Abnormal liver enzymes

Objectives:

- Approach to liver enzymes
- Selected disease

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Resources: 436slides + 435 team + Davidson + kumar + Recall questions step up to medicine.

- Editing file
- Feedback

Dr. Saad: the most important things that I want you to know from this lecture are: 1. How to read liver enzyme and to determine which pattern it represents (hepatocellular or cholestatic)

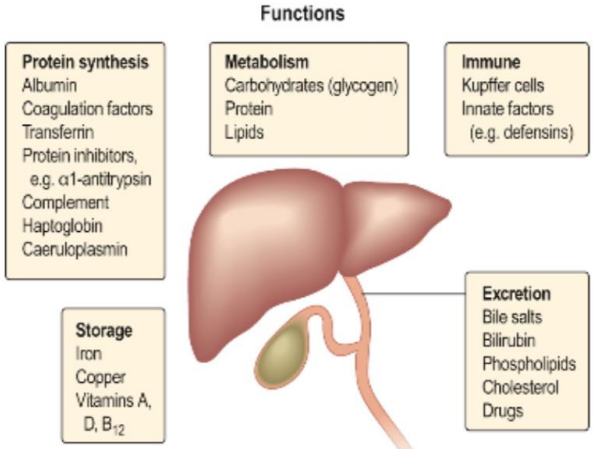
2. to spot Jaundice and to determine whether the bilirubin is direct or indirect and to know the causes of each

3. to carefully read the diagram of cholestatic pattern

4. to know about Hepatitis A, B and Auto immune hepatitis

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.



Liver biochemistry and function tests: serum levels

Biochemistry
- ***From hepatocytes***
  ALT (alanine transferase)
  AST (aspartate transferase)
  γGT (gamma glutamyl transpeptidase)
- ***From bile canalicular membranes***
  ALK (alkaline phosphate)

Function
Albumin
Prothrombin time

Liver disease is under one of the following categories :

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
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

liver function test (LFT)

★ liver enzymes :

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 patient 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 a useful indicator as well:

1. **If ALT and AST levels are mildly elevated** (low hundreds), think of chronic viral hepatitis, acute alcoholic hepatitis or NASH (usually never exceeds a few hundred)
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 most important diseases that usually present with >1000 are:
   1-ischemia
   2- hepatitis B
   3-Drugs (even multi vitamins could elevate liver enzymes. We have to check every drug the patient has taken in the past 6 months because he could have elevated liver enzymes for a few months then suddenly presents with jaundice)
   4- AIH
   5- Wilson's disease[1]

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

1. Autoimmune hepatitis
2. Hepatitis B
3. Hepatitis C
4. Drugs or toxins
5. Ethanol
6. Fatty liver (triglyceridemic)
7. Growths (tumors)
8. Hemodynamic disorders (e.g., CHF)
9. Iron (hemochromatosis), copper (Wilson's disease), or AAT deficiency

[1] Wilson disease is a rare **autosomal recessive** inherited disorder of copper metabolism that is characterized by excessive deposition of copper in the liver, brain, and other tissues

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.

	notes
Alkaline phosphatase (ALK-P) (IN THE DUCTS)	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**.

➔ **Anti-Nuclear Antibodies (ANA), Anti smooth muscles Antibodies (ASMA) And IgG** can be found in serum, often in high titer, in patients with **autoimmune hepatitis**

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

Anti-neutrophil cytoplasmic antibodies (ANCA) can be found in the serum of patients with **primary sclerosing cholangitis**[2]

★ common causes of liver diseases and abnormal liver enzymes:

1- **Hepatocellular causes**

2- **Cholestatic causes**

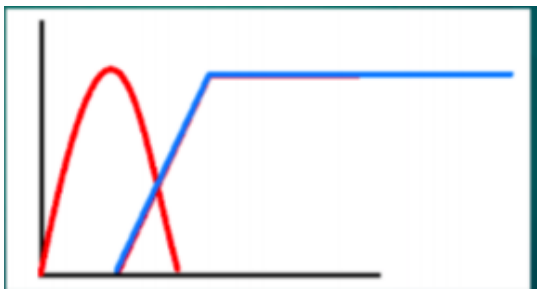
3- **Mixed**

[2] Which is associated with IBD

★ No other differentials for abnormal liver enzymes

When reading liver enzymes, to have an idea about the origin you should look for the dominant pattern, what does this mean? It means that if the AST and ALT (which indicate hepatocellular damage) were way higher than their upper limits[3] (for example 7 times as much)
And alkaline phosphate was not as high[4] (2 times as much) then the dominant pattern is a hepatocellular one. But if alkaline phosphatase was significantly high and AST and ALT weren't as high this means that the dominant pattern is cholestatic.

Example: 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. (which is the dominant pattern)

Hepatocellular causes	Cholestatic causes
	A- Extrahepatic = obstructive more common.
• Viral hepatitis (Acute or chronic): Non-alcoholic steatohepatitis (**NASH**) and alcoholic steatohepatitis (**ASH**) • Drugs eg. Tylenol OD, idiosyncratic reaction • Toxins eg. cocaine • **Vascular injury:** such as in hypotension, vascular outflow obstruction (budd-chiari syndrome) • Autoimmune Hepatitis / Primary biliary cirrhosis/celiac • Metabolic disease • Passed stone • Pregnancy related .	1. Biliary stone Pattern of biliary stone[5] (the red and blue lines represent transaminases (AST and ALT) and Alkaline phosphatase respectively:  2. Stricture: Malignant: Peri-ampullary tumors [6] Primary Sclerosing Cholangitis, AIDs cholangiopathy
	B-Intra-hepatic = non-obstructive
	1. Primary biliary cholangitis / Primary

[3] AST upper limit(40IU/L), ALT upper limit(55IU/L),
[4] Alk-P upper limit(140IU/L).
[5] In case of gallbladder stone first thing you see is elevation of AST and ALT (Because it overflows to the hepatocytes first) then it will drop to normal and ALK-P (it will start damaging the ducts) will go up. If the stone Passes early you may not see an ALK-P elevation. But if the obstruction continues then you will see ALK-P and high direct bilirubin This is so important you will not find it in the books I want you to understand it very well.

