City & Hackney CCG

Abnormal Liver Function Tests (LFTs) in Adults

Interpreting abnormal liver function tests (LFTs) and trying to diagnose any underlying liver disease is a common scenario in Primary Care.

Chronic liver disease is often asymptomatic and the first sign of liver damage may be a raised liver enzyme in an otherwise well patient. It is therefore important for clinicians to investigate appropriately in order to diagnose and treat such patients. Alternatively, there may be nothing wrong with the liver at all - traditionally 'normal' values are defined as being within ± 2 standard deviations meaning that 2.5% of a healthy population will have LFTs outside the normal range.

This is a guideline to assist GPs in deciding how to proceed when confronted with abnormal LFTs.

The adult reference ranges for liver function tests are as follows:

- Bilirubin 0-17 µmol/L
- ALT 5-40 IU/L
- ALP 25-115 IU/L
- Total Protein 60 – 85 g/L
- Albumin 38 – 50 g/L
- gGT 0-32 IU/L

Individual LFTs

Bilirubin

Hyperbilirubinaemia can be broadly defined due to the whether the increase is conjugated or unconjugated. Many patients have a mixed picture. Enzyme analysis will point to the correct diagnosis and appropriate referral. Slight increases in bilirubin (17-50 µmol/L) are not unusual and usually not clinically significant.

The actual determination of conjugated (Direct) and unconjugated (Indirect) bilirubin is seldom required in adults, except when the rise in bilirubin is isolated, i.e. the liver enzymes are within the reference range.

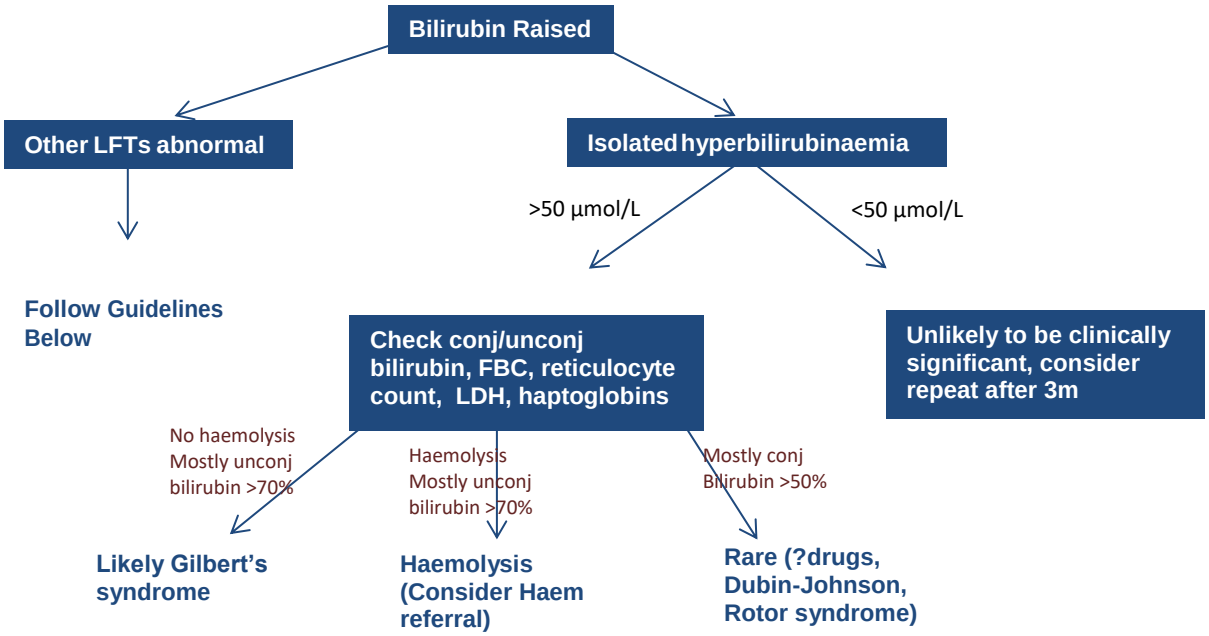
Causes of isolated unconjugated hyperbilirubinaemia:

- Gilbert's syndrome (bilirubin level usually < 70 µmol/L)
- Stress/fasting
- Drugs e.g. rifampicin, sulfonamides
- Haemolytic disease

This is the most common cause and effects 2 – 7 % of the population

Causes of isolated conjugated hyperbilirubinaemia*:*

- Drugs e.g. phenothiazines, sulfonamides and carbimazole
- Dubin-Johnson syndrome
- Rotor's syndrome



Alanine Transferase (ALT)

ALT is a cytosolic enzyme, which is expressed predominantly in liver cells and is used as a marker to assess liver cell damage.

