

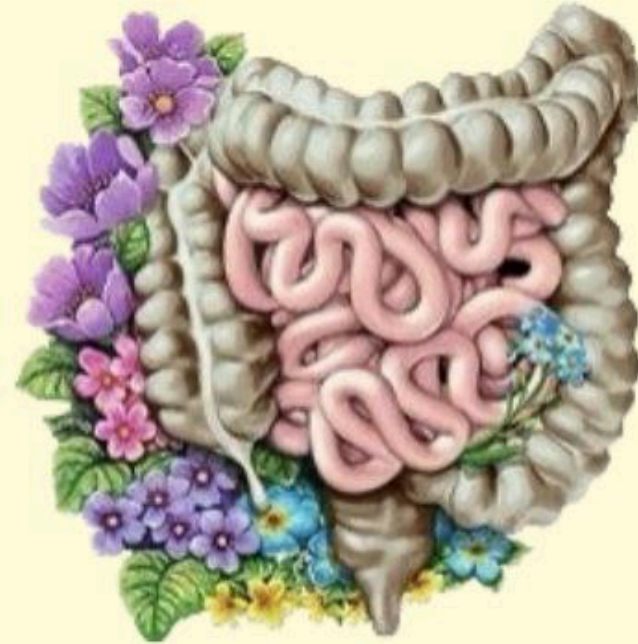


GIT SYSTEM

Subject : Pharmacology

Lecture : Lec 7

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وَقُلْ رَبِّ زِدْنِي عِلْمًا

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

GIT- system module
Pharmacology 7
Drug used in treatment of liver cirrhosis
and hepatic encephalopathy

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Liver Cirrhosis

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

هسا ال cirrhosis اخذناه بالبائو وهي لما يكون عندي severe fibrosis وما يتم علاجه بشكل كويس
فبيتحول ل cirrhosis

- Leading to the **disruption of liver function and structure**
- Resulting in **abnormal blood vessels** and **bile duct architecture**.

Liver Cirrhosis

Common etiologies:

Alcohol consumption

Viral hepatitis

Obesity

Metabolic syndrome leading to non-alcoholic steatohepatitis

Complications :

