chemotherapy
  - Fulminant liver failure (early stages)

Ischemic hepatitis

=Shock liver, acute hepatic circulatory insufficiency.

- **low-flow hemodynamic state**
  - **hypotension, sepsis, cardiac arrhythmia, MI, HF, hemorrhage, extensive burns, severe trauma, heat stroke**
- **hypotension often not documented**
- **usually subclinical**

Ischemic hepatitis

- sudden and massive (>2000) elevation of liver enzyme, tend to decrease rapidly and return normal within 1 wk.
- mild and transient elevation of bilirubin (80% < 2 mg/dl) and ALP
- Rx and prognosis α underlying disease

Ischemic hepatitis

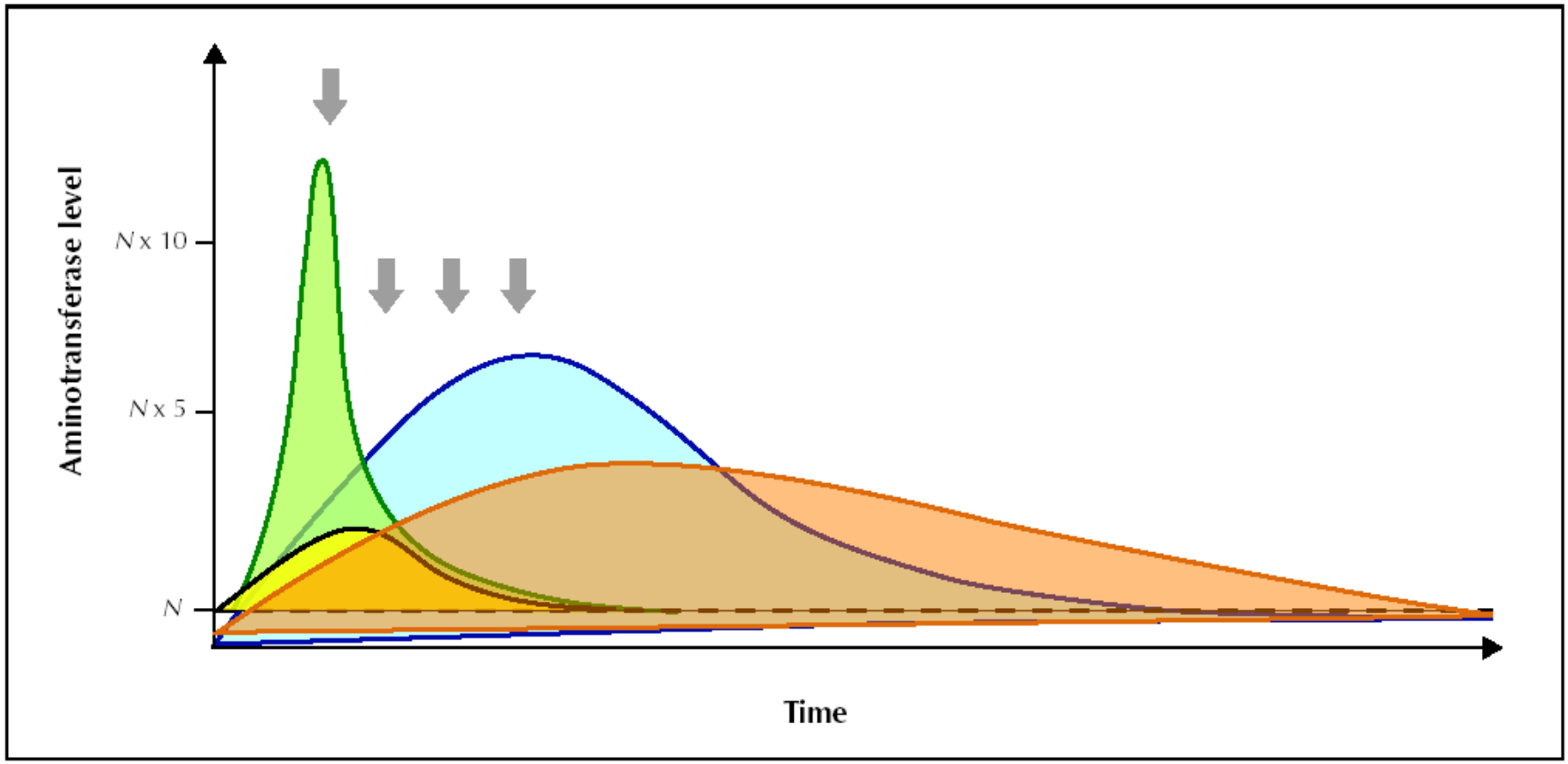


Fig. 3: Schematic representation of the rate of change of aminotransferase and bilirubin levels in a patient with acute ischemic hepatitis (green area, yellow area respectively) and acute viral hepatitis (blue area, orange area respectively). It is important to underscore that the pattern of enzyme alteration may vary and occasionally appear similar if a single observation point is taken into consideration (arrows).

SGPT & SGOT

- Cirrhotic patients may have normal enzymes.
- Severe lipemia can cause elevation in SGPT, less elevation in SGOT, but does not affect GGT.