[6] Pancreatic carcinoma in the head of pancreas

	sclerosing cholangitis (small duct) / cystic fibrosis 2. Sepsis, Total parenteral nutrition, Drugs 3. Infiltrative: • Granulomatous diseases such as TB, sarcoidosis, lymphoma • Amyloidosis 4. intrahepatic cholestasis of pregnancy

Primary biliary cholangitis (primary liver cirrhosis) (PBC)[7] 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

[7] Primary biliary cholangitis (primary liver cirrhosis)

DDx of jaundice (do an Ultrasound to identify the cause)

- ★ if a patient comes to you with jaundice always look for 2 essential things:
  1- pattern of bilirubin
  2- the liver enzymes (hepatocellular or cholestatic pattern)

1-Direct Hyperbilirubinemia (Hepatic, Post-hepatic): Hepatobiliary disease

The liver can conjugate bilirubin but it cannot transport it to the bile due to parenchymal injury

Acute jaundice in the presence of an ALT of greater than 1000 U/L is highly suggestive of an infectious cause (e.g. hepatitis A, B),

2- Indirect Hyperbilirubinemia (pre-hepatic): Hemolytic anemia[8], Hematoma, Massive transfusion, rifampin, Gilbert's syndrome[9]

3-Pseudo-Jaundice due to Carotenamia, in which case the sclera is intact

يجيكم المريض يحب الجزر

how to approach patients with suspected liver disease

If Hepatocellular pattern

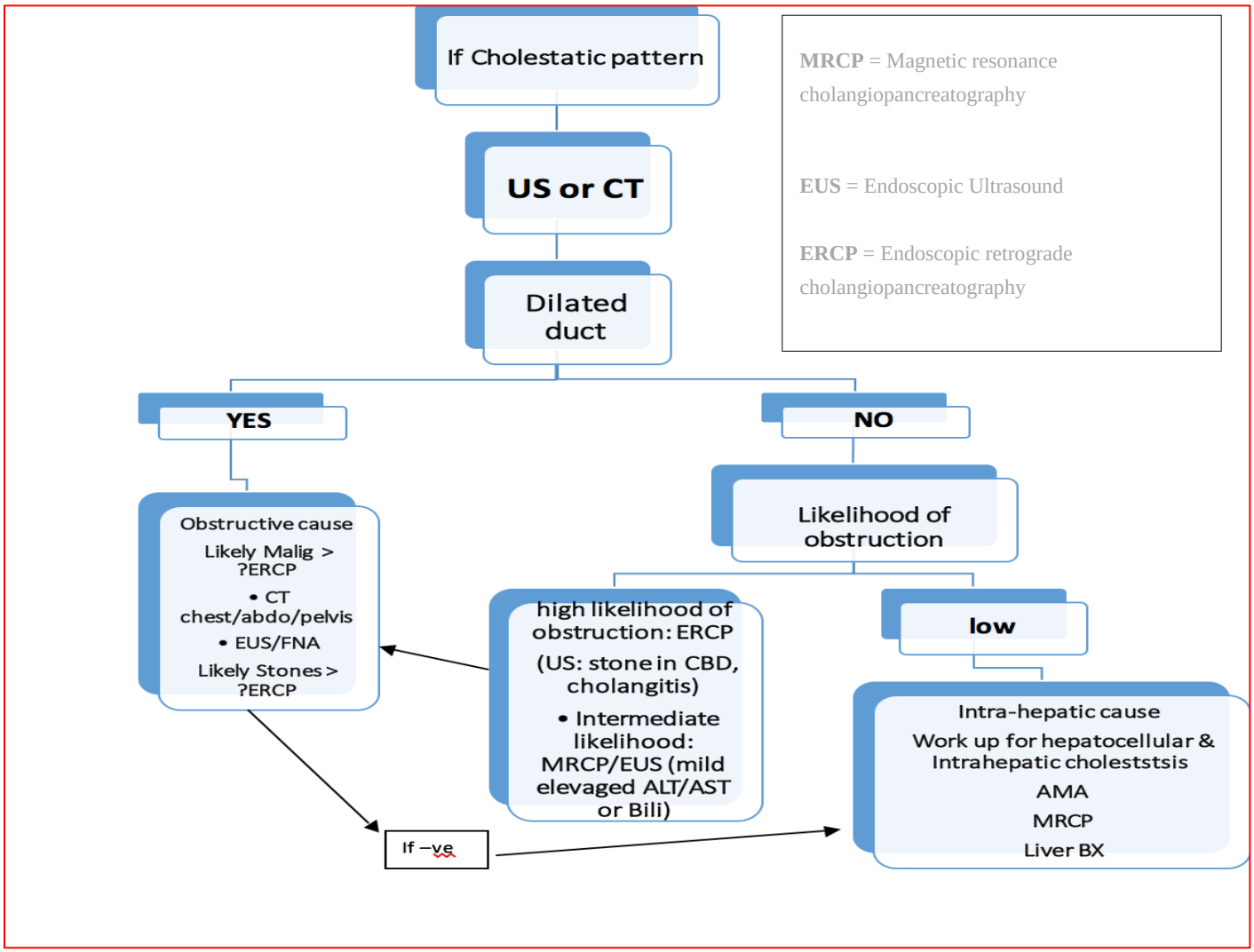
- Viral Hepatitis serologies

  Alcohol level AST:ALT normally in acute viral hepatitis, ALT is higher than AST but in alcoholic hepatitis is it the opposite
- US – for fatty liver or cirrhosis
- Drug level for Tylenol, phenytoin
- Urine toxins: cocaine
- Doppler US
- ANA, ASMA, IgG, AMA, celiac screen
- Serum ceruloplasmin
- Liver Biopsy to be considered if needed Fibro scan

6hr of severe RUQ pain with ALT 400 & AST 300 & ALP 140
> US abdomen

[8] The excessive bilirubin overwhelms the liver(which can compensate up to a certain point). it cannot conjugate all the bilirubin, this leads to an increase in indirect (unconjugated) bilirubin!