Please remember that some patients can have severe liver disease with only slightly abnormal liver enzymes.

Common causes:

- Alcohol
- Viral hepatitis
- Steatosis
- Medications/toxins e.g. NSAIDs, antibiotics, statins, antiepileptics, antituberculosis drugs

Less Common causes:

- Autoimmune hepatitis
- Haemochromatosis
- Alpha$_1$-antitrypsin deficiency
- Wilson's disease

(A1AT and Wilsons disease are very rare conditions generally diagnosed in younger patients, and should be investigated in secondary care only. Initial tests to look for these have been removed from the primary care pathway)

Non-hepatic causes of raised ALT (usually small rises, <120 U/L):

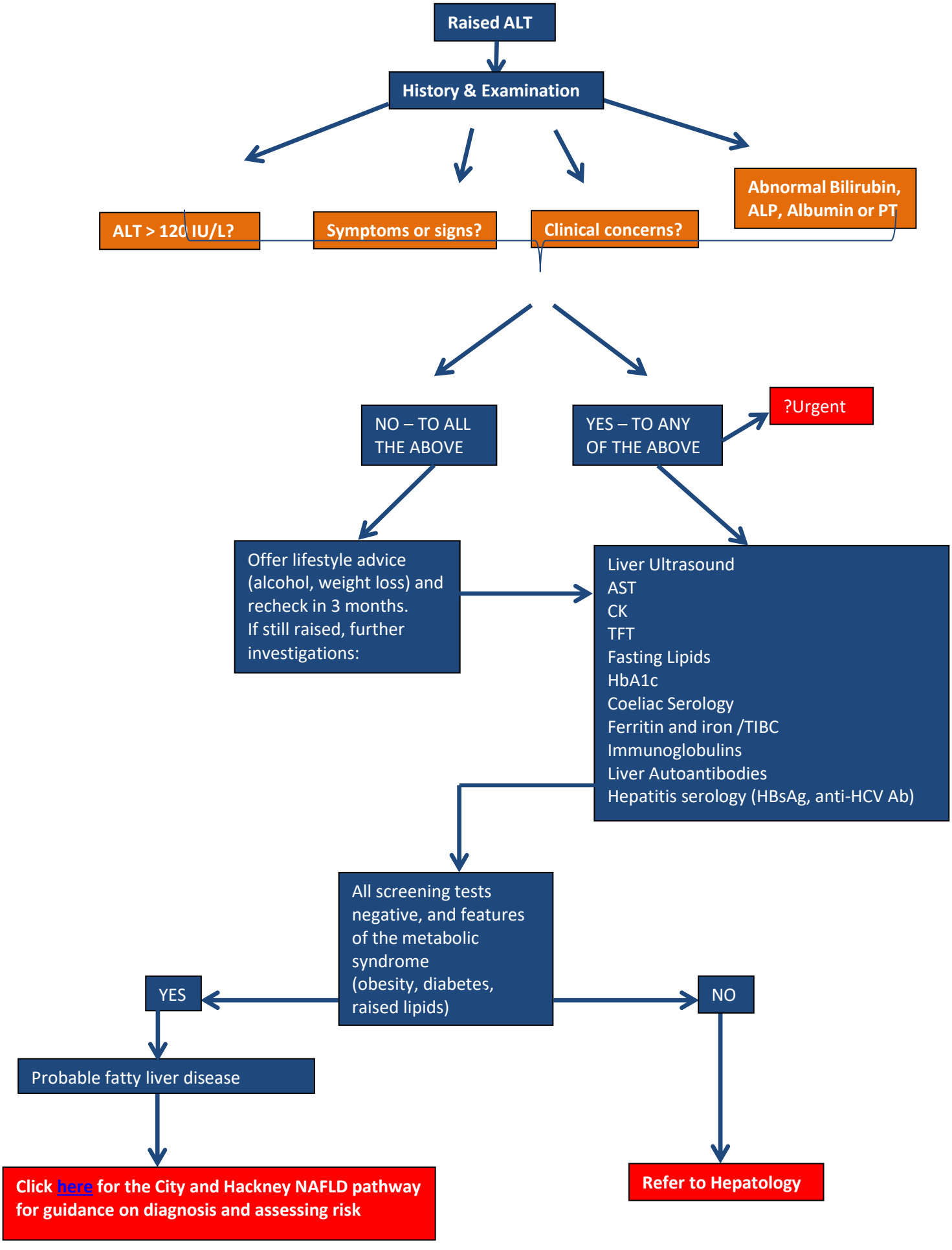
- Coeliac disease
- Strenuous exercise
- Muscle disease
- Endocrine disease e.g. Hypo- and hyper-thyroidism

Aspartate Aminotransferase (AST)

AST is expressed in the liver, as well as in the heart, skeletal muscle, kidneys, brain and red blood cells and therefore is not as liver specific as ALT. AST and ALT differ in their cellular location within the liver, as ALT is predominantly cytoplasmic and AST is present in both cytoplasm and mitochondria.

