# Abnormal Liver Chemistry Studies

## Objectives (Regarding the Blueprint):

1. Describe and interpret abnormal liver enzymes.
2. Develop a differential diagnosis for abnormal liver enzymes and jaundice.
3. Describe the approach plan for patients with abnormal liver enzymes and jaundice.
4. To recognize the common causes for acute liver failure, understand the pathophysiology, clinical presentation, and formulate the work-up and management plan.


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### Color Index

- Slides / Reference Book
- Doctor notes
- OnlineMeded / Amboss
- Important
- Extra

# Describe and interpret abnormal liver enzymes.

## Liver enzymes

### 1. Aminotransferases- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST):

- ALT is found in cytoplasm of hepatocyte, and AST is found in cytoplasm & mitochondria of hepatocytes.
- There levels are increased in hepatocellular damage, ALT is more specific for hepatocellular damage than AST.
- AST & ALT normal range: 0-35 U/L.

### 2. Alkaline phosphatase (ALP):

- ALP includes enzymes that are widely distributed in the body e.g. liver, GIT , bone, placenta and kidney (not specific).
- In the liver they are located in cell membranes of the hepatic sinusoids and the biliary canaliculi (bile ducts). Accordingly, levels rise with intrahepatic and extrahepatic biliary obstruction and with sinusoidal obstruction (as in infiltrative liver disease).
- ALP normal range: 36-92 U/L.

### 3. γ-glutamyl transferase (GGT):

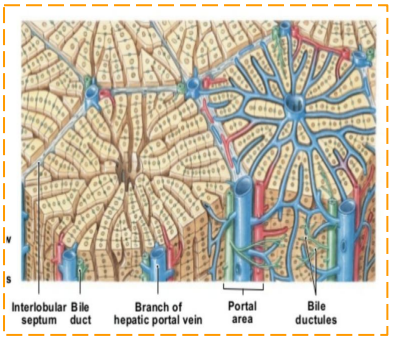
- Microsomal enzyme found in many cells and tissues of the body, but the highest concentrations is in the liver.
- It is produced by hepatocytes and by the epithelium lining small bile ducts
- Large increases in ALP and GGT activity favours biliary obstruction and is described as 'cholestatic' or 'obstructive'.
- Isolated elevation of GGT is common and occur during ingestion of microsomal enzyme-inducing drugs, including alcohol, but also in Non-alcoholic fatty liver disease.

# Develop a differential diagnosis for abnormal liver enzymes and jaundice.

## Approach to abnormal liver enzymes

**Hepatocellular causes** VS **Cholestatic causes:** **Isolated ALP and rule of GGT** VS **Mixed**

- Hepatocellular picture **(Hepatitis)** :
  - **ALT** and **AST** are elevated more than ALP and GGT e.g. If the upper limit of normal for AST and ALT is 35 and the upper limit of normal ALP is 150 and the results of LFT were as followed:
  - AST and ALT = 200 (That's quadruple the normal level)
  - ALP = 200 (Not increased much compared to the normal level)
  - So this case has a hepatocellular dominant picture
- Cholestatic picture : **ALP** elevated more than ALT and AST; apply the same concept here as well.



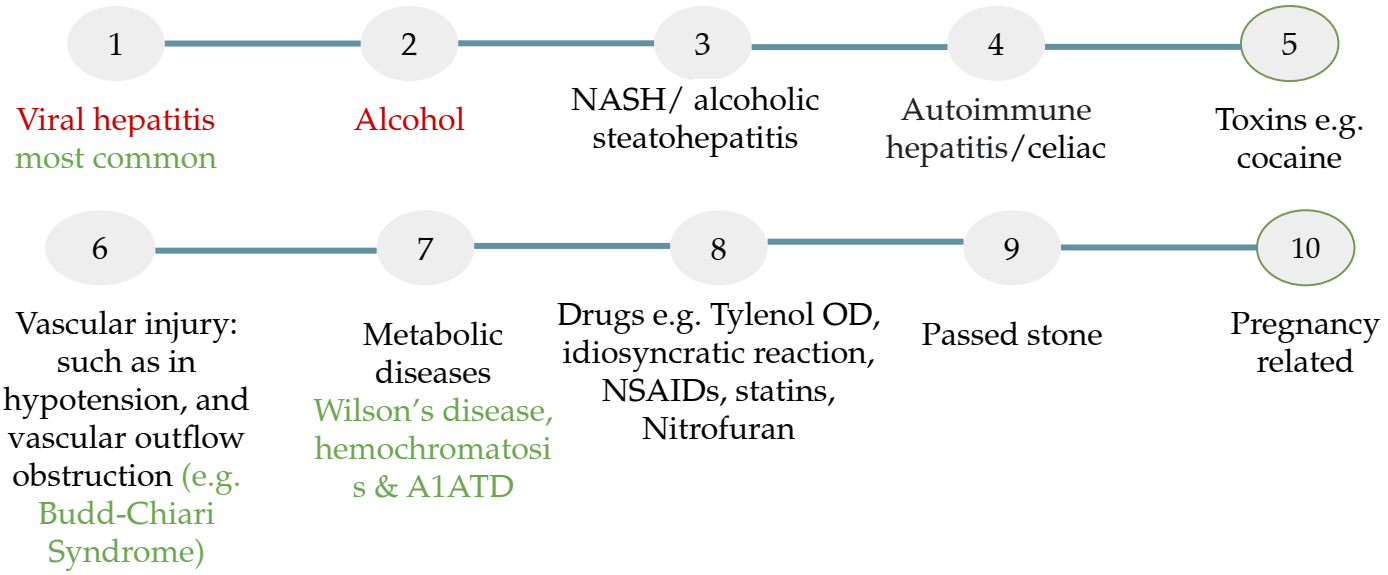

## DDx of jaundice

**The degree of transaminases elevation could be a useful indicator as well :**

| **Minor elevation (<100 U/L)** Direct Hyperbilirubinemia (Hepatic, Post-hepatic) | **Moderate elevation (100-300 U/L)** | **Major elevation (>300 U/L) (Thousand range (>1000)** |
|---|---|---|
| • Chronic hepatitis (B,C)<br>• Haemochromatosis<br>• Fatty liver disease | • Alcoholic hepatitis<br>• Non-alcoholic steatohepatitis<br>• Autoimmune hepatitis<br>• Wilson's disease | • **Drugs**: Tylenol, anticonvulsants, and paracetamol<br>  ○ 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 present with jaundice)<br>• Toxins: amanita phalloides poisoning.<br>• **Acute viral hepatitis (A ,B)**<br>• **Autoimmune** liver disease (hepatitis)<br>• Ischemic liver<br>• Vascular injury e.g. hypotension in ICU pts |

# Cont..

## Hepatocellular causes




## Cholestatic causes

### Extrahepatic = Obstructive

- Biliary stone
- Stricture:
  - Malignant: Periampullary tumors
  - PSC, AIDs cholangiopathy

### Intrahepatic = non-obstructive

- Primary biliary cholangitis
- Primary sclerosing cholangitis: small duct
- Cystic fibrosis
- Sepsis, Total parenteral nutrition, Drugs
- Infiltrative:
  - Granulomatous diseases such as TB, sarcoidosis, and lymphoma
  - Amyloidosis
- Intrahepatic cholestasis of pregnancy

