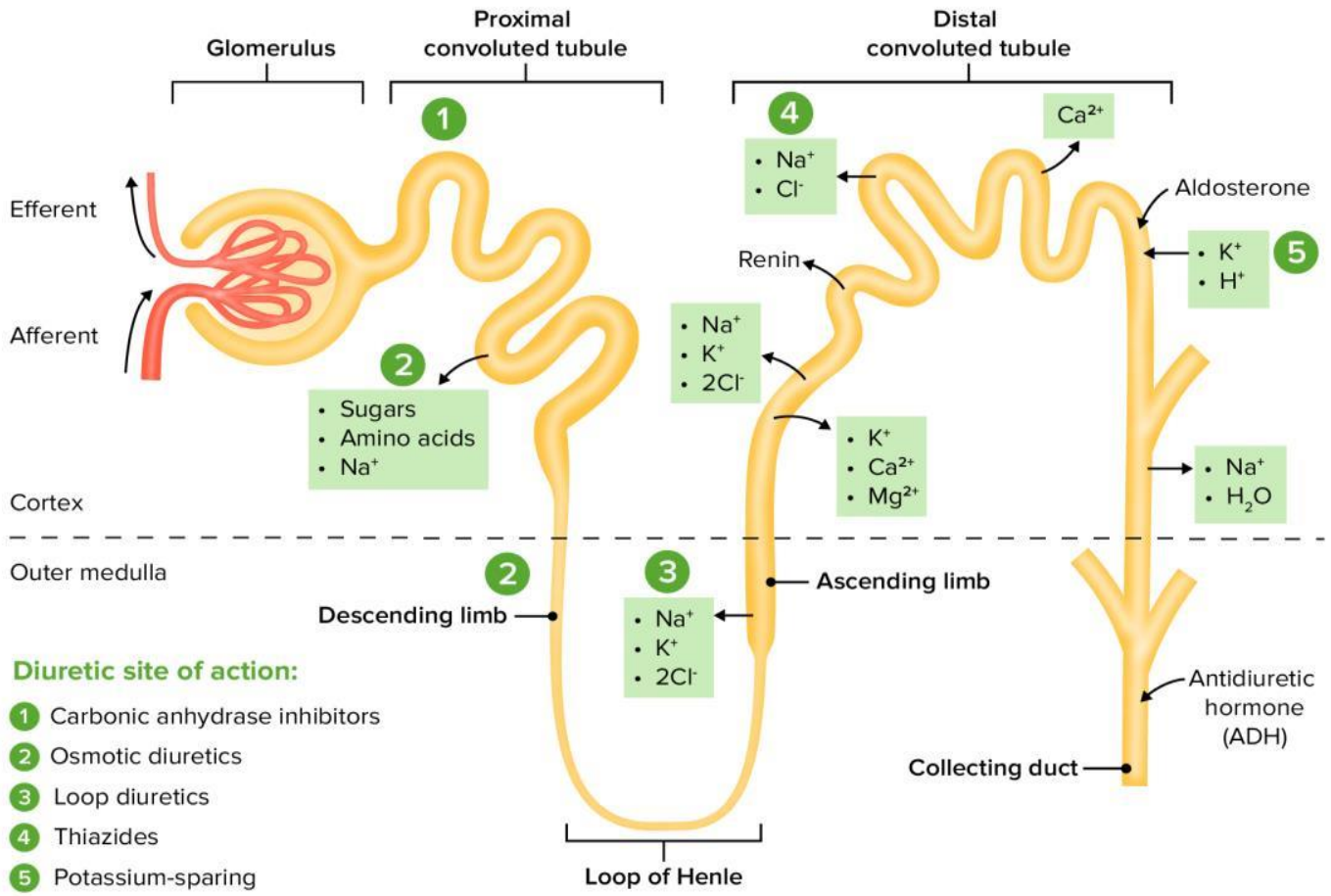
Diuretics in liver dse

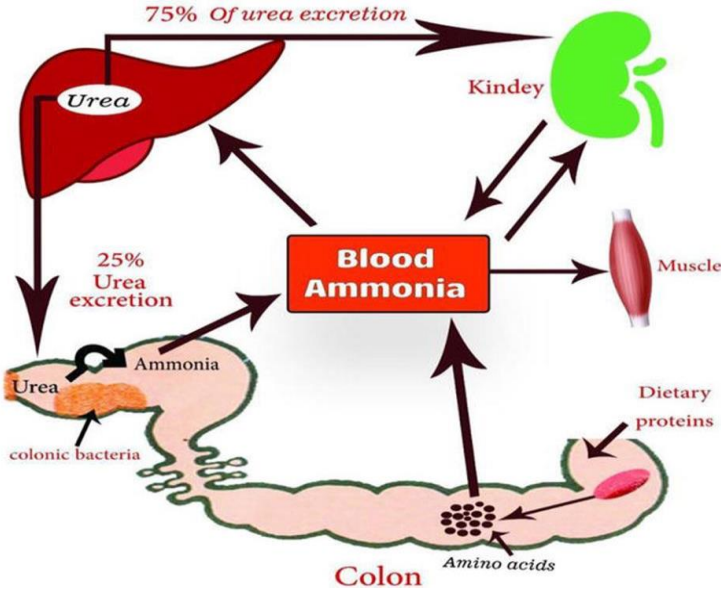
- *The combination of **spironolactone and furosemide** is recommended as initial diuretic therapy for patients with ascites.*

