Bachelor of Chinese Medicine Year IV

2024 - 2025

BCHM4608 – Fundamentals of Diagnosis (Pathology)

Use of Biochemical Laboratory Tests:

Liver Function Test

19 March 2025

14:30 – 16:20

(T6-035)

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Learning Objectives

- Purpose of requesting a laboratory test.
- General concept of reference intervals.
- What tests in general constitute a Liver Function Test profile in clinical practice.
- Interpret and recognize common patterns of abnormalities in liver function test results.
- Interpret and select appropriate tests for assessment of liver derangements.
- Recognize the hepatic and non-hepatic causes of hyperbilirubinaemia.
- Recognize the limitations of Liver Function Tests in the diagnosis of liver disease.

Why do we need to initiate a laboratory test request?

1. To CONFIRM a diagnosis.
2. To AID differential diagnosis.
3. To REFINE a diagnosis.
4. To MONITOR disease progress.
5. To ASSESS the severity of disease.
6. To DETECT complications of disease or side effects of treatment.
7. To MONITOR therapy.

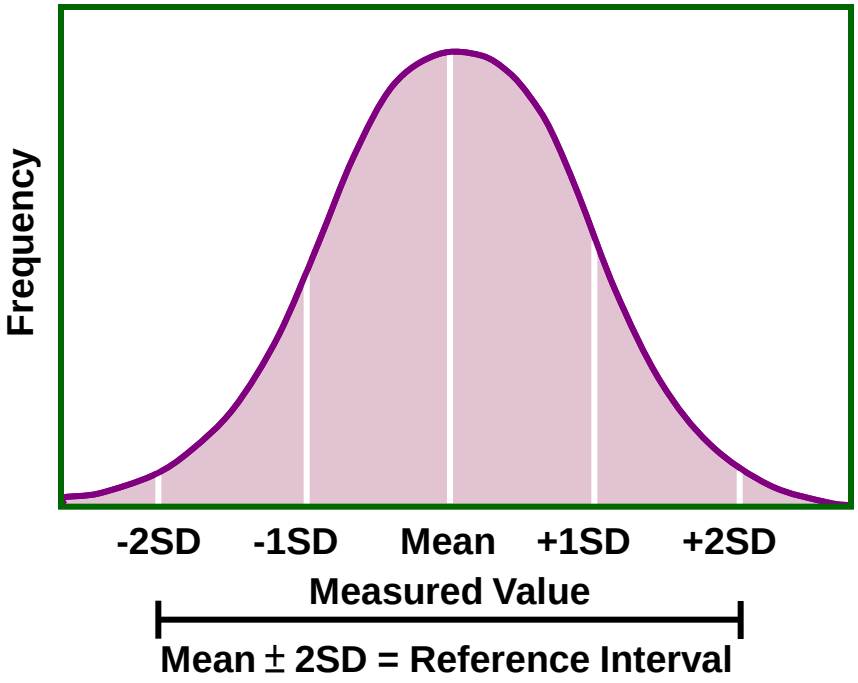
Points to ponder before initiating a test:

- √ **Why do I request this test?**
- √ **What will I look for in the result?**
- √ **If I find what I am looking for, will it affect my diagnosis?**
- √ **How will this investigation affect my management of the patient?**
- √ **Will this investigation ultimately benefit the patient?**

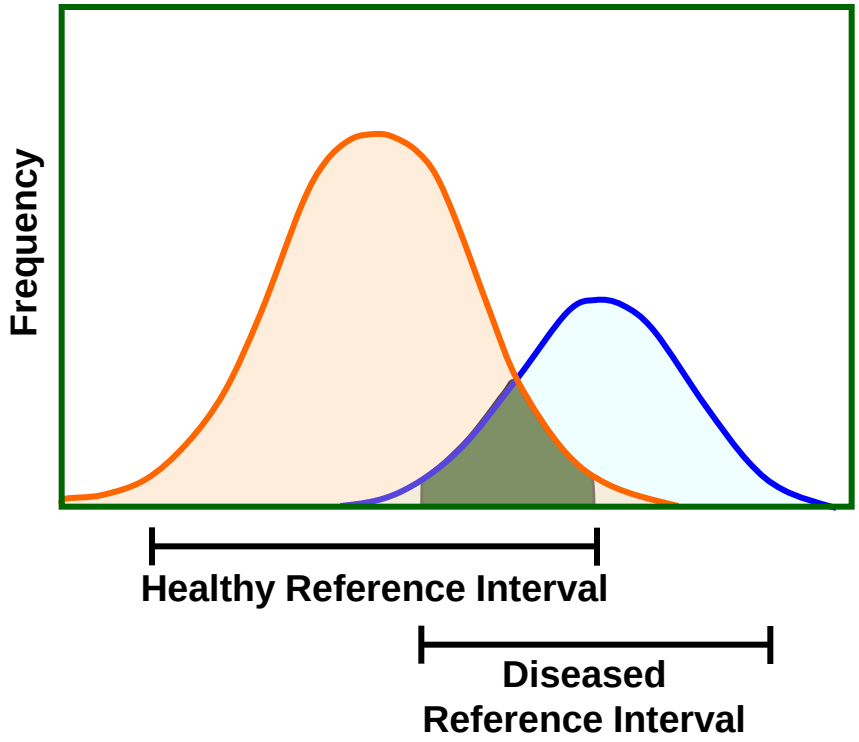
"Primum non nocere"
(first do no harm)

Reference Intervals ("normal ranges")

- Test results which would be obtained in the normal population; based on findings obtained from a representative sample of "healthy" individuals (reference population).
- Mean $\pm$ 2 SD (normal distribution).
- Between 2.5 - 97.5 centiles.
- Depends on age, gender, race and test methodology - values quoted in literature may not be generally applicable.
- As "Reference Interval" in general represents the 2.5 - 97.5 %tile or the central ~95%, thus invariably 5% of normal subjects will have test results outside the reference interval.
- Therefore, deviation from "reference intervals" does NOT necessarily mean the presence of disease, and *vice versa*; they should always be interpreted in the proper clinical context.



Reference Interval in a Normal Healthy Population



Overlap of Biochemical Results in Health and Disease

Interpretation of Laboratory Test Results

The clinical significance of an abnormal clinical biochemistry test result can only be appreciated when it is interpreted in light of the clinical context and against the background of a broad knowledge of the various factors that may affect these results.