# Cont..

## Hepatocellular pattern

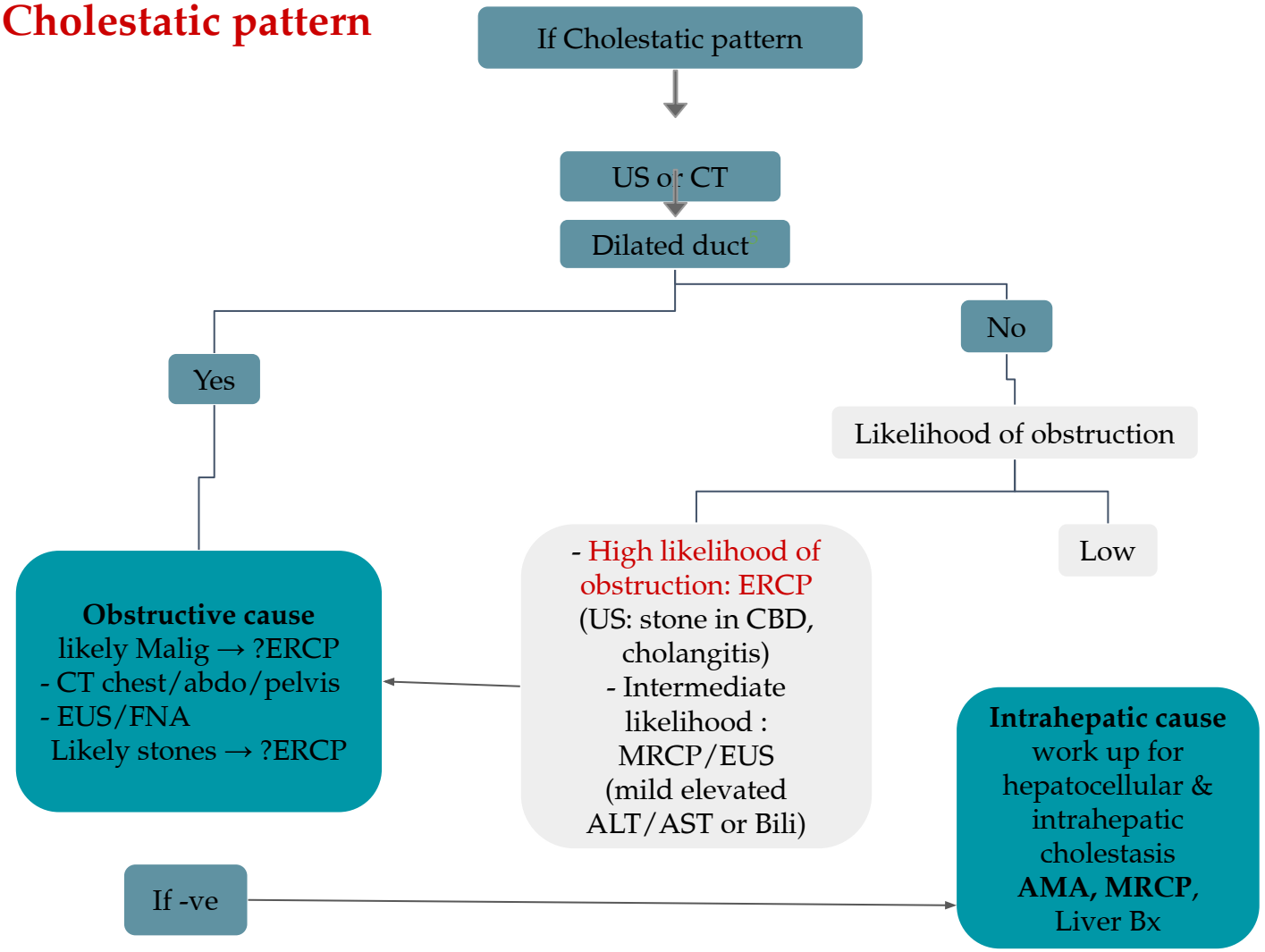
- Viral Hepatitis serologies
- Alcohol level
- US – for fatty liver or cirrhosis
- Drug level for Tylenol,pheytoi
- Urine toxins: cocaine
- Doppler US
- ANA, ASMA,IgG, AMA, celiac screen
- Serum ceruloplamin
- Liver Bx to be considered if needed
- Fibroscan

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

**US abdomen**

When you see cholestatic pattern the first thing you should do is rule out obstructive jaundice by US as the best initial bc we usually suspect stones to be the cause. Better to avoid CT scan

## Cholestatic pattern



# Cont..

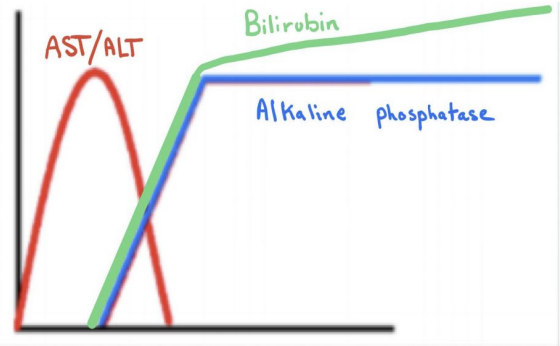
## Isolated elevated ALP

- **Isolated ALP and role of GGT:** If ALP is elevated alone ( normal AST,ALT), look at the GGT, if it is elevated as well then it's probably a liver problem, if not (GGT is normal) then the elevated ALP is probably due to another cause (Pregnancy, Bone disease, etc..). So, When testing for ALP levels measure GGT as well **to make sure the elevation is hepatic (obstructive)** in origin **(rather than bone or intestinal).**

## Alcohol **Alcohol can cause hepatic or cholestatic picture but usually hepatocellular**

| How to ask? | AST:ALT | Bilirubin | IgA, ACE, Anti-ttg |
|---|---|---|---|
| Don't ask the patient in front of people. You have to know how to ask in the right way. do not jump directly to the question | AST is double or triple ALT levels. leading to a reversed AST:ALT ratio to 2:1 (characteristic feature) | 100, elevated out of proportion. | |

### Bile duct stone




Expected liver enzymes pattern:
ALT and AST get elevated first (in the 1st six hours) then the go down. then:

- if the stone persists long enough thereafter (~24hrs) ALP will elevate (500-thousands)as well as direct bilirubin (obstructive jaundice)
- if the stone passes early (before ALP elevation) ALP will not get elevated.
- At the beginign it is hepatocellular pattern then it become cholestatic pattern

# Describe the approach plan for patients with abnormal liver enzymes and jaundice.

## Management of abnormal LFTs in asymptomatic patients

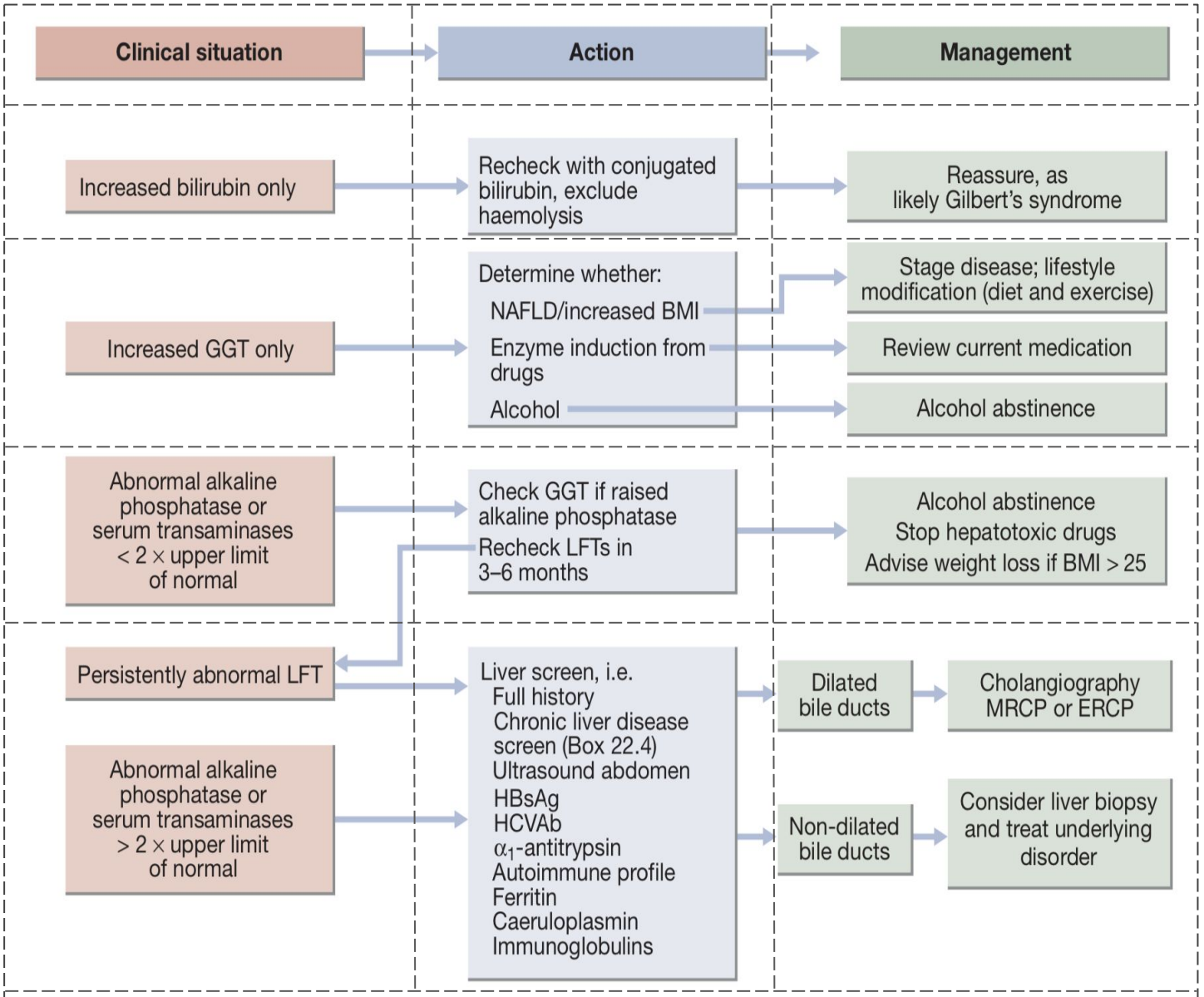



**Fig. 22.14 Suggested management of abnormal liver function tests in asymptomatic patients.** *No further investigation needed. ($\alpha_1$AT = alpha$_1$ antitrypsin; BMI = body mass index; ERCP = endoscopic retrograde cholangiopancreatography; GGT = γ-glutamyl transferase; HBsAg = hepatitis B surface antigen; HCVAb = antibody to hepatitis C virus; MRCP = magnetic resonance cholangiopancreatography; NAFLD = non-alcoholic fatty liver disease)

**To recognize the common causes for acute liver failure, understand the pathophysiology, clinical presentation, and formulate the work-up and management plan.**

## Background for Acute Hepatic Failure

- Is a clinical syndrome that results from the sudden loss of hepatic parenchymal and metabolic functions results in altered mentation and coagulopathy in individuals without known pre-existing liver disease.
- Acute liver failure often affects young persons.
- ALF is a rare condition.
- Because of its rarity, ALF has been difficult to study in depth and very few controlled therapy trials have been performed.

