Faculty of Pharmacy- Clinical Pharmacy Program - level 5 - Spring 2016

Gastroenterology

Second Lecture: **Hepatitis**

Prof.Dr. Hasan El-Asklany

Professor of internal medicine, Gastroenterology & Hepatology

Faculty of medicine Mansoura University

Hepatitis

- **Definition:** Hepatitis is an inflammation of the liver.
- **Etiology:**
  - Hepatitis can be caused by both infectious (viral, bacterial, fungal, and parasitic organisms) and non-infectious (alcohol, non-alcoholic fatty liver disease, toxins, drugs, autoimmune diseases, and metabolic diseases)
  - Worldwide, viral hepatitis is the most common cause of liver inflammation. Hepatotropic viruses causing viral hepatitis include hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus(HDV) (which requires hepatitis B to cause disease) and hepatitis E virus (HEV).
- **Acute versus chronic viral hepatitis:**

  Hepatitis is acute when it lasts less than six months duration and chronic when it persists longer.

Acute viral hepatitis

- **Epidemiological and clinical features of hepatitis viruses:**

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Synonym	Infectious hepatitis	Serum hepatitis	Hepatitis C	Delta hepatitis	Hepatitis E
Type of virus	ssRNA	dsDNA	ssRNA	ssRNA	ssRNA
Incubation period	2–7 weeks	1–6 months	2–26 weeks	2–12 weeks	6–8 weeks
Transmission	Faecal–oral	Predominantly parenteral	Parenteral	Parenteral	Faecal–oral
Carrier state	No	Yes	Yes	Yes	No
Severity of hepatitis	±	++	+	+	±
Immunity					
Passive immunization	Hyperimmune globulin	Hyperimmune globulin	None	Hyperimmune globulin	None
Active immunization	Vaccine (hepatitis A)	Vaccine (hepatitis B)	None	Vaccine (hepatitis B)	None

ss, single-stranded; ds, double-stranded.

- **C/P:** Acute infection with a hepatitis virus may result in conditions ranging from:
  - subclinical disease (asymptomatic), to
  - self-limited symptomatic disease, to
  - Fulminant hepatic failure.
- **Typical symptoms of acute hepatitis are:**
  - Fever: non-specific and flu-like;
  - Appetite loss= anorexia;
  - Nausea and vomiting;
  - Abdominal pain; and
  - Jaundice (yellowish colour on the skin and eyeballs); and dark urine.
- **Fulminant hepatic failure (FHF)**
  - Defined as acute liver failure (within 8 weeks of onset) that is **complicated by** hepatic encephalopathy, coagulopathy, and multisystem organ failure. FHF may occur in as many as 1% of cases of acute hepatitis. FHF may result in death unless liver transplantation is performed in time.

Chronic viral hepatitis

- **Definition:** inflammation of the liver continuing without improvement longer than 6 months
- Hepatitis A and hepatitis E **never** progress to chronic hepatitis, either clinically or histologically.
- Chronic hepatitis can be demonstrated in
  - Approximately 90-95% of cases of acute **hepatitis B** in neonates, 5% of cases of acute hepatitis B in adults.
  - Approximately 85% of cases of acute **hepatitis C**.

- **Symptoms of chronic hepatitis**: Chronic hepatitis may cause nonspecific symptoms such as malaise, tiredness, and weakness. Extrahepatic manifestations of the disease (eg,polyarteritis nodosa, cryoglobulinemia, and glomerulonephritis) may develop in Chronic hepatitis B& C patients.
- It is commonly identified on blood tests performed either for screening or to evaluate nonspecific symptoms.
- Approximately 20% of patients with chronic hepatitis eventually develop **cirrhosis**, as evidenced by the histologic changes of severe fibrosis and nodular regeneration. The clinical illnesses of chronic hepatitis and cirrhosis may take months, years, or decades to evolve.