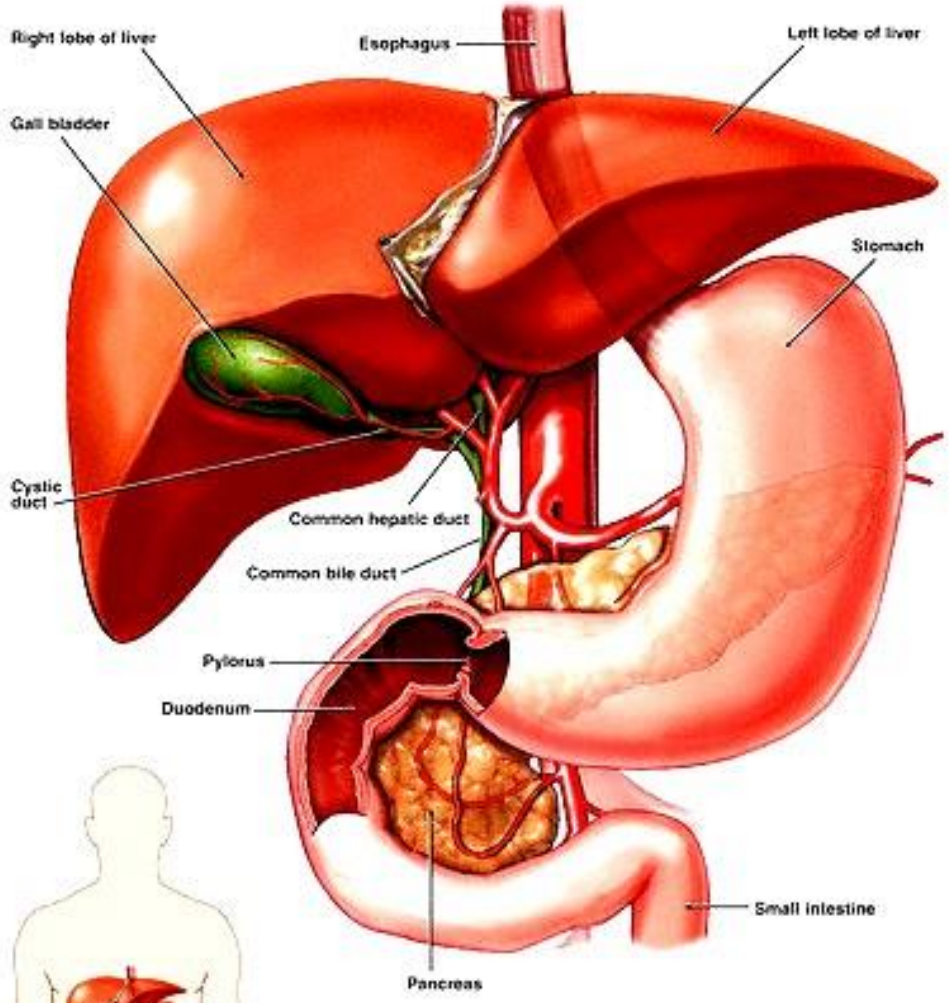
Interpretation of Laboratory Results (1)

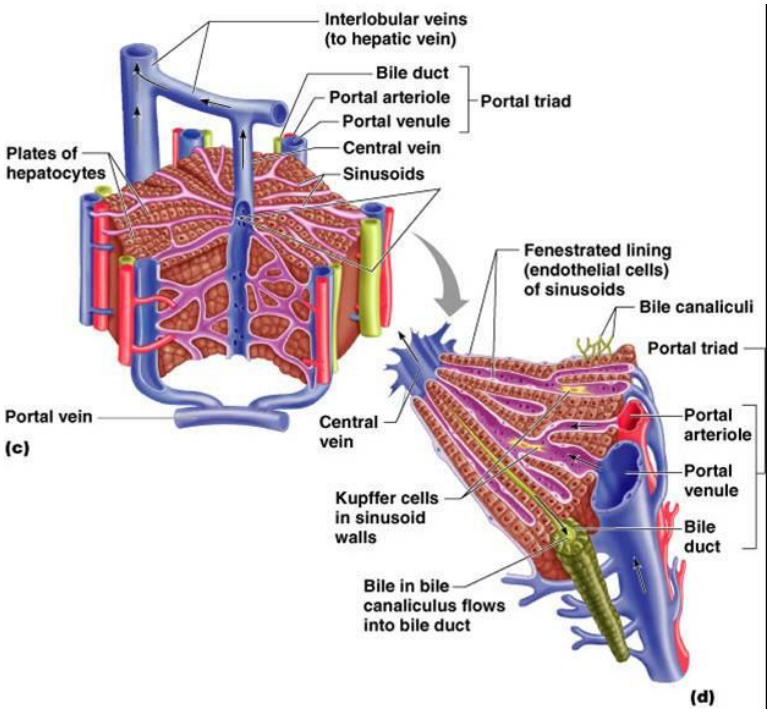
- Biochemistry results are often reported as concentration or activity (for enzymes) of the analyte; the value of concentration / activity changes if the absolute amount of the analyte in question changes and / or if the volume of the solution changes.
- Variability of results is caused by biological factors (i.e., physiological & pathological), analytical and pre-analytical factors.
- The Reference Interval (RI) supplied with the corresponding result is only a guide to the probability of the result being statistically "normal" or "abnormal".

- Different Reference Intervals (e.g., due to change in assay methodology, sampling conditions) observed in cumulative reports (displaying serial results of the tested subject chronologically) when placed in clinical context are as important as the absolute value of the result – many reference intervals are age, sex and ethnicity dependent (age and sex-specific reference intervals are often provided but not race-specific ones).

- If a result does not accord with that expected of the patient, the finding should be discussed with the laboratory (i.e., possibility of pre- and analytical issues, e.g., sample mix-up, deterioration due to improper delivery, handling, sampling, such as sampling from a site close to an intravenous line) and a repeat analysis or sampling is to be arranged where necessary.

The Liver


Right lobe of liver
Esophagus
Left lobe of liver
Gall bladder
Stomach
Cystic duct
Common hepatic duct
Common bile duct
Pylorus
Duodenum
Small intestine
Pancreas


Interlobular veins (to hepatic vein)
Bile duct
Portal arteriole
Portal venule
Portal triad
Central vein
Sinusoids
Plates of hepatocytes
Portal vein
(c)
Fenestrated lining (endothelial cells) of sinusoids
Bile canaliculi
Portal triad
Central vein
Portal arteriole
Portal venule
Kupffer cells in sinusoid walls
Bile duct
Bile in bile canaliculus flows into bile duct
(d)

Liver Functions

Synthesis:

* Transport Proteins (for vitamins, trace metals, hormones)
* Plasma Albumin
* Coagulation Factors
* Glycogen
* Urea

Lipoproteins
Bile Salts
Phospholipids
Cholesterol

Detoxification / Excretion:

* Bilirubin
* Alcohol
* Drugs & Toxins

Bile Salts
Steroids
Ammonia

Storage:

* Carbohydrates
* Vitamins (B_{12}, A, D, E, K)

Lipids
Iron, Copper

Biochemical Indices in Hepatobiliary Disease

- Laboratory tests for hepatobiliary diseases involve examination of the Plasma/Serum, Urine and very rarely, Faeces.
- The term "**Liver Function Test**" (**LFT**) conventionally refers to a profile of analytes in serum or plasma measured by automated multi-channel analyzers that are interrelated and reflect the status of the organ.
- Coagulation profile, conventionally grouped under "Haematology Tests", reflects the synthetic function of the liver for functional proteins with short plasma half-life involved in blood coagulation (i.e., clotting factors):-

  PT (INR) and **APTT** are sensitive indices for acute changes in functional status of the liver.

Liver Function Test Profile ("LFT")

- Liver function tests (LFT) are amongst the most frequently requested panels of clinical biochemistry tests in clinical practice.
- The term "**Liver Function Tests**" (**LFT**) usually refers to a **profile** of biochemical parameters comprising:

  - **Bilirubin** (total, conjugated, unconjugated)
  - **Alkaline Phosphatase** (ALP)
  - **γ-Glutamyl Transferase** (GGT)
  - **Alanine Transaminase** (ALT, SGPT)
  - **Aspartate Transaminase** (AST, SGOT)
  - **Total Protein** (albumin + globulins)
  - **Albumin**
  - **Lactate Dehydrogenase** (LDH) – NOT included in the conventional LFT profile but is a useful adjunct in some circumstances (very sensitive but non-specific).