- in a patient without preexisting cirrhosis & with an illness of <26 weeks' duration with the following three criteria:
    - Massive cellular necrosis
    - Any degree of mental alteration (encephalopathy)
    - Coagulation abnormality, INR >= 1.5
- Can develop:
    - Infectious complications
    - Multi-organ failure
    - Cerebral edema (Most serious complications of acute liver failure)

## Classification (not important)

- Terms used signifying length of illness, such as "hyperacute" (<7 days), "acute" (7-21 days) and "subacute" (>21 days and <26 weeks), are popular but not particularly helpful since they do not have prognostic significance distinct from the cause of the illness.

## Causes

- Viral Hepatitis
- DILI
- Toxins/herbs
- Vascular injury
- AIH
- Wilson's disease
- HELLP/Acute fatty liver
- Malignant infiltration

# Cont..

## Initial evaluation

Conduct complete relevant history and physical exam.

- History:
  - Review of possible exposures to viral infection and drugs or other toxins.
  - If severe encephalopathy is present, the history may be provided entirely by the family or may be unavailable.
  - Further history….
- Px:
  - RUQ tenderness is variably present.
  - An enlarged liver may be seen early in viral hepatitis, but is particularly noteworthy for malignant infiltration, or acute Budd-Chiari syndrome.
  - CLD signs.

## Management

### Investigations :

- CBC, Lyte, urea , Cr, Glucose.
- All liver enzymes, INR, Albumin, Bilirubin.
- ABG.
- Pregnancy test in females.
- Plasma ammonia: A detailed analysis of serum ammonia in patients with ALF identified a concentration of 75 lM as an important threshold below which patients rarely develop intracranial hypertension (ICH). Conversely, arterial ammonia levels of >100 lM on admission represent an independent risk factor for the development of high-grade hepatic encephalopathy, and a level of >200 lM predicts ICH.
- Viral Hepatitis A-E
  - Anti-HAV IgM
  - HBsAg, anti-HBc IgM
  - Anti-HCV, HCV RNA
  - Anti-HEV IgM
  - HSV IgM
  - VZV
  - CMV
- Acetaminophen level or any other suspected drug.
- Urine toxin & Toxicology screen.
- Autoimmune Hepatitis: ANA, ASMA, Immunoglobulin levels.
- Serum ceruloplasmin (very low ALP suggest WD…..Hemolysis).
- US with doppler: Imaging: could suggest "cirrhosis," but this is often an overcall by radiology, because a regenerating massively necrotic liver will give the same nodular profile as cirrhosis.
- Liver biopsy, most often done via the transjugular route because of coagulopathy, is indicated when certain conditions such as autoimmune hepatitis need to be ruled out.

### Treatment :

- Supportive.
- Treat the cause.
- Consult liver transplant service : **Liver transplantation** remains the only definitive treatment for patients who fail to demonstrate recovery.

# Cont..

## ICU Management

- **Admit patient to ICU if evidence of elevated INR** or altered MS.
- Monitor for:
  - Hypoglycemia.
  - Encephalopathy & Cerebral edema.
  - Coagulopathy +/- DIC —> daily INR/PTT, Give **vit K**.
  - Infection — daily pan-culture & low threshold to for **ABx**.
  - MOF: renal failure, hemodynamic collapse.

## Liver support systems :

- Despite great early interest in liver support systems, the field has had little forward movement. Both artificial (i.e., sorbent-based) and bio-artificial (i.e., cell-based) systems have been tested. There has been **no good evidence that any artificial support system reliably reduces mortality in the setting of ALF.**

- Currently available liver support systems are not recommended outside of clinical trials; their future in the management of acute liver failure remains unclear.

## Prognosis :

- To date, it often remains **difficult to predict** which ALF patients will ultimately require transplantation.
- The model for end-stage liver disease (MELD) score, have not improved our accuracy, not found to be superior to that of the INR or the King's College Hospital criteria.

- **Etiology** of ALF provides one of the best indicators of prognosis:
  - Acetaminophen toxicity or ischemic hepatopathy, both of which have good initial recovery rates.

- Etiology with **poor** prognosis:
  - Idiosyncratic drug injury
  - Mushroom poisoning.
  - Budd-Chiari syndrome.
  - Autoimmune hepatitis.
  - Wilson disease.
  - Indeterminate cause.

# Cont..

## 1. Acetaminophen hepatotoxicity

- It is suggested by historic evidence for excessive ingestion either as:
  - intended suicidal overdose.
  - the inadvertent use of supratherapeutic quantities of pain medications.

- It is a dose-related toxin:
  - most ingestions leading to ALF exceed 10 gm/day. (20 tablet per day)
  - However, severe liver injury can occur rarely when doses as low as 3-4 gm/day are taken.

- Very high **aminotransferase** levels are typically seen:
  - serum levels exceeding 3,500 IU/L are highly correlated with acetaminophen poisoning.
  - should prompt consideration of this etiology even when historic evidence is lacking.

- Acetaminophen is the leading cause of ALF (at least in the United States and Europe) and there is an available antidote, acetaminophen levels should be drawn in all patients presenting with ALF.

### Management :

- Activated **charcoal**:
  - useful for gastrointestinal decontamination.
  - while it is most effective if given within one hour of ingestion, it may be of benefit as long as 3 to 4 hours after ingestion.

- N-acetylcysteine (**NAC**): Begin NAC promptly in all patients where the quantity of acetaminophen ingested, serum drug level or rising aminotransferases indicate impending or evolving liver injury.
  - NAC should be given as early as possible, but may still be of value 48 hours or more after ingestion.
  - May be given orally or IV.
  - If administered within 12 hours & possibly in 16 hours of acetaminophen ingestion, Chances of severe liver injury are virtually abolished.
  - Controversy exists over when to stop use of NAC, whether a standard 72-hour period is optimal or continuation until liver chemistry values have improved.
  - Has few side effects occasionally (nausea and vomiting, rare urticaria or bronchospasm).
  - Allergic reactions are infrequent and are successfully treated with discontinuation, antihistamines and epinephrine if bronchospasm is present.

- NAC may be used in cases of acute liver failure in which acetaminophen ingestion is possible or when knowledge of circumstances surrounding admission is inadequate but aminotransferases suggest acetaminophen poisoning.

- Low or absent levels of the parent compound, acetaminophen, do not rule out hepatotoxicity since the time of ingestion may be relatively remote or unknown, especially when overdose may have been unintentional or occurred over several days.

# Cont..

## 2. Drug Induced Liver Injury

- Determination of a particular medication as the cause of ALF is a diagnosis of exclusion. Other causes of ALF should still be ruled out even if a drug is suspected.
- Many prescription and over-the-counter medications have been associated with acute liver injury and liver failure.
- Most examples of idiosyncratic drug hepatotoxicity occur within the first 6 months after drug initiation. A potentially hepatotoxic medication that has been used continually for more than 1 to 2 years is unlikely to cause de novo liver damage.
- Certain herbal preparations, weight loss agents and other nutritional supplements have been found to cause liver injury, Classes of drugs commonly implicated include:
    - Antibiotics,
    - NSAIDs
    - Anticonvulsants
- Rx: Stop suspected Meds & supportive treatment.

## 3. Mushroom Poisoning

- Mushroom Poisoning (usually Amanita phalloides) may cause ALF.
- Initial history should always include inquiry concerning recent mushroom ingestion.
- There is no available blood test to confirm the presence of these toxins, but this diagnosis should be suspected in patients with a **history of severe gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal cramping), which occur within hours to a day of ingestion.**
- If these effects are present, it may be early enough to treat patients with **gastric lavage and activated charcoal via nasogastric tube.**
- Traditionally, very low rates of survival have been reported without transplantation.

## 4. Wilson's Disease

- is an uncommon cause of ALF.
- Early identification is critical because the fulminant presentation of Wilson disease is considered to be uniformly fatal without transplantation.
- Usually in young patients.
- Finding support the diagnosis:
    - Coombs negative hemolytic anemia
    - Low ALP
- To exclude Wilson disease one should obtain:
    - Serum ceruloplasmin
    - 24hr urinary copper levels
    - Slit lamp examination for Kayser-Fleischer rings
    - Liver Biopsy: to assess hepatic copper levels if feasible

# Cont..

## 5. Viral Hepatitis

- **Acute hepatitis A** ---99% self-limited, rarely cause fulminant hepatic failure.

- **Acute Hepatitis B** :
  - Age: Infant vs adult
  - Reactivation of chronic or inactive hepatitis B may occur in the setting of chemotherapy or immunosuppression, Nucleos(t)ide analogues should be considered for hepatitis B-associated acute liver failure and for prevention of post-transplant recurrence.

- Although controversial, **hepatitis C alone does not appear to cause ALF**.

- **Acute hepatitis D** may occasionally be diagnosed in a hepatitis B positive individual.

- **Acute Hepatitis E**
  - **is a significant cause of liver failure in countries where it is endemic.**
  - Tends to be more severe in **pregnant women**.
  - This virus should be considered in anyone with recent travel to an endemic area such as **Russia, Pakistan, Mexico, or India**.

- **Herpes virus infection rarely causes ALF.**
  - **Immunosuppressed patients or pregnant women** (usually in the third trimester) are at increased risk, but occurrences of herpes virus ALF have been reported in healthy individuals.
  - Liver biopsy is helpful in making the diagnosis.
  - Treatment: Acyclovir.