[9] It's a benign autosomal dominant disease that is characterized by a decrease in Glucuronyl transferase which leads to a decrease in bilirubin uptake. It is the only liver disease that causes **Indirect Hyperbilirubinemia**


If Cholestatic pattern
US or CT
Dilated duct
YES
NO
Obstructive cause
Likely Malig > ?ERCP
• CT chest/abdo/pelvis
• EUS/FNA
Likely Stones > ?ERCP
Likelihood of obstruction
high likelihood of obstruction: ERCP
(US: stone in CBD, cholangitis)
• Intermediate likelihood: MRCP/EUS (mild elevaged ALT/AST or Bili)
low
If –ve
Intra-hepatic cause
Work up for hepatocellular & Intrahepatic cholestsis
AMA
MRCP
Liver BX
MRCP = Magnetic resonance cholangiopancreatography
EUS = Endoscopic Ultrasound
ERCP = Endoscopic retrograde cholangiopancreatography

HAV		
Route of transmission	**The primary route of transmission** of HAV is the fecal-oral route, by either Person-to-person contact or Ingestion of contaminated food or water. Infection with HAV does not result in chronic infection, only in an acute self-limited episode of hepatitis. Complete clinical recovery is achieved in 2-6 months for almost everyone.	
History	• Prodromal[10] symptoms in patients with acute hepatitis A include fatigue, weakness, anorexia, nausea, vomiting, and abdominal pain. • Less common symptoms are fever, headache, arthralgias, myalgias, and diarrhea. • Symptoms may last from a few days to 2 weeks and usually **decrease with the onset of clinical jaundice.**	
Physical examination	• Right upper quadrant tenderness and mild liver enlargement are found on physical examination in 85% of patients • splenomegaly and cervical lymphadenopathy are each present in 15%.	
Clinical presentation	Adults with HAV infection usually present with one of the following five clinical patterns: 1. Asymptomatic 2. Symptomatic with jaundice and self-limited after approximately 8 weeks 3. Rarely Cholestatic, with jaundice lasting 10 weeks or more 4. 10% of symptomatic patients, relapsing, with two or more bouts of acute HAV infection occurring over a 6- to 10-week period 5. fulminant hepatic failure (Rarely)	Children ➔ If younger than 2 years are usually asymptomatic (80%). ➔ If 5 years or older symptoms develop in most children (80%).
Treatments	Treatment is symptomatic. (supportive) اهم شيء تعرفون انه اغلب الناس يتعافون منه	
Note	• Neither the cholestatic variant nor relapsing hepatitis A is associated with an increase in mortality. • Acute hepatitis A, unlike hepatitis E, is not associated with a higher mortality rate in pregnant women.	

[10] Relating to or denoting the period between the appearance of initial symptoms and the full development of a rash or fever

<table>
<tr><th colspan="3">HBV
the doctor heavily discussed the red colored material</th></tr>
<tr><td>Route of transmission</td><td colspan="2">Vertical Transmission: Transmission of infection from an HBV carrier mother to her neonate accounts for the majority of new infections in the world today.

If HbeAg +ve: 80% of HBsAg-positive mothers who are HBeAg -positive transmit the disease to their offspring.
HbeAg –ve: whereas mothers who are positive for antibody to HBeAg (anti-HBe) transmit the disease less frequently (20%)

• Other common sources of infection are:
1. High risk Sexual behavior (very important)
2. Receipt of blood products or organs.
3. Intravenous Drug Use
4. tattooing, body piercing
5. Household contact with an HBV carrier.
6. Hemodialysis
7. Needle stick injury</td></tr>
<tr><td>Prevalence</td><td colspan="2">The prevalence of hepatitis B varies markedly around the world. In highly endemic regions (8% or more of the population are chronic HBV carriers), such as Southeast Asia (excluding Japan), China, and much of Africa,.</td></tr>
<tr><td>Acute vs chronic (the age of which a person becomes infected with HBV is a principle determinant of the clinical outcome)</td><td>chronic
• In adults: only 1% to 5% of these persons become chronically infected when get HBV infection
• By contrast, as many as 95% of infected neonates become chronic HBV carriers because of immunologic tolerance to the virus.
• Resolved CHB infection is defined by clearance of HBsAg with acquisition of antibody to HBsAg.
• Approximately 0.5% of persons with inactive CHB will clear HBsAg yearly; and most will develop antibody to HBsAg (anti-HBs).
• Low levels of HBV DNA are transiently detected in the serum in the minority of persons achieving</td><td>Acute
• In adults, fulminant liver failure caused by acute hepatitis B occurs in less than 1% of cases .

Acute Hepatitis B in adults:
➔ Acute infections are heralded by a serum sickness–like prodrome of fever, arthralgia or arthritis, and rash, which is most commonly maculopapular or urticarial, in 15% of patients.

➔ These features generally abate before the manifestations of liver disease which include jaundice and peak serum aminotransferase elevations are observed. Clinical symptoms and jaundice generally disappear after one to three months.</td></tr>
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	seroclearance. **Clinical presentation:** • Asymptomatic • Fatigue • Symptoms and signs of CLD **Extrahepatic Manifestations:** • arthritis, • dermatitis • glomerulonephritis • polyarteritis nodosa • cryoglobulinemia, • papular acrodermatitis • polymyalgia rheumatica. **Acute Flares in Chronic Hepatitis B:** Spontaneous Flares Immunosuppressive Therapy-Induced Flares	➔ In general, elevated serum ALT levels and serum HBsAg titers decline and disappear together, and in approximately 80% of cases.
Diagnosis	• HBsAg (indicates infection, if it persists more than 6 months then it is considered chronic) • IgM and IgG HBcAb (IgM indicates recent exposure and it is the way to diagnose patients in an early stage of acute hepatitis because it appears early and it persists longer than the surface antigen) Always order total core (both IgM and IgG) never order them individually. • HbsAb Tests for co-infection: • HCV • HDV • HIV • **HbsAg:** ➔ Appears in serum 2 to 10 weeks. ➔ Persistence of HBsAg for >6 months implies progression to chronic HBV infection. ➔ In self-limited acute hepatitis, HBsAg usually becomes undetectable after 4-6 months. ➔ The disappearance of HBsAg is followed several weeks later by the appearance of anti-HBs. ➔ Anti-HBs may not be detectable during a window period of several weeks to months after the disappearance of HBsAg.	