1. Portal hypertension

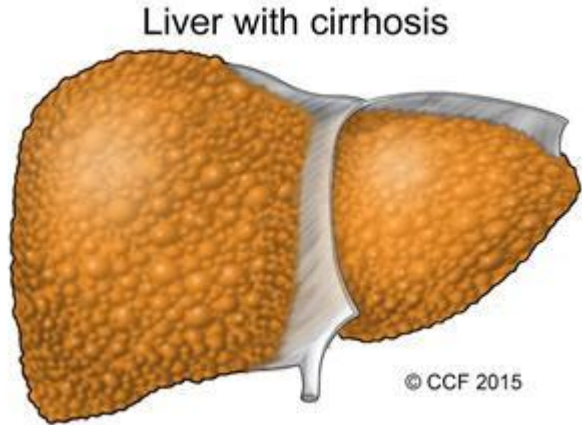
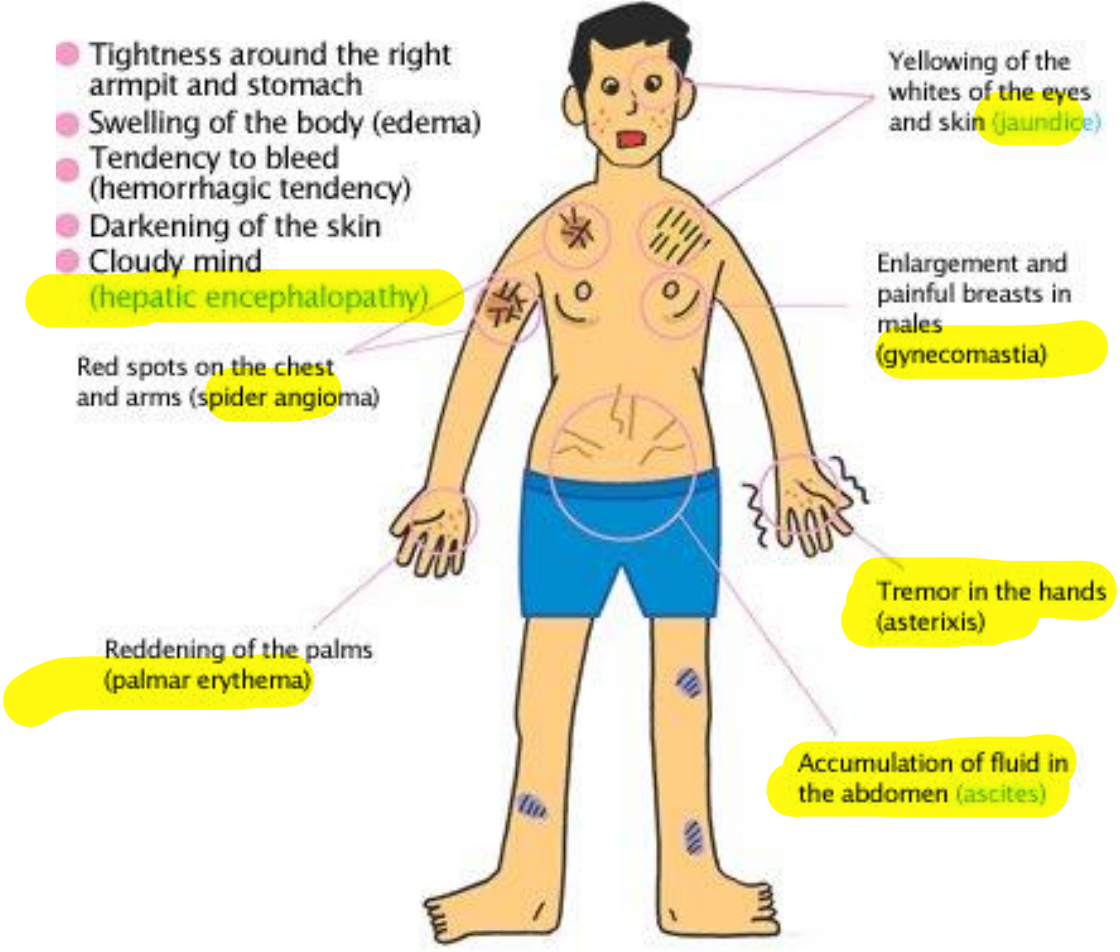
2. Ascites

3. Hepatic encephalopathy رَح نَحْكِ عِنَه

4. Organ failure

5. Hepatocellular carcinoma (HCC)

Liver Cirrhosis



Treatment of Liver Cirrhosis

Ursodiol (ursodeoxycholic acid): a secondary bile acid

هو not cure هو بس يقلل من ال toxicity لل bile acid

- **Mechanism:** Bile acid that is orally absorbed, conjugated in liver, excreted in bile with extensive enterohepatic circulation (It increases bile acid pool in bile)
 - 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.