EXTRA

# Hepatitis A virus

The primary route of transmission of HAV is the fecal-oral route, by either:

1 Person-to-person contact

2 Ingestion of contaminated food or water

- Infection with HAV does not result in chronic infection, only in acute self-limited episode of hepatitis.
- Complete clinical recovery is achieved in **2-6 months** for almost everyone.

## Clinical presentation

### Adults

usually present with one of the following five clinical patterns:

- Asymptomatic
- Symptomatic with jaundice and self-limited after approximately 8 weeks
- Rarely Cholestatic with jaundice lasting 10 weeks or more
- 10% of symptomatic patients, relapsing, with two or more bouts of acute HAV infection occurring over a 6- to 10 week period
- Rarely Fulminant Hepatic Failure (FHF)

### Children

- If younger than 2 years → are usually asymptomatic (80%)
- If 5 years or older → symptoms develop in most children (80%)

| History (Hx) | Physical examination | Investigation | Prescription (Rx) |
|---|---|---|---|
| • Prodromal symptoms in patients with acute hepatitis A include: fatigue, weakness, anorexia, nausea, vomiting, and abdominal pain,<br>• Less common symptoms are fever, headache, arthralgias, myalgias, and diarrhea.<br>• Symptoms may last from a few days to 2 week, and usually decrease with the onset of clinical jaundice. | • Right upper quadrant tenderness and mild liver enlargement are found on physical examination in 85% of patients.<br>• Splenomegaly and cervical lymphadenopathy are each present in 15%. | • HAV antigen (the only antigen)<br>• Anti-HAV: IgM type is diagnostic for acute HAV infection, and IgG type marker of previous infection and indicates immunity. | • Treatment is symptomatic.<br>• Neither the cholestatic variant nor relapsing hepatitis A is associated with an increase in mortality.<br>• Pregnancy: Unlike hepatitis E, Acute hepatitis A is not associated with a higher mortality rate in pregnant women. |

EXTRA

# Hepatitis B virus

## Prevalence

- Highly endemic regions (8% or more of the population are chronic HBV carriers), such as:

1. Southeast Asia (excluding Japan)
2. China
3. Much of Africa

## Transmission

**Vertical Transmission:** Transmission of infection from an HBV carrier mother to her neonate accounts for the majority of new infections in the world today.

High risk of sexual behavior.

Receipt of blood products or organs.

Needle stick injury, IVDU, Tattooing, and body piercing.

Household contact with an HBV carrier and Hemodialysis.

**If HbeAg +ve:**

- 80% of HbsAg-positive mothers who are HBeAg-positive transmit the disease to their offspring.
- Whereas mothers who are positive for antibody to HBeAg (anti-HBe) transmit the disease less frequently (20%)

## Clinical presentation

### Acute Hepatitis B in Adult

- 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. In general, elevated serum ALT levels and serum HBsAg titers decline and disappear together, and in approximately 80% of cases.

### Chronic Hepatitis B in Adult

- Asymptomatic or fatigue
- Symptoms and signs of CLD
- Extrahepatic Manifestations: arthritis, dermatitis, glomerulonephritis, polyarteritis nodosa, cryoglobulinemia, papular acrodermatitis, and polymyalgia rheumatica.

- Acute Flares in Chronic Hepatitis B:
  - Spontaneous Flares
  - Immunosuppressive Therapy-Induced Flares

# EXTRA

## Diagnosis

1. HbsAg
2. HbcAB: IgG vs IgM
3. HbsAB
4. Tests for co-infection: HCV, HDC, and HIV

### Acute or Chronic hepatitis B

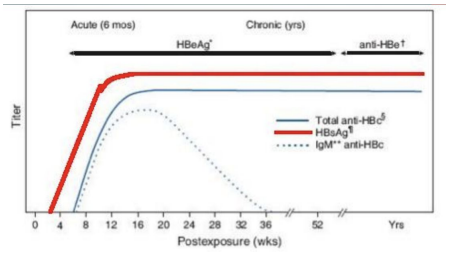
- Coexistence of HBsAg and anti-HBs in serum has been reported in approximately 25% of HBsAg-positive persons and occurs more commonly in persons with chronic hepatitis B than in those with acute hepatitis B.
- Persistence of HBeAg[3] three or more months after the onset of illness indicates a high likelihood 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.

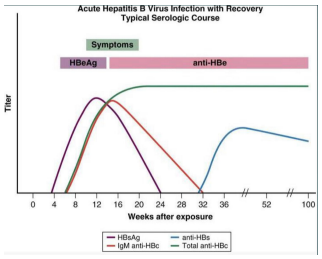
### HBsAg

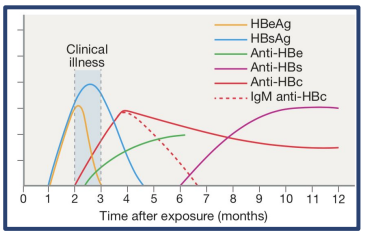
- Appears in serum 2 to 10 weeks.
- Persistence of HBsAg for >6 months implies progression to chronic HBV infection.
- In self-limited acute hepatitis, HBsAg usually becomes undetectable after 4-6 months.
  - The disappearance of HBsAg is followed by several weeks later by the appearance of anti-HBs.
  - Anti-HBs may not be detectable during a window period of several weeks to months after the disappearance of HBsAg.

### HBcAB

- 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 arrely 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)




22.38 How to interpret the serological tests of acute hepatitis B virus infection

| Interpretation | HBsAg | Anti-HBc IgM | Anti-HBc IgG | Anti-HBs |
|---|---|---|---|---|
| Incubation period | + | + | – | – |
| Acute hepatitis | | | | |
| Early | + | + | – | – |
| Established | + | + | + | – |
| Established (occasional) | – | + | + | – |
| Convalescence | | | | |
| (3–6 months) | – | ± | + | ± |
| (6–9 months) | – | – | + | + |
| Post-infection | – | – | + | ± |
| Immunisation without infection | – | – | – | + |

+ = positive; – = negative; ± = present at low titre or absent.
(anti-HBc IgM/IgG = antibody to hepatitis B core antigen of immunoglobulin M/G type; anti-HBs = antibody to HBsAg; HBsAg = hepatitis B surface antigen)

# EXTRA

## HBV scenarios

**1**
- HBsAg +ve
- HbcAb +ve
- HBsAb –ve

→ **Patient has an active HBV and requires further work up**

**2**
- HBsAg -ve
- HbcAb +ve
- HBsAb +ve

→ **Had HBV and recovered**

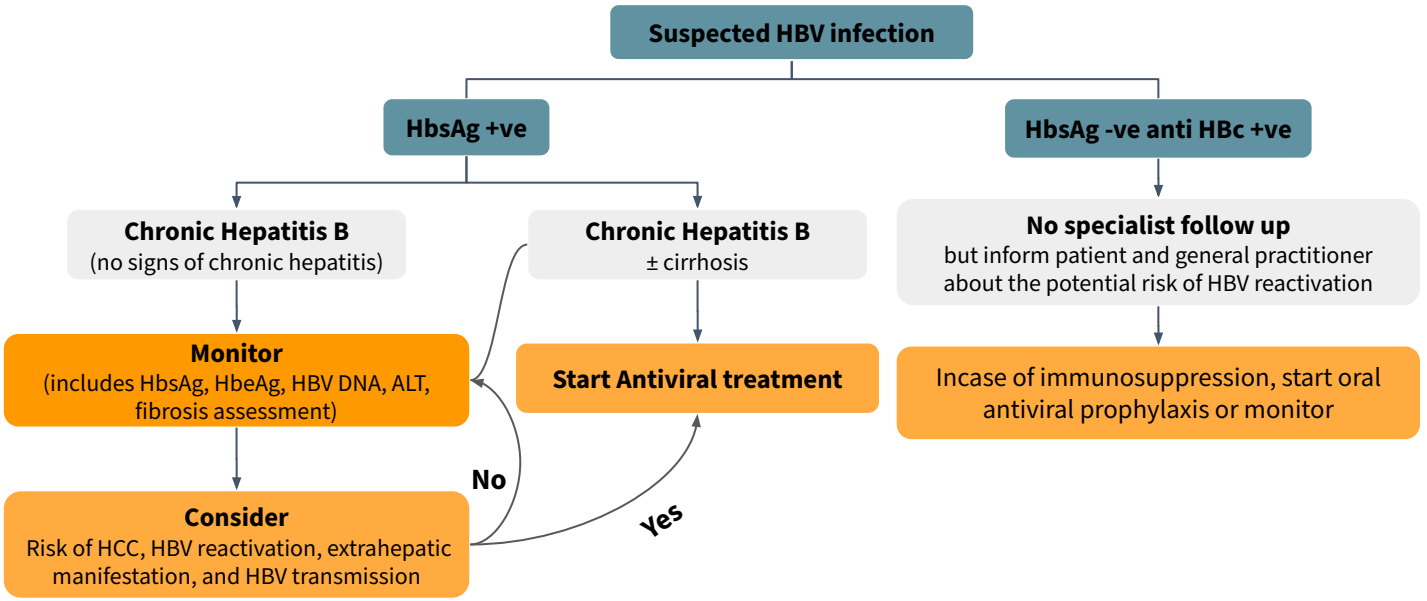
**3**
- HBsAg -ve
- HbcAb -ve
- HBsAb +ve