	• **HbcAB IgM vs IgG** ➔ During the window period, the diagnosis of acute HBV infection is made by the detection of IgM anti-HBc in serum. IgM class is usually detectable for 4 to 6 months after an acute episode of hepatitis or during exacerbation of chronic hepatitis B and rarely for up to two years. ➔ IgG Anti-HBc persists in persons who recover from acute hepatitis B and CHB. ➔ The accurate diagnosis of acute hepatitis B require testing with immunoglobulin (Ig) M antibody to hepatitis B core antigen (HBcAg) (IgM anti-HBc) • Coexistence of HBsAg and anti-HBs in serum has been reported in approximately 25% of HBsAg-positive persons and occurs more commonly in persons with chronic hepatitis B than in those with acute hepatitis B. • **HbeAg** ➔ Persistence of HBeAg three or more months after the onset of illness indicates a high likelihood of transition to chronic HBV infection. ➔ The finding of HBeAg in the serum of an HBV carrier indicates greater infectivity, a high level of viral replication, and the need for antiviral therapy.
monitoring & treatments	➢ The measurement of serum HBV DNA is commonly used to evaluate a patient's candidacy for antiviral therapy and to monitor response during treatment. ➢ Owing to the fluctuating nature of CHB, the accuracy of one high HBV DNA level at a single time point in predicting prognosis is poor and regular monitoring of disease status is imperative to determine need for antiviral therapy. ➢ ALT ➢ Fibroscan: noninvasive methods to assess fibrosis severity. ➢ Liver biopsy provides an assessment of the severity of necroinflammation and fibrosis and may be especially useful for persons who lack clear-cut indications for treatment. Whereas liver biopsy is regarded as the best method to assess the severity of inflammatory activity and fibrosis, noninvasive methods to assess fibrosis severity are also useful. ➢ US: HCC screening Pegylated interferon (Peg-IFN): • Short duration of therapy • Before pregnancy • Side effects • Nucleos(t)ide analogs (NAs) therapy. Overall, all NAs have an excellent safety profile across a wide spectrum of persons with CHB, including those with decompensated cirrhosis.

HCV not very common in clinical practice nowadays	
Definition	• Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. • The long-term impact of HCV infection is highly variable, ranging from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC).
Route of transmission	Modes of transmission of HCV can be divided into 1. Percutaneous (blood transfusion and needle stick inoculation). 2. Non-percutaneous (sexual contact and perinatal exposure). 3. The risk of sexual transmission is negligible in monogamous couples that do not engage in high-risk sexual practices. However, epidemiologic studies have shown that persons with multiple sex partners have a higher prevalence of HCV infection. the risk of perinatal transmission of HCV infection is low, averaging 5.1% to 6.7% for HCV-monoinfected patients. The Centers for Disease Control and Prevention have concluded that breastfeeding by HCV-infected mothers is generally safe.
Genotypes	1. Genotypes 1, 2, and 3 are most common in North America and Europe 2. Genotype 4 is most common in the Middle East 3. Genotypes 5 and 6 are most common in Southeast Asia
clinical features	**Acute hepatitis C** • is rarely seen in clinical practice because nearly all cases are asymptomatic. • The rate of viral persistence after acute infection varies, ranging from 45% to more than 90%. • Younger and female patients having the lowest rates of chronicity. Other factors that may play a role include the source of infection and size of inoculum. • Anti-HCV will be detected between Week 2 and month 3. • HCV RNA is detectable within 2 to 3 weeks of exposure In patients whom the infection resolves spontaneously, loss of HCV RNA from serum usually occurs within 3 to 4 months of the onset of clinical disease
Extrahepatic Manifestations	Symptoms and signs include : 1. Fatigue 2. Arthralgias, arthritis 3. Purpura 4. Raynaud's phenomenon 5. Vasculitis 6. Peripheral neuropathy 7. nephropathy. Among HCV-infected patients 19% to 50% have cryoglobulins in serum, but clinical manifestations of cryoglobulinemia are reported in only 5% to 10% of these patients and are more common in patients with cirrhosis.
Diagnosis	1. Anti-HCV antibodies are the first-line diagnostic test for HCV infection. 2. If anti-HCV antibodies are detected, HCV RNA should be done.

	3. If detectable viral load, HCV Genotyping should be done. **HCV RNA testing should be part of the initial evaluation, in the case of suspected** ➔ **acute hepatitis C or in immunocompromised patients** The *diagnosis of acute and chronic HCV infection is based on the detection of HCV RNA* by a sensitive molecular method limit of detection <15 international units [IU]/ml). In patients with acute Hepatitis C, HCV RNA should be retested 3 to 4 months after clinical presentation.
Treatment	Researcher have recently made significant advances in treatment for hepatitis C using new, "direct-acting" anti-viral medications, sometimes in combination with existing ones. As a result, people experience: 1. Better outcomes 2. Fewer side effects 3. Shorter treatment times. The choice of medications and length of treatment depend on: 1. Presence of Cirrhosis 2. The hepatitis C genotype 3. Prior treatments 4. Renal function

Autoimmune hepatitis[11] The doctor said that this disease is very important	
Definition	AIH is a chronic liver disease that affects mainly young women is characterized by : 1. Hypergammaglobulinemia 2. Circulating autoantibodies (ANA, ASMA, IgG are the most important) 3. Interface hepatitis on liver histology 4. A favorable response to immunosuppression. The disease, if untreated, often leads to cirrhosis, liver failure and death. The disease can also affect males and may present at any age and in all ethnic groups.
Subclassification	➢ The clinical implications arising from this sub- classification are uncertain ➢ Indirect immunofluorescence is the test of choice for all auto-antibodies except ASLA. Immunoassays (ELISA/Western blotting) are the tests of choice for the detection of SLA/LP. Methods and cut- off values should be reported by the laboratory.