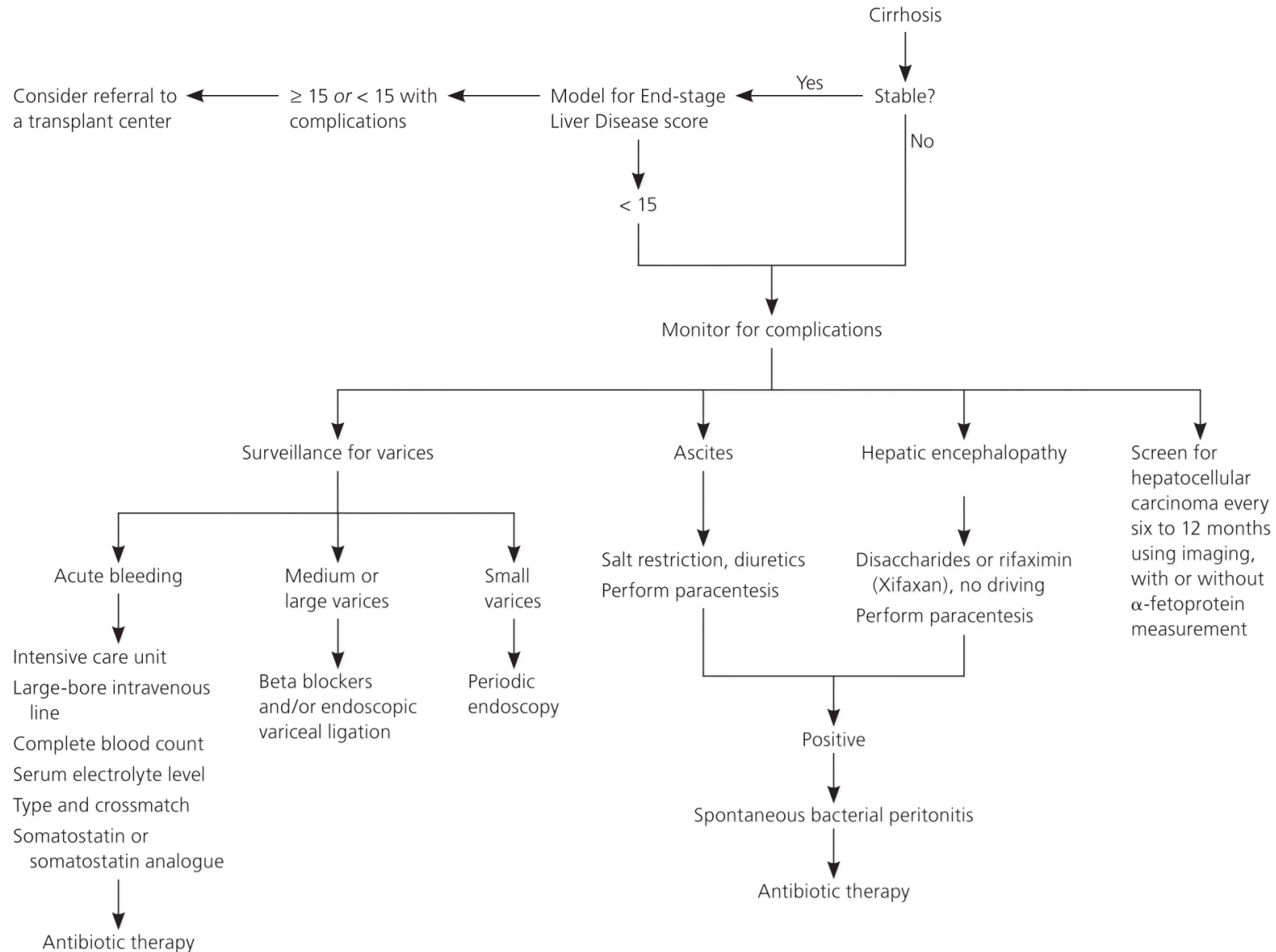
Treatment of Liver Cirrhosis

هذا يقلل من ال portal pressure اللي هي احدى ال complication لل liver cirrhosis

Drugs decreasing portal pressure (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

Managements of Liver Cirrhosis



الدكتورة قرأته قراءة
وما شفت هالشي المهم اللي فيه
بس انه اعرفوا انه اذا كان اكبر
من 15 سم او اقل من 15 سم مع
liver complication بتحتاج
transplan
ف اذا كانت اقل من 15 انت لازم
تشوف ال complication
وتعالجهم او تخفف منهم

Hepatic encephalopathy (HE)

- Brain dysfunction caused by liver insufficiency.
- Associated with a greater risk of death
- 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.**
- Recurrent episodes are possible.
- Overt hepatic encephalopathy affects 30–45% of patients with cirrhosis

Hepatic encephalopathy

Mechanism

Gut bacteria on dietary proteins, produce urease which converts proteins into ammonia and Glutaminase which converts glutamine into glutamate and ammonia.

Normally:

Ammonia is converted into urea in the liver. And glutamate is converted into glutamine by glutamine synthase in brain astrocytes.

In hepatic encephalopathy:

↑ ammonia

This → brain edema & neuropsychiatric manifestations.

In fasting: glycogenolysis is not sufficient to ↑ blood glucose.