Diagnosis of viral hepatitis

- Diagnosis is made by assessing an individual's symptoms, physical exam, and medical history, in conjunction with blood tests. Blood testing includes liver blood chemistry& serology.
- **Liver Function Test (Liver chemistry test): classified in 3 groups:**
    - **Synthetic function :** albumin, PT(Prothrombin time)
    - **Hepatocyte injury :** aminotransferases: Aspartate transaminase (AST), Alanine transaminase (ALT), bilirubin
    - **Cholestasis (obstruction of bile flow) :** bilirubin, Alkaline phosphatase(ALP), Gamma-glutamyl transpeptidase (GGT)
        - ☒ Very high aminotransferase values (>1000 U/L) and hyperbilirubinaemia are often observed in acute viral hepatitis patients, while mildly high aminotransferase values (300 U/L) are observed in chronic viral hepatitis patients.
- **Serological tests= viral hepatitis markers:**

A. Diagnosis of **HAV** is by demonstration of HAV antigen in feces. Serological tests demonstrate immunoglobulin **M (IgM)** class anti-HAV antibodies in serum during the acute or early convalescent phase which disappears several months after the initial infection. The presence of immunoglobulin G (**IgG**) anti-HAV merely demonstrates that an individual has been infected with HAV at some point in the past.

B. **HBV:** Detection of IgM for hepatitis B core antigen (**IgM anti-HBc**) in serum is required to make the diagnosis of acute hepatitis B virus (HBV) infection. Testing with a polymerase chain reaction (**PCR**)-based assay for **HBV DNA** Hepatitis B surface antigen (**HBsAg**) may be present in acute infection or in patients who are chronic carriers. Its presence in patients with symptoms of acute hepatitis strongly suggests acute HBV infection. The presence of **HBsAg in the serum for 6 months or longer indicates chronic infection**.

C. There are 2 types of assays for detecting the presence of **HCV infection**:

- Serologic assays to detect antibody to HCV (**anti-HCV**) using enzyme-linked immunosorbent assay (ELISA) and Enzyme immunoassays (EIA). IgG anti-HCV antibodies appears **4-10 weeks** after acute HCV infection.
- Molecular tests for the presence of viral particles: Qualitative polymerase chain reaction (**PCR**) assay for presence of viral particles and positive **1 week** after acute HCV infection.

D. A serologic diagnosis of **HDV** infection is made by using **IgM anti-HDV** and IgG anti-HDV tests. **IgM anti-HBc** should be used to help distinguish between coinfection (positive for IgM anti-HBc) and superinfection (negative for IgM anti-HBc). Detecting HDV RNA in serum is also possible.

E. A serologic diagnosis of hepatitis E virus **(HEV)** infection is made by using **IgM** antibody to HEV (anti-HEV) and IgG anti-HEV. HEV RNA can be detected in the serum and stool of infected patients.

Treatment of viral hepatitis

A) Treatment of Acute viral hepatitis

❖ **Approach Considerations for acute viral hepatitis:**

- Most patients with viral hepatitis can be monitored on an outpatient basis. Ensure that patients can maintain adequate hydration, and arrange close follow-up care. Instruct patients to avoid using any potential hepatotoxins (eg, ethanol or acetaminophen). Advice patients to avoid prolonged or vigorous physical exertion until their symptoms improve.
- No specific emergency department (ED) treatment is indicated, other than supportive care that includes intravenous (IV) rehydration.
- Admit patients with hepatitis if they are showing any signs or symptoms suggestive of severe complications (? **FHF**):
  - hepatic encephalopathy any patients with altered mental status, agitation, behavior or personality changes, or changes in sleep-wake cycle.
  - criteria that are suggestive of severe disease include a prothrombin time (PT) longer than 3 seconds, a bilirubin level greater than 30 mg/dL, and hypoglycemia,
  - intractable vomiting, significant electrolyte or fluid disturbances.