→ **Immunity due to vaccination**

## Chronic HBV: Monitoring

- 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.

| | | | |
|---|---|---|---|
| **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 | **Liver enzyme** | • ALT |
| **Pegylated interferon (Peg-IFN)** | • Short duration of therapy<br>• Before pregnancy<br>• 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. |



# EXTRA

- **Management of acute hepatitis B:**
  - Treatment is **supportive with monitoring**. There is no definitive evidence that antiviral therapy reduces the severity or duration of acute hepatitis B.
- **Management of chronic hepatitis B:**
  - Treatments are still limited, as no drug is able to eradicate hepatitis B infection completely. (i.e. render the patient HBsAg-negative).
  - The goals of treatment are **HBeAg seroconversion, reduction in HBV-DNA and normalisation of the LFTs**.

| Features | **Pegylated interferon alfa (PegIFNα)** | **Nucleos(t)ide analogs:** Entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide |
|---|---|---|
| Route of admin | Subcutaneous injection | Oral |
| Treatment duration | 48 weeks | **first-line agents: long-term until HBsAg loss (stopping NA after some years might be considered in selected cases)** |
| Tolerability | Low | High |
| Long term safety concern | Very rarely persistence of on treatment adverse event (psychiatric, neurological, endocrinological) | **Probably not (uncertainties regarding kidney function, bone disease for some NA)** |
| Contraindications | Many (i.e. decompensated disease, comorbidities etc.) **contraindicated in cirrhosis, as it may cause a rise in serum transaminases and precipitate liver failure.** | **None (dose adjustment according to eGFR)** |
| Strategy | **Induction of a long term immune control by finite treatment** | **Stopping hepatitis and disease progression by inhibiting the viral replication** |
| Level of viral suppression | Moderate (variable response pattern) | Universally high |
| Effect on HBeAg loss | Moderate, depending on baseline characteristic | low in the first year, increase to moderate during long term treatment |
| Effect of HbsAg levels | Variable, depending on the baseline characteristic (overall higher as compared to NA) | low: slowly increase with treatment time in HBeAg +ve patient; usually very low in HBsAg -ve patient |
| Risk of relapse after treatment cessation | low for those with sustained response 6-12 months after therapy | **Moderately in consolidation treatment provided after HbeAg seroconversion. High for HbeAg -ve disease** |
| Early stopping rules | Yes | **No** |
| Risk of viral resistance | No | **Minimal to none** |

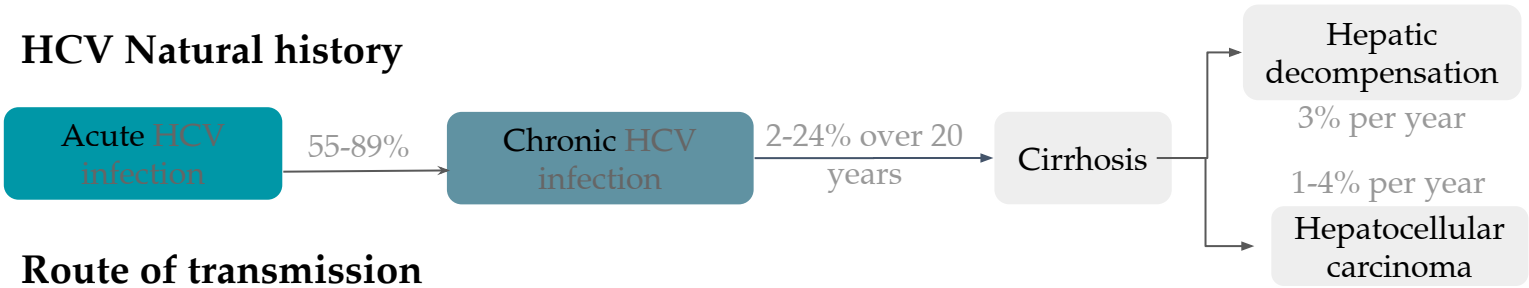
EXTRA

# Hepatitis C virus

## 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).

## HCV Natural history




## Route of transmission

- Modes of transmission of HCV can be divided into:
  1. Percutaneous (blood transfusion and needle stick inoculation, dental procedures).
  2. Non-percutaneous (sexual contact and perinatal exposure).
- 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

| Genotypes 1, 2, and 3 | Genotypes 4 | Genotypes 5 and 6 |
|---|---|---|
| Most common in North America and Europe | Most common in Middle East | Most common in Southeast Asia |

## Clinical features

### Acute Hepatitis C

- Rarely seen in clinical practice because nearly all cases are **asymptomatic** until progression to cirrhosis occurs.
- 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.

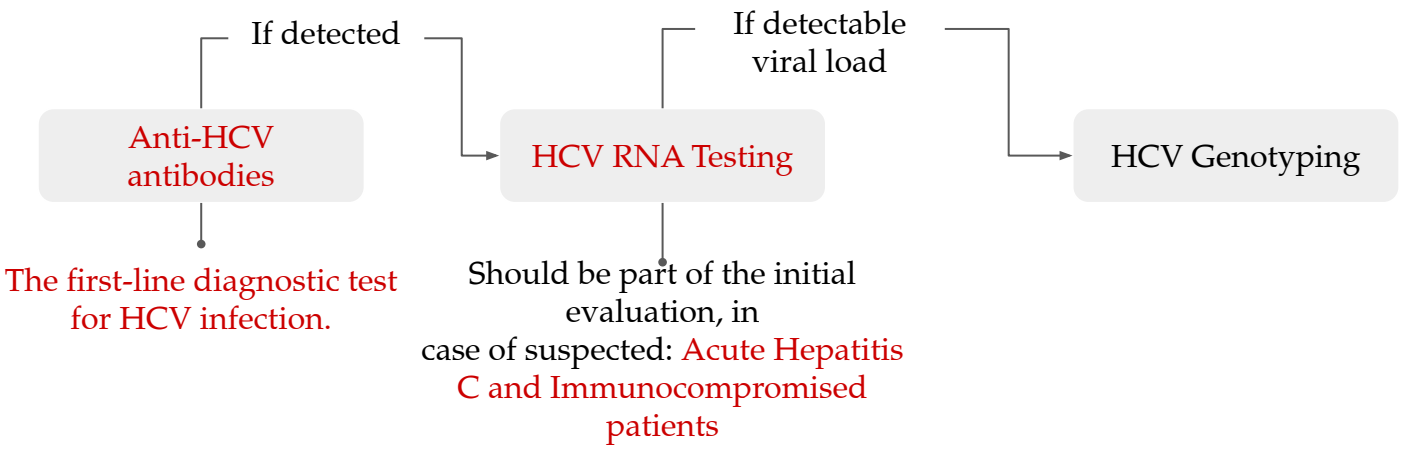
### Extrahepatic Manifestation:

| | | | | | | |
|---|---|---|---|---|---|---|
| Fatigue | Arthralgias and arthritis | Purpura | Raynaud's phenomenon | Vasculitis | Nephropathy | Peripheral neuropathy |

- 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.

# EXTRA

## Diagnosis




- 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" antiviral 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 depends on:**

1. Presence of Cirrhosis and HCV genotype
2. Prior treatments
3. Renal function

| Drug class | Therapeutic target | Selected drugs |
|---|---|---|
| **Protease inhibitors (PIs)** | Non-structural viral protein NS3/4A (protease that cleaves the HCV polyprotein) | Telaprevir<br>Boceprevir<br>Simeprevir<br>Paritaprevir<br>Grazoprevir |
| **Nucleoside polymerase inhibitors (NPIs)** | Non-structural viral protein NS5B (RNA-dependent RNA polymerase needed for viral replication) | Sofosbuvir |
| **Non-nucleoside polymerase inhibitors (NNPIs)** | Non-structural viral protein NS5B (RNA-dependent RNA polymerase needed for viral replication) | Dasabuvir |
| **NS5A replication complex inhibitors** | Non-structural viral protein NS5A (assembly of viral replication complex) | Daclatasvir<br>Velpatasvir<br>Ledipasvir<br>Ombitasvir<br>Elbasvir |
| **Host-targeting antiviral drugs (HTAs)** | Cyclophilin (pharmacological inhibitor targets host cell functions involved in the HCV life cycle) | Alisporivir |

# Cont..

## 6. Autoimmune hepatitis

### Characteristics

- Hypergammaglobulinemia (IgG in particular).
- A favorable response to immunosuppression.
- Circulating autoantibodies (ANA, ASMA, IgG are the most important).
- Interface hepatitis on liver histology.

### Clinical presentation

- Symptoms: Broad range from asymptomatic to acute/severe or even fulminant.
- Any age.
- Both sexes (female-male 3:1).
- Onset: Acute (25%) or insidious.

**Insidious onset** is the most common clinical phenotype of the disease (two thirds of patients):

- either without any apparent symptom
- with one or more of the following non-specific symptoms:
  - **Fatigue (General ill health).**
  - **Right upper quadrant pain.**
  - **Anorexia, Weight loss, Nausea.**
  - **Amenorrhea is also common.**
  - **Fluctuating jaundice.**
  - **polyarthralgia involving the small joints <u>without arthritis.</u>**

Signs of acute liver failure (one third of patients):

- Jaundice.
- Fever.
- Hepatomegaly.
- Splenomegaly.
- Ascites.
- RUQ pain.