- They are useful for the diagnosis and monitoring of hepatobiliary diseases especially when considered **collectively**.

Indications for Liver Function Test

- History or physical examination suggestive of liver disease:
  - History of poisoning (e.g., paracetamol, potentially or known hepatotoxic herbs and mushroom)
  - History of alcohol abuse, known carrier of HBV, HCV
  - Family history of haemochromatosis (very rare in Chinese)
  - Signs of chronic liver disease, e.g., jaundice, ascites, splenomegaly, gynaecomastia, caput medusae, spider naevi, palmar erythrema, Duputren's contracture, finger clubbing, pitting pedal oedema.
- Screening for populations at high risk of blood borne virus infection:
  - Contact tracing in cases of hepatitis
  - Illicit drug use
  - History of frequent blood transfusion
- Significant non-liver disease that may affect liver function:
  - Malignancies
  - Hypoxia, hepatic congestion from congestive heart failure
- Monitoring medications that are potentially hepatotoxic or principally metabolized by the liver:
  - Valproate, Methotrexate, immunosuppressants, cytotoxic drugs, anti-fungal agents, etc.

Hospital Authority
Queen Mary Hospital

Urgent

Division of Chemical Pathology
LG238, Block K, 102 Pokfulam Road, Hong Kong
Tel. 22553175 Fax. 28194179

Lab No: 23C3[redacted]
Name: HUNG [redacted]
(孔[redacted]
HKID No: D48[redacted]
Hosp No: HN23[redacted]
Location: QMH/MED3/A2 Bed: 01A
Sex/Age: M/63Y DOB: 05[redacted]9
Req. Loc.: QMH/MED3/A2
Doctor: Dr. MOK [redacted]

Patient Hospital: Queen Mary Hospital

Collect Date :	23/03/23	24/03/23	25/03/23	26/03/23	**27/03/23**		
Collect Time :	08:55	08:58	08:35	14:15	**10:24**		
Request No. :	C32[redacted]	C32[redacted]	C32[redacted]	C32[redacted]	**C32**[redacted]		
Remark :	deranged liver function	deranged liver function	deranged liver function	deranged liver function	deranged liver function	Ref. Interval	Units
Total Protein	68	66 L	67 L	68	77	68 - 84	g/L
Albumin	34 L	34 L	36 L	35 L	39	39 - 50	g/L
Globulin	34	32	31	33	38 H	24 - 37	g/L
Total Bili	70 H	37 H	30 H	22	43 H	4 - 23	umol/L
Direct Bili					36 H	< 6	umol/L
ALP	351 H	356 H	337 H	294 H	623 H	42 - 110	U/L
ALT	422 H	434 H	440 H	375 H	579 H	8 - 58	U/L
AST	227 H	223 H	221 H	165 H	330 H	15 - 38	U/L
GGT	565 H	505 H	428 H	342 H	651 H	11 - 62	U/L
Amylase			95		67	25 - 124	U/L

Comment:
23C3271494 Amylase is useful in acute pancreatitis but often unhelpful in other abdominal emergencies.
Test result(s) analytically verified: TBIL ALP

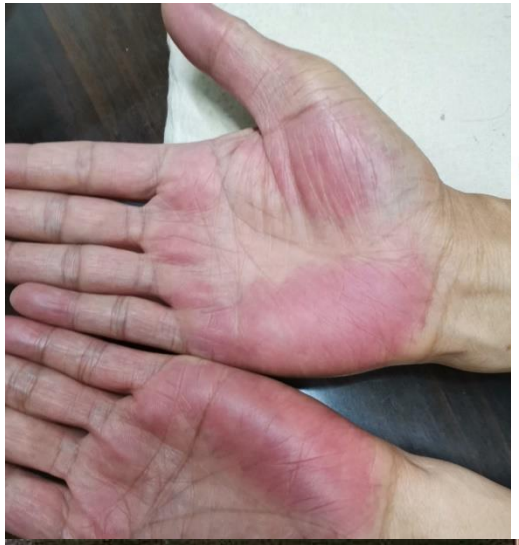
Authorized By: Tam, Sidney

Consultant Chemical Pathologist: Prof. C W Lam
This laboratory is accredited by the College of American Pathologists,
CAP Accreditation Number 71755-25

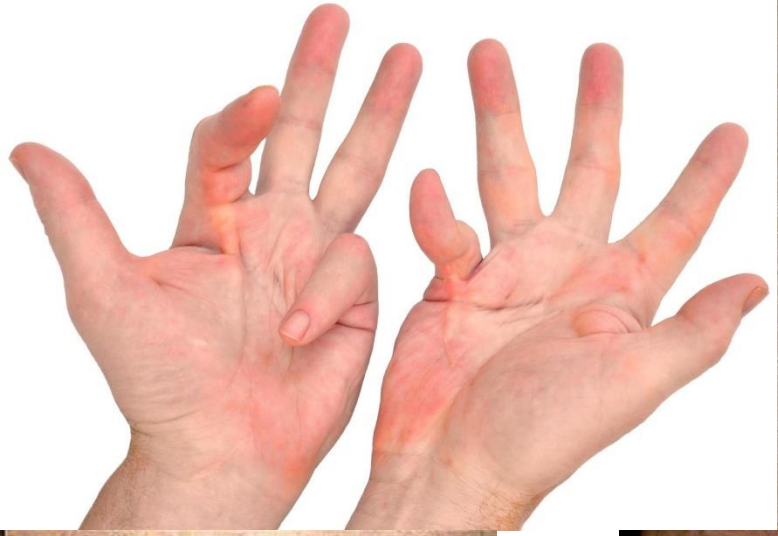
Report Date & Time: 27/03/2023 14:09 Generated on: 27/03/2023 14:09
Report Destination: QMH/--/A2 - A2, Medicine