❖ **Management of Acute HBV Infection**

- As is the case for acute HAV infection, no well-established antiviral therapy is available for acute HBV infection. Supportive treatment recommendations are the same for acute hepatitis B as for acute viral hepatitis.
- **Lamivudine**, **adefovir**, and **other antiviral therapies** appear to have a positive impact on the natural history of ***severe cases*** of acute HBV infection.

❖ **Management of Acute HCV Infection**

- **12 weeks of peginterferon monotherapy** recommended
- **Peginterferon alfa-2a** should be dosed at 180 µg/wk, and **peginterferon alfa-2b** should be dosed at 1.5 µg/kg/wk
- Therapy should be delayed **12-16 weeks** to allow for spontaneous clearance

B) Treatment of chronic viral hepatitis

- **For chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infections**: the goals of therapy are to decrease viral replication or eradicate virus, reduce liver inflammation and fibrosis and to prevent progression to cirrhosis and its complications e.g. HCC .
- **Chronic Hepatitis B:**
  - Candidates for antiviral therapy must have evidence of active HBV infection. Before therapy is started, patients should undergo testing with a polymerase chain reaction (PCR)-based assay for HBV DNA. At present, the typical threshold for treatment is a viral load of 2 × 104 IU/mL or more .
  - Agents currently used to treat hepatitis B include PEG- Interferon (IFN alfa-2a) and the oral nucleoside or nucleotide analogues (lamivudine, adefovir, entecavir, telbivudine, and tenofovir).
  - Typically, PEG-IFN treatment is continued for 48 weeks for both HBeAg-positive and HBeAg-negative chronic hepatitis. Treatment with PEG-IFN alfa-2a offers the hope of a finite course of treatment and the potential for achieving HBsAg negativity.
  - Oral nucleoside and nucleotide analogues may be used for as little as 1-2 years; however, most HBeAg-positive chronic hepatitis patients and almost all HBeAg-negative chronic hepatitis patients require indefinite therapy with these agents. Oral agents are often prescribed for indefinite periods
  - Nucleos(t)ide analogs in hepatitis B treatment

Agent	Advantages	Disadvantages
Lamivudine	Long-term data on clinical efficacy Studied in ESLD patients Studied extensively in pregnant women	High rate of resistance
Adefovir	Studied in ESLD Data in lamivudine failures	Lower potency Moderate rate of drug resistance
Entecavir	High potency High genetic barrier for resistance in treatment-naïve patients	Decreased response and increased resistance in patients with lamivudine-resistant HBV
Telbivudine	Moderate potency Category B in pregnancy	Not active against lamivudine-resistant HBV
Tenofovir	High potency Category B in pregnancy Studied in HIV-coinfected Low rates of resistance	Renal toxicity

- **Treatment of Hepatitis D**
  - Treatment of patients coinfected with HBV and HDV has demonstrated that patients with HBV-HDV coinfection are less responsive to IFN therapy than patients with HBV infection alone.
  - Treatment with PEG-IFN alfa-2b produced HDV RNA negativity in only 17-19% of patients. Lamivudine appears to be ineffective against HBV-HDV coinfection.

❖ Chronic Hepatitis C

- **Until mid-2011** the standard treatment regimen for chronic hepatitis C virus (HCV) infection was ***pegylated interferon (PEG-IFN) and ribavirin (RBV).*** There was, however, with interferon and ribavirin, a high incidence of adverse events. Treatment took a long time, up to 48 weeks, with high failure rate.
- **May 2011** the approval by the US Food and Drug Administration (FDA) of 2 direct-acting antiviral agents (DAAs), the first-generation NS3/NS4a protease inhibitors telaprevir and boceprevir. The introduction of DAAs for the treatment of HCV infection is the most significant development since the pegylation of interferon (INF) and the addition of RBV to PEG-IFN in the late 1990s.
- **2014** was a year of revolution in hepatitis C treatment. For more than 20 years, we were able to treat chronic hepatitis C virus (HCV) infection patients with interferon-based treatment regimens only, and ***from 2014 onwards***, we are able to give chronic hepatitis C virus (HCV) infection patients also ***interferon-free treatment regimens***.

