Abnormal liver enzymes

Objectives:

- Approach to liver enzymes
- Selected disease

[Color index : Important | Notes | Extra]

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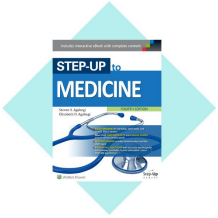
Resources:

- 435 slides



★ This lecture was made based on last year's slides and objectives (LFT and **jaundice**), unfortunately the doctor decided to change the content and added some **selective diseases** **(Most of them are mentioned in Liver Cirrhosis lecture)** rather than jaundice and due to the short notice we couldn't cover all of them.

★ We tried to cover the approach to LFT and its interpretation much as we could, and we made sure that all the diagnostic tests for the selected diseases are mentioned in this file.

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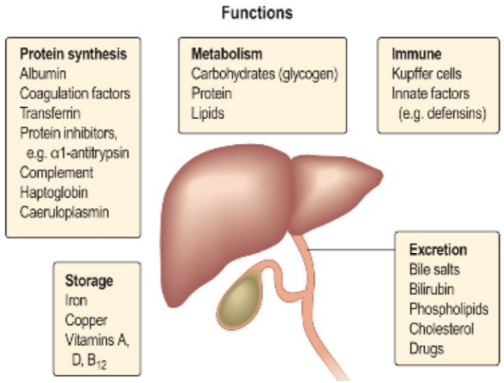
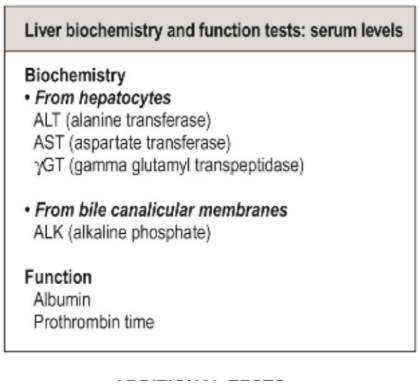
Abnormal liver enzymes

Routine blood sample sent to the laboratory for liver biochemistry to measure serum levels of bilirubin, **aminotransferase (AST/ALT)**, **alkaline phosphatase (ALP)**, **gamma-glutamyl (GGT)** transpeptidase and total proteins. These tests are often referred to as liver function tests but this term is misleading as they don't accurately reflect how well the liver is functioning. These tests are best referred to as liver blood tests. Liver synthetic function is determined by measuring the prothrombin time and serum albumin.

- When you see abnormal liver enzymes you should think first of the possible cause? the pathology could be either due to:
  1-Hepatocellular disease 2- Cholestatic disease 3-Mixed
- ALT & AST are hepatocellular enzymes
- ALK-P & GGT represent obstructive or (Cholestatic) disease
- The AST & ALT and ALK-P test are most useful to make the distinction between hepatocellular and cholestatic diseases
- If you see ALT & AST elevated out of proportion (Extremly) compared to ALK-P → Hepatocellular disease
- Upper limit of normal serum ALT (30 IU/L), ALK (130 IU/L)
- Example (1): ALT & AST =200 (ALT & AST levels greater than 7 times the upper limit of normal) ALK-P 200 (increased approximately 1 time) so what is the cause ? a Hepatocellular cause
- Example (2): ALK-P =(500) ALT= (60) AST= (70) ? a Cholestatic cause

Sometimes it can be mixed, so don't get confused go back and see the clinical scenario and the you can decide





Liver Function Tests

Liver disease is under one of the following category :

1. **Hepatocellular** injury with predominant increase in AST and ALT +/- increase in alkaline phosphatase and Direct bilirubin (due to injury in duct system) Indirect bilirubin[1]
2. **Obstruction** with predominant increase in Alkaline phosphatase and direct bilirubin +/- increase in AST and ALT
3. **Jaundice** (pre-hepatic, Intra-hepatic and post-hepatic)
4. **Infiltrative diseases** with predominant increase in Alkaline phosphatase +/- Direct bilirubin

[1]May increase in advanced liver disease

- **Here's a list of some of the common causes of liver diseases and abnormal liver enzymes:**

  go through them before we talk about the interpretation of the specific tests.

