APPROACH TO ABNORMAL LFT'S

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LFT’S

- Reflect different functions of liver
- Bilirubin: Excrete anions & waste metabolites
- Aminotransferases: Hepatocellular integrity
- Bilirubin & ALKP: Formation & subsequent free flow of bile
- Albumin: Protein synthesis
- PT/INR: Synthesis of coagulation factors by liver

Commonly available LFT'S

- ALT : alanine aminotransferase
- AST: aspartate aminotransferase
- ALKP: alkaline phosphatase
- GGT: gamma glutamyl transferase
- Bilirubin: direct & indirect
- Albumin
- Prothrombin Time
- Other tests: 5 Nucleotidase, Glutamate dehydrogenase, Isocitrate dehydrogenase, LDH, Sorbitol dehydrogenase

- When faced with abnormal LFT’S in an asymptomatic individual it is imperative to establish there is an abnormality
- Normal value is the mean value in a group of healthy individuals +/- 2SD
- Repeat tests to confirm
- Take appropriate steps

Clinical assessment

- Detailed history
- Full physical examination
- Particular emphasis on:
  - alcohol consumption
  - risk factors for viral hepatitis: IV drug use
- Medication use
- herbal or alternative remedies
- Occupational exposure

sexual promiscuity
homosexual relationship
tattoos
ear or body piercing
blood transfusion
baby boomers(1945-1965)

Normal Values

- ALT: 13-40 IU/L
- AST: 13-31 IU/L
- ALKP: 30-120 IU/L
- GGT: 0-30
- Bilirubin: T bili: 1-1.5mg/dl direct : 0.4-0.8 mg/dl
  Indirect: 0.4-0.8 mg/dl
- PT: 10.9-12.5
- Albumin: 3.5- 4.5 gm/dl

ALT values

- Since many diseases of liver are asymptomatic in early stages careful definition of true normal ranges is important in screening patients for liver diseases

- ALT more specific than AST in liver diseases
- Levels depend on body mass and gender
- ALT: ULN for male : 30 IU/L
  female : 19 IU/L
- Sensitivity for detecting HCV patients improved from 55% to 76% using these limits compared to 40 & 30 IU for men & women

- Treatment decisions for chronic viral hepatitis particularly HBV use ALT elevation above ULN to determine appropriateness of treatment

Bilirubin

- Breakdown product of senescent red cells
- Toxic waste product
- Extracted & bio transformed in liver
- Excreted in bile & urine
- Unconjugated bilirubin → transferred to liver bound to albumin
- Conjugated in liver to bilirubin glucuronide (water soluble)
- Canalicular excretion → bile & gut
- Intestinal flora → urobilinogen → urine & gut
- Stercobilinogen into feces gives yellow color