SGPT & SGOT

- **SGOT/SGPT > 1**
  - **Alcoholic (**If AST > 500 consider other cause).
  - **Wilson D.**
  - **Advanced cirrhosis**
  - **D.D.B. treatment**

The aspartate aminotransferase platelet ratio (APRI) index

You divide AST by the ULN of AST, divide this result by the platelet count (with the last three zeros chopped off), and multiply by 100. As a formula it's (AST/ULN)/platelets x 100.

Here's an example of how it works, for an AST of 63(UNL=42) and a platelet count of 137,000/dl

63/42 = 1.5
1.5/137 = 0.109
0.109 x 100 = 1.09 (APRI)

What does an APRI score of 1.09 tell me?

APRI comes with two cut-offs: a lower one, 0.5, and a higher one, 1.5.

If the APRI score is less than or equal to 0.5, you have no fibrosis or just a little.

If your APRI score is 1.5 or above, you probably have cirrhosis.

APRI scores between 0.5 and 1.5 are related to progressive fibrosis stages, like Metavir F1-to-F3.

Alkaline phosphates (ALP)

- ***Sources:*** **Liver, bone, kidneys, small bowel & placenta**
- **Non hepatic causes of ALP elevation**
  - **Old age**
  - **Females after menopause**
  - **Third trimester of pregnancy**
  - **After heavy fatty meal**
  - **Benign familial elevation**