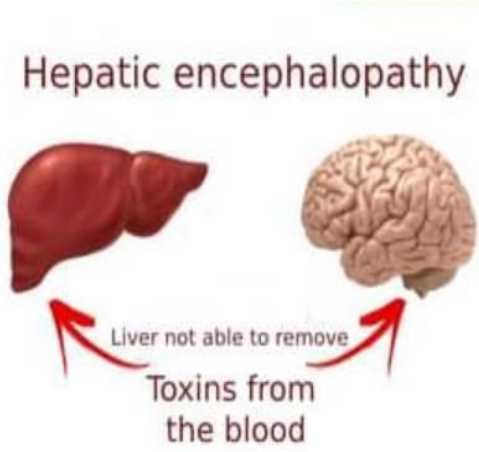
Advantages of diuretics:	Disadvantages of diuretics:
• *Correction of **fluid retention.*** • *Spironolactone antagonizes **aldosterone.***	• *Aggressive use of diuretics can precipitate **hepatorenal syndrome.*** • *Aggressive use of diuretics can precipitate **hyperammonemia** and **hepatic encephalopathy***

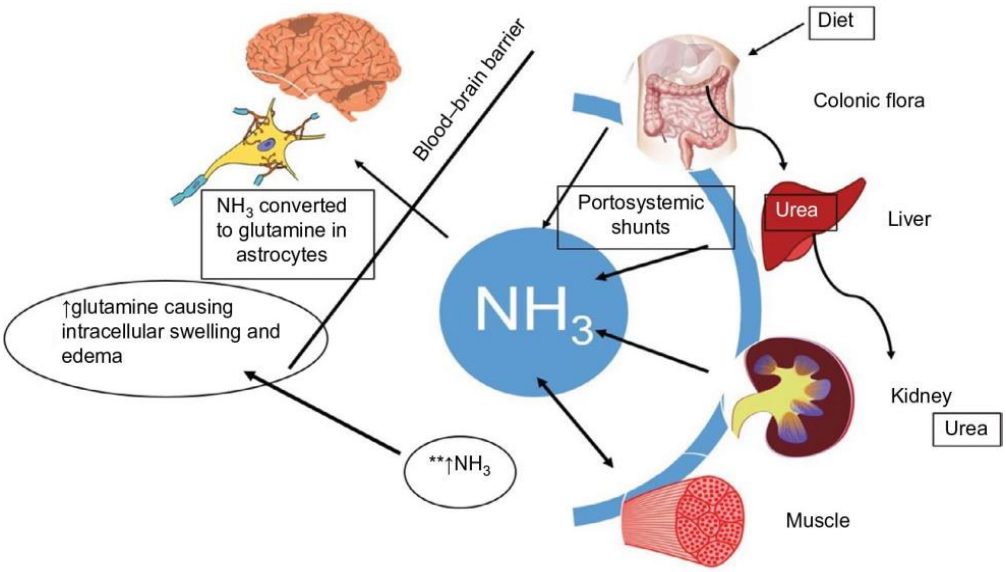


Hepatic encephalopathy

- **Definition:**
  - *is a functional disturbance of the brain caused by **liver insufficiency** or **portal systemic shunting***
- **Pathogenesis:**
  - *It results from an **accumulation** of **gut-derived nitrogenous substances** due to decreased hepatic functioning.*
  - *Once these substances enter the **CNS**, they cause alterations of neurotransmission that affect **consciousness and behavior.***
  - ***Ammonia** is the most important in the pathogenesis of HE, but glutamine, benzodiazepine receptor agonists, and aromatic amino acids have role.*