Hepatocellular causes	Cholestatic causes
• Viral hepatitis (Acute or chronic)	**A- Extrahepatic = obstructive**
• Non-alcoholic steatohepatitis (**NASH**) and alcoholic steatohepatitis (**ASH**)	• Biliary stone
	• **Stricture:** Malignant: Peri-ampullary tumors[2], Primary Scleroaing Cholangitis, AIDs cholangiopathy
• Drugs eg. Tylenol OD, idiosyncratic reaction	**B-Intra-hepatic = non-obstructive**
• **Vascular injury:** such as in hypotension, vascular outflow obstruction	PBC/ PSC (small duct) / cystic fibrosis
• **Autoimmune Hepatitis /** Primary biliary cirrhosis/celiac	Sepsis, Total parenteral nutrition, Drugs
• Metabolic disease	**Infiltrative**: • **Granulomatous diseases** such as TB, sarcoidosis, lymphoma • **Amyloidosis**
• Passed stone	intrahepatic cholestasis of pregnancy
• Pregnancy related	Some Hepatocellular causes

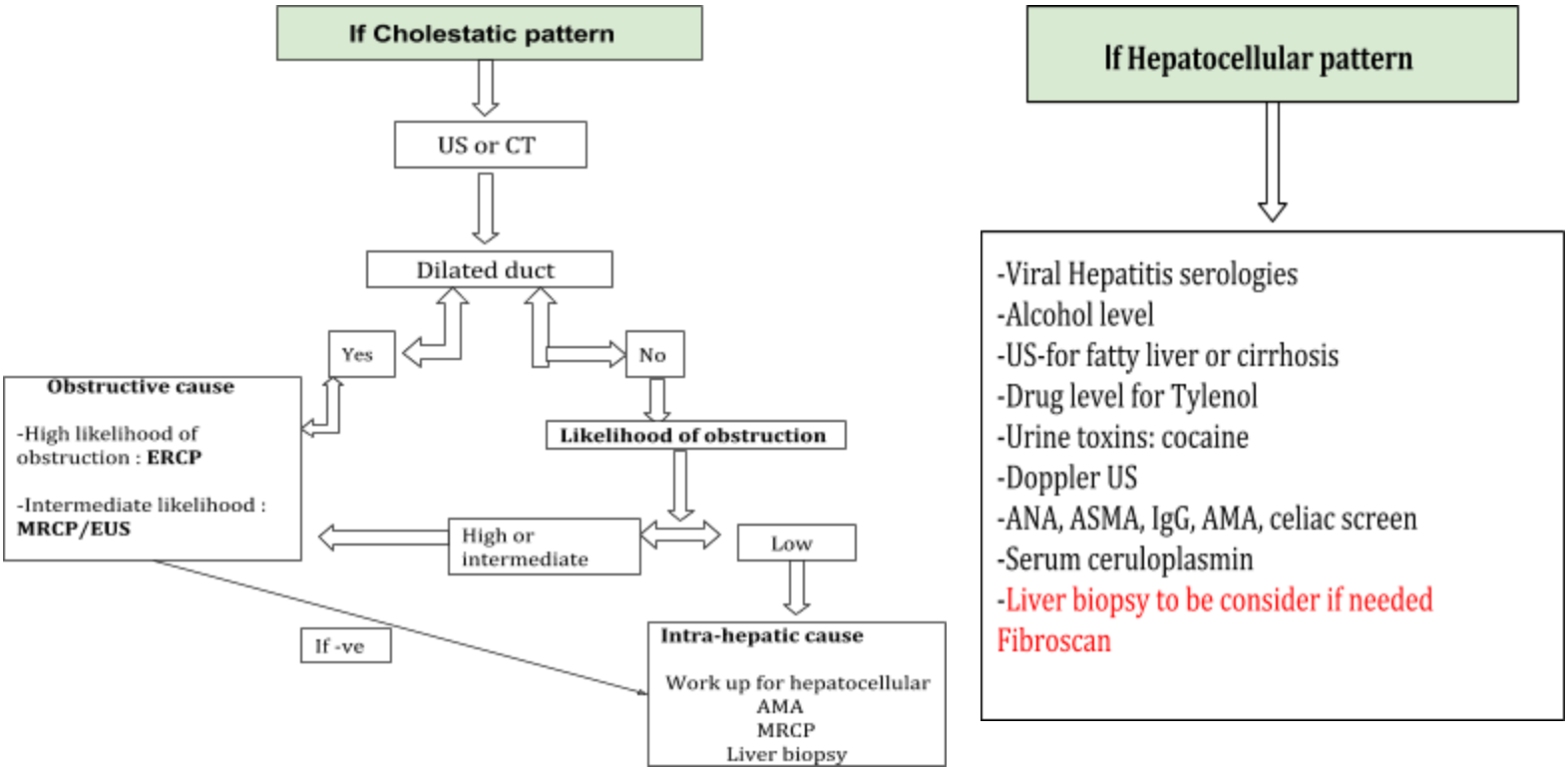
★ PBC[3] is a **cholestatic disease**, yet we can see some increase in hepatocellular enzymes because of some degree of periportal and lobular necrosis.