- GGT may be necessary to evaluate the origin of ALP

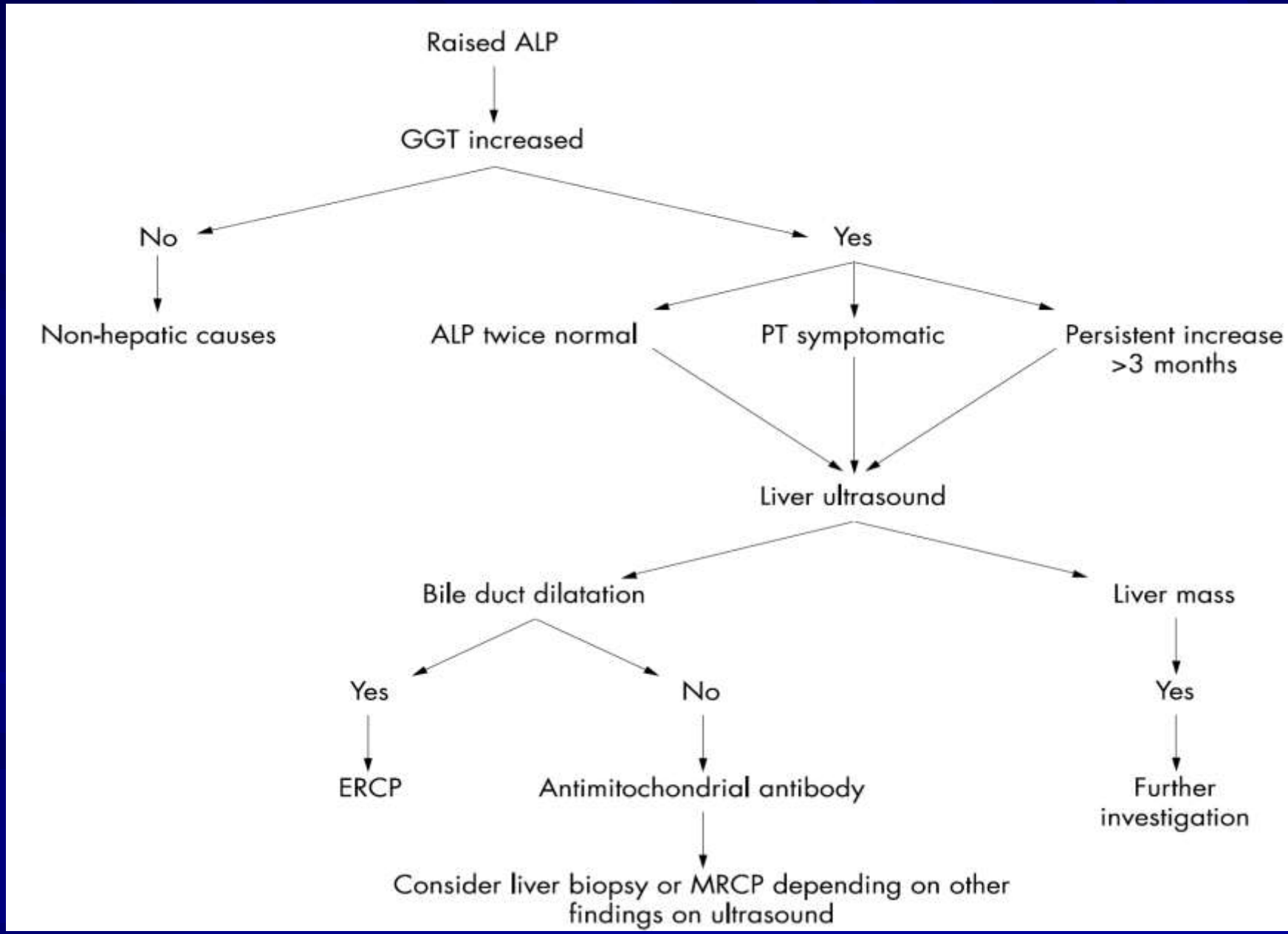
Alkaline phosphates (ALP)

- Hepatic causes of ALP elevation
  - Cholesatic
    - CBD stones
    - PBC
    - PSC
    - Drugs
  - Infiltrative
    - Tumours
    - T.B
    - Sarcoidosis

Alkaline phosphates (ALP)

- Depressed ALP
  - Hypothyroidism
  - Pernicious anaemia
  - Zinc deficiency

Suggested algorithm for evaluating a raised s.alkaline phosphatase



GGT

- GGT is a sensitive indicator of hepatobiliary disease
- It is not specific
- GGT elevation excludes a bone source of ALP
- Isolated increased GGT may be of no benefit.

- Gamma-GT – hepatocytes and biliary epithelial cells, pancreas, renal tubules and intestine
- Very sensitive but Non-specific
- Raised in ANY liver disease either hepatocellular or cholestatic
- Usefulness limited
- Confirm hepatic source for a raised ALP
- Alcohol
- Isolated increase does not require any further evaluation

GGT

- GGT increased in:
  - -Hepatic metastasis
  - – Renal failure
  - – Myocardial infarction
  - – Pancreatic diseases
  - – Diabetes mellitus
  - – Drugs