Stigmata of Chronic Liver Disease

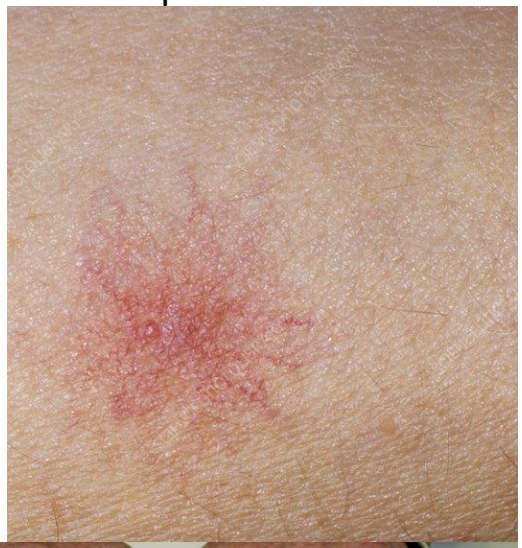
Palmar Erythema



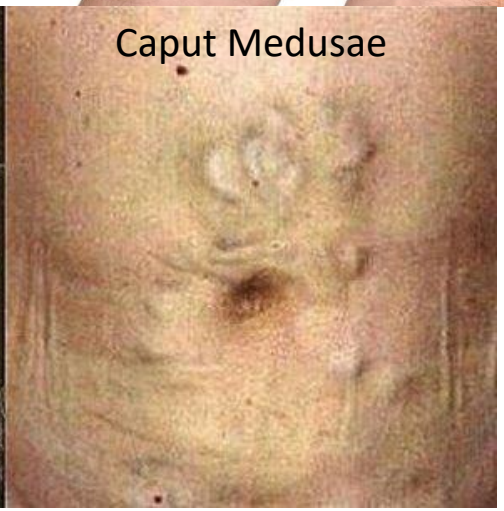
Dupuytren contracture



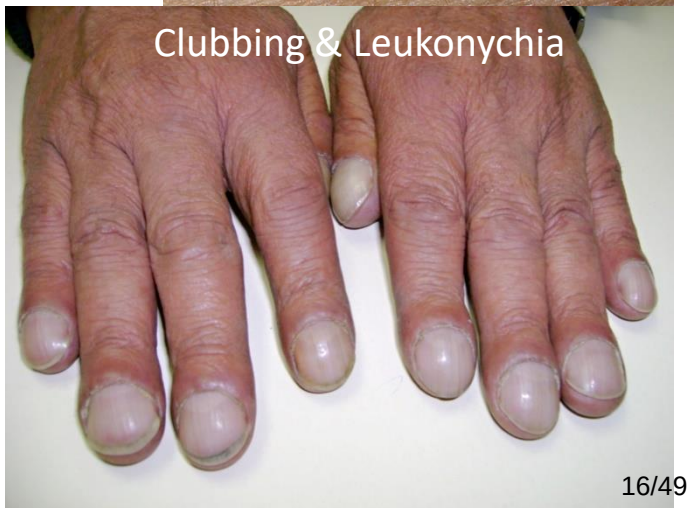
Spider naevi



Caput Medusae



Clubbing & Leukonychia



Activity of an enzyme in blood represents a BALANCE between its:

- Rate of **release** into the extracellular fluid (ECF) compartment (e.g., blood) and
- Rate of **clearance** or **uptake** from the ECF (e.g., blood).
- Enzymes in blood of healthy individuals are mainly derived from the metabolic breakdown and normal turnover of cells and tissues habouring the enzymes in question.
- Concentration **gradient** between the intracellular and extracellular compartments often exceeds 100 or more for most enzymes, thus they will readily get out of the cell into the extracellular fluid when the plasma membrane integrity is compromised or disrupted.
- **Integrity** of the cellular plasma **membrane** therefore plays a crucial role in retaining enzymes (e.g., AST, ALT) within the cell.

Factors Causing Elevated Enzyme Levels in Blood

Plasma membrane integrity is jeopardized and permeability increased by:

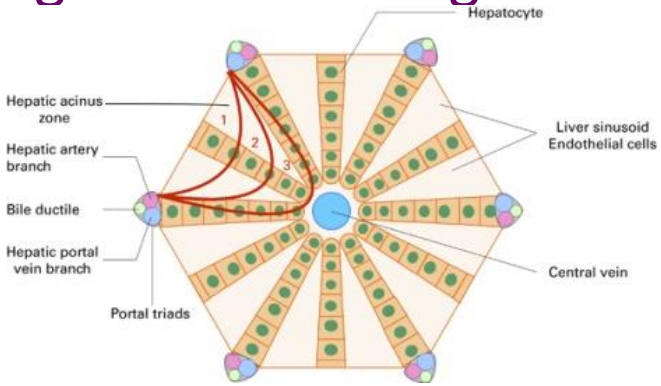
Anoxia, Ischaemia, Toxin, Infection, Trauma

NB: Other conditions causing raised blood enzyme levels that are *not* associated with membrane dysfunction or cellular injury:-

- Drugs: some drugs, e.g., promethazine and chlorpromazine, acts directly upon cell membrane to **accelerate enzyme release**.
- **Enzyme induction** can lead to elevation in blood enzyme levels in the absence of cellular injuries, e.g., anti-epileptic drugs, sedatives and hypnotics are potent enzyme inducers that cause increased Alkaline Phosphatase (ALP), γ-Glutamyl Transferase (GGT) and 5'-Nucleotidase (regarded redundant and not included in the routine LFT Profile in most clinical labs).

Important Clues for Proper Interpretation of Liver Function Test (LFT) - 1

- Liver has a great reserve capacity for most of its functions and a remarkable ability to regenerate.
- A hepatocyte generally can survive and recover up to the point of mitochondrial damage.
- A liver acinus can regenerate as long as a layer of cells in zone 1 survive.



- Significantly different plasma half-life between the various analytes in the LFT profile (e.g., $T_{1/2}$ of ALT >> AST) partly accounts for the chronological changes in the deranged LFT pattern.

Important Clues for Proper Interpretation of Liver Function Test (LFT) - 2

- Metabolic, synthetic, and secretory processes are interdependent functions of the liver, therefore time factors have to be considered, and both the history and clinical findings all have to be taken in proper context for the interpretation of liver function test.

- Judged independently, many tests have a relatively low sensitivity and specificity. However when all the relevant factors are considered in the proper context **collectively**, they often bring a high level of probability to a clinical decision.

- History, physical examination and relevant laboratory tests enable a proper diagnosis of hepatobiliary diseases in ~75% to 80% of cases; ancillary investigations, e.g., imaging studies, have to be resorted to in the remaining ~ 20%.

Organ/Tissue Locations of "Liver" Enzymes

Enzyme	Organs with Relatively High Concentrations
AST (SGOT)	Liver, heart, muscle, kidney
ALT (SGPT)	Liver (major), kidney
LDH	Liver, RBC, WBC, heart, muscle, kidney, tumours
ALP	Liver, bone, intestine, placenta
GGT	Liver, pancreas, kidney, prostate

Relative Activity ("concentration") of Transaminases

Botros M & Sikaris KA

Table 1. Relative activity of transaminases in human tissues.*

	AST Activity	ALT Activity	AST/ALT Ratio	Weight (kg)	AST Total	ALT Total
Liver	7,100	2,850	2.5	1.5	10,650	4,275
Kidney	4,500	1,200	3.8	0.25	1,125	300
Heart	7,800	450	17	0.3	2,340	135
Muscle	5,000	300	17	30	150,000	9,000
Serum	1	1	1.0	3	3	3

