GI pharma summary lec 7 Liver cirrhosis

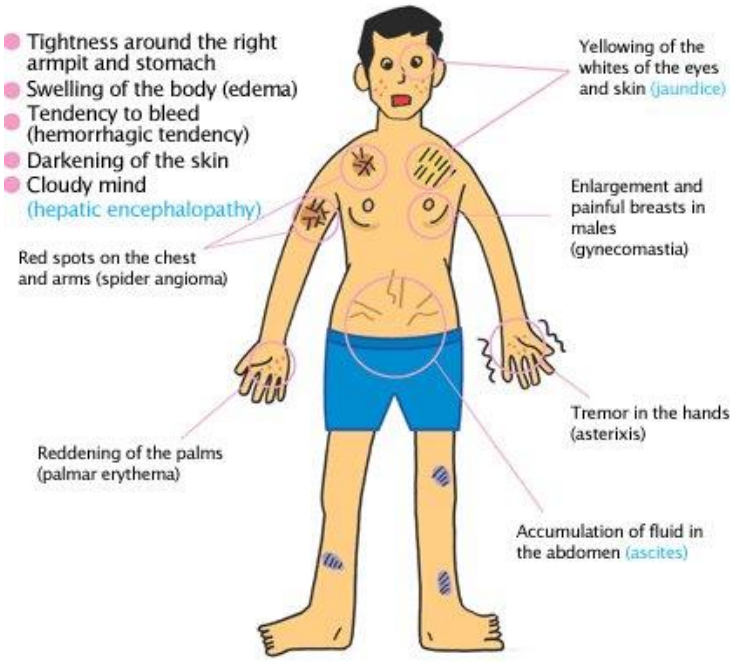
Summary prepared by Dr: Ahmad Almohtaseb

Liver cirrhosis is a chronic progressive disease characterized by **extensive degeneration and destruction of liver parenchyma resulting in the replacement of normal liver tissue with diffuse fibrosis.**

There is no radical cure except for liver transplant

So treatment aims at improving symptoms and reducing complications

Common etiologies: Alcohol consumption, Viral hepatitis ,Obesity, Metabolic syndrome leading to non-alcoholic steatohepatitis



A 65-year-old man is brought to the emergency room for abdominal pain. He has a history of alcohol abuse. He reports that he has felt fatigued, itchy, and "out of it" for the past several weeks. His wife also noticed that his skin looks more orange. On exam, his abdomen is distended with a positive fluid wave.(ascites) Dermatologic exam reveals jaundice, palmar erythema and spider angiomata. A hepatic ultrasound shows nodularity and fibrosis of the liver.

A 63-year-old male with a history of alcohol abuse is admitted to the hospital after his wife found him to be confused. On exam, he is disoriented and fatigued. The whites of his eyes and his skin have a yellow hue**(jaundice)**
Furthermore, his hands flap when he holds his arms out straight in front of him and extends his wrists**(asterixis).** His abdomen is distended with muffled bowel sounds and a fluid wave**(ascites).** His abdominal exam is remarkable for the finding of abnormal masses as shown in Figure A. Which of the following processes is most likely responsible for the finding seen in this clinical photograph?

Treatment of liver cirrhosis

Ursodiol (ursodeoxycholic acid): a secondary bile acid

• Mechanism: **Bile acid that is orally absorbed, conjugated in liver, excreted in bile with extensive enterohepatic circulation (It increases non-toxic bile acid pool in bile and replaces the toxic hydrophobic ones):-**

1) Protection of injured cholangiocytes against toxic effects of bile acids

2) Stimulation of impaired biliary secretion

3) Stimulation of detoxification of hydrophobic bile acids

4) Inhibition of apoptosis of hepatocytes.

Drugs decreasing portal pressure cirrhosis complication (for esophageal varices):

1. **Octreotide: Somatostatin analogue, act by inducing mesenteric arterial vasoconstriction, thus reducing portal venous flow (PVF) and portal pressure.**

2. **β blockers: reducing portal venous flow (PVF) and portal pressure**

3. **Vasopressin: potent arterial vasoconstriction**

4. **Nitrates: decrease hepatic venous pressure by venodilation**

Hepatic encephalopathy (HE):-

• **Brain dysfunction** caused by **liver insufficiency in detoxifying ammonia →ammonia accumulation in brain**

• **Manifests as: a wide spectrum of neuropsychiatric abnormalities, from mild subclinical changes (eg, inversion of sleep cycle) to marked disorientation, confusion, and coma.**

• Overt hepatic encephalopathy may develop over a period of hours or days and **can occur spontaneously or following an event, such as gastrointestinal bleeding, infection, dehydration, or constipation.**

Mechanism of hepatic encephalopathy:-

Gut bacteria produce urease, which converts dietary proteins into **ammonia.**

Gut bacteria also produces Glutaminase which converts glutamine into glutamate and ammonia.