Bilirubin Metabolism

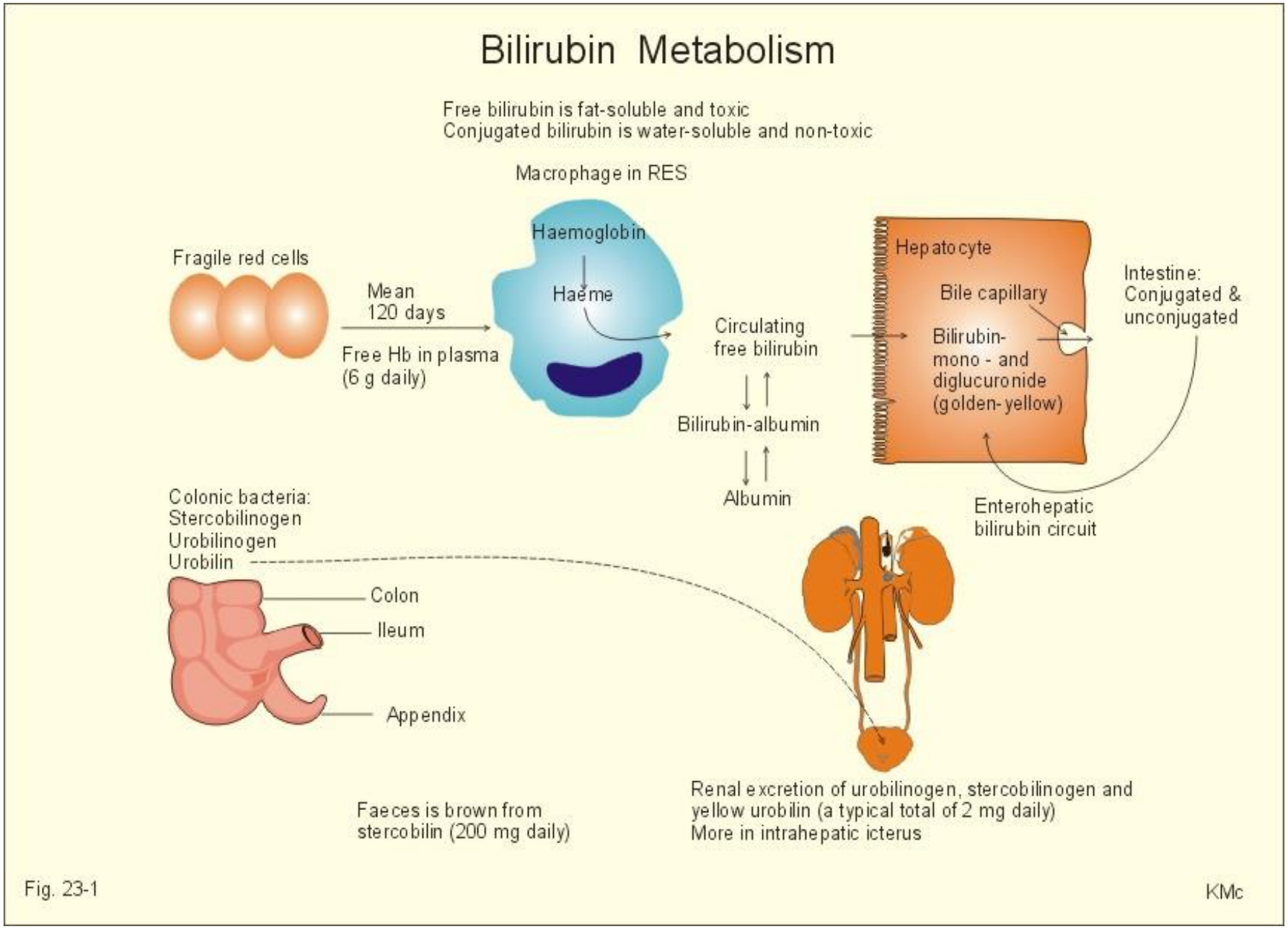


Fig. 23-1

KMc

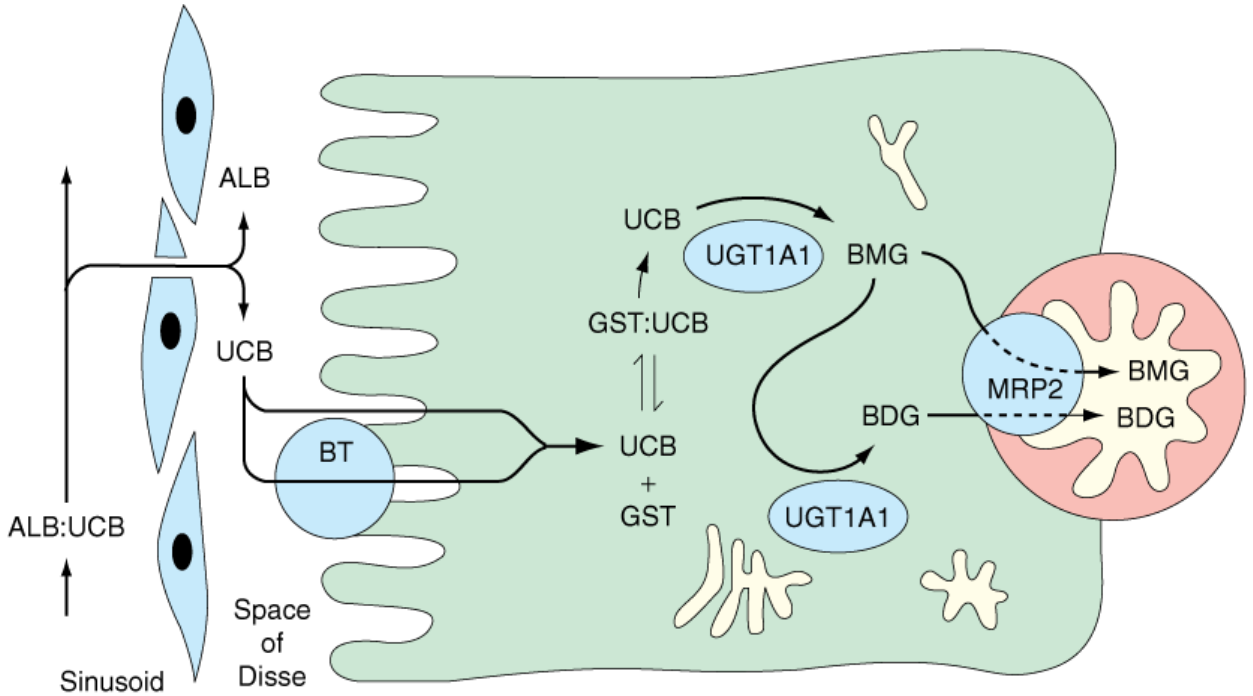


Figure 6.5 Hepatocellular transport of bilirubin. Efficient transfer of bilirubin from blood to bile is dependent on normal sinusoidal architecture, plasma membrane transport processes, and intracellular binding and conjugation. Albumin-bound bilirubin in sinusoidal blood passes through endothelial cell fenestrae to reach the hepatocyte surface, entering the cell by both facilitated and simple diffusional processes. Within the cell it is bound to glutathione-*S*-transferase (GST), and conjugated by bilirubin–uridine diphosphate (UDP) glucuronosyl-transferase (UGT1A1) to mono- and diglucuronides, which are actively transported across the canalicular membrane into the bile. ALB, albumin; BDG, bilirubin diglucuronide; BMG, bilirubin monoglucuronide; BT, proposed bilirubin transporter; MRP2, multidrug resistance-associated protein 2; UCB, unconjugated bilirubin. (Reproduced from Berk and Wolkoff [69] with permission from McGraw-Hill.)

Significance of elevated bilirubin

- Elevated Unconjugated Bilirubin: (0.8-1.2mg/dl)
  - hemolysis
  - ineffective erythropoiesis
  - hematoma, muscle injury
  - familial : Gilbert's, Criggler-Najjar (syndromes)
  - physiological jaundice of newborn
  - medications : Rifampin, HIV protease inhibitors

- Unconjugated bilirubin never appears in urine as it is too small to permit ultrafiltration

- Pre-hepatic jaundice→ no bilirubin in urine

Significance of elevated bilirubin

- Elevated conjugated bilirubin: (0.4-0.8mg/dl)
  -parenchymal disease
  -biliary obstruction
  -familial: Dubin-Johnson, Rotor (syndromes)

- Conjugated bilirubin can be excreted by kidney and is absolute indicator of conjugated hyper-bilirubinemia

- obstructive jaundice→ no urinary urobilinogen

Prognostic significance of bilirubin

- Alcoholic hepatitis (discriminant function)