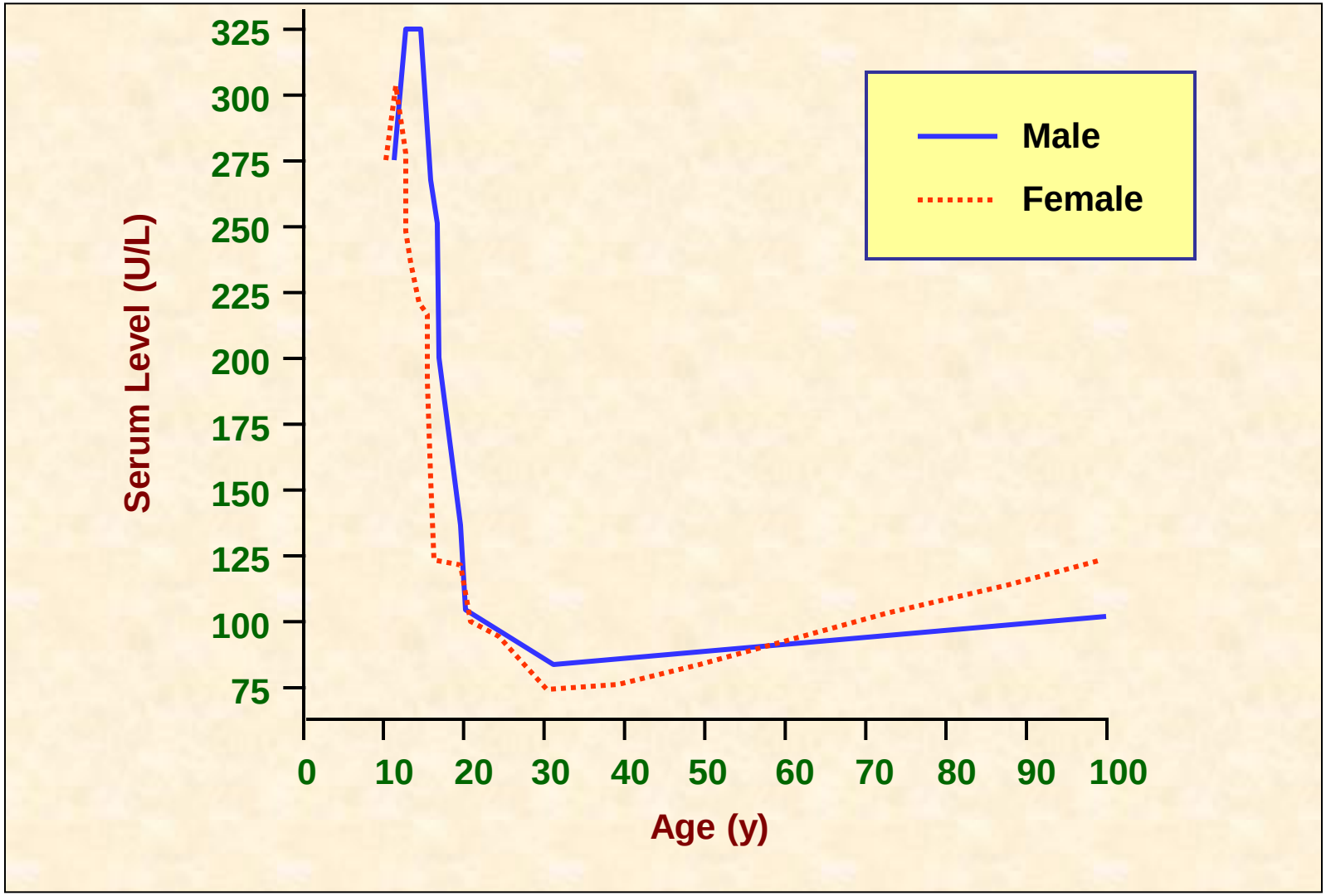
*Adapted from King J. Practical Clinical Enzymology, 1965.[3]

Clin Biochem Rev, Vol 34, November 2013: 117 – 130

Alkaline Phosphatase (ALP) and γ-Glutamyl Transferase (GGT)

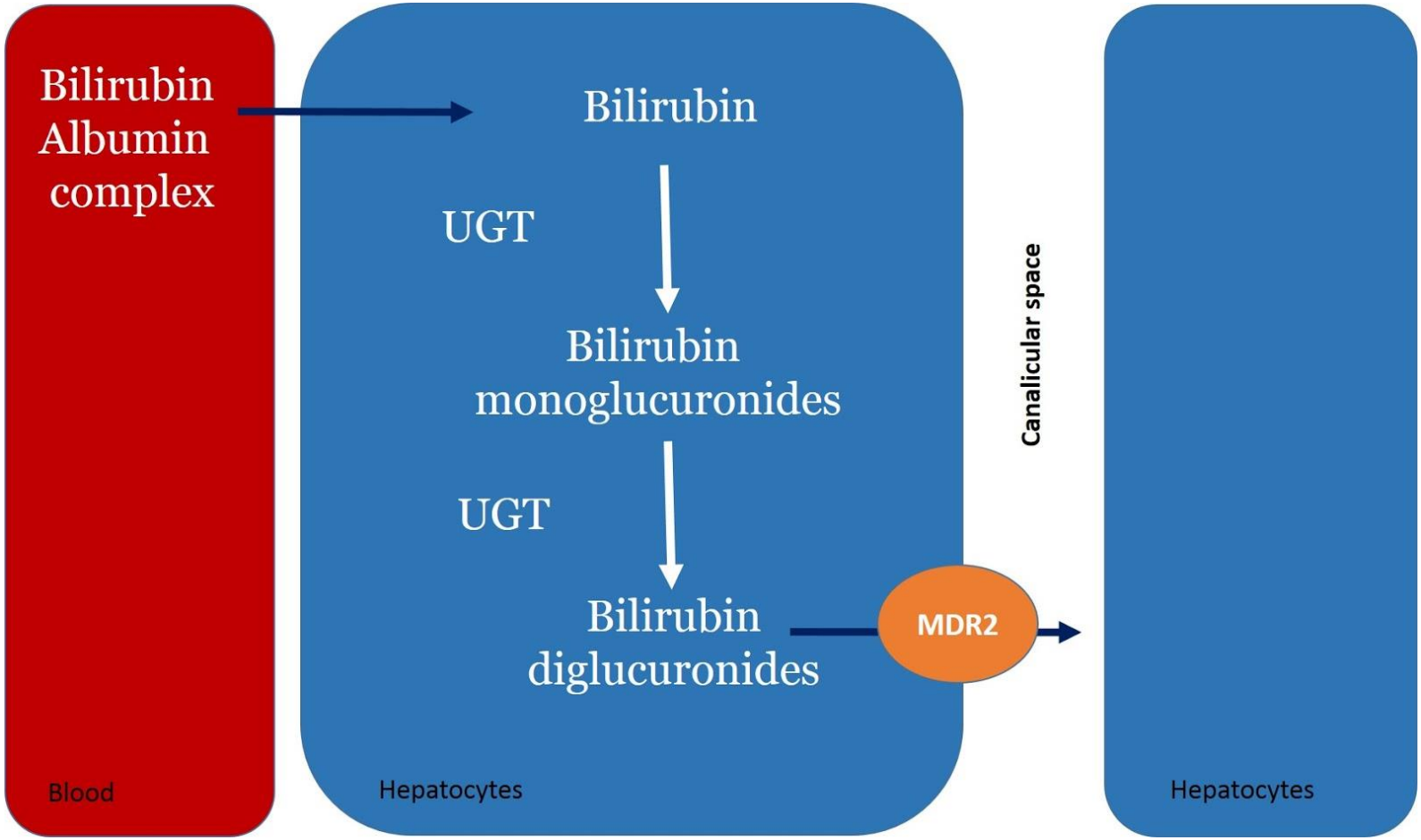
- There are several isoenzymes of **ALP** (i.e., **liver**, **bone**, **intestine** and **placenta**).
- **Liver** or **bone** pathologies are the most common causes for elevated ALP levels in blood.
- **ALP** and **GGT** are found on the membranes, rather than inside the cells, of the bile canaliculi and ducts.
- Therefore, if a raised ALP is of **liver** origin, it often indicates cholestasis and/or infiltrative disease and is usually accompanied by a raised **GGT**.
- **Isolated** increase in ALP can be **physiological**, e.g., rapid bone growth (healing fracture, pubertal growth spurt – the isoenzyme from bone), pregnancy (isoenzyme from placenta), certain individuals (mostly of Blood Group O or B) after fatty meals (only transient and mild increase).
- When the above conditions are excluded, a **bone** pathology should be considered when there is an **isolated increase** in ALP.
- **Alcohol** and **drugs** are amongst the most common causes for isolated elevation of GGT in clinical setting.