Remember:

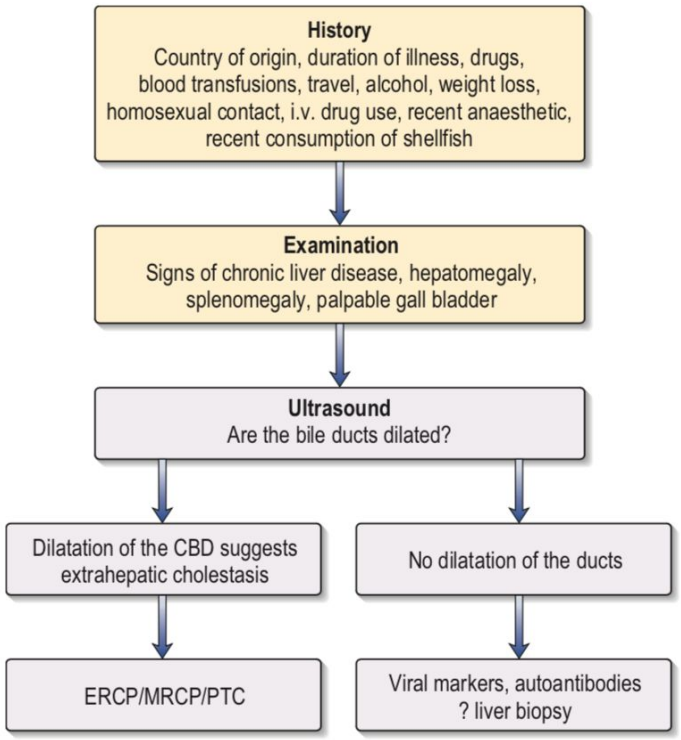
- **Cholestatic LFTs:** markedly elevated alkaline phosphatase and GGT; ALT and AST slightly elevated
- **Hepatocellular necrosis or inflammation:** normal or slightly elevated alkaline phosphatase; markedly elevated ALT and AST

[2] Pancreatic carcinoma in the head of pancreas
[3] Primary biliary cholangitis (primary liver cirrhosis)

★ **Follow the mind-map below to learn how to approach patients with suspected liver disease: IMPORTANT**



★ Another form of the previous mind map:



- **MRCP** = Magnetic resonance cholangiopancreatography
- **EUS** = Endoscopic Ultrasound
- **ERCP** = Endoscopic retrograde cholangiopancreatography

• AMINOTRANSFERASES (AST/ALT):

These enzymes (often referred to as transaminases) are contained in hepatocytes and leak into the blood with liver cell damage.

➔ ***Aspartate aminotransferase*** **(AST)** is primarily a mitochondrial enzyme (80%; 20% in cytoplasm) and is also present in heart, muscle, kidney and brain. High levels are seen in hepatic necrosis, myocardial infarction, muscle injury and congestive heart failure.