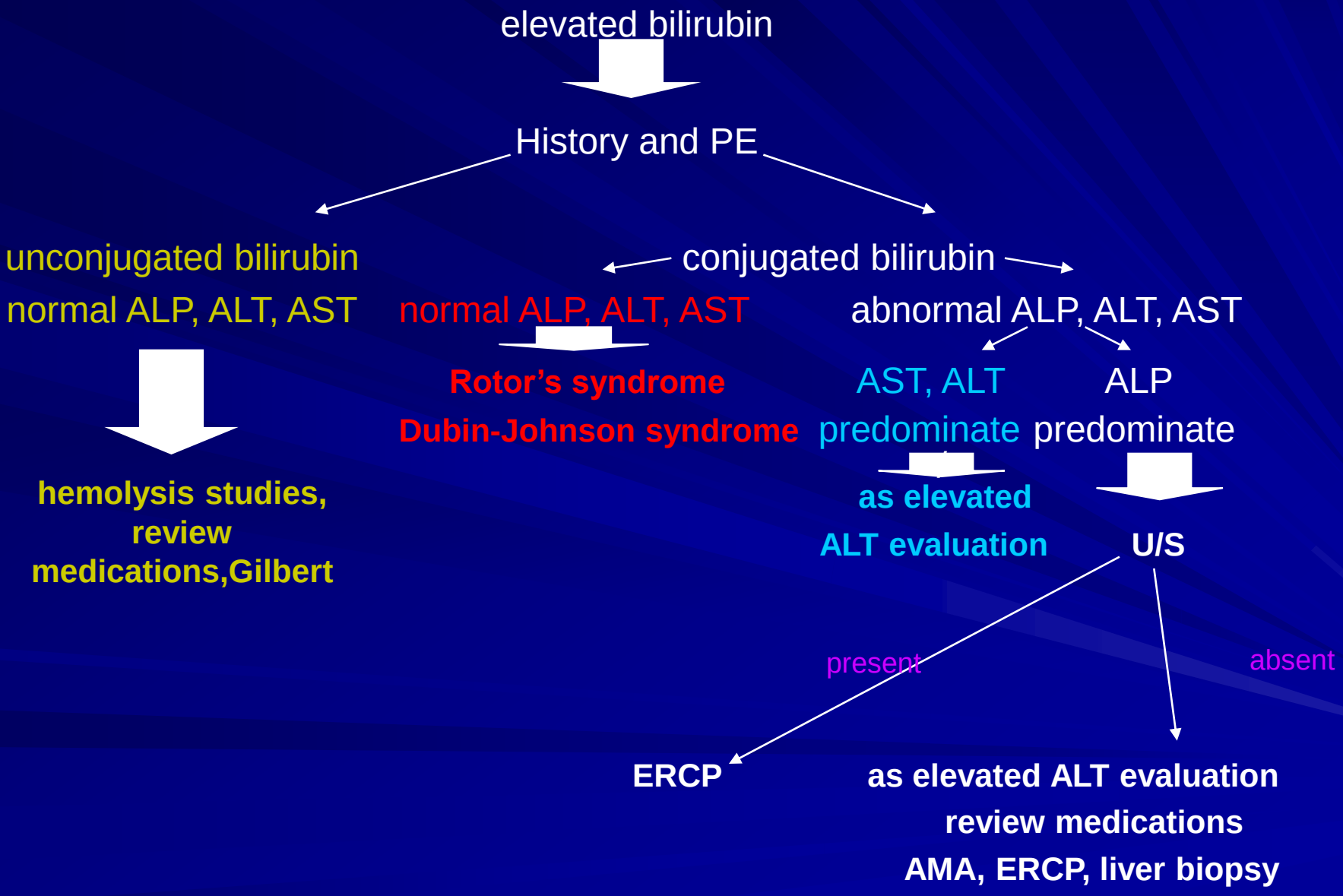
Bilirubin

- Product of hemoglobin breakdown
- 2 Forms
  - Unconjugated (indirect)- insoluble
    - ↑ in hemolysis, Gilbert syndrome, meds
  - Conjugated (direct)- soluble
    - ↑ in obstruction, cholestasis, cirrhosis, hepatitis, primary biliary cirrhosis, etc.

S.bilirubin

- Increased in both cholestatic and hepatocellular disease with rise of liver enzymes.
- Unconjugated bilirubin is increased with normal enzymes in Gilbert's disease

Diagnostic approach in elevated serum bilirubin



S.albumin

- **S.albumin:**
  - Accounts for 65% of S. proteins.
  - Normal liver produces 10-12gm/day
  - Cirrhotic liver produces 4 gm/day
  - Albumin half life is 22 days
  - Patient with fulminant hepatitis may die with normal s. albumin.