### Classification

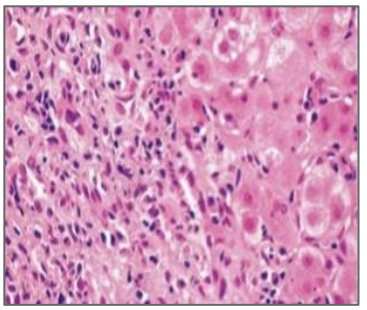
| AIH 1 | AIH 2 | AIH 3 |
|---|---|---|
| • prevalence: The more frequent type of AIH (almost for 90% of AIH cases).<br>• Detected by: antinuclear antibodies (ANA), or anti-smooth muscle antibodies (ASMA)<br>• Associated with: HLA DR3, DR4 and DR13. | • prevalence: accounts for up to 10% of AIH cases.<br>• Detected by: anti-LKM1, anti-LC1 and anti-LKM3 (rarely).<br>• Associated with: HLA DR3 and DR7.<br>• Onset: usually in childhood and young adulthood. | • ASLA/LP positive. |

# Investigation

**The diagnosis of AIH relies particularly on the presence of:**

- **Hypergammaglobulinemia** (A selectively elevated IgG in the absence of IgA and IgM elevation is particularly suggestive of AIH).
- **Autoantibodies:**
  **Indirect immunofluorescence:** the test of choice for all auto-antibodies except ASLA.
- **Immunoassays (ELISA/Western blotting)**: the tests of choice for the detection of SLA/LP. Methods and cut-off values should be reported by the laboratory.
- **Typical or compatible histology.**
  (Discussed in the box below)

- There are no morphological features that are pathognomonic of AIH, but some features could be suggestive of AIH, such as:
  - interface hepatitis:
    - not disease specific (patients with drug-related, viral or immune-mediated disease may show similar features).
    - with dense plasma cell-rich lymphoplasmacytic infiltrates, is the typical hallmarks of AIH.
  - periportal necrosis
  - rosetting of hepatocytes
- Plasma cells: typically abundant at the interface and throughout the lobule, but their paucity in the inflammatory infiltrate does not preclude the diagnosis.



## Laboratory findings :

Bilirubin & Aminotransferases

The typical biochemical profile of the disease is a predominantly hepatitis pattern:

- Bilirubin concentrations and aminotransferases: from just above the upper limits of normal to >50 times these levels (Degree of ALT/AST elevations does not reliably reflect severity of AIH at the histological level).
- Usually normal or only moderately elevated cholestatic enzymes.

Acute presentation

In some patients with acute presentation of AIH:

- Immunoglobulin G (IgG) levels: may be within the normal range.
- Antinuclear (ANA) and/or smooth muscle antibodies (SMA): first screening may be negative.

Immunoglobulins

- high IgG levels: very distinctive feature.
- IgA and IgM levels: 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.

- Adult patients with AIH and cholestatic lab changes: should be considered for MRCP to recognize sclerosing cholangitis.
- In severe coagulopathy: 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.

# Management

## Treatment of AIH should be aimed to obtain:

**01** Complete biochemical (ALT/AST & IgG) resolution **02** 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 subclinical 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. 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 cirrhosis.
3. Treatment options: **glucocorticoids** is life-saving in autoimmune hepatitis, particularly **during exacerbations** of active and symptomatic disease:
   a. **prednisolone**: 30 mg is given daily for at least 2 weeks, followed by a slow reduction and then a maintenance dose of 10–15 mg daily.
   b. **Azathioprine:** should be added, 1–2 mg/kg daily, as a steroid-sparing agent and in some patients as sole long-term maintenance therapy. Levels of thiopurine methyltransferase should be obtained.
   c. **Mycophenolate, ciclosporin and tacrolimus:** have been used in resistant cases. He
   d. **Budesonide:** 3 mg × 2 or 3 daily has fewer side-effects than prednisolone and is now the preferred treatment.

# Cont..

## 7. Acute Fatty Liver of Pregnancy/HELLP Syndrome

- HELLP syndrome is a **life-threatening form of preeclampsia[1] characterized by Hemolysis, Elevated Liver enzymes, and Low Platelets.**
- Features of pre-eclampsia such as hypertension and proteinuria are common, but it may occur without hypertension or proteinuria.
- Generally confined to the last trimester.
- **Expeditious delivery** of the infant is recommended.
- Recovery is typically rapid after delivery, and supportive care is the only other treatment required.
- **Transplantation** may need to be considered if hepatic failure does not resolve quickly following delivery.

## 8. Acute Ischemic Injury

- A syndrome often referred to as **"shock liver" may occur after cardiac arrest**, any period of significant hypovolemia/hypotension, or in the setting of severe congestive heart failure.
- Long-term outcome depends on the underlying cardiac process.
- Rx: supportive.

## 9. Budd-Chiari Syndrome

- The Budd-Chiari syndrome is **acute hepatic vein thrombosis**, and it can also present as ALF.
- **Abdominal pain, ascites and striking hepatomegaly** are often present.
- Diagnosis: should be **confirmed with hepatic imaging studies** (computed tomography, Doppler ultrasonography, venography, magnetic resonance venography).
- Overall, **the prognosis in this condition is poor if hepatic failure is present, and transplantation may be required** as opposed to venous decompression .

## 10. Malignant Infiltration

- In patients with acute liver failure who have a previous cancer history or massive hepatomegaly, consider underlying malignancy and obtain imaging and liver biopsy to confirm or exclude the diagnosis .
- Malignant infiltration of the liver may cause ALF.
- Diagnosis should be made by **biopsy**.
- Acute severe hepatic infiltration occurs with breast cancer, small cell lung cancers, lymphoma, melanoma, and myeloma.

1. It's a new-onset gestational hypertension with proteinuria or end-organ dysfunction.

# Cont..

## 11- Primary sclerosing cholangitis (PSC)

- 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 (The cause of PSC is unknown), thus differentiating PSC from secondary sclerosing cholangitis.
- Association: Many, if not most cases of PSC are associated with IBD, particularly ulcerative colitis.
- Prevalence: in UC has been estimated to be ~5%. PSC was also more common in young men and those with pancolitis.

### Signs and symptoms:

Asymptomatic

- A large number of patients present without symptoms and come to attention simply by a finding of persistently abnormal liver tests.
- PSC may be asymptomatic for long periods but may also have an aggressive course, leading to:
  - Recurrent biliary tract obstruction.
  - Recurrent episodes of cholangitis.
  - Cirrhosis/ESLD.

Symptomatic

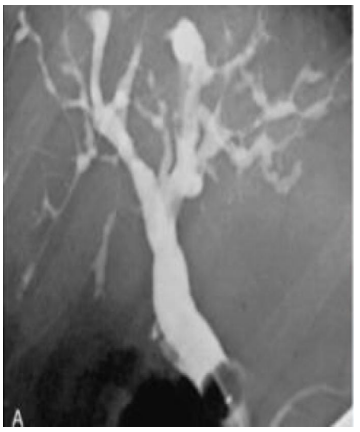
- Fatigue: When symptoms occur, fatigue maybe the most commonly noted finding.
- Pruritus: Sudden onset of pruritus should signal the possibility of obstruction of the biliary tree.
- Other patients may experience chronic right upper quadrant discomfort.
- Other Common symptoms: intermittent jaundice, weight loss.

### Diagnostic criteria:

The generally accepted diagnostic criteria are:

- Generalised beading and stenosis of the biliary system on cholangiography.
- Absence of choledocholithiasis (or history of bile duct surgery).
- Exclusion of bile duct cancer.

## Investigations:



- 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.
- 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: often normal at the time of diagnosis..

## Treatment:

- At this time, there is no established medical treatment for patients with PSC.
- We treat **complications** of the disease.
- MRCP & CA19-9 annually.
- Annual colonoscopy if known to have UC.

## Complications:

| **Acute attacks of cholangitis** | **Obstruction to the extrahepatic bile ducts on cholangiography** | **cholangiocarcinoma** | **Metabolic bone disease** |
|---|---|---|---|
| give Broad-spectrum antibiotics. (e.g. ciprofloxacin) | mechanical relief by stent or balloon dilatation using ERCP. | | (usually osteoporosis) due to fat soluble Vit malabsorption: Fat-soluble vitamin replacement. |

# 12. Indeterminate Etiology

- When the etiology of ALF cannot be determined after routine evaluation, **biopsy using a trans-jugular approach** may be helpful in diagnosing:
    - Malignant infiltration.
    - Autoimmune hepatitis.
    - Certain viral infections.
    - Wilson disease.
- **Lack of a clear diagnosis suggests that the history may have been inadequate regarding toxin or drug exposures.**

# Cont..

## Complications of ALF

### CNS complications:

1. Hepatic encephalopathy.
2. Cerebral edema & ICH.

### Other complications:

1. Infection.
2. Coagulopathy.
3. Thrombocytopenia.
4. Portal hypertension.
5. Hemodynamic (hypotension).

### Hepatic Encephalopathy:

- **Frequent neurological assessments** should be performed.
- Transfer to an **ICU** should occur promptly if the level of consciousness declines.
- Head imaging with computerized tomography (**CT**) may be used to exclude other causes of decline in mental status such as intracranial hemorrhage.
- Sedation is to be avoided, if possible; unmanageable agitation may be treated with short-acting **benzodiazepines** in small doses.
- **Lactulose** may be used either orally or rectally.
- As patients progress to severe encephalopathy**, intubation and mechanical ventilation** are mandatory.