➔ ***Alanine aminotransferase*** **(ALT)** is a cytosol enzyme, **more specific to the liver**, so that a rise only occurs with liver disease.

The ALT : AST ratio is a useful clinical indicator:

- **In viral hepatitis**, ALT is greater than AST unless cirrhosis is present, in which case AST is greater than ALT. (Eg. a patients with viral hepatitis, an AST : ALT ratio of more than 1 indicates cirrhosis)
- In alcoholic liver disease and steatohepatitis, the AST is often greater than the ALT

The degree of enzymes elevation could be an useful indicator as well:

1. **If ALT and AST levels are mildly elevated** (low hundreds), think of chronic viral hepatitis or acute alcoholic hepatitis
2. **If ALT and AST levels are moderately elevated** (high hundreds to thousands), think of acute viral hepatitis.
3. **If ALT and AST levels are severely elevated** (>10,000), extensive hepatic necrosis has occurred. Typical cases are:
   A- Ischemia, shock liver (prolonged hypotension or circulatory collapse)
   B- Acetaminophen toxicity
   C- Severe viral hepatitis

The following can cause an elevation in ALT or AST levels in asymptomatic patients:

A. Autoimmune hepatitis
B. Hepatitis B
C. Hepatitis C
D. Drugs or toxins
E. Ethanol
F. Fatty liver (triglyceridemia)
G. Growths (tumors)
H. Hemodynamic disorders (e.g., CHF)
I. Iron (hemochromatosis), copper (Wilson's disease), or AAT deficiency

★ **Note that** liver transaminases are often normal or even low in patients with cirrhosis (without any active cell necrosis) or metastatic liver disease, because the number of healthy functioning hepatocytes is markedly reduced.

• Alkaline phosphatase (ALK-P):

Alkaline phosphatase (ALP) is present in hepatic canalicular and sinusoidal membranes, and also in **bone, intestine and placenta**. (Not specific)

- ❖ ALK-P is elevated when there is obstruction to bile flow (e.g., **cholestasis**) in any part of the biliary tree. Normal levels make cholestasis unlikely.
- ❖ If levels are very high (10-fold increase), think of extrahepatic biliary tract obstruction or intrahepatic cholestasis (e.g., PBC or drug-induced cirrhosis).
- ❖ If levels are elevated, measure the gamma-glutamyl-transferase (GGT) level to make sure the elevation is hepatic (obstructive) in origin (rather than bone or intestinal). If the GGT level is also elevated, this strongly suggests a hepatic origin. If the GGT level is normal but ALK-P is elevated, consider pregnancy or bone disease.

• γ-GLUTAMYL TRANSPEPTIDASE (GGT)

- ➔ Often used to confirm that the ALK-P elevation is of hepatic origin.
- ➔ Useful guide to alcohol intake

• Albumin

This is a marker of synthetic function and is useful for gauging the severity of chronic liver disease: a falling serum albumin is a bad prognostic sign.

- ➔ Decreased in chronic liver disease, nephrotic syndrome, malnutrition, and inflammatory states (e.g., burns, sepsis, trauma)

• Prothrombin time

Prothrombin time (PT) is also a marker of synthetic function. Because of its short half-life, it is a sensitive indicator of both acute and chronic liver disease.

- ➔ The liver synthesizes clotting factors I, II, V, VII, IX, X, XII, and XIII, the function of which is reflected by PT.
- ➔ PT is not prolonged until most of the liver's synthetic capacity is lost, which corresponds to advanced liver disease.