S.albumin

- **Factors affecting s. albumin:**
  - **Chronic liver disease**
  - **Renal insufficiency**
  - **Urinary protein losses**
  - **Gastrointestinal losses.**

Modified Child-Turcotte-Pugh prognostic classification for grading degree of hepatic dysfunction in patients with cirrhosis

Factor	Points*		
	1	2	3
Encephalopathy (grade)	0	1-2	3-4
Ascites	None	Slight	Moderate
Bilirubin (mg/dL)	1-2	2-3	>3
Albumin (g/dL)	≥3.5	2.8-3.5	<2.8
Prothrombin time (sec)	1-4	5-6	>6

**Total points = 5 or 6, grade A; 7 to 9, grade B; 10 to 15, grade C.*

Nonhepatic causes of abnormal liver function test results

Test result	Nonhepatic causes	Discriminating tests
Decreased serum albumin level	Protein-losing enteropathy	Serum globulins, alpha$_1$-antitrypsin clearance
	Nephrotic syndrome	Urinalysis, 24-hr urinary collection for protein
	Congestive heart failure	Cardiac examination, two-dimensional echocardiogram
Elevated AST level	Myocardial infarction	ECG & CK.
	Muscle disorders	CK, ESR
Elevated ALP level	Bone disease	GGT, serum leucine aminopeptidase, 59-nucleotidase
	Pregnancy	GGT, 59-nucleotidase, hCG in serum and urine
	Malignant tumor	Alkaline phosphatase electrophoresis
Elevated bilirubin level	Hemolysis	Reticulocyte count, peripheral smear, LDH, haptoglobin
	Sepsis	Clinical setting, blood cultures
	Ineffective erythropoiesis	Peripheral smear, urine bilirubin, hemoglobin electrophoresis, bone marrow aspiration and biopsy

FibroTest
&
ActiTest

FibroTest

- Combines the blood measurement of five indirect markers of fibrosis
  - Alpha 2-macroglobulin.
  - Haptoglobin
  - Apolipoprotein A1
  - Total bilirubin
  - Gamma glutamyl transpeptidase (GGT) adjusted for age and sex

ActiTest

- FibroTest (combines the same markers with)
- Alanine aminotransferrase (SGPT)
- The algorithm adjusts the results for age and sex

Fibrosis stage (Metavir score)

F0:	No Fibrosis
F1:	Portal Fibrosis
F2:	Bridging Fibrosis with few septa
F3:	Bridging Fibrosis with many septa
F4:	Cirrhosis

Necroinflammatory activity grade (Metavir score)

A0:	No activity
A1:	Minimal activity
A2:	Moderate activity
A3:	Severe activity

What are the most frequent causes of FibroTest - ActiTest false positives?

An isolated very abnormal value of one component of FibroTest - ActiTest is suspect.

- Hemolysis, which decreases haptoglobin as observed with ribavirin treatment, or cardiac prosthesis.
- Gilbert syndrome, which increase total bilirubin.
- Extra-hepatic cholestasis, which increases GGT and total bilirubin.
- Drugs which increase total bilirubin as atazanavir.
- During combined treatment (IFN) & ribavirin therapy.

What are the most frequent causes of FibroTest - ActiTest false negatives?

- An isolated very abnormal value of one component of FibroTest - ActiTest is suspect.
- Acute inflammation, which increases haptoglobin as observed with acute sepsis.

Investigation of Abnormal LFTs

PRINCIPLES

- 2.5% of population have raised LFTs
- Normal LFTs do not exclude liver disease
- Interpret LFTs in clinical context
- Take a careful history for risk factors, drugs (inc OTCs), alcohol, comorbidity, autoimmunity
- Physical examination for liver disease
- If mild abnormalities and no risk factors or suggestion of serious liver disease , repeat LFTs after an interval (with lifestyle modification)

Investigation of Abnormal LFTs - Raised ALT / AST

- In Egypt please do Hepatitis serology markers (B, C)
- Iron studies – transferrin saturation + ferritin
- Autoantibodies & immunoglobulins
- Consider caeruloplasmin
- Alpha-1- antitrypsin