ALP Interpretation



Physiological elevations of ALP occur with bone growth and during pregnancy owing to ALP coming from the bone and placenta respectively

Overview of Bilirubin Metabolism



Bilirubin

- Plasma **total** bilirubin consists of the **conjugated** and **unconjugated** forms.
- Unconjugated bilirubin ("**indirect**" bilirubin) is a metabolic by-product of **haem** metabolism, and is relatively water insoluble.
- Unconjugated bilirubin formed is then conjugated by the liver (conjugated or "**direct**" bilirubin), rendering it more water soluble, to facilitate its excretion in the bile.
- The capacity of liver to **conjugate** bilirubin normally far exceeds that of **excretion** of conjugated bilirubin into biliary canaliculi.
- Therefore, most liver pathologies are associated with **conjugated hyperbilirubinaemia** except when there are enzyme deficiencies in the bilirubin conjugation pathway (e.g., *Crigler-Najjar Syndrome*)
- Haemolytic disorders are also associated with **unconjugated hyperbilirubinaemia** as a result of rapid release of haemoglobin from the damaged erythrocytes.
- When a haemolytic condition is excluded or deemed unlikely, mild fluctuating unconjugated hyperbilirubinaemia is often due to *Gilbert's syndrome* (~1 - 5 % of population).

Differential Diagnosis of Jaundice

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 gamma glutamyl transpeptidase	Normal	Normal

(Adapted from Harrison's Internal Medicine-16th Ed)

How do Liver Function Tests reflect liver pathologies?

Patterns of Abnormal Liver Function Tests:

I] Predominantly Hepatic –

- ALT and AST most markedly elevated tests.
- An isolated raised ALT can be transient due to an intercurrent illness such as a viral infection or an intervention (results should normalise after a few weeks if that is the case).
- Other causes of a hepatic picture are Viral Hepatitis, NAFLD, Autoimmune Hepatitis or Alcohol-related liver disease, hepatotoxins (e.g., toxic mushrooms) and hepatotoxic medications (including herbal medications).
- AST:ALT ratio >1 can signify a higher risk of fibrosis or cirrhosis in the long term.
- ALT (and more so AST) can also come from muscle, so consider testing for Creatine Kinase (CK) if no other cause apparent.

II] Cholestatic

- Alkaline phosphatase (ALP) increased significantly more than ALT (ALP is an enzyme present in high levels in the liver and bones; smaller amounts in the kidneys, intestine and placenta).

- Raised ALP can occur in patients with biliary pathology; if suspicious of malignancy, presence of marked or progressive cholestasis or severe unintentional weight loss, then rigorous and prompt investigations for underlying pathology is warranted.

- Need to determine the source of raised ALP (especially hepatic vs skeletal).

- Repeating LFT's with a γ-Glutamyl Transferase (GGT) (and vitamin D status for high risk individuals as long term vitamin D deficiency may cause elevated ALP) will usually differentiate between liver and bone being the predominant source of elevated ALP.

- Liver or biliary pathology is supported by a raised GGT; common biliary causes include biliary obstruction (stones, strictures, neoplasms), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), others like hepatic congestion and medications.

II] Cholestatic *(con'td)*

- When a bone source is suspected (normal GGT), vitamin D should be tested as vitamin D deficiency is a relatively common cause of non-liver raised ALP due to aging population.

- Subjects at risk of vitamin D deficiency (e.g., strict vegan, homebound, elderly, dark skin, marked obesity, Crohn's disease, celiac disease, chronic pancreatic insufficiency).

- Thyrotoxicosis may also cause elevated ALP, the condition is often clinically evident (signs and symptoms may be more subtle in elderlies); test for TSH and free thyroid hormone (i.e., FT4, FT3) to confirm / exclude the diagnosis.

- **ALP isoenzymes** (tests mostly unavailable in this locality); "**Heat-stability test**" of ALP may help differentiate between predominantly bone or hepatic origin of elevated ALP but the test is not sensitive if the ALP < 200 U/L; Liver ALP is more heat resistant than Bone ALP (Placental ALP is most heat resistant).

III] Mixed

- Usually associated with raised ALT, AST, ALP, GGT and Bilirubin.
- Such a pattern is often evident when the liver insult is prolonged.
- Prolonged biliary obstruction may lead to significant secondary liver cell destruction due to back pressure and the resultant damage on liver parenchyma.
- Acute hepatitis may give rise to a severe cholestatic element as disease progresses due to hepatic congestion and impaired excretion of bilirubin into biliary canaliculi by the damaged hepatocytes – Bilirubin peaks after transaminases.
- Infiltrative liver diseases, e.g., amyloidosis, sarcoidosis, haematological and lymphoid malignancies, may give a similar pattern of liver derangement.

What other information can be gained from the Liver Function Tests?

Albumin

- Albumin is predominantly synthesized by the liver parenchymal cells (i.e., hepatocytes).
- Hypoalbuminaemia in liver disease is due to both reduced hepatic albumin synthesis and haemodilution consequent to generalised oedema from fluid retention.
- Hypoalbuminaemia in association with liver pathology is a marker indicative of the **chronic** nature of the illness.
- Albumin is also a negative acute phase reactant, therefore a reduced level can be due to infective, inflammatory conditions and major systemic illnesses, independent of liver derangement.
- Apart from hepatic dysfunction, excessive renal (e.g., nephrotic syndrome) or gastrointestinal loss (e.g., inflammatory bowel disease) and severe malnutrition can also cause significant hypoalbuminaemia – the degree of hypoalbuminaemia may be masked by the concomitant dehydration.

Besides the LFT panel of tests, there are other tests which are also useful in the assessment of the hepatic derangement:

- Prolongation of **Prothrombin Time** (PT, INR) is reflective of the severity of liver disease as the **Clotting Factors** I, II, V, VII, IX and X are produced by the liver (II, VII, IX, X via a vitamin K dependent pathway).
- Most of these Clotting Factors have very short plasma half-life (in terms of hours) and therefore **PT** is a sensitive index of the current status of the synthetic function of the liver, e.g., steady improvement in PT heralds the recovery from severe hepatic insults, e.g., toxic hepatitis.
- Please note that **vitamin K deficiency** due to fat malabsorption secondary to biliary obstruction or chronic pancreatic insufficiency also gives rise to PT prolongation.
- Plasma **Ammonia** (NH_3) is measured in the assessment of hepatic encephalopathy as NH_3, which is neurotoxic, is normally detoxified by the liver through conversion to **urea** and is subsequently excreted by the kidney, significantly elevated NH3 levels in blood is a biochemical hallmark for fulminant hepatic failure.

Plasma Half-life of Different Proteins Synthesized by the Liver

Protein	Half-life
Albumin	**21 days**
Transferrin	6 days
Pre-albumin	2 days
Factor VII	**6 - 8 hours**

Helpful Hints for Interpreting Liver Function Tests (1)

Situation	Comments
Mildly elevated **ALT** and **AST** levels (<1.5 ×ULN)	ALT and AST values could be normal for gender, ethnicity or physical habitus. Consider muscle injury, myositis or myopathy, (e.g., prolonged strenuous exercise can also cause transient elevation: ↑ AST > ALT).
Alcoholic Hepatitis	Laboratory values can appear predominantly cholestatic, and symptoms can also mimic cholecystitis. Mild elevations of AST and ALT often occur where ↑ AST > ALT (AST:ALT ratio >2 – De Ritis ratio)

Helpful Hints for Interpreting Liver Function Tests (2)

Situation	Comments
AST level greater than 8 - 10 x ULN	The AST elevation is unlikely to result from alcohol intake alone. In a chronic heavy drinker, also consider paracetamol toxicity (a relatively common overdose) as they are more susceptible due to the frequently associated bodily glutathione depletion.
Common ductal stone	Laboratory picture can mimic acute hepatitis. AST and ALT may become elevated shortly, followed by a more prominent increase of ALP and GGT, and often a rise in bilirubin (may be transient or intermittent).
Isolated elevation of **GGT** level	This situation may be induced by alcohol and aromatic medications, usually with no actual liver disease.