• Serum autoantibodies

- ➔ ***Anti-mitochondrial antibody (AMA)*** in serum is found in over 95% of patients with **PBC**.
- ➔ ***Nucleic, smooth muscle (actin), liver/kidney microsomal antibodies (SMA)*** can be found in serum, often in high titre, in patients with **autoimmune hepatitis**
- ➔ ***Anti-nuclear cytoplasmic antibodies (ANCA)*** can be found in the serum of patients with **primary sclerosing cholangitis**[4]

[4] Which is associated with IBD

Useful blood and urine tests for certain liver diseases:

Test	Disease
Anti-mitochondrial antibody	Primary biliary cholangitis
Anti-nuclear, smooth muscle (actin), liver/kidney microsomal antibody	Autoimmune hepatitis
Raised serum immunoglobulins:	
IgG	Autoimmune hepatitis
IgG4	Autoimmune hepatitis/cholangiopathy and pancreatitis
IgM	Primary biliary cholangitis
Viral markers	Hepatitis A, B, C, D, E and others
α-Fetoprotein	Hepatocellular carcinoma
Serum iron, transferrin saturation, serum ferritin	Hereditary haemochromatosis
Serum and urinary copper, serum caeruloplasmin	Wilson's disease
α_1-Antitrypsin	α_1-Antitrypsin deficiency (cirrhosis (± emphysema))
Anti-nuclear cytoplasmic antibodies (ANCA)	Primary sclerosing cholangitis