### Cerebral edema and ICH:

- The occurrence of **cerebral edema and ICH** in ALF is related to the severity of hepatic encephalopathy.
- Cerebral edema is seldom observed in patients with grade I-II encephalopathy, but increases to 25% to 35% with progression to grade III, and 65% to 75% or more in patients reaching grade IV coma.
- **Intracranial pressure monitoring** is recommended in ALF patients with high grade hepatic encephalopathy, in patients awaiting and undergoing liver transplantation.
- In the absence of ICP monitoring, **frequent (hourly) neurological evaluation is recommended** to identify early evidence of intracranial hypertension (III).
- The pathogenic mechanisms leading to the development of cerebral edema and intracranial hypertension in ALF are not entirely understood.
- Seizures increase ICP, and must be promptly controlled with:
    - Phenytoin
    - Short-acting benzodiazepines should be administered in phenytoin-refractory cases.
    - Prophylactic phenytoin is not recommended.

## Infection:

- **All ALF patients are at risk for bacterial or fungal infection**, which may preclude liver transplantation or complicate the postoperative course.
- Periodic surveillance cultures are recommended to detect bacterial and fungal pathogens as early as possible.
- **Antibiotic treatment** should be initiated promptly according to surveillance culture results at the earliest sign of active infection or deterioration (progression to high grade hepatic encephalopathy or elements of the SIRS).
- Prophylactic antibiotics and antifungals have not been shown to improve overall outcomes in ALF and therefore cannot be advocated in all patients, particularly those with mild hepatic encephalopathy.

## Coagulopathy:

- The synthesis of **coagulation factors is universally decreased**, while consumption of clotting factors and platelets also may occur.
- In the absence of bleeding, it is not advisable to correct the INR with plasma, since clinically significant blood loss is rare, and **correction obscures trends in the INR an important marker of prognosis**.
- **Vitamin K** (5-10 mg subcutaneously) should be administered routinely, since vitamin K deficiency has been reported in patients with ALF.

## Thrombocytopenia:

- Replacement therapy for thrombocytopenia and/or prolonged prothrombin time is recommended only in the setting of:

1. **Hemorrhage** or
2. **Prior to invasive procedures** or
3. **PLT < 10,000**

- Experience in patients without ALF suggests that platelet counts of 10,000/mm3 are generally well tolerated.
- When **invasive procedures** must be performed in patients with ALF, **platelet counts of 50-70,000/ mm3** have been considered adequate.
- Patients who **develop significant bleeding with platelet levels below approximately 50,000/mm3** should generally be **transfused with platelets** provided no contraindication (such as thrombotic thrombocytopenic purpura or heparin-induced thrombocytopenia).

## Portal hypertension:

- The hepatic venous pressure gradient of ≥ 6 mm Hg.
- Although portal hypertension occurs in acute liver injury due to architectural collapse of the liver**, but bleeding from esophageal varices almost never occurs.**

## Hemodynamic (hypotension):

- Hemodynamic derangements occur frequently in patients with ALF and contribute **peripheral tissue oxygenation** and **multi-organ system failure.**
- The fundamental hemodynamic abnormality in ALF, similar to cirrhosis or sepsis, is **low systemic vascular resistance**.

OnlineMedEd

| | |
|---|---|
| Prehaptic | Hemolysis<br>Hematoma |
| IntraHepatic | Gilbert's<br>Crigler-Najjar<br>Dubin-Johnson<br>Rotor's<br>Cirrhosis |
| PostHepatic | Gallstones<br>Pancreatic Cancer<br>PBC<br>PSC |

Introduction and Differential

Jaundice is a clinical finding where there's **yellowing** of the sublingual region (1st), the **sclera** (2nd) and then the **skin** (3rd). It's a result of elevated **bilirubin** in the blood. Bilirubin is processed by the liver and excreted into the small intestine by the biliary tree. Defects in any three regions can cause a build up of bilirubin: 1) **PreHepatic,** which essentially means **hemolysis** producing an unconjugated bilirubinemia from increased RBC turnover, 2) **Intrahepatic**, a defect in anything involving **uptake**, **metabolism**, or **excretion** of bilirubin producing an unconjugated bilirubin, and 3) **PostHepatic**, typically a **mechanical obstruction** preventing efflux of conjugated bilirubin.

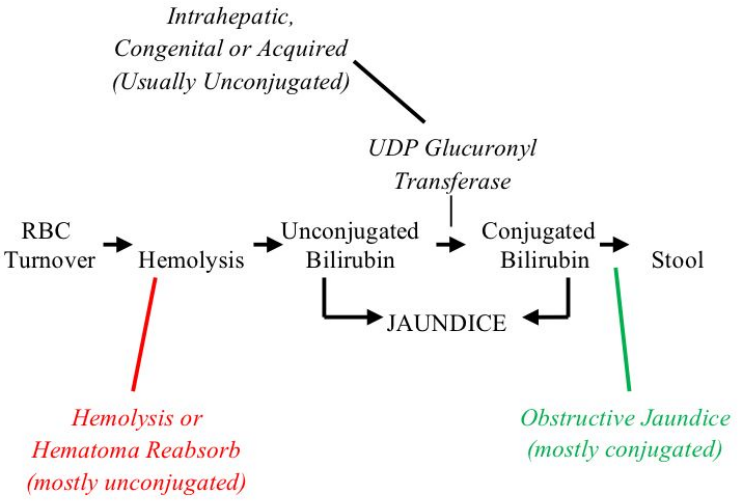
Conjugated vs Unconjugated

Unconjugated bilirubin comes from broken down red blood cells. Glucuronyl Transferase is an enzyme in the liver that **conjugates** the unconjugated bilirubin. Conjugated bilirubin can then be excreted in the GI tract. **Unconjugated** is generally the "worse" type. It **can't be renally excreted** and **can cross the blood brain barrier** because it's lipid-soluble. **Conjugated** on the other hand is water-soluble and **is renally excreted,** but **can't cross the blood brain barrier**. A conjugated hyperbilirubinemia will therefore present with **dark urine**.

| ***UNCONJUGATED*** | ***CONJUGATED*** |
|---|---|
| Lipid-Soluble | Water-Soluble |
| Crosses BBB | Ø Cross BBB |
| Ø Urinary Excreted | ⊕ Urinary Excretion |
| ⊕ Kernicterus | Ø Kernicterus |

1) Hemolysis

See the heme section for all hemolytic anemias. Look for a **history of transfusions**, culpable medications (like **Dapsone**), or **African Americans**. Since actual hemolytic anemia rarely causes jaundice, look only for a mild elevation of the bilirubin. A **blood smear** and **Hgb Electrophoresis** can distinguish hemolytic subtypes.




2) Gilbert's and Crigler-Najjar

Disease of uptake of bilirubin. They're either **fatal early** (Crigler-Najjar) or present as **asymptomatic jaundice** when the body is **stressed** (infection, dehydration, etc). Because bilirubin can't enter the liver or get conjugated, there's an ↑ **unconjugated bilirubin**. The enzyme deficiencies are for step 1 and aren't required.

3) Dubin-Johnson and Rotor syndrome

Diseases of excretion of already conjugated bilirubin, these cause an **asymptomatic jaundice** when the body is **stressed** just like Gilbert's. However, there's **conjugated hyperbilirubinemia** so the urine will be **dark** and ⊕ **for blood** (representing the bilirubin, not actually hematuria). Being able to separate these two diseases isn't necessary.

4) Gallstones

Discussed in gallbladder pathology. The patient will present with a history of **colicky RUQ pain** and will have either **hemolytic anemia** or be **fat, fertile, + forty**. Diagnosis is made with **ultrasound** then treated/confirmed with **ERCP** to remove stones. Gallbladder jaundice is painful obstructive jaundice.

5) Pancreatic / Biliary Tract Cancer

There will be a painless **obstructive jaundice** with a conjugated hyperbilirubinemia. An **ultrasound** will show a **thin-walled, distended gallbladder**. See surgery videos for more information on obstructive jaundice.

6) Primary Biliary Cirrhosis

**PBC** is for **B**itches, an **autoimmune** disease affecting **females** and **intrahepatic ducts**. Conjugated bilirubin can't get out, causing a **conjugated hyperbilirubinemia**. The only diagnostic tool is a **biopsy** and treatment is **transplant**. See cirrhosis.

7) Primary Sclerosing Cholangitis

An **autoimmune** disease affecting **MALES** with an association with **ulcerative colitis** (p-ANCA). This affects **extrahepatic** ducts, causing a macroscopic pattern of disease. A diagnostic **MRCP** can be used to see a **beads-on-a-string** pattern. Biopsy (not needed) via ERCP will show **onion-skin fibrosis**.