- Cirrhosis (MELD) (MELD-Na)
- Fulminant liver failure(King’s College Criteria)

Delta Bilirubin

- Prolonged conjugated hyperbilirubinemia in plasma binds covalently to albumin & called delta bilirubin
- Does not appear in urine
- Disappears from plasma in 14-21 days

- Accounts for slow rate of clearance of conjugated bilirubin as hepatitis or biliary obstruction resolves

Aminotransferases

- AST/ALT: markers of hepatocellular injury
- AST: present in cytosolic & mitochondrial iso-enzymes of liver
  - 80% of AST is from mitochondrial iso-enzymes
  - Also present in: cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, RBC
- Less sensitive & specific for liver disease

Aminotransferases

- ALT: Cytosolic enzyme found in highest concentration in liver
  - More specific for liver disease
  - Hepatocellular injury & not cell death is the trigger for release of aminotransferases
  - Rapid decrease in aminotransferases is usually a sign of recovery from disease
  - May be a poor prognostic sign in liver failure

When faced with abnormal AST/ALT

- Assess degree of abnormality
- Repeat if mild
- Investigate if repeat tests abnormal
- High levels > 4 x ULN → prompt further tests without delay

Causes of AST/ALT elevation

- NAFLD
- Alcoholic liver disease
- Chronic hepatitis B & C
- AIH
- DILI
- Congestive hepatopathy
- Ischemic hepatitis
- Hemochromatosis
- Wilson’s disease
- Alpha 1 antitrypsin deficiency
- Celiac disease
- Hypothyroidism
- Addison’s disease
- Skeletal muscle disorders
- Glycogen storage disorders

Alcoholic liver disease

- Reliable history/difficult in reality
- Clues:

➢ AST/ALT = 2:1 at least (low level of activity of ALT in alcoholics) pyridoxal 5 phosphate deficiency

➢ GGT: twice normal with AST/ALT 2:1 highly suggestive

➢ GGT cannot be used as isolated test

➢ Typically AST & ALT < 300 unless other insults such as viral, drugs etc.. superimposed