So ↑ gluconeogenesis → ↓ amino acids, ↑ ammonia

هسا ليش بتصير ال hepatic encephalopathy

بتصير بسبب الامونيا المهم احكيلكم كيف ، هسا بالحالة الطبيعية لما تاكل بروتين المعدة فيها بكتيريا بتفرز urease بكسر ال ال بروتين ل ammonia والامونيا بتروح لل liver عشان تحولها ل urea ، بس لما يكون عندي cirrhosis ال liver بتكون معطوبة وما رح تقدر تحول الامونيا ف عشان هيك رح تتراكم الامونيا وتروح للدماغ وتعمل هاي الاشياء

وبحالة ال fasting الجسم رح يصير يكسر البروتينات عشان يطلع glucose ولما تتكسر البروتينات تطلعلي امونيا

Precipitating factors:

1. GIT infection. بتزيد البكتيريا ف رح يزيد ال urease ف رح يزيد تكسير البروتينات

2. Increased dietary proteins.

3. Hypokalemia.



😊 احفظوهم حفظا

4. GIT bleeding.

Managements of Hepatic encephalopathy (HE)

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.

هسا انا ما لازم اقلل من اكل البروتين اخليه بالمستوى الطبيعي

Managements of Hepatic encephalopathy (HE)

Treatment of precipitating factors:

Gastrointestinal bleeding

انا لازم اعالج السبب اللي بيزيدلي من الامونيا

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.

Managements of Hepatic encephalopathy (HE): Lower blood ammonia

1- Lactulose: In the colon, lactulose (beta-galactosidofructose) and lactitol (beta-galactosidosorbitol) are catabolized by the bacterial flora, resulting in an acidic pH. The reduction in pH favors the formation of the nonabsorbable NH_4^+ from NH_3 , trapping NH_4^+ in the colon and thus reducing plasma ammonia concentrations.

مبدأ عمله انه يقلل من ال pH
وبخليه اكثر حمضية وهذا الاشئ
بحول الامونيا NH_3 to NH_4^+

Other effects that may contribute to the clinical effectiveness 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 non-urease-producing *Lactobacillus*.
يغير البكتيريا اللي بتطلع ال urease ل بكتيريا ما بتفرزه.
3. Cathartic 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 .

النقطتين هذول تقدر تحكي انهم بزيدوا
من الحركة الامعاء وبقلوا من الوقت
اللي بقضيه الامونيا بال colon يعني
بسرعوا عنلية الاخراج بكونوا ك
laxatives

Lactulose is also used for prevention of recurrent hepatic encephalopathy.

Managements of Hepatic encephalopathy (HE): Lower blood ammonia

2- Antimicrobial therapy:

Non absorbed antibiotics against urease- producing & glutaminase - producing gut bacteria.