8) Stricture

Stricture is the **other painless obstructive jaundice**. It presents just like a cancer (insidious, dilated ducts, conjugated hyperbilirubinemia), but there isn't cancer or PSC. Strictures are diagnosed with MRCP, confirmed by ERCP and treated with stenting (do not stent PSC, only stents). To identify a potential stricture look for iatrogenic causes - especially a history of manipulation of the biliary tree surgically or with ERCP.

| *Disease* | *Bilirubin* | *Dysfunction* | *Patient Picture* | *Diagnosis* | *Treatment* |
|---|---|---|---|---|---|
| Hemolysis or Hematoma | Unconjugated | PreHepatic | African American, Transfusions, Medications | Heme/Onc Lectures | |
| Cirrhosis (any acquired form) | Unconjugated | IntraHepatic | EtOH, Viral, Wilson's, Hemochromatosis, Acetaminophen toxicity, etc. etic. | Diagnose underlying dz | Supportive Care |
| Gilbert's Crigler-Najjar | Unconjugated | IntraHepatic | Asx, Unconjugated Hyperbili, Death In Infancy | Genetics Biopsy | Asx, ØTx |
| Dubin-Johnson Rotor | Conjugated | IntraHepatic | Asx Conjugated Hyperbili | MRI, Biopsy | Asx, ØTx |
| Gallstones | Conjugated | PostHepatic | h/o colicky pain, RUQ worse with fatty food, Female, Fat, Forty, or Hemolysis | U/S RUQ ERCP, HIDA | ERCP |
| Pancreatic Cancer | Conjugated | PostHepatic | Weight Loss and Asx Jaundice | U/S RUQ CT Scan | Surgery |
| Primary Sclerosing Cholangitis | Conjugated | PostHepatic | MALE with Ulcerative Colitis Extrahepatic Dilation | p-ANCA MRCP ~~Biopsy~~ | Transplant |
| Primary Biliary Cirrhosis | Conjugated | PostHepatic | FEMALE with conjugated hyperbili | AMA Biopsy | Transplant |
| Cancer | Conjugated | PostHepatic | Weight loss, Painless Jaundice | CT scan EUS biopsy | Resection |
| Stricture | Conjugated | PostHepatic | Previous manipulation of the biliary system, painless jaundice | U/S RUQ MRCP | Stent |

Introduction

Viral Hepatitis is an umbrella categorization of the different viruses that can cause an infection of the liver. Some are chronic, others acute, some can be prevented, others only avoided. Let's talk about each.

Hepatitis A

This is an **Acute** form of hepatitis spread by fecal-oral contamination. It has a 2-6 week incubation and is carried in contaminated water, shellfish, and daycares. It produces a **nonbloody diarrhea** and a **modest LFT** ↑. Since it's self-limiting a diagnosis is rarely required. However, serologies will show **IgM** for active infection while **IgG** indicates immunity. A **vaccine** is available and given as a child. Boosters are recommended for travel to endemic regions >2 wks before the trip. **Post Exposure Prophylaxis** with IgG can be started **with vaccine** within 2 weeks of exposure.

*Fecal Oral*
*RNA*
*Vaccine* ⊕
*IgM = Active Infxn*
*IgG = Immunity*
*PPX = IgG w/I 2 weeks of exposure*

Hepatitis B

This can be **both** acute and chronic. The stronger the immune response the less likely it's in the chronic carrier state and more likely it's a devastating hepatitis case. **Adults** acquire it through **Sex** more than **IVDA**. Because adults are generally healthy (an intact immune system) they suffer **jaundice**, **LFTs in the 1000s**, and only the acute phase without chronic carrier state. **Fulminant Hepatitis** is rare (and nearly fatal). **Babies** acquire it through the **birth canal** (vertical transmission) and will likely have **Ø symptoms** (a poor immune system), but are almost always **chronic carriers**. Since there's chronic inflammation infection of the chronic carrier may result in **cirrhosis** or **hepatocellular carcinoma**. **Screen for HCC** with **Alfa-fetoprotein** (AFP) and **Ultrasound**. To treat the hepatitis infection give **peg IFN-α-2a** for 48 weeks coupled with antivirals (lamivudine, adefovir, telbivudine, entecavir) with the goal of eliminating HBeAg. There's a vaccine against Hep B so **vaccinations** are a must to prevent chronic illness. If a patient isn't vaccinated and gets stuck, give them **vaccine** and **ppx IgG**. Understanding serology is critical. **IgG** indicates either past exposure or immunity. **IgM** is only during acute infection. The virus has a **s**urface antigen (HB**s**Ag), a **c**ore antigen (HB**c**Ag), and a protein of infectivity (HBeAg). **IgG HBsAb** ⊕ **ONLY** is a sign of **vaccination**. **IgG HBeAb** but without the presence of Antigen is a sign of immunity following exposure. **HBsAg** ⊕ (the presence of antigen, not antibody) occurs early and denotes infection. **HBeAg** ⊕ indicates active infection and **infectivity**. During the **window period** where the Antibodies and Antigens cancel each other out (binding to each other prevents binding of the test antigen), Anti-HBc is the only indicator of infection. Incubation is generally **1-6 months**.

*IVDA/Sex = Adult = Acute*
*Baby = Vertical = Chronic*
*HCC/Cirrhosis if chronic*
*HBsAg initial infxn*
*HBeAg infectivity*
*IgM HBxAg window period*
*IgG HbeAb waning infection / infectivity*
*IgG HBsAb long term immunity*
*Vaccine* ⊕
*PPx = IgG*
*DNA Virus*
*Peg-IF-α-2a + antivirals = ↓ HCC Transformation*

Hep C

Hep C is the **chronic** hepatitis that has **no vaccine**. Until recently there was also no treatment. Hepatitis C is on its way to eradication. Good thing too - chronic hepatitis is chronic inflammation, leading to **cirrhosis** after 20-30 years. Cirrhosis progresses to **hepatocellular carcinoma** at a rate of 2-5%. Even in the absence of cirrhosis, chronic Hep C can lead to hepatocellular carcinoma. Hep C is transmitted by **blood** and essentially not at all by sex (people who sleep with people who do IV drugs tend to also do IV drugs, which is how they get the virus). Blood transmission means **IVDA** and **Blood Transfusions**. The goal with all Hep C is to **prevent further inflammation** by abstaining from alcohol and to **screen for HCC** with annual Ultrasound and AFP.

*IVDA//Blood Transfusions = Chronic*
*HCC/Cirrhosis*
*Antibody ⊖ and HCV RNA ⊕ = Early Infection*
*Antibody ⊕ and HCV RNA ⊖ = Resolution (rare)*
*Antibody ⊕ and HCV RNA ⊕ = Chronic*
*NO Vaccine*
*PPx = IgG*
*RNA Virus*
*Peg-IF-α-2a + Ribivarin = Remission and ↓ HCC*
*Direct Acting Antivirals = Hep C cure (~12 week regimen)*

There are two treatments for Hep C. If genotype 1b, we can use **Pegylated Interferon with Ribavirin** which causes psychosis, depression, and flu-like symptoms for a year. If genotype 2 or 3, we have the new **Direct Acting Antivirals** which all end in –vir. There are many of them and more are coming (they're extremely effective, but also extremely expensive – expect to talk about them).

Viral serology is either **acute** (Ø Anti-HCV, ⊕ HCV RNA), **resolved** (⊕ Anti-HCV, Ø HCV RNA), or most commonly, **chronic** (⊕ Anti-HCV and ⊕ HCV RNA).

Hep D

This is essentially **mini-B.** It requires the presence of **Hep B** (reliant on one of Hep B's proteins) and is transmitted the same way. It causes a **more severe hepatitis** and a **faster progression to cirrhosis**.

*Requires coinfection with Hep B*
*makes B worse*

Hep E

Pregnant ladies in third world countries contract it through fecal-oral route. Think of this as Hep A of women in the 3rd world.

*Pregnant ladies in third world countries*

| *Hepatitis* | *Route* | *Acute* | *Chronic* | *Cancer* | *RNA/DNA* | *Vaccine* | *Serology* |
|---|---|---|---|---|---|---|---|
| **Hep A** | Fecal-Oral | Always | Never | Never | RNA | >2 weeks before endemic travel | N/A |
| **Hep B** | IVDA, Sex, Vertical through birthing | Strong Immune = Acute | Weak Immune = Chronic | HCC, Only with chronic infxn | Incomplete DNA | All @ risk, especially health care providers | See Above |
| **Hep C** | IVDA, Horizontal, or through blood transfusions | Never | Always | HCC | RNA | None | See Above |
| **Hep D** | IVDA, Sex, requires Hep B | Never | Always | HCC | RNA | None | - |
| **Hep E** | Fecal-Oral | - | - | - | - | - | |

# Lecture Quiz

1:A / 2:C / 3:C

**Q1: 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. gallstone
B. Viral hepatitis
C. Alcoholic hepatitis
D. Autoimmune hepatitis

**Q2:You see a 56-year-old woman who presents with a two-month history of jaundice. Associated symptoms include lethargy and polyarthralgia. Her LFTs reveal a bilirubin of 46 iu/L, AST 200, ALT 175, ALP 104. On examination, the patient is jaundiced and has finger clubbing. There are several spider naevi on the front and back of the trunk. Her abdomen is soft and there is a smooth hepatomegaly. Prior to her onset of symptoms, the patient has been fit and well. Viral serology is normal and anti-soluble liver antigen (SLA) is detected. You decide to start this patient on treatment. The most appropriate treatment is:**

A. Liver transplantation
B. Methotrexate
C. prednisolone
D. Cyclosporin

**Q3: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 41 iu/L, AST 111 iu/L, ALT 55 iu/L and ALP 98 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. ramorol
C. Amiodarone
D. bendroflumethiazide