AST is not part of the initial LFT, but the ratio of AST to ALT may provide useful information about the possible cause of liver disease:

AST:ALT ratio ≥ 2.1 may be suggestive, but not diagnostic of alcohol related liver disease, while AST:ALT ratio < 2.1 may suggest hepatic steatosis or chronic viral hepatitis.


Raised ALT
History & Examination
ALT > 120 IU/L?
Symptoms or signs?
Clinical concerns?
Abnormal Bilirubin, ALP, Albumin or PT
NO – TO ALL THE ABOVE
YES – TO ANY OF THE ABOVE
?Urgent
Offer lifestyle advice (alcohol, weight loss) and recheck in 3 months. If still raised, further investigations:
Liver Ultrasound
AST
CK
TFT
Fasting Lipids
HbA1c
Coeliac Serology
Ferritin and iron /TIBC
Immunoglobulins
Liver Autoantibodies
Hepatitis serology (HBsAg, anti-HCV Ab)
All screening tests negative, and features of the metabolic syndrome (obesity, diabetes, raised lipids)
YES
NO
Probable fatty liver disease
Click here for the City and Hackney NAFLD pathway for guidance on diagnosis and assessing risk
Refer to Hepatology

Alkaline Phosphatase (ALP)

The two main sources of ALP are liver and bone, although there are also intestinal and placental isoforms.

Elevations may be physiological or pathological. Common causes for raised ALP.

Physiological

- Third trimester of pregnancy
- Adolescents, due to bone growth
- Benign, familial

Pathological

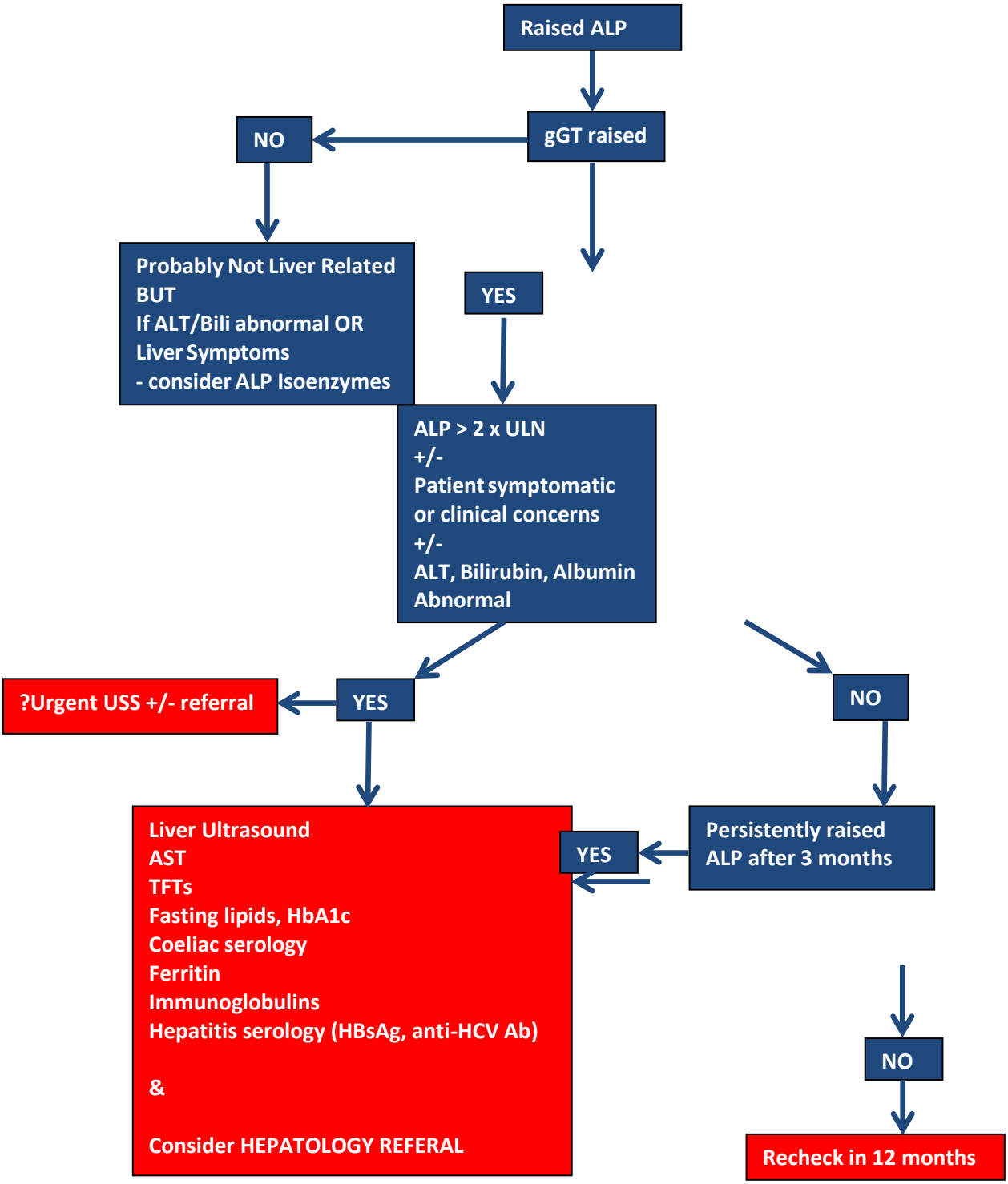
- Bile duct obstruction
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Drug induced cholestasis, e.g. anabolic steroids
- Metastatic liver disease
- Bone disease e.g Pagets
- Heart failure