➢ Normal ALT in severe disease

➢ AST > 8 x ULN & ALT > 5 x ULN → rare in alcoholic livers

NAFLD

- NAFLD: normal LFT'S NASH: elevated LFT'S
- NASH: asymptomatic elevation
  - BMI
  - DM
  - dyslipidemia
  - no alcohol use

  Metabolic Syndrome
- AST/ALT elevation : mild, < 4 x ULN, < 1:1
- Most common cause of mild AST/ALT elevation
- Bilirubin & Albumin usually normal unless advanced
- Thrombocytopenia & leukopenia = portal HTN/cirrhosis

Medications(DILI)

- NSAID'S
- Antibiotics: Augmentin most common
- Statins : Relatively safe medications based on studies
- Anti epileptics: phenytoin, carbamazepine, Valproic acid
- Anti tuberculous therapy: INH
- Herbal remedies (HILI)
- Alternative medications (SILI)
- Tylenol:

➢ most common cause of massive aminotransferase elevation

➢ Usually >10gm or lower dose if combined with alcohol or other drugs

➢ Livertox.com (a good resource for DILI)

Viral hepatitis

- Hepatitis B:

  -HBSAg +ve : acute or chronic infection. 2-8 weeks before biochemical evidence of jaundice

  -IgM anti HBC: best marker of acute hepatitis B(2-4 weeks of appearance of HBSAg
  if +ve indicates acute infection: repeat HBSAg & HBSAb in 6 months

  -Chronic infection: HBSAg +ve HBSAb –ve

  -HBeAg & HbeAb: Determine if actively replicating or quiescent

  -Screen family members → vaccinate if HBSAb -ve

Viral hepatitis

- Hepatitis C:

  -HCV Ab +ve ELISA: indicates contact with virus

  -False +ve HCV Ab: not uncommon

  -If -ve : unlikely has infection except acute HCV

  -HCV RNA : PCR gold standard for active infection & replication

  -If Ab +ve & PCR –ve : retest in 3 months

Autoimmune Hepatitis

- Female: Male = 4:1
- Young to middle age
- 80% have hyper gammaglobulinemia
- IgG > 2 x ULN : highly suggestive

Type 1

-ANA/ASMA
-most common
-<40 years
-30% have other autoimmune disorders

Type 2

-anti LKM1 Ab
-children 2-14
-DM-1, vitiligo thyroiditis
-low IgA

Type 3

-SLA antibodies
-least established

Hemochromatosis

- Autosomal recessive
- Whites/Celtics 1:250/1:70
- Increased iron absorption due to decreased hepcidin expression in liver
- Iron deposition in liver, pancreas, pituitary, joints
- Young white male with Pigmentation, DM, Monoarthritis
- Fasting Transferrin sats > 45%
- Elevated ferritin: not useful for screening: acute phase reactant
- Liver biopsy: hepatic iron index
- HFE C282Y homozygosity
- C282Y/H63D compound heterozygosity
- Can occur in non HFE patients
- Screen adult family members
- HCC risk only if cirrhotic ?

Wilson's Disease

- Age 5-25 up to 40 years
- Ceruloplasmin reduced in 85% of cases
- Kayser Fleisher rings, sunflower cataracts
- Low Alkp & Bilirubin/Alkp ratio > 2 suggestive
- 24 Hour urine copper: > 100 micrograms suggestive
- Liver biopsy: copper > 250 micrograms/gm
- Isolated unconjugated hyperbilirubinemia in fulminant Wilson's
- Hemolysis due to copper release into the circulation