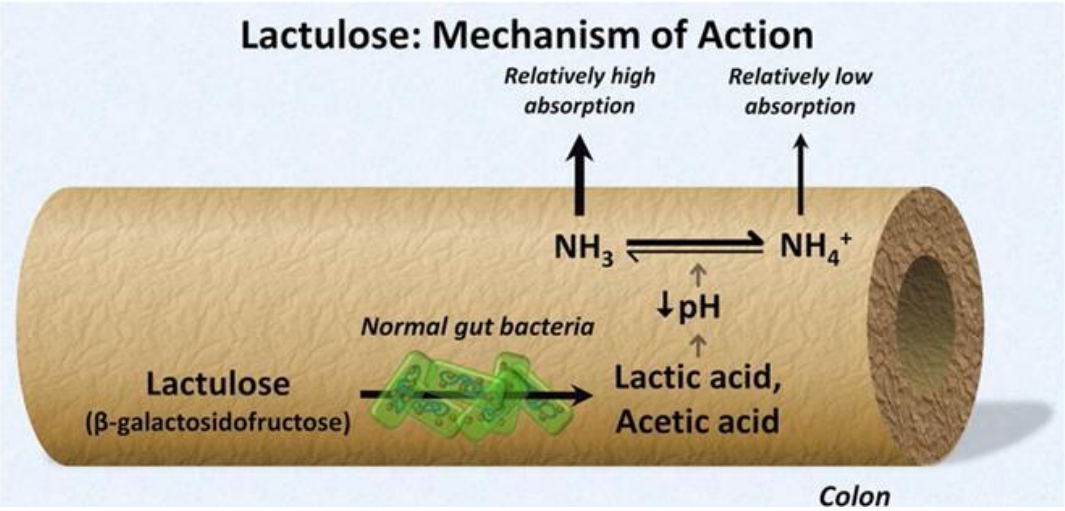






Management of hepatic encephalopathy

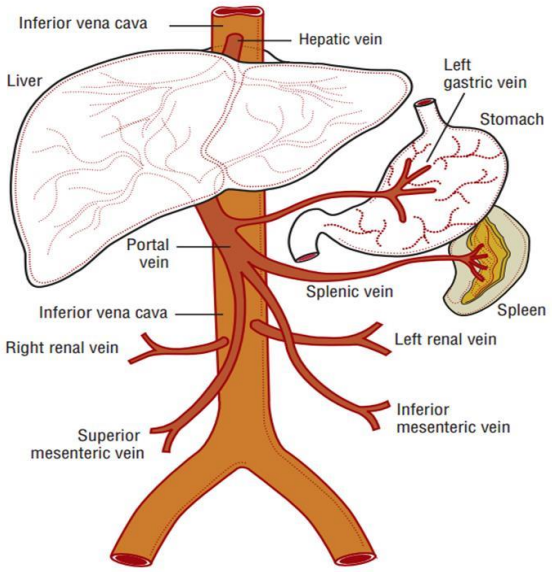
- ***Aim:*** *Treatment is aimed at reduction of* ***hyperammonemia.***
- ***Management:***

Diet:	• ***Protein restriction*** *to decrease formation of ammonia by intestinal bacteria.* • ***Vegetable*** *protein is better tolerated than animal protein.* • *The rationale and benefit of dietary protein restriction is* ***controversial.***
Enemas:	• *Cleansing of the colon is a* ***rapid*** *and* ***effective*** *method to remove ammoniagenic substrates.* • *It can be done with* ***lactulose*** *or tape water.*
Lactulose:	• *It is synthetic non-absorbable disaccharide. In the colon, it is transformed by bacteria into* ***lactic and acetic acids*** *→↓ pH of the colonic medium leading to:* ➢ *Inhibition of* ***intestinal bacteria*** *→↓ production of ammonia.* 

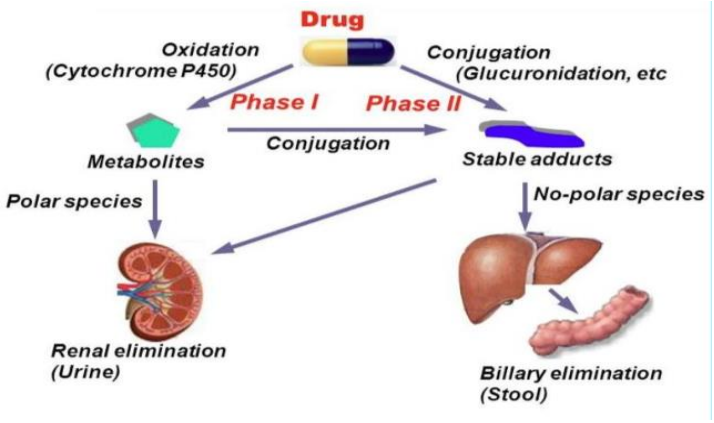
Oral antibiotics:	• **Neomycin:** ➢ *It is **non-absorbable** aminoglycoside antibiotic.* ➢ *It ↓ blood ammonia by **killing intestinal bacteria** that generate ammonia.* ➢ *It is used in a dose of 1-2 g 4 times daily **orally** or as **retention enema**.* ➢ *Small amounts of neomycin may be absorbed (~1%) and result in **ototoxicity** and **nephrotoxicity** especially in patients with renal impairment.* • **Metronidazole:** ➢ *Acts on **anaerobic** bacteria.* ➢ *It is the **preferred option** if there is fear from adverse effects of neomycin (but given for short term).* • **Rifaximin:** *is non-absorbable and better **tolerated** antibiotic.*