[11] You will find that ALT and AST are elevated then you will do other tests to confirm the diagnosis.

	AIH-1: the more frequent type of AIH (accounts almost for 90% of AIH cases). detection of ANA[12], or ASMA[13] association with HLA[14] DR3, DR4 and DR13.	AIH-2: accounts for up to 10% of AIH cases. detection of anti-LKM1[15], anti-LC1 and rarely anti-LKM3. association with HLA DR3 and DR7. onset usually in childhood and young adulthood	AIH-3: ASLA/LP[16] positive
Clinical presentation	• Any age • Both sexes(female-male 3:1) • Broad range from asymptomatic to acute/severe or even fulminant Most common clinical phenotype of the disease (two thirds of patients) is characterized by an insidious onset • either without any apparent symptom • with one or more of the following non-specific symptoms: 1. fatigue 2. general ill health 3. right upper quadrant pain 4. anorexia 5. weight loss 6. nausea 7. fluctuating jaundice and polyarthralgia involving the small joints without arthritis 8. Amenorrhea is also common. • Acute onset of AIH does exist (about 25% of patients)		
Laboratory findings	**-the typical biochemical profile of the disease is a predominantly hepatitic pattern:** • with bilirubin concentrations and aminotransferases ranging from just above the upper limits of normal to more than 50 times these levels, with usually normal or only moderately elevated cholestatic enzymes, Degree of ALT/AST elevations does not reliably reflect severity of AIH at the histological level. • Of note, in some patients with acute presentation of AIH, immunoglobulin G (IgG) levels may be within the normal range and antinuclear (ANA) and/or smooth muscle antibodies (SMA) as first screening may be negative. • The presence of high IgG levels is a very distinctive feature (IgA and IgM levels are usually normal). Increased IgA or IgM levels suggest different diseases such as alcoholic steatohepatitis and PBC, respectively. • It is important to underline that the range within which c- globulins and IgGs are considered normal is wide. This may explain why a proportion of patients may show apparently ‘‘normal’’ IgG levels at diagnosis. Many, if not most of these patients have IgG levels in the upper range of normal, and show a marked fall upon initiation of therapy, sometimes even to levels below the normal range . • the level of immunoglobulins is an important and useful marker in monitoring the response to treatment and the achievement of remission.		

[12] Antinuclear antibody
[13] Anti-smooth muscle antibody
[14] Human leukocyte antigen
[15] Liver kidney microsome type 1

[16] Anti-soluble liver antigen/liver-pancreas antibody

Diagnosis	• The diagnosis of AIH relies particularly on the presence of 1. Hypergammaglobulinemia (A selectively elevated IgG in the absence of IgA and IgM elevation is particularly suggestive of AIH) 2. Autoantibodies 3. Typical or compatible histology. DO a liver biopsy! • Adult patients with AIH and cholestatic lab changes should be considered for MRCP to recognize sclerosing cholangtitis • When severe coagulopathy is present the transjugular approach can be used, in particular, in acute/fulminant onset of the disease. • the simplified criteria for AIH are user-friendly and a good tool for daily clinical practice but without a diagnostic ‘‘gold standard’’ the clinicians must regard any diagnostic score only as an aid to diagnosis of AIH and the criteria should be used alongside clinical judgment.
Histology	• there are no morphological features that are pathognomonic of AIH, but interface hepatitis, periportal necrosis, and rosetting of hepatocytes are suggestive of AIH. **Interface hepatitis with dense plasma cell-rich lymphoplasmocytic infiltrates is the typical hallmarks** of AIH . (A rich plasma interface) • Plasma cells are typically abundant at the interface and throughout the lobule, but their paucity in the inflammatory infiltrate does not preclude the diagnosis . • Interface hepatitis is not disease specific and patients with drug-related, viral or immune- mediated disease may show similar features.
Treatments	• immunosuppressant: steroids, Imuran • Treatment of AIH should be aimed to obtain: 1. complete biochemical (ALT/AST & IgG) & histological resolution of the disease • In mild asymptomatic older patients with mild necroinflammatory activity on liver biopsy: 1. is there any benefits of immunosuppressive therapy? 2. Treatment related side effects should be counterbalanced to the risk of sub-clinical disease. • Points to support observation: 1. Ten-year survival in untreated patients with mild disease was reported to be 67–90% and in an uncontrolled study untreated asymptomatic patient had similar survival to those receiving immunosuppression. Thus, a decision not to treat might be justified, especially if there are relative contraindications to the use of steroids. 2. In addition, spontaneous resolution of AIH may occur. • Points to support treatment: 1. As AIH is a lifelong disease, and progressive fibrosis may take many years to become clinically apparent, the observational studies published may have been too short and may have included too few patients in order to demonstrate the benefit of immunosuppressive therapy in milder disease. 2. AIH has a fluctuating, unpredictable disease behaviour and a substantial proportion of asymptomatic patients become symptomatic during the course of their disease follow-up, and progression towards end-stage liver disease with liver cirrrhosis.