Non hepatic causes

- Metastatic disease
- Tuberculosis
- Sarcoidosis
- Amyloidosis

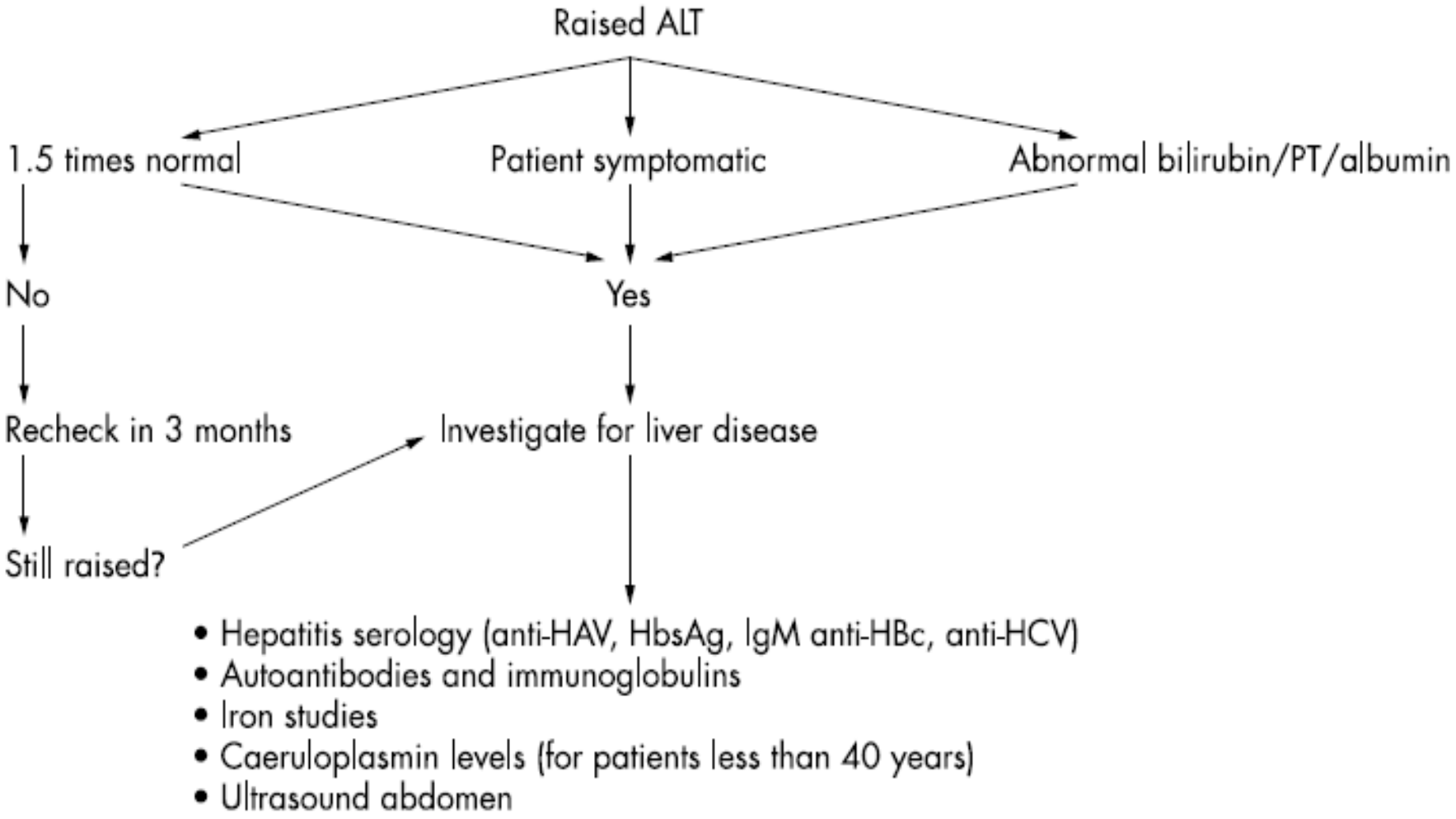
-Up to a 3-fold increase in AST/ALT and a 20-fold increase in ALKP

-Occult celiac sprue: anti gliadin Ab, anti endomysial Ab, TTG

Very high amino transferases

- Typically seen in:
  - Ischemic liver injury
  - Acute viral hepatitis
  - Drugs or toxins
  - Acute obstructing choledocholithiasis

Suggested algorithm for elevated ALT



Alkaline phosphatase

- Main source : Liver & bone
- Other sources: intestine, kidney, placenta, leukocytes

➢ Physiological increase:

- tissues undergoing Metabolic stimulation
- 3rd trimester: placental ALKP release
- adolescents: 2 times normal for adults due to growth
- benign familial elevation in blood groups B & O due to intestinal ALKP after a fatty meal (check fasting level)

Alkaline phosphatase

- Canalicular/luminal domain of bile duct epithelium
- May not rise until 1-2 days after obstruction (rise due to increased synthesis & not from trapping)
- ½ life 1 week→ persistent elevation even after relief of obstruction
- Can be elevated in malignancies without liver or bone involvement: “Reagan Enzyme” → lung cancer
- Genetic : Unknown cause of elevation