Summary

<table>
<tr><th colspan="2">Markers of liver dysfunction</th><th colspan="2">Markers of hepatocellular injury</th><th colspan="2">Markers of cholestasis</th></tr>
<tr><td>Bilirubin (serum)</td><td>• High bilirubin levels are observed in gallstones, acute and chronic hepatitis
• It is the yellowish pigment observed in jaundice:
Types of jaundice:
1- Pre-hepatic or hemolytic
⬆ Unconjugated → hemolytic anemia
2- Hepatic or Hepatocellular
⬆ Unconjugated and conjugated → hepatitis
3- Post-hepatic
⬆ conjugated →gallstones</td><td>Aspartate aminotransferase (AST)</td><td>• A marker of hepatocellular damage
• High serum levels are observed in chronic hepatitis, cirrhosis and liver cancer</td><td rowspan="2">Alkaline phosphatase (ALP)</td><td rowspan="2">• Modearte elevation observed in Infective hepatitis, alcoholic hepatitis and hepatocellular carcinoma
• High levels are observed in Extrahepatic obstruction (obstructive jaundice) and intrahepatic cholestasis
• Very high levels are observed in Bone diseases</td></tr>
<tr><td>urobilinogen(UBG) and urine bile salts(urine)</td><td>• Normally : bile salts are not present in the urine and only a little amount of UBG is present in the urine
• High UBG and the presences of bile salts in the urine indicates biliary obstruction</td><td rowspan="5">Alanine aminotransferase (ALT)</td><td rowspan="5">• More liver-specific than AST
• High serum levels are observed in acute hepatitis
• Moderate elevation is observed in alcoholic hepatitis
• Minor elevation is observed in cirrhosis, hepatitis C and non-alcoholic steatohepatitis
• Appears in plasma many days before clinical signs appear
• A normal value does not always indicate absence of liver damage</td></tr>
<tr><td>Albumin(Serum)</td><td>• decreases in all chronic liver diseases</td><td rowspan="3">g-glutamyltransferase (GGT)</td><td rowspan="3">• Moderate elevation observed in Infective hepatitis and prostate cancers
• GGT is increased in alcoholics despite normal liver function tests
• Highly sensitive in detecting alcohol abuse</td></tr>
<tr><td>Globulin(Serum)</td><td>High serum g-globulins are observed in chronic hepatitis and cirrhosis:
• IgG in autoimmune hepatitis
• IgA in alcoholic liver disease</td></tr>
<tr><td>Albumin to globulin (A/G) ratio</td><td>• Globulin levels increase in hypoalbuminemia as a compensation
• The ratio decreases</td></tr>
<tr><td>Prothrombin Time (PT)</td><td>• PT is prolonged only when liver loses more than 80% of its reserve capacity
• Vitamin K deficiency also causes prolonged PT</td><td colspan="2"></td></tr>
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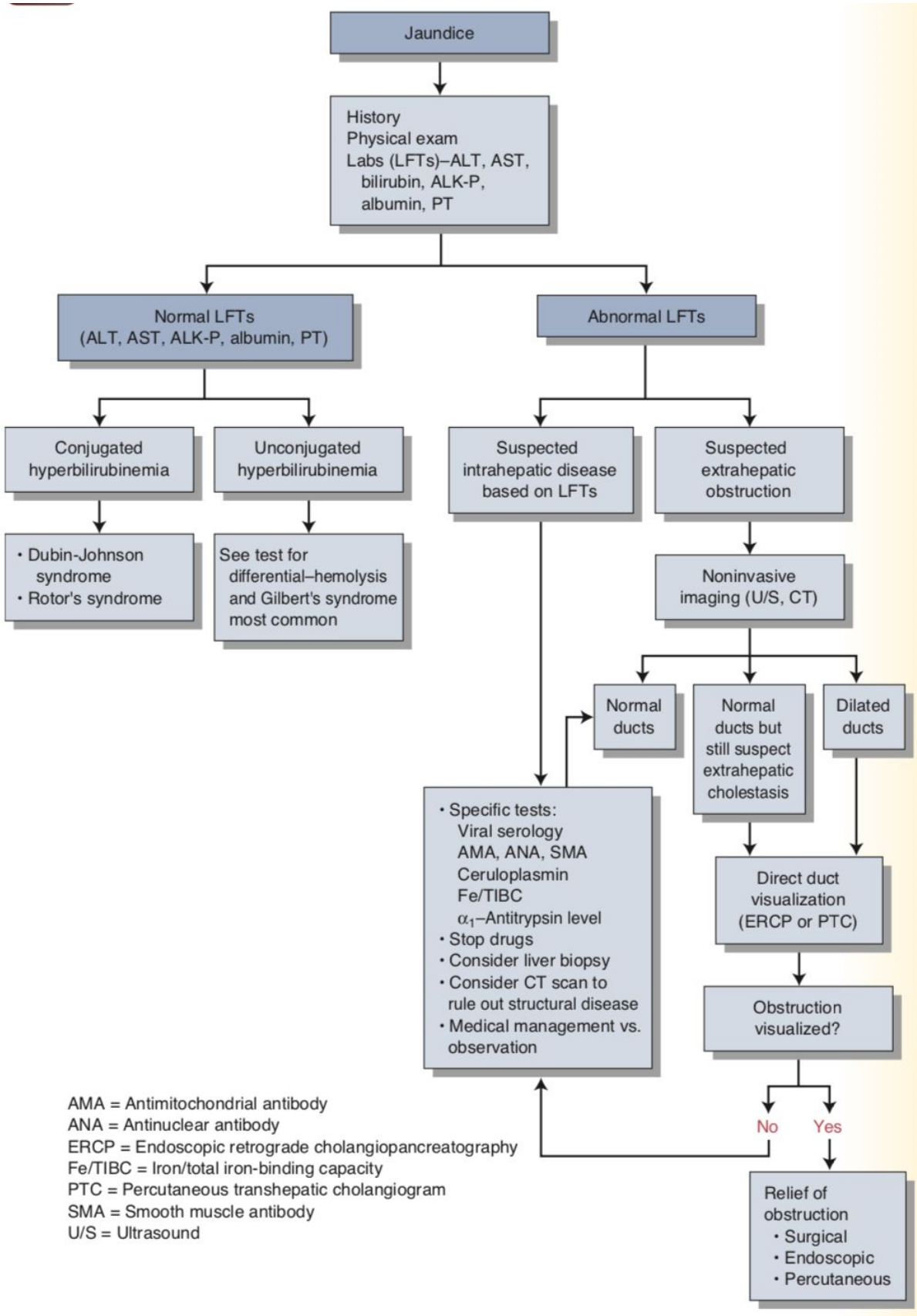
Jaundice
History
Physical exam
Labs (LFTs)–ALT, AST, bilirubin, ALK-P, albumin, PT
Normal LFTs (ALT, AST, ALK-P, albumin, PT)
Abnormal LFTs
Conjugated hyperbilirubinemia
Unconjugated hyperbilirubinemia
Suspected intrahepatic disease based on LFTs
Suspected extrahepatic obstruction
• Dubin-Johnson syndrome
• Rotor's syndrome
See test for differential–hemolysis and Gilbert's syndrome most common
Noninvasive imaging (U/S, CT)
Normal ducts
Normal ducts but still suspect extrahepatic cholestasis
Dilated ducts
• Specific tests:
Viral serology
AMA, ANA, SMA
Ceruloplasmin
Fe/TIBC
α_1–Antitrypsin level
• Stop drugs
• Consider liver biopsy
• Consider CT scan to rule out structural disease
• Medical management vs. observation
Direct duct visualization (ERCP or PTC)
Obstruction visualized?
No
Yes
Relief of obstruction
• Surgical
• Endoscopic
• Percutaneous
AMA = Antimitochondrial antibody
ANA = Antinuclear antibody
ERCP = Endoscopic retrograde cholangiopancreatography
Fe/TIBC = Iron/total iron-binding capacity
PTC = Percutaneous transhepatic cholangiogram
SMA = Smooth muscle antibody
U/S = Ultrasound