Normally: Ammonia is converted into urea in the liver.

. In hepatic encephalopathy: ↑ammonia

This → brain edema & neuropsychiatric manifestations.

In fasting: glycogenolysis is not sufficient to ↑blood glucose. So ↑gluconeogenesis → ↓amino acids, ↑ammonia

Treatment includes:

1. **Correcting any predisposing conditions**
2. **Lowering blood ammonia levels with medications**
3. **Restricting dietary protein is not recommended for the majority of patients**

treatment of Predisposing conditions/precipitating factors:

- **Gastrointestinal bleeding Infection (including spontaneous bacterial peritonitis and urinary tract infections)**
- **Hypokalemia and/or metabolic alkalosis**
- **Renal failure**
- **Hypovolemia**
- **Sedative or tranquilizer use**
- **Hypoglycemia**
- **Constipation**
- **When possible, these precipitating causes should be treated.**

Lowering blood ammonia for hepatic encephalopathy treatment:-

Lactulose: In the colon, lactulose (beta-galactosidofructose) and lactitol (betagalactosidosorbitol) are catabolized by the bacterial flora, resulting in an acidic pH.

The reduction in pH favors the formation of the nonabsorbable NH4+ from NH3 , trapping NH4+ in the colon and thus reducing plasma ammonia concentrations.

Other effects that may contribute to the clinical effectiveness of lactulose include:

1. **Increased incorporation of ammonia by bacteria for synthesis of nitrogenous compounds.**

2. **Modification of colonic flora, resulting in displacement of urease-producing bacteria with nonurease-producing Lactobacillus.**

3. **Cathartic(water drawing) effects of a hyperosmolar load in the colon that improves gastrointestinal transit, allowing less time for ammonia absorption.**

4. **Increased fecal nitrogen excretion due to the increase in stool volume .**

Lactulose is also used for prevention of recurrent hepatic encephalopathy

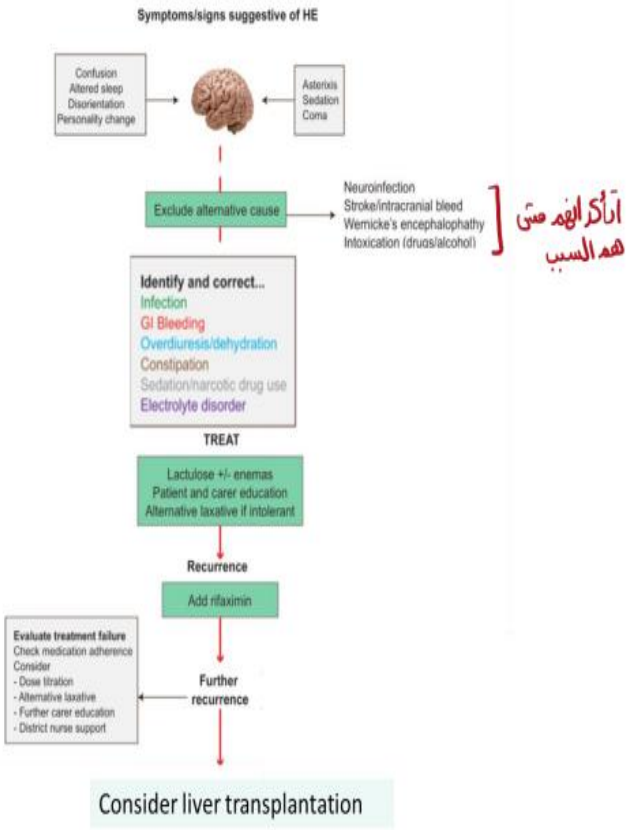
2- **Antimicrobial therapy: Non absorbed antibiotics against urease- producing & glutaminase - producing gut bacteria.**

a. **Rifaximin: Antimicrobial of 1st choice because it is not absorbed, broad spectrum, with low adverse effects.**

b. **Neomycin: decrease bacterial glutaminase.**

side effects: ototoxicity & nephrotoxicity(at high doses)

فهم عام



Drugs induce liver injury (DILI)

• **Common and nearly all classes of medications can cause liver disease.**

Most cases of DILI are benign and improve after drug withdrawal.

• It is important to recognize and remove the offending agent as quickly as possible to prevent the progression to chronic liver disease and/or acute liver failure.