Gamma-Glutamyl Transferase (γGT)

γGT is a sensitive marker for hepatobiliary disease, but its use is limited by poor specificity. Causes of raised γGT:

- Hepatobiliary disease (often with other liver enzyme abnormalities)
- Pancreatic disease
- Alcoholism
- Chronic obstructive pulmonary disease
- Renal failure
- Diabetes
- Myocardial infarction
- Drugs, e.g. carbamazepine, phenytoin and barbiturates and oral contraceptive pill

The use of γGT is in supporting a hepatobiliary source for other raised liver enzymes, e.g. ALP. It has limited utility as a primary liver test. If an isolated raised γGT is found, consider retesting after 3m if mildly raised (<5 times ULN). Consider ultrasound if γGT is >5x ULN.


Raised ALP
gGT raised
NO
Probably Not Liver Related
BUT
If ALT/Bili abnormal OR
Liver Symptoms
- consider ALP Isoenzymes
YES
ALP > 2 x ULN
+/-
Patient symptomatic
or clinical concerns
+/-
ALT, Bilirubin, Albumin
Abnormal
?Urgent USS +/- referral
YES
NO
Liver Ultrasound
AST
TFTs
Fasting lipids, HbA1c
Coeliac serology
Ferritin
Immunoglobulins
Hepatitis serology (HBsAg, anti-HCV Ab)
&
Consider HEPATOLOGY REFERAL
YES
Persistently raised
ALP after 3 months
NO
Recheck in 12 months

Albumin
Albumin synthesis is an important function of the liver. When the functioning capacity of the liver decreases, falls in plasma albumin can be seen. However, there are many other causes of decreasing albumin levels.

Causes of low albumin:
- Decreased Synthesis - severe liver disease, malabsorption, malnutrition, acute phase reaction
- Haemodilution - pregnancy, iv therapy, congestive cardiac failure, cirrhosis, antidiuresis
- Altered distribution - injury, infection, inflammation, malignancy, cirrhosis
- Loss from body - skin (burns), gut (protein losing enteropathy) and renal (nephrotic syndrome)
- Increased catabolism - acute/chronic illness, malignancy, pregnancy

History and Investigations
A detailed clinical assessment is very important for patient management and should include the following:

- Alcohol Consumption
- Medications
- Past history of autoimmune conditions
- Occupational exposure to toxins
- Family history of liver disease
- Risk factors for viral hepatitis:
  - intravenous drug use
  - travel history
  - non-sterile ear or body piercing
  - tattoos
  - health care intervention in developing nations
  - country of birth

Second Line Tests (Liver screen):
- Liver Ultrasound
- AST
- γGT
- Immunoglobulins
- CK
- Ferritin
- TFTs
- Fasting Lipids
- Glucose / HbA1c
- Coeliac Serology
- Hepatitis serology (HBsAg, anti-HCV Abs)
- Liver Autoantibodies

References

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