Helpful Hints for Interpreting Liver Function Tests (3)

Situation	Comments
Isolated elevation of **ALP** level (normal GGT, may be asymptomatic)	Accelerated bone growth, healing fracture, Paget's disease, osteomalacia, rickets, vitamin D def, hyperparathyroidism, pregnancy (ALP from placenta)
Blood **Ammonia** level	Blood ammonia values are not necessarily elevated in patients with hepatic encephalopathy; a normal value does not exclude the diagnosis (NB: NH_3 level is significantly higher in CNS than in blood) (NB: pre-analytical factors can lead to spurious results, and hyperammonaemia can be due to drugs, e.g., Valproate) Measurement of blood ammonia levels is useful in patients with altered mental status of new onset or unknown origin.

Helpful Hints for Interpreting Liver Function Tests (4)

Situation	Comments
Low **Albumin** level	Low albumin is most often caused by acute or chronic inflammation, infection, renal loss, severe malnutrition or liver diseases; it is sometimes caused by gastrointestinal loss (e.g., colitis or some uncommon small bowel disease, e.g., Crohn's disease). Normal values are lower in pregnancy (esp. 2nd trimester) due to fluid retention.
Isolated elevation of **Unconjugated Bilirubin**	Consider *Gilbert's syndrome* (asymptomatic), or haemolysis (reduced haemoglobin, low or absent haptoglobin level, increased LDH, increased reticulocytes in peripheral blood).

Deranged LFT is often encountered, especially in hospital inpatients, and the individuals may be asymptomatic and from extra-hepatic causes.

Common causes of Abnormal LFT:

- Non-alcoholic fatty liver disease (NAFLD)
- Alcohol-related liver disease (ARLD)
- Drug-induced (including herbal medicine)
- Viral hepatitis

Less common causes of Abnormal LFT:

- Primary liver cancer (hepatocellular carcinoma)
- Liver metastasis
- Liver abscess
- Hepatic congestion, e.g., congestive heart failure
- Infiltrative diseases, e.g., haemochromatosis, amyloidosis, sarcoidosis, lymphoproliferative diseases, glycogen storage disease
- Thyrotoxicosis (severe)
- Autoimmune hepatitis
- Haemolysis, muscle injuries (e.g., rhabdomyolysis, myositis), inflammatory bowel disease
- Primary biliary cholangitis
- Primary sclerosing cholangitis (PSC)
- Wilson's disease
- Haemochromatosis
- Inherited liver disorders, e.g., α-1 antitrypsin deficiency

Non-pathological causes:

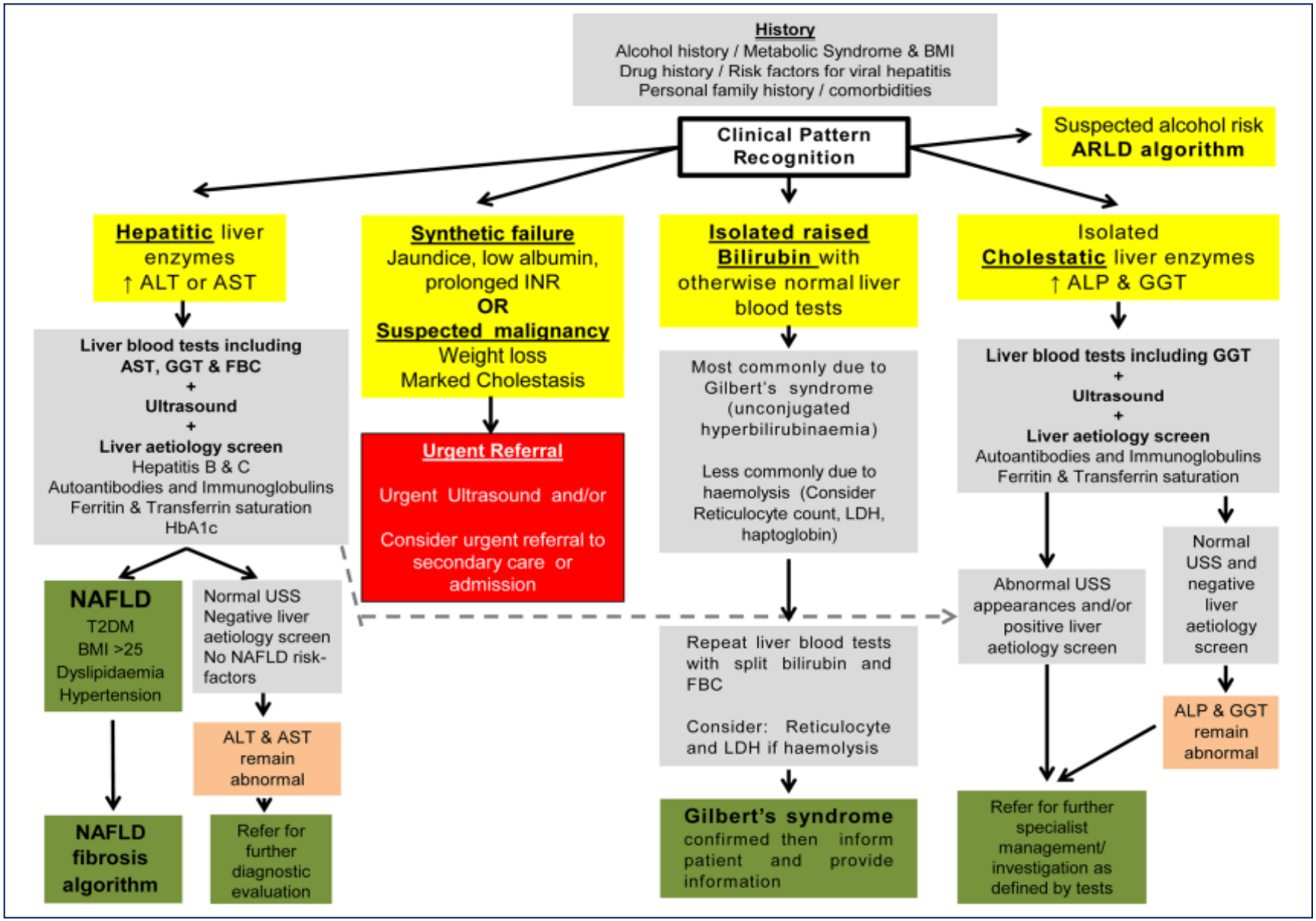
- Gilbert's syndrome
- Strenuous exercise (transitory).

Abnormal liver function tests (LFT's) are frequently detected in asymptomatic patients. This may be due to the nature of liver disease often being "silent" and that increased frequency of testing now automated assays are readily available.

Interpretation of abnormal Liver Function Test results should be made in the context of previous results, past medical history, current medical conditions, symptoms and signs, and drug history.