• **Treatment of drug and herbal-induced liver injury consists of rapid drug discontinuation and supportive care targeted to alleviate unwanted symptoms.**

Risk factors for drug-induced liver injury

• **Age :hepatic drug reactions are rare in children**.

Elderly persons are at increased risk of hepatic injury.

• **Sex** : although the reasons are unknown, **hepatic drug reactions are more common in females.**

• **Alcohol ingestion**

• **Genetic factors: a unique gene encodes each P-450 protein. Genetic differences in the P-450 enzymes can result in abnormal reactions to drugs(genetic polymorphisms)**

• **Other comorbidities**: **Persons with AIDS, persons who are malnourished.**

• **Drug formulation: Long-acting drugs may cause more injury than shorter-acting drugs**.

Pathophysiology of drugs induce liver injury:-

The pathophysiologic mechanisms of hepatotoxicity are still being explored and **include both hepatocellular and extracellular mechanisms.**

• **Disruption of the hepatocyte**

• **Cytolytic T-cell activation**: **Covalent binding of a drug to the P-450 enzyme acts as an immunogen, activating T cells and cytokines and stimulating a multifaceted immune response.**

• **Apoptosis of hepatocytes**

• **Mitochondrial disruption**

• **Disruption of the transport proteins:** Drugs that affect transport proteins at the canalicular membrane can **interrupt bile flow causing cholestasis.**

• **Bile duct injury:** Toxic metabolites excreted in bile may cause injury to the bile duct epithelium.

Drug name	Class
Acetaminophen Panadol	Antipyretic, Pain medication
NSAID e.g., diclofenac	NSAID
Ciprofloxacillin	Antibiotics
Erythromycin	Antibiotics
Amoxicillin	Antibiotics
Fluconazole	Antifungal
Chlorpromazine	CNS
Valproic acid	CNS
phenytoin	CNS
Methotrexate	Chemotherapy and immune system suppressor
Statins	HMG-CoA reductase inhibitors
Oral contraceptives	Oral contraceptives
Methyldopa	Antihypertensive
Halothane	Anesthetic

• The management of DILI is based upon **proper diagnosis, recognition of the offending agent, and its withdrawal.**

• **The decision to discontinue the medication is based on the values of liver enzymes.**

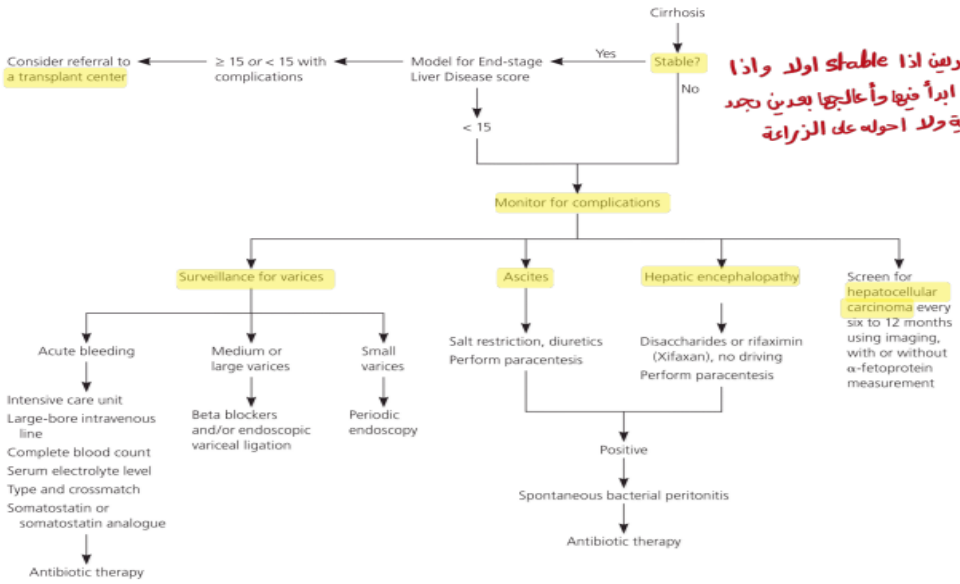
Even after stopping the drug, the outcome may vary from complete resolution to acute liver failure and death.

• **Acetaminophen intoxication is treated with N-acetylcysteine (no other specific antidotes are currently employed.)**

• Severe cases that progress to acute liver failure may require liver transplantation.

Managements of Liver Cirrhosis

الدكتورة حكت افهموها



* باختصار بشوف حالة المريض اذا stable اولا واذا عنده complication لازم ابدأ فيها وأعالجها بعدين بجدد اذا بمشي حاله مع الادوية ولا احوله على الزراعة