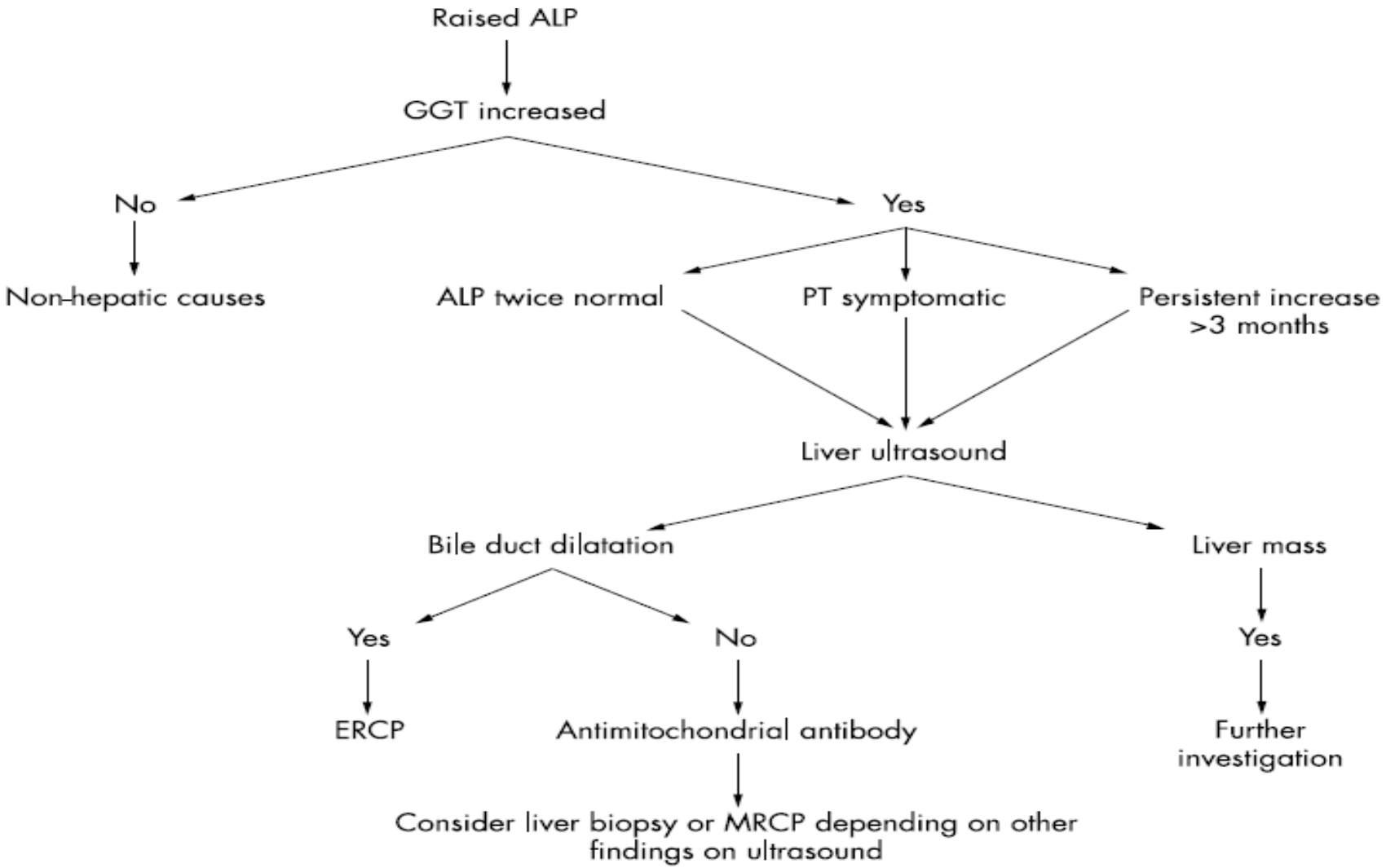
Approach to elevated AlKP

- Identify source
- Isoenzymes: Very specific but expensive, not routinely available
- 5’ nucleotidase & GGT : liver specific
- If coming from liver US indicated

Common causes of elevated ALKP

- Extra hepatic obstruction
- Infiltrative disease
- Metastasis
- PBC
- PSC
- Sarcoidosis
- Drugs (anabolic steroids) clue: bodybuilders
- Ductopenia (old transplant or no compliance with ISP)
- Bone disease

Suggested algorithm for elevating ALKP



Hepatocellular vs cholestatic

- ALT/ALKP : > 5 indicates hepatocellular process
- ALT/ALKP : < 2 Cholestatic picture
- ALT/ALKP : >2 & < 5 mixed picture