Portal hypertension

- ***Non-selective β-blocker** reduces portal pressure.*
- ***Non-selective β-blocker therapy plus endoscopic varices ligation (EVL)** is the best therapeutic option for prevention of recurrent variceal bleeding.*



▪ Altered drug pharmacokinetics and pharmacodynamics in liver disease:

Pharmacodynamics in liver disease:	• *There is increased sensitivity to the effects of **certain drugs** including opiates, benzodiazepines, and nonsteroidal anti-inflammatory drugs (NSAIDs).* 
Pharmacokinetics in liver disease	• *Reduced hepatic blood flow, lower first-pass extraction, and portosystemic shunting result in **higher bioavailability** and serum levels of drugs.* • *Hypoalbuminemia results in **higher concentrations** of free drug due to less protein binding.* • *Ascites **increases volume of distribution** of hydrophilic drugs.* • *Serum levels of various drugs can be higher after normal dosing secondary to **impaired biliary and renal excretion** that is possible in cirrhosis.* • ***Reduced enzymatic clearance by hepatocytes** can also lead to reduced first-pass metabolism and reduced hepatic clearance.* 

Drugs For Viral Hepatitis

	1- Interferons	2- Ribavirin
Nature	• *They are **natural antiviral glycoproteins.*** • *They were called so because they **interfere** with replication of the virus in tissue culture.* • ***Interferons are of three major classes:*** ➢ ***Alpha** synthesized by leucocyte.* ➢ ***Beta** produced by fibroblasts.* ➢ ***Gamma** formed by lymphocytes.* • *Exogenous interferon used clinically is **alpha** interferon produced by using recombinant DNA technology.*	• *It is a **synthetic purine nucleoside** that possesses broad antiviral inhibitory activity against respiratory syncytial, herpes simplex and influenza viruses.*
MOA	***1)** The natural interferons attach to surface receptor on membrane of infected cell and then inhibit synthesis of protein & DNA that **block viral replication**. Also interferon **blocks viral assembly and release**.* ***2) Suppress cell proliferation.*** ***3) Interferon has immunomodulating effects:** It enhance phagocytosis by macrophages and increases the cytotoxicity exerted by lymphocytes*	• *Ribavirin has **anti-metabolite activity**, which interfere with synthesis of viral messenger RNA and ribonucleic protein synthesis.*

Uses:	**1) Treatment of viral infections**, especially, chronic hepatitis B and C viruses and prevents chronic liver toxicity, AIDS and genital (venereal) warts. **2) Human cancer** shows some response to interferon e.g. certain leukemias, lymphomas and laryngeal papillomatosis	**1)** Ribavirin aerosol is used in the treatment of infants and young children with severe lower respiratory tract infection due to **syncytial virus**. **2)** If it is used within 24 hrs. of appearance of influenza A and B symptoms it reduces fever and systemic symptoms. **3)** High dose IV is used in Lassa fever. **4)** Hepatitis B ,C
Adverse effects:	**1) Flu-like symptoms:** Fatigue, depression, muscle weakness, weight and appetite loss, and change in thyroid function and cardiotoxcity. **2)** High dose or chronic therapy causes **bone marrow suppression**, **neurotoxicity** and progressive fatigue. **3)** Plasma concentration of **hepatic enzymes** increase. **4)** The metabolism of other drugs can be **reduced** by interferon action on microsomal enzyme.	**1) Rash, conjunctivitis.** **2) Dyspnea and chest soreness and decline of pulmonary** function if used in adult who have chronic respiratory disease.

	3- Adefovir	4- Entecavir	5- Lamivudine
MOA	• *It is phosphorylated by cellular kinases to the **active diphosphate metabolite** and then **competitively inhibits HBV DNA polymerase** to result in chain termination after incorporation into the viral DNA.*	• *Competitively **inhibits all three functions of HBV** DNA polymerase, **including** base priming, reverse transcription of the negative strand, and synthesis of the positive strand of HBV DNA.*	• ***Inhibits HBV DNA polymerase** and **HIVreverse transcriptase.***
Uses	• *Adefovir is **active in vitro** against a wide range of DNA and RNA viruses, including HBV, HIV, and herpesviruses.*		
Kinetics		• ***Oral bioavailability approaches 100%** but is decreased by food; therefore, entecavir should be taken on an empty stomach.* • *The intracellular half-life of the active phosphorylated compound is **15 hours**.* • *It is excreted by the **kidney**, undergoing both glomerular filtration and net tubular secretion.*	