Cases

1. You see a 19-year-old Caucasian man in your clinic who presents with a history of transient jaundice. On direct questioning, you ascertain that the jaundice is noticeable after periods of increased physical activity and subsides after a few days. The patient has no other symptoms and physical examination is unremarkable. Full blood count is normal (with a normal reticulocyte count) and liver function tests reveal a bilirubin of 37 µmol/L. The most appropriate management is:

A. Reassure and discharge
B. Start on a course of oral steroids
C. Request abdominal ultrasound
D. Request MRCP
E. Refer to Haematology

2. You see a 54-year-old woman, referred to accident and emergency through her GP, with a week's history of jaundice and right upper quadrant abdominal pain. Associated symptoms include dark urine and pale stools. There is no history of weight loss and the patient does not consume alcohol. Her liver function tests reveal a bilirubin of 40 µmol/L, ALT of 40 iu/L, AST 50 iu/L and ALP of 350 iu/L. The most likely diagnosis is:

A. Gallstones
B. Viral hepatitis
C. Alcoholichepatitis
D. Carcinoma of the head of the pancreas
E. Autoimmunehepatitis

3. You are asked by your registrar to request an imaging investigation for a 49-year- old woman with jaundice and abdominal pain. She has a past medical history of gallstones and you suspect this is a recurrence of the same problem. The most appropriate imaging investigation is:

A. Abdominal x-ray
B. Abdominal ultrasound
C. Abdominal CT
D. Magnetic resonance imaging (MRI)
E. Endoscopic retrograde cholangiopancreatography (ERCP)

4. A 46-year-old woman presents to your clinic with a week's history of jaundice. Her past medical history includes long standing atrial fibrillation and hypertension. Physical examination reveals hepatomegaly. You assess her liver function which shows a bilirubin of 41iu/L, AST 111iu/L, ALT 55iu/L and ALP98 iu/L. There is no history of travel. You have a look at the patient's medication history. Which of the following drugs below is likely to have caused the derangement in the patient's liver function?

A. Aspirin
B. Ramipril
C. Amiodarone
D. Bendroflumethiazide E. Amlodipine

Answers

1. **A.** This patient has Gilbert's syndrome, an autosomal recessive (although some heterozygous cases have been reported in the Asian population) disorder characterized by unconjugated hyperbilirubinaemia. Genetic mutations in the gene responsible for coding for the enzyme uridine-diphosphoglucuronate glucuronosyltransferase results in decreased conjugation of bilirubin.
Patients usually present in their adolescence with asymptomatic jaundice which is noticed after fasting, intercurrent illness (e.g. viral URTI), exercising or lack of sleep. In addition, exposure to certain drugs (e.g. chemotherapy) may precipitate jaundice. No treatment is usually required for Gilbert's syndrome. Therefore, from the answers, (A) is the most appropriate. The fact that the reticulocyte count is normal indicates that there is no haemolysis and hence there would be no need to refer to a haematologist (E) or start a course of oral steroids (B). Requesting an MRCP (D) or abdominal ultrasound (C) would not reveal any positive findings and is therefore not required.