Gamma glutamyl transferase

- Present in hepatocytes & biliary epithelial cells
- Lack specificity
- Increased levels in; pancreatic disease, MI, renal failure,
  COPD, DM,
- Medication induced: Dilantin, Tegretol
- Combine with other enzymes for diagnosing specific conditions

Albumin

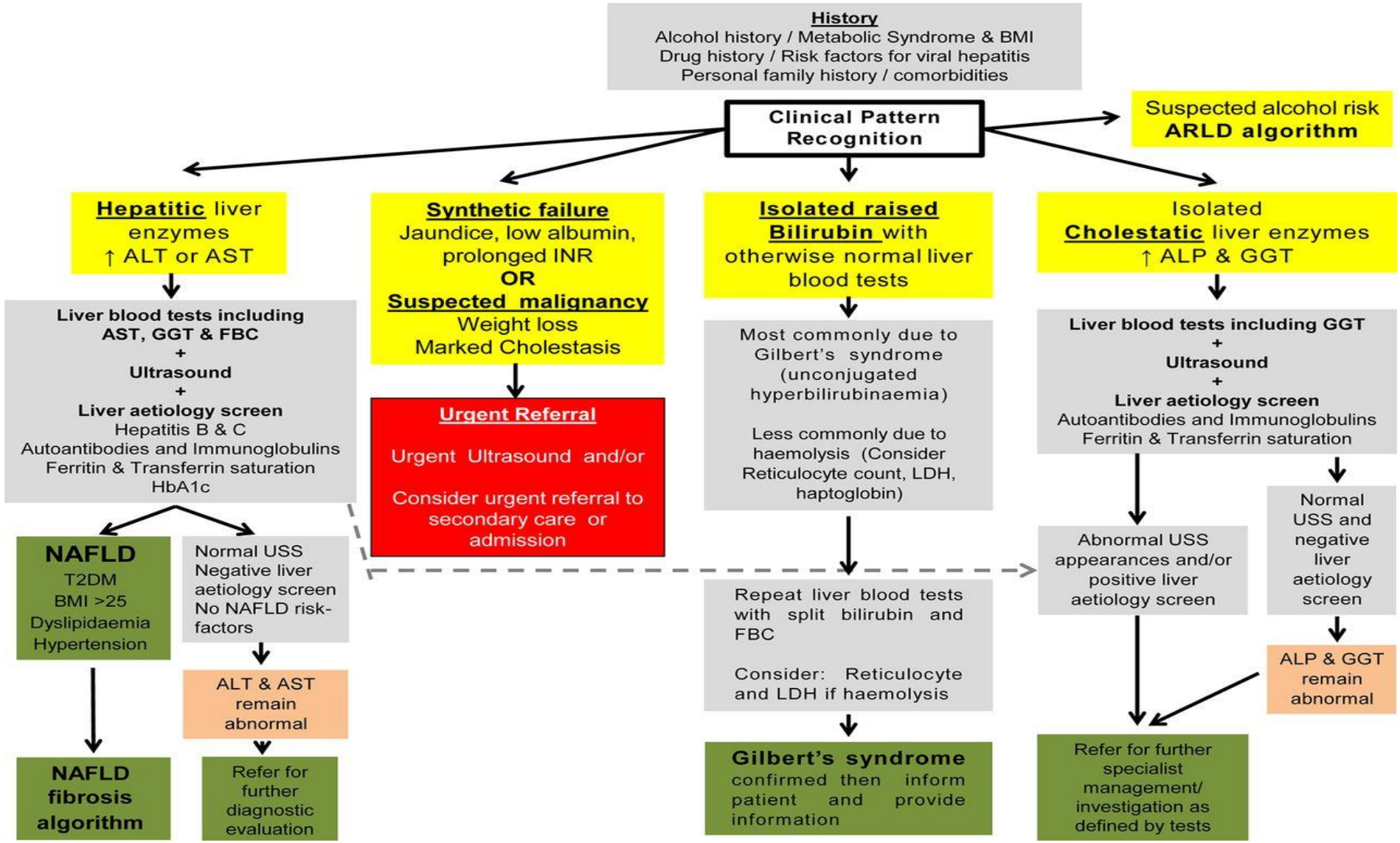
- Important synthetic function of liver
- 15gm synthesized per day and secreted
- Low levels indicate advanced disease
- Other factors should be taken into account :
  - nutritional status
  - catabolism
  - hormonal factors
  - nephropathies
  - enteropathies
- Does correlate with prognosis in liver disease