Primary sclerosing cholangitis (PSC) Not very important according to the doctor	
Definition	It is a chronic cholestatic liver and biliary tract disease, defined as the presence of beading and stricture formation of the intra and/or extrahepatic bile ducts that cannot be ascribed to another cause, thus differentiating PSC from secondary sclerosing cholangitis. Many, if not most, cases of PSC are associated with IBD. The prevalence of PSC in UC has been estimated to be ~5%. PSC was also more common in men and those with pan-colitis.
Signs and symptoms	➢ PSC may be asymptomatic for long periods but may also have an aggressive course, leading to: 1. Recurrent biliary tract obstruction 2. Recurrent episodes of cholangitis 3. Cirrhosis/ESLD ➢ A large number of patients present without symptoms and come to attention simply by a finding of persistently abnormal liver tests. ➢ When symptoms occur, fatigue maybe the most commonly noted finding. ➢ Sudden onset of pruritus should signal the possibility of obstruction of the biliary tree. other patients may experience chronic right upper quadrant discomfort.
Diagnosis	The diagnosis of PSC requires the following: • Chronic cholestatic liver test abnormalities, in particular elevations of serum ALP level • Cholangiographic (MRCP or ERCP) evidence • of multifocal strictures and saccular dilatation of the intrahepatic and extrahepatic bile ducts, which may lead to a “beaded” appearance • A liver biopsy, if performed: • characteristic “onion skin” fibrosis, which is almost pathognomonic for the disease, is seen infrequently. • Small duct PSC makes up 5% of cases GGT will be elevated and the aminotransferases are often times only modestly elevated. Bilirubin and albumin levels are often normal at the time of diagnosis.
Treatment	At this time, there is no established medical treatment for patients with PSC. However, we treat complications of the disease. MRCP & CA19-9 annually, Annual colonoscopy if known to have UC

Primary biliary cirrhosis Not very important according to the doctor	
Definition	is a chronic cholestatic disease with a progressive course. The etiology of PBC is thought to be due to a combination of genetic predisposition and environmental triggers.
Clinical Manifestations	Fatigue: is the most common symptom. Pruritus: a more specific symptom of PBC.
Liver Biochemical Tests	Most patients with PBC have abnormal liver tests including: ➢ elevations of ALP. ➢ mild elevations of aminotransferases activity. ➢ increased levels of immunoglobulins (mainly immunoglobulin M [IgM]). The degree of elevation in ALP is strongly related to the severity of ductopenia and inflammation. the increase in aminotransferase activity and IgG levels reflects mainly the degree of periportal and lobular necrosis and inflammation.
Autoantibodies	➢ AMA[17] is found in nearly 95% of patients with PBC. ➢ ANA[18] and ASMA are found in nearly half of patients with PBC. ➢ In approximately 5%-10% of the patients, AMA antibodies are absent or present only in low titer (1/80), when immunofluorescent techniques are used.
Histology	● PBC is characterized by ➢ chronic, nonsuppurative cholangitis that mainly affects interlobular and septal bile ducts. ➢ When focal lesions show intense inflammatory changes and necrosis around bile ducts, the term “florid duct lesion” is often used. ➢ Bile duct paucity or ductopenia. ● The size of the liver biopsy specimen is important. The probability of observing cholangitis and bile duct destruction increases with the number of portal tracts because of the typical patchy distribution of the lesions. At least 10-15 portal tracts should be present.
Diagnosis	The diagnosis of PBC should be suspected in the setting of chronic cholestasis after exclusion of other causes of liver disease. The diagnosis is suspected based on •cholestatic serum liver tests and largely confirmed with tests for AMA. •A liver biopsy can be used to further substantiate the diagnosis if needed. The diagnosis of PBC can be established when two of the following three criteria are met: Biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation. Presence of AMA. Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts .
Treatment	UDCA in a dose of 13-15 mg/kg/day is the only therapy for PBC approved by the U.S. Food and Drug Administration. The drug is initiated gradually and generally given in two divided doses.

[17] anti-mitochondrial antibody
[18] antinuclear antibody

Cases

Case 1

A 24-year-old woman presents with acute onset of right upper quadrant pain, and increased abdominal girth. She has no known past medical history. She has no risk factors for liver disease. Family history is unremarkable. Her only medication is a birth control pill. Exam reveals tender hepatomegaly and obvious ascites.
Labs reveal mildly increased bilirubin and alkaline phosphatase only. Imaging studies reveal hepatomegaly (especially the caudate lobe) and ascites.

1- What is the most likely diagnosis?
Acute Budd-Chiari syndrome[19]
Hepatomegaly is unusual and, in the presence of a sudden onset of ascites, suggests venous outflow obstruction as the cause (Budd–Chiari syndrome).

Case 2

You see in consultation a 43-year-old man because of jaundice. He has been drinking 1 pint a day (sometimes more) of whiskey for the past 4 months. He denies other risk factors for liver disease. Examination reveals a blood pressure 110/80, pulse 110; respirations 16, temperature 37°C. He is jaundiced, has multiple spider telangectasias, and parotid gland swelling, but no muscle wasting. Abdominal examination reveals a liver 4 finger breadths below right costal margin, a palpable spleen tip, but no shifting dullness. Laboratory studies:
Bilirubin 150 mmol/l , mostly direct, AST 212 U/L , ALT 63 U/L (normal: 0-35 U/L), ALP 140 U/L (normal: 36-92 U/L), INR 1.5 , Ferritin 480 ng/mL

1-What is the pattern?
Direct hyperbilirubinemia with hepatocellular pattern (AST and ALT are significantly raised)

2-Do you need to do work up?
Viral hepatitis, Fibroscan[20]

[19] Budd-Chiari syndrome is an uncommon condition induced by thrombotic or nonthrombotic obstruction of the hepatic venous outflow and is characterized by hepatomegaly, ascites, and abdominal pain.

[20] is a non-invasive device that assesses the 'hardness' (or stiffness) of the liver via the technique of transient elastography. Liver hardness is evaluated by measuring the velocity of a vibration wave (also called a 'shear wave') generated on the skin.

Case 3

A 35-year-old woman is referred to you for elevated liver enzymes. She was found to have:
• ALT 255 U/L , AST 205 U/L , Alkaline phosphatase 121 U/L
• Total bilirubin 18 mmol/l
Her ANA is positive at a 1:80 & IgG is elevated. Her albumin and INR are at normal levels. She has mild tenderness over her right upper quadrant. She is otherwise healthy, with the exception of being treated intermittently with nitrofurantoin for recurrent urinary tract infections. Viral serologies against hepatitis A, B, C, and E are all negative. ultrasound revealed a heterogenous echotexture of a normal-sized liver.