The pattern and degree of changes along with the overall clinical picture can provide hints to the underlying causes for the deranged LFT.

Approach to Abnormal LFT



Gut 2018;67:6 - 19

Key Messages and Caveats (1):

- A detailed medical history is very important in the evaluation of a patient with abnormal LFT findings. The history should include consumption of alcohol, medications (including herbal medicine), recent travel and other risk factors for viral hepatitis transmission like blood transfusion, needle drug use, tattoos, unprotected intercourse, haemodialysis, family history of liver diseases (e.g., Wilson's disease, α-1 Antitrypsin deficiency, haemochromatosis – latter 2 very rare amongst Chinese).
- Abnormal LFT can be broadly categorized into that of predominantly hepatocellular injury, cholestatic or mixed injury based on the pattern of derangement.
- The common laboratory tests for evaluating liver derangement can be divided into those that evaluate synthetic function (i.e., albumin, PT/INR), hepatocyte integrity (i.e., ALT, AST) and bile excretion and conjugation (i.e., bilirubin – total, conjugated, unconjugated, ALP, GGT).
- Beware of the primarily non-hepatic causes for deranged LFT, such as intravascular haemolysis, congestive hepatopathy secondary to heart failure, shock (ischaemic injury), muscle diseases, thyroid disorders (both hyper- and hypothyroidism may increase AST).
- Elevated blood NH3 in liver disease heralds hepatic encephalopathy though normal NH3 does not necessarily exclude it.
- Look for stigmata of chronic liver diseases on physical examination.

Key Messages and Caveats (2):

- **Potential pitfalls and common errors** –
  - Inadequate history taking.
  - Frivolous or haphazard use of a wide net of assorted tests instead of a targeted approach guided by the medical history and clinical context.
  - Failure to consider extrahepatic causes for elevated analytes in the LFT profile, e.g.,
    - ALP can be elevated in bone diseases, healing fracture, rapid growth, pregnancy, vitamin D deficiency;
    - Elevated bilirubin (predominantly unconjugated) can be due to haemolysis (often accompanied by increased AST);
    - AST can be elevated in muscle injury, after strenuous exercise (transitory increase), myositis, myopathy, and myocardial infarction.
  - To initiate exhaustive investigations for liver disease just based on a single episode of abnormal LFT findings, which may be transient, or an isolated elevation of GGT.

Laboratory assessment of the patient with suspected or clinically obvious liver disease is context dependent. For example, the acutely ill jaundiced patient with a history of prolonged alcohol ingestion requires a different laboratory assessment than the well patient in whom one or more standard liver test results are discovered to be abnormal during routine testing.

In Summary……

- Laboratory assessment of the patient with suspected or clinically obvious liver disease is **context dependent**, e.g., the acutely ill jaundiced patient with a history of prolonged alcohol ingestion requires a different laboratory assessment than the well patient in whom one or more standard liver test results are discovered to be abnormal during routine testing.
- A detailed **medical history** is key and generally the most important step in the evaluation of a patient with abnormal liver tests.
- Liver enzyme elevation can be broadly categorized into **hepatocellular** injury, **cholestatic** injury, or **mixed** injury based on **patterns** of relative elevation of different liver enzymes.
- Laboratory tests to diagnose liver disease can be divided into test parameters which evaluate liver **function** (INR, albumin), those which primarily evaluate hepatocyte **integrity** (AST, ALT) and those which predominantly assess abnormalities of bile ducts and **bile flow** (bilirubin, AP, GGT).
- The **differential diagnosis** of abnormal liver tests is very broad and includes infectious (viral hepatitis), metabolic (non-alcoholic fatty liver disease, Wilson's disease, haemochromatosis, α-1 antitrypsin deficiency), toxin- and drug-induced (alcohol, western medicines, toxic mushrooms, herbal medicinal products), immunological (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, overlap syndromes), infiltrative, vascular (Budd-Chiari syndrome), traumatic and neoplastic diseases.
- **Non-hepatic causes** of elevated liver enzymes, such as congestive hepatopathy, shock liver (ischaemic injury), muscle diseases, thyroid disorders (hyper- or hypothyroidism), or celiac disease have to be excluded.

(WARD ENQUIRY)

Hospital Authority
Queen Mary Hospital

Urgent

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Name: HUNG [redacted]
(孔[redacted]
HKID No: D48[redacted]
Hosp No: HN23[redacted]
Location: QMH/MED3/A2 Bed: 01A
Sex/Age: M/63Y DOB: 05[redacted]9
Req. Loc.: QMH/MED3/A2
Doctor: Dr. MOK [redacted]

Patient Hospital: Queen Mary Hospital

Collect Date :	23/03/23	24/03/23	25/03/23	26/03/23	**27/03/23**		
Collect Time :	08:55	08:58	08:35	14:15	**10:24**		
Request No. :	C32[redacted]	C32[redacted]	C32[redacted]	C32[redacted]	**C32[redacted]**		
Remark :	deranged liver function	deranged liver function	deranged liver function	deranged liver function	deranged liver function	Ref. Interval	Units
Total Protein	68	66 L	67 L	68	77	68 - 84	g/L
Albumin	34 L	34 L	36 L	35 L	39	39 - 50	g/L
Globulin	34	32	31	33	38 H	24 - 37	g/L
Total Bili	70 H	37 H	30 H	22	43 H	4 - 23	umol/L
Direct Bili					36 H	< 6	umol/L
ALP	351 H	356 H	337 H	294 H	623 H	42 - 110	U/L
ALT	422 H	434 H	440 H	375 H	579 H	8 - 58	U/L
AST	227 H	223 H	221 H	165 H	330 H	15 - 38	U/L
GGT	565 H	505 H	428 H	342 H	651 H	11 - 62	U/L
Amylase			95		67	25 - 124	U/L

Comment:
23C3271494 Amylase is useful in acute pancreatitis but often unhelpful in other abdominal emergencies.
Test result(s) analytically verified: TBIL ALP

Authorized By: Tam, Sidney

Consultant Chemical Pathologist: Prof. C W Lam
This laboratory is accredited by the College of American Pathologists,
CAP Accreditation Number 71755-25

Report Date & Time: 27/03/2023 14:09 Generated on: 27/03/2023 14:09
Report Destination: QMH/--/A2 - A2, Medicine Page No.: 2/2

What is your interpretation?

Suggested Supplementary Reading

- Newsome PN, et al. “Guidelines on the management of abnormal liver blood tests”. *Gut* 2018; 67(1):6-19.
- “AGA Technical Review on the evaluation of liver chemistry tests.” *Gastroenterology* 2002;123:1367– 84.
- Giannini EG, et al. “Liver enzyme alteration: a guide for clinicians.” *CMAJ* 2005; 172(3): 367 – 79.
- Pratt DS, Kaplan MM. “Evaluation of abnormal liver enzyme results in asymptomatic patients”. *New England Journal of Medicine* 2000;342(17): 1266 – 1271.
- Gopal DV, Rosen HR. “Abnormal findings on liver function tests.” *Postgraduate Medicine* 2000; 107 (2):100 – 104
- Kamath PS. “Clinical approach to the patient with abnormal liver test results.” *Mayo Clinic Proceedings* 1996; 71:1089 – 1095.
- Johnson PJ. “Role of the standard ‘Liver Function Tests’ in current clinical practice.” Review Article. *Ann Clin Biochem* 1989; 26:463 – 471.

END

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