Prothrombin Time

- Synthesis of coagulation factors in liver
- Factors II, VII, IX & X
- Vitamin K required for gamma carboxylation of factors
- PT may be prolonged in Vitamin K deficiency, warfarin use, liver disease & consumptive coagulopathy
- Chronic cholestasis can lead to malabsorption of fat-soluble vitamins→ Vitamin K corrects PT indicating malabsorption & not advanced liver disease

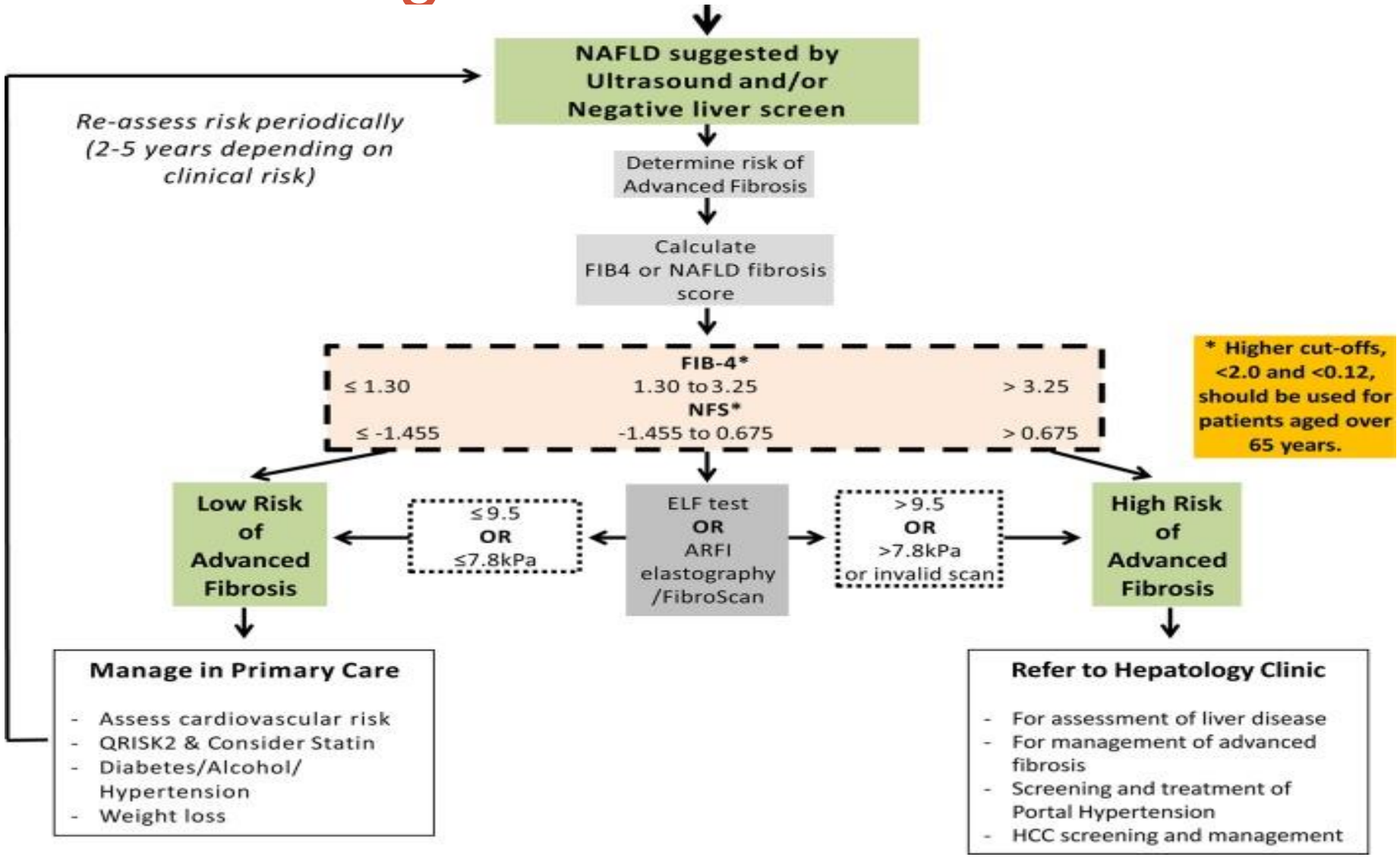
- INR: standardize reporting of PT to prevent inter lab variability: patient PT/ mean control PT
- Important prognostic marker in cirrhosis & fulminant hepatic failure

Suggested algorithm & when to refer ?



Ref: Newsome PN etal, BMJ gut; Nov 2017

NAFLD algorithm



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thank
you!