a. **Rifaximin** هو اكثر واحد بفضل استعماله من هاي العائلة

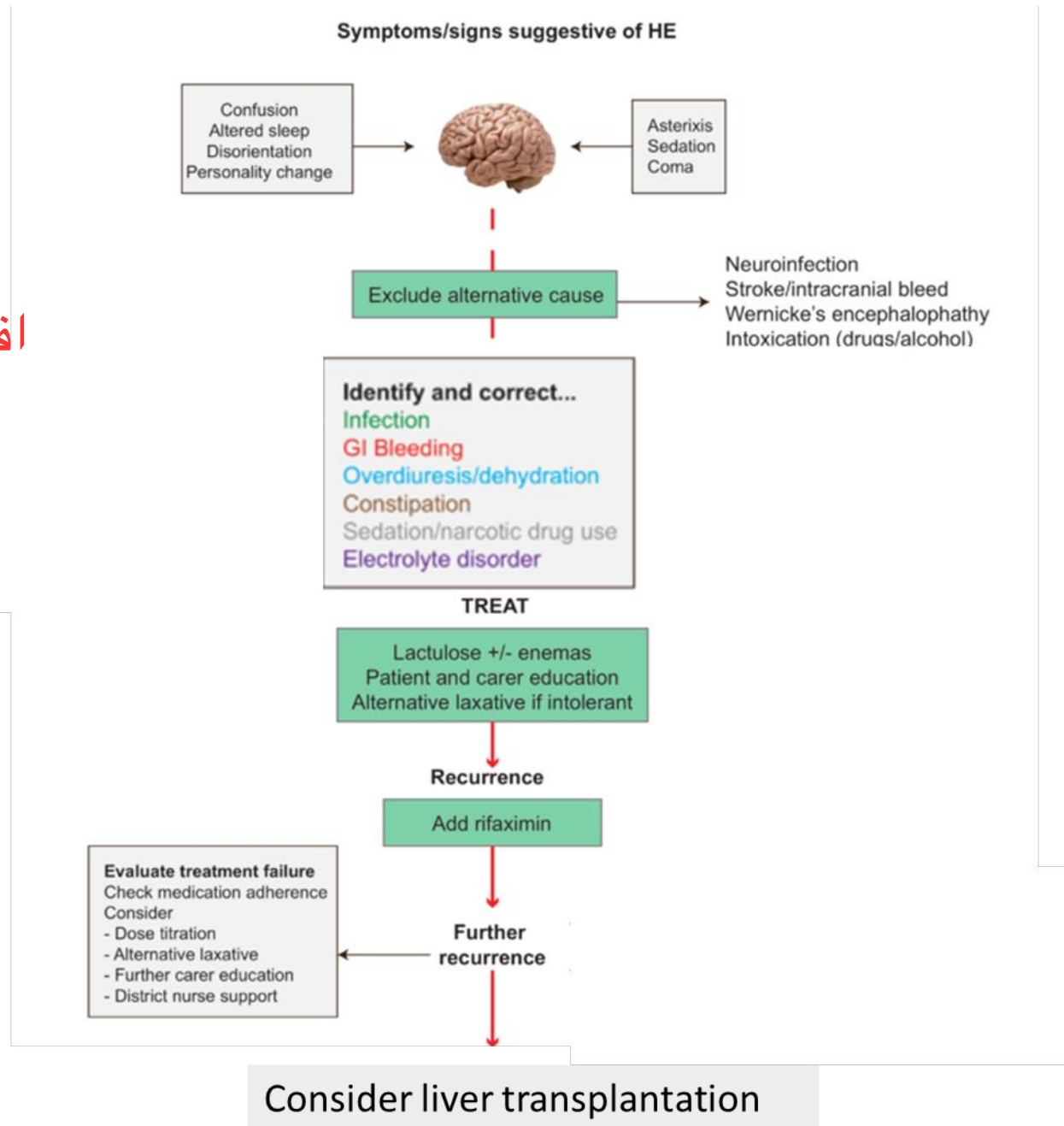
Antimicrobial of 1st choice because it is not absorbed, broad spectrum, with low adverse effects.

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

side effects: ototoxicity & nephrotoxicity.

ما يحب استخدمه لانه بصيرله absorbtion فيعمل adverse effect

افهموها فهم



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.

هسا انا في ادوية بتعمل liver injury فانا عشان اعالج ال liver injury الناتج من هاي الحال الادوية اول اشئ لازم اوقف استخدام هاي الادوية واعالج الاعراض واخفف منها

Risk factors for drug-induced liver injury

هاي العوامل اللي بتخلي استخدام بعض الادوية يعمللي liver injury بال

- **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.
- **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**
- **Disruption of the transport proteins:** Drugs that affect transport proteins at the canalicular membrane can interrupt bile flow causing **cholestasis.**
- **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**
- **Bile duct injury:** Toxic metabolites excreted in bile may cause injury to the bile duct epithelium.

اعرفوا واحفظوا هاي الادوية اللي بتعمل liver injury ، الدكتور حكت حبيب عليهم سؤال

Drugs induce liver injury (DILI)

Drug name	Class
Acetaminophen	Antipyretic, Pain medication
NSAID e.g., diclofenac	NSAID
Ciprofloxacin	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

Managements of drugs induce liver injury

- The management of DILI is based upon proper diagnosis, recognition of the offending agent, and its withdrawal. *بشوف ايش الدوا اللي سبب ال injury ويوقفه*
- 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.

هسا انا بقرر انه اوقف الدوا اللي سبب ال injury او لا بناء على ال liver enzymes

ال N-acetylcysteine هو ال antidot لل Acetaminophen

هاي اخر محاضرة فارما بال GI بعنذر عن اي تقصير
وموفقين يارب ، وما تنسوا تدعوا ل اهلنا بغزة ♡

Thank
you

