The Doctor in the lecture emphasized on some information and told us to not focus on anything else. I will be mentioning what we need to know only.

Drugs Used in Hepatitis

1- Hepatitis B virus:

- HBV causes **chronic**/acute hepatitis, **cirrhosis** of the liver and hepatocellular **carcinoma**. **Asians** are mostly affected.
- It is considered a **human carcinogen** causing up to 80% of hepatocellular carcinoma.
- The virus particle (Dane) consists of an outer lipid envelope and a nucleocapsid core which encloses the viral DNA (thus it **has a vaccine**) and a DNA polymerase with a reverse transcriptase activity similar to retroviruses.
- The surface envelope expresses a hepatitis B surface antigen (**HBsAg**), it is considered a **marker**.
- **Tx:**
  1- **Immunomodulatory therapies**, including: Interferon alpha (IFN-α) and pegylated IFN-α.
  2- **Nucleosides analogs**, including: Lamivudine, Entecavir, Telbivudine and emtricitabine.
  3- **Nucleotides analogs**, including: Adefovir and Tenofovir.
- Not everyone is treated, treatment is only for patients in **active phases of HBV**.
- Drugs will be mentioned according to their date of approval:

Drug	Notes
1- Interferon 1991	- **First** approved therapy for chronic HB, but it's no longer used. - **Seroconversion** from HBeAg into anti-HBe marks the transition from the active phase of infection to the **inactive carrier state**. This occurred in **20**%, and in early trials, 8% became inactive carriers. - Trials of IFN-α were disappointing, suppressing HBV **transiently** but never resulting in antiviral response.
2- Lamivudine 1998	- The **first** nucleoside analog, it **inhibits** reverse transcriptase activity of both **HIV** and **HBV**. - It is potent and effective in treating **chronic hepatitis B**. It is taken **orally** with limited side effects. - It is used **until** seroconversion occurs (HBeAg conversion into anti-HBe). - It used among patients with **cirrhosis** or **advanced fibrosis**; it reduces the risk of hepatic decompensation and Hepatocellular carcinoma. - Due to the need for long treatment courses, **low barrier to resistance**, and less efficacy from later anti-virals, it is no longer recommended.
3- Adefovir 2002	- It is a **nucleotide analog**, **inhibiting** reverse transcriptase activity as well. - Continued treatment is **required** to maintain anti-viral response; thus, it is no longer recommended. - Among patients with **co-infections of HIV and HBV** with normal T-cell counts, Adefovir dipivoxil is effective. It is also effective in **Lamivudine-resistant patients**. - When Lamivudine resistance occurs, adding Adefovir maintaining Lamivudine to prevent the emergence of adefovir resistance is **better** than switching to it completely. - It is found to be **nephrotoxic** at high doses. **Creatine level elevations**, rarely encountered, indicate renal toxicity.
4- Pegylated Interferon 2005	- It is the **only interferon approved** for the treatment of chronic HB. - It is given **SC**, once weekly for 48 weeks.

5- Entecavir 2005	- **Oral cyclopentyl guanosine analog** and **polymerase inhibitor**. - It is the **most potent** of HBV antivirals and is **well tolerated.** - It is effective in **Lamivudine-resistant HBV**. - 0.5mg daily and up to 1mg daily in case of **liver cirrhosis**. - It has an excellent clinical profile but may worsen the rate of **osteoporosis**.
6- Telbivudine 2006	- **Cytosine analog**, similar to Entecavir in efficacy, but **less potent** in suppressing HBV DNA. - **Side effects**: Creatinine elevations, peripheral neuropathy, lactic acidosis, and may also worsen osteoporosis. - It is neither recommended as first-line therapy nor widely used.
7- Tenofovir 2008	- **Acyclic nucleotide analog**, **potent** antiviral in HIV infections similar to Adefovir but **more potent**. - It is given **once** daily (300mg). - **First-line therapy** for chronic hepatitis B and as an add-on therapy for **Lamivudine-resistant infections**. - The administration is reduced in patients with **impaired creatinine clearance**.

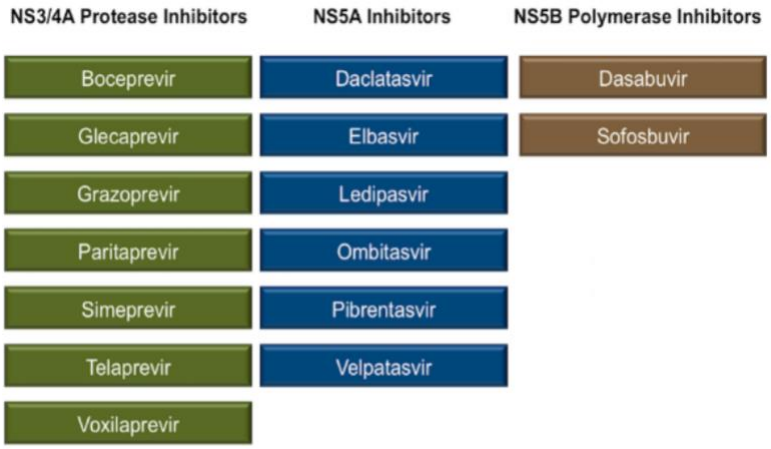
2- Hepatitis C virus:

- Half of the liver transplants due to **cirrhosis** is secondary to **HCV infections.**
- It is an **RNA virus** (thus has no vaccine) with **6** genotypes of different geographical prevalence and treatment. 70% of North America has genotype 1, while genotype 4 is common in Egypt and the Middle East.
- Frequent mutations may happen in the same person (**Quasispecies**).
- It is mostly transmitted by **blood**, which is much more than being sexually transmitted 20%.
- **Serologic Tests:**
  1- **HCV RNA** is detected within 2 weeks, it is a **marker of active infection** (Gold standard).
  2- **Anti-HCV** is detected by ELISA, it is positive up to 6 weeks and may become absent after recovery. It is used in patients with **undetectable HCV RNA.**
  3- **HCV RIBA** is used to confirm.
- Treatment can be for **any patient**, whether being in the active or inactive phase of the infection.
- The **non-structural part** of HCV RNA is the target of treatments.

Drug	Notes
1- Ribavirin	- **Guanosine nucleoside analog** with in-vitro antiviral activity. - **Monotherapy** has **no** significant effect on serum HCV RNA. - It is combined with **peg-interferon** and now with new **DAAs** (discussed below) to **reduce relapse**. - **Side effects**: dose-dependent hemolytic anemia, renal failure, **teratogenic** for both males and females, nausea and pruritic rash.
2- Interferon	- Combined with **Ribavirin for HCV treatment**. - **Types**: peg-interferon alpha 2-a and peginterferon alpha 2-b. - **Sustained Virologic Response (SVR)**: 40% in genotype **1**, 80% in genotype 2 and 3. - Used with **DAAs** as a **second-line therapy** to **shorten** the duration of therapy. Infection may **relapse** 20% after therapy discontinuation. - **Side effects**: worsening underlying psychiatric diseases.

3- Direct-acting antiviral agents (DAA) *The doctor didn't mention them all in details. He mainly focused on their target.*	- In contrast to the **nonspecific activity of peg-interferon** and **Ribavirin**, **DAAs** are designed to inhibit **viral proteins** involved in the HCV life cycle, acting on the non-structural part of HCV RNA.	
	Boceprevir, Telaprevir	- Inhibitors of HCV nonstructural protein (**NS3/4A**) serine protease and the **first** DAAs to be approved. - Used with Ribavirin and interferons to **enhance SVR**. - **Side effects**: anemia and skin rash.
	Simeprevir	- Second DAA generation, **NS3/4A inhibitor**. - Used with Ribavirin and interferons for **genotype 1.** - Used with Sofosbuvir for **minimal side effects.** - **Contraindicated** in **decompensated cirrhosis**.
	Sofosbuvir	- Prodrug that acts on **NS5B**. - Used in **all** genotypes in combination with other DAAs. - Renally cleared, not used if **GFR is less than 30ml/min**.
	Ledipasvir	- **NS5A inhibitor**. - Approved efficacy in combination with Sofosbuvir. May have efficacy on **all** genotypes and **HIV co-infections**.
	Ombitsavir, Paritaprevir, Ritonavir, Dasabuvir	- **For genotype 1.** - **Ombitasvir**: NS5A inhibitor with pan-genotypic activity. - **Paritaprevir**: NS3/A4 protease inhibitor. - **Ritonavir**: CYP3A inhibitor which increases the serum level of Paritaprevir. - **Dasabuvir**: NS5B RNA polymerase inhibitors. It is combined with Ribavirin for genotype 1a only not 1b. It is not used in decompensated cirrhosis patients.
	Daclatasvir	- NS5A inhibitor, used in combination with Sofosbuvir for genotype 3. - Does not need renal nor hepatic adjustment.
	Elbasvir, Grazoprevir	- Effective in genotypes 1,2,4,5,6. - Used in genotype 1 with patients with ESRD. - Elbasvir is an NS5A inhibitor, while Grazoprevir is an NS3/A4 inhibitor.
	Velpastasvir, Voxilaprivir, Pebrentasvir	- *The doctor didn't explain them, refer to their respective 2 slides if you want.*

- HBV is a DNA virus with a vaccine, treatment is for patients in active phase only, while HCV is an RNA virus with no vaccines, treatment is for all patients.
- Know the combinations and what are they used for.
- Know what drugs may develop resistance.
- Memorize this table knowing each DAAs' target in treatment to eradicate HCV:



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