1-What is the pattern?
Hepatocellular (similar to case 2, AST and ALT are significantly raised) with normal bilirubin

2- What should you do next for the diagnosis or treatment of this patient?
This pattern is consistent with an autoimmune hepatitis-like presentation induced by nitrofurantoin. Simply stopping the offending medication will usually result in normalization of her liver enzyme values. Of note, an ANA that is positive at 1:80 dilution is fairly non-specific, and may be seen in 30% of adults, especially women, without disease.

Case 4

A 45-year-old woman presents for evaluation of elevated liver tests. She has a past medical history of diabetes, & hypertension. She does not drink alcohol or use tobacco. Her medical regimen consists of insulin, metformin, & lisinopril. On physical exam, BMI is 39, blood pressure is 160/98. Abdominal exam reveals an obese abdomen without hepatosplenomegaly, masses, hernias, or ascites. Her evaluation included:
AST 330 U/L , ALT 380 U/L, Alkaline phosphatase 80 ,Total bilirubin is normal
ANA 1:640, ASMA 1:160, IgG is elevated, AMA negative, Hepatitis A IgM negative, HbsAg negative, HCV antibody negative, Abdominal ultrasound shows mild echogenic liver of 14 cm with normal spleen size and no focal masses or ascites, A liver biopsy shows 50% macrovesicular steatosis, interface hepatitis comprised of lymphocytes, prominent plasma cells, and periportal fibrosis Metavir stage 2.

1-What is the pattern?
Hepatocellular with normal bilirubin
2-What is the diagnosis?
AIH & NASH[21]

[21] is strongly associated with obesity, dyslipidemia, insulin resistance and type 2 (non-insulin dependent) diabetes mellitus, and so may be considered to be the hepatic manifestation of the 'metabolic syndrome'

Case 5

A 53-year-old woman presents for evaluation of elevated liver tests. She has a past medical history of diabetes mellitus treated with insulin and hyperlipidemia treated with atorvastatin, 20 mg daily. She does not drink alcohol and does not use tobacco. On exam, her BMI is 32, weight is 90 kg, BP is 130/80, heart rate is 88. On abdominal exam, there is no hepatosplenomegaly, ascites, masses, or hernias. Blood work shows:
ALT 221 U/L, AST 90 U/L , Total bilirubin is normal, Alkaline phosphatase 220 U/L (normal: 36-92 U/L)
ANA 1:160 , ASMA is negative, IgG, is mildly elevated Hepatitis C antibody negative, Hepatitis B surface antigen negative, Hepatitis A IgM negative, Normal US

1-What is the pattern?
Hepatocellular or may be mixed with normal bilirubin

2-What is the most appropriate next step in her management?
Liver biopsy +/- MRCP
Up to 20% of patients with nonalcoholic fatty liver disease may have positive autoantibodies, and autoantibodies alone should not be used to establish the diagnosis of autoimmune hepatitis.

Case 6

An 66-year-old man is found collapsed at a home. He is found to be in asystole. After CPR and other emergency treatments, a pulse is restored and she is taken to the hospital. His only known medications are furosemide, and insulin. On admission, her LFTs are normal. Twenty-four hours later, her AST is 12,500 U/L and ALT is 7,450 U/L.

1-What is the pattern?
hepatocellular
2-What is the diagnosis?
Shocked liver[22]
3-Treatment:
Supportive

[22] Ischemic hepatitis, also known as ischemic hepatopathy or **shock liver**, is a condition defined as an acute **liver** injury caused by insufficient blood flow (and consequently insufficient oxygen delivery) to the **liver**. The decreased blood flow (perfusion) to the **liver** is usually due to **shock** or low blood pressure.

Case 7

A 65-year-old woman presents with malaise of 2 weeks and is found to have elevated ALT/AST. Her past medical history is significant for hypertension, hypothyroidism, and osteoarthritis. Her medications include lisinopril 10 mg daily, levothyroxine 100 micrograms daily, diclofenac 75 mg daily, and acetaminophen 500 mg, twice a day. On physical exam, her sclera are icteric, abdomen is soft with mild right upper quadrant tenderness, no hepatosplenomegaly, masses, or ascites. Labs reveal:
AST 350 U/L , ALT 480 U/L Total bilirubin 45 mmol/L, Alkaline phosphatase 180 U/L (normal: 36-92 U/L) • ANA 1:640 (positive: titer of ≥1:160), ASMA –ve & IgG normal • Hepatitis C antibody negative, Hepatitis B surface antigen negative, Hepatitis A IgM negative

1-What is the pattern?
hepatocellular
2-What is the diagnosis?
Drug induced liver injury. Diclofenac is the most common NSAID associated with DILI.
The most immediate intervention is to stop the diclofenac and monitor the patient for resolution of the injury. Half the cases of diclofenac hepatotoxicity present with an autoimmune phenotype characterized by the presence of serum autoantibodies with or without typical histologic features on liver biopsy.
Liver biopsy and abdominal ultrasound may be indicated and provide important information if stopping diclofenac does not normalize the LFTs. Steroids can also be considered if there is no improvement after discontinuation of the offending drug.

Case 8
A33-year-old woman with acute liver failure. The patient has no prior history of liver disease and was well until 1 month ago. There is no family history of liver disease. Physical examination reveals jaundice and ascites; Grade 2 encephalopathy is present. Laboratory tests are as follows:
ALT 500 U/L AST 1,220 U/L , Total bilirubin 50 mmol/l that is mostly direct Alkaline phosphatase 40 U/L • INR 1.7 Hb 9 with evidence of hemolysis but Coombs test negative Ceruloplasmin 24 mg/dL (normal: 20-40 mg/dL) Ferritin 1,200 ng/mL (normal: 15-200 ng/mL)

1-What is the pattern?
Hepatocellular
2-What is the diagnosis?
This is a classic presentation for acute fulminant Wilson disease. The constellation of a Coombs-negative hemolytic anemia, acute liver failure and the age of the patient all point to this diagnosis.
A positive slit lamp exam would confirm the diagnosis of Wilson disease, however, if negative does not rule out the disease.
The ceruloplasmin is falsely elevated into the low normal range due to an acute phase response.
The serum iron studies are increased because of release of iron from the liver.
Liver biopsy may demonstrate increased copper concentration because of the relatively high serum bilirubin level.