Direct-acting antiviral drugs (DAAs):

❖ There are 3 classes of DAAs:

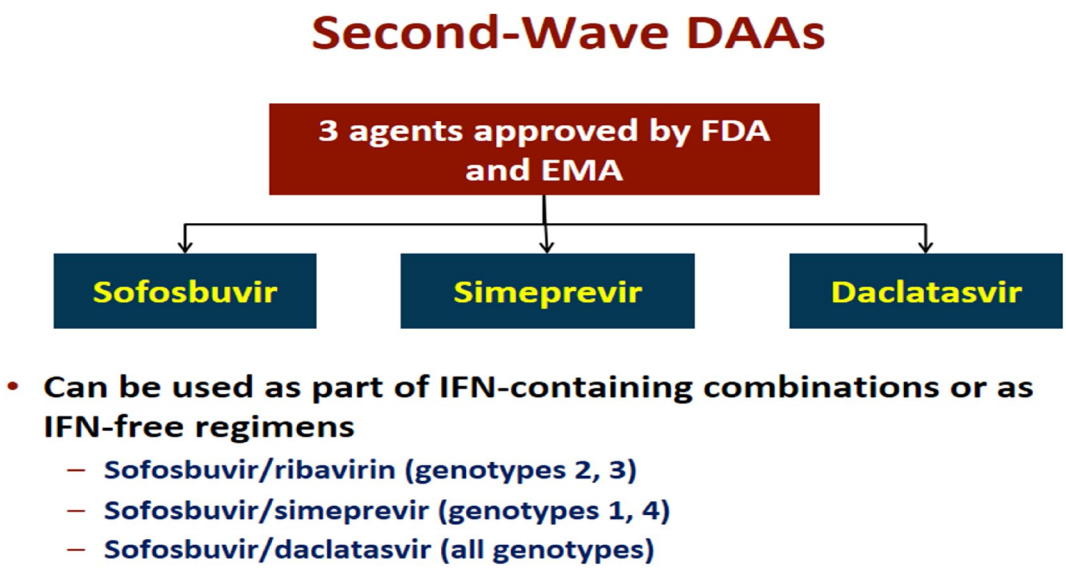
- protease inhibitor,
- polymerase inhibitor
- NS5A replication complex inhibitor.

❖ Direct-acting antivirals target specific steps of the HCV life cycle:

- RNA replication is inhibited by **sofosbuvir** ***a nucleotide NS5B polymerase inhibitor*** that competitively binds to the catalytic site of RNA polymerase.
- **Dasabuvir** and **Beclabuvir** are ***non-nucleoside NS5B polymerase inhibitors*** that work through allosteric inhibition.
- Polyprotein processing is targeted by ***NS3/NS4 serine protease inhibitors***, including **Boceprevir, Telaprevir, Simeprevir, Paritaprevir, Asunaprevir, and Grazoprevir.**
- ***Inhibitors of NS5A***, which likely modulates viral RNA replication, include **Ledipasvir, Ombitasvir, Daclatasvir, and Elbasvir**.

❖ **Specific Updates Hepatitis C Treatment Guidelines:**

- IFN-free regimens with ***direct-acting antivirals*** have quickly become the mainstay of treatment for HCV infection
- The primary goal of HCV treatment is cure, defined as ***sustained virologic response*** (SVR), that is, undetectable circulating HCV-RNA, 12 weeks after treatment completion.
- All patients with chronic HCV infection ***should be treated*** with the exception of those with short life expectancies as a result of comorbid conditions.
- Based on available resources, patients at high risk for liver-related complications should be given high priority for immediate treatment.



Centers for Disease Control and Prevention (CDC). Progress toward prevention and control of hepatitis C virus infection – Egypt, 2001–2012. Morb Mortal Wkly Rep 2012; 61(RR29):545–549.