2. **A.** From the history, it is clear that the patient is suffering conjugated hyperbilirubinaemia with symptoms of jaundice coupled with dark urine and pale stools. The liver function tests support a diagnosis of cholestasis – bilirubin of 40μmol/L, with an unparalleled rise in ALP (350iu/L). AST and ALT are mildly elevated in comparison. Therefore, from the list of possible answers, gallstones (A) are the most likely diagnosis. With viral (B), alcoholic hepatitis (C) and autoimmune hepatitis (E) one would expect elevation in ALT and AST enzymes due to hepatocellular damage. There is no history of weight loss which makes pancreatic carcinoma (D) unlikely.

3. **B.** The most appropriate imaging modality for the investigation of gallstones is abdominal ultrasound (B). This remains the imaging modality of choice. It is highly sensitive (gallstones are echogenic and will usually cast a 'shadow' on US), fast, non-invasive, free from radiation exposure and is relatively cheap compared to CT and MRI. Although patients who are admitted via accident and emergency with an acute abdomen will usually have an abdominal x-ray (A), this investigation is not done in attempting to detect gallstones as only 10 per cent are radiopaque. CT scanning (C) has been shown to be less sensitive than ultrasound scanning in the detection of gallstones and, in addition, delivers a very large quantity of radiation which can be avoided in this case. MRI (D) is not routinely performed for gallstone detection as it is costly, time consuming and, again, not as sensitive as ultrasound scanning. ERCP (E) is useful in the detection of gallstones within the common bile duct, but cannot clearly identify stones within the gallbladder and, being quite an invasive procedure, would not be recommended as first-line imaging in this scenario.

4. **C.** This patient is suffering from drug-induced liver cirrhosis secondary to chronic amiodarone therapy. Amiodarone (C) along with other drugs, such as methyldopa and methotrexate, are known to induce liver cirrhosis. Liver cirrhosis is characterized, histologically, by a loss of the normal hepatic architecture coupled with bridging fibrosis and nodular regeneration. The causes of liver cirrhosis include chronic alcoholism, non-alcholic steatohepatitis, chronic hepatitis B and C infections, autoimmune conditions (e.g. auto-immune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis), genetic disorders (e.g. haemachromatosis, Wilson's disease), cryptogenic (in approximately 20 per cent), Budd–Chiari syndrome.

In some cases, patients do not present with clinical signs although LFTs may show derangement. Some patients may show signs of chronic liver disease such as leuconychia, clubbing, palmer erythema, hyperdynamic circulation, Dupuytren's contracture, spider naevi, xanthelasma, gynaecomastia, atrophic testes, loss of body hair, hepatomegaly (occurs in initial stages then shrinks in late disease).
Investigations include:

- blood: FBC, LFTs, clotting studies (there is a decline in synthetic function of the liver leading to an elevated INR), iron studies, hepatitis serology, immunoglobulins, autoantibodies, AFP, caeruloplasmin , α1-antitrypsin
- liver ultrasound and duplex
- MRI
- ascitic tap for MC&S (spontaneous bacterial peritonitis (SBP)), protein content, LDH, glucose, cell count and biochemistry
- liver biopsy – confirms diagnosis.

Complications of liver cirrhosis include: (1) Hepatic failure leading to conditions such as coagulopathy, encephalopathy, hypoalbuminaemia, sepsis and hypoglycaemia; (2) Portal hypertension leading to ascites, splenomegaly, oesophageal varices and other portosystemic shunts; (3) Increased risk of hepatocellular carcinoma. Management is targeted towards stopping/removing the underlying causative factor and to treat symptoms (e.g. colestyramine can be used for pruritus, interferon-α treatment for HCV-induced cirrhosis, penicillamine for Wilson's disease). Ascites can be managed through fluid restriction, low salt diet, diuretics (e.g. spironolactone). If SBP is suspected (i.e. on a clinical basis before the MC&S results of the ascitic tap are obtained), antibiotic treatment should commence.
Definitive treatment for liver cirrhosis is liver transplantation which increases the five-year survival from 20 to 70 per cent in end-stage disease.