Case 9

A 53-year-old woman underwent hysterectomy and oophorectomy for stage 2 ovarian cancer which was complicated by a colonic perforation with intra-abdominal infection and abscess requiring drainage and broad-spectrum antibiotics. She was treated initially piperacillin-tazobactam and vancomycin for 2 weeks and then amoxicillin clavulanate for an additional 2 weeks. She was discharged home following completion of the antibiotics and is readmitted for mild jaundice and pruritus 1 week later. A recent abdominal/pelvic CT scan shows normal appearing liver without biliary duct dilatation and improved intra-abdominal abscess.

Time	AST (U/L)	ALT (U/L)	ALKP (U/L)	Total bilirubin (mg/dl)
28 days	30	40	119	0.9
14 days	40	50	199	0.8
7 days	55	65	243	1.9
3 days	68	74	398	3.3
Today	70	83	488	3.9

1-What is the pattern?
Cholestatic with direct hyperbilirubinemia

2-What is the likely Diagnosis?
Amoxicillin/clavulanate may be associated with hepatotoxicity, typically with a cholestatic (ALP predominant increase in liver enzymes). A mixed hepatocellular and cholestatic pattern of liver injury may also be observed
The onset of drug-induced liver injury from amoxicillin/clavulanate may be as little as a few days to as long as 8 weeks post-exposure.
Treatment for antibiotic associated drug-induced liver injury is withdrawal of the drug and supportive care.

Case 10
A 58 year-old overweight Hispanic man with diabetes has been referred to you for evaluation of persistently mildly elevated liver enzymes with his ALT/AST ranging between 60 and 140 over the last year. As part of the evaluation, you are able to rule out viral, autoimmune, and metabolic liver diseases. He drinks alcohol occasionally. He is not on medications. US showed evidence of fatty liver. Normal liver function tests & CBC

1-What is the likely Dx ?
NASH or ASH
2-What is the next step?
Fibroscan
Liver biopsy reveals moderate steatosis, hepatocellular ballooning, Mallory bodies, and both lobular and portal-septal inflammation, consistent with steatohepatitis.

Case 11

You are asked to see a 14-year-old boy who suddenly developed itching and jaundice. He started taking minocycline for acne about 6 weeks ago. This is now stopped. Laboratory studies demonstrate AST 13 , ALT 15 , Alkaline phosphatase 620 ,Total bilirubin 90 mmol/l
Serum albumin and INR are normal.

1-What is the pattern?
Cholestatic with direct hyperbilirubinemia
2-What is the next step?
US: The liver and biliary tree appeared normal on ultrasound.
3-What should you tell the parents about their child?
Pure cholestatic drug reactions almost always resolve within 6 weeks of stopping the medication. We just need to monitor.

CASE 12

You are asked to see a 45-year-old woman who developed elevations in liver transaminases after initiating a statin. Over the past 3 months,
AST has been 65 U/L, 75 U/L, and 85 U/L (normal: 0-35 U/L). ALT has been 86 U/L, 88 U/L, and 95 U/L (normal: 0-35 U/L). Alkaline phosphatase and total bilirubin were normal. The primary care physician was concerned that the liver transaminases were rising and so he stopped the statin. The AST is now 45 U/L and ALT 50 U/L.

1-What is would you recommend?
Adaptation phenomena vs True hepatotoxicity
Adaptation phenomena : In these patients the liver transaminases elevate to values under 3 times the ULN and then remain stable for variable periods of time before declining back to the normal range. This process is referred to as adaptation and is commonly seen with many medications.
True hepatotoxicity is associated with progressive stepwise elevations in liver transaminases to values greater than 3 times the upper limit of normal. When this occurs, the risk of liver toxicity is significant, medications must be stopped and not restarted.
Although statins can cause hepatotoxicity this is relatively uncommon. However, it is not unusual for statins to cause mild elevations in liver transaminases when first initiated.
In this patient, the mild fluctuations in AST and ALT are not significant stepwise elevations.

Summary

Test	Pattern	Causes
Aminotransferases (**ALT** + **AST**)	Hepatocellular	Elevated >1000s in: • Viral hepatitis (HAV, HBV) • Drugs • Toxins • AIH • Vascular injury (hypotension) • Wilsons disease

Alkaline Phosphatase (**ALP**)
Gamma Glutamyl Transpeptidase (**GGT**)
	Cholestatic	• Extra-hepatic (obstructive)
		  ○ Biliary stone or stricture.
		• Intra-hepatic (nonobstructive)
		  ○ PBC, PSC, CF, sepsis, drugs, etc..

Bilirubin	-	• ↑ Direct → Hepatobiliary disease (post/intra-hepatic). • ↑ Indirect → Prehepatic (hemolytic anemia) / Gilbert syndrome.
Autoantibodies	-	• AMA → PBC • ANA + ASMA → AIH • ANCA → PSC

Disease	Test to dx
Biliary stone	• Liver enzyme pattern: start as hepatocellular (↑AST&ALT) then become cholestatic (↑ALP±GGT) if blockage continues, (if stone leaves everything will go down). • Further work up: US, CT, ± ERCP/MRCP/EUS.
Alcohol	Reversed ALT:AST ratio + elevated bilirubin out of proportion to liver enzymes
HAV	IgM Antibody
HBV	HBsAg (best for chronic), HBcAB (IgM → acute), HBsAb, test for co-infection (HCV, HDV, HIV)
HCV	1. Anti-HCV antibodies. 2. HCV RNA (PCR). 3. HCV Genotyping.
Auto-immune Hepatitis (AIH)	1. Hypergammaglobulinemia (elevated IgG + absence of IgA ang IgM) 2. Autoantibodies. Typical or compatible histology (liver biopsy).
Primary sclerosing cholangitis (PSC)	• ↑ ALP + GGT • MRCP / ERCP • Liver biopsy (onion skin fibrosis)
Primary ciliary cirrhosis (PBC)	• Cholestatic pattern mainly ALP. • Autoantibodies: AMA.