Inflammatory cholestasis	Viral hepatitis-like pattern
Chlorpromazine.	Isoniazid.
Chlorpropamide.	Phenytoin.
Erythromycin.	Methyldopa.

2.a. Immunoallergic Idiosyncratic Hepatotoxicity :

Drug or its metabolite binds to hepatic membranes or proteins ➔act as hapten to induce a variety of immune reactions

interfere with bilirubin metabolism (it causes cholestasis like symptoms) (Damaging the biliary system)	Interfere with protein synthesis (it causes hepatocellular damage – viral hepatitis like symptoms)
Erythromycin	Corticosteroids
Rifampicin	Tetracycline

2.b. Metabolic Idiosyncratic Hepatotoxicity :

The metabolite of the offending drug interferes with hepatic metabolism as that of bilirubin or protein synthesis.

Type of hepatotoxins

1-Intrinsic hepatotoxin type A (increased dose)

2-Idiosyncratic hepatotoxin type B(normal dose)

1- Direct hepatotoxicity caused by intrinsic hepatotoxin:

Type A: Dose-dependent hepatotoxicity

2-.Indirect hepatotoxicity caused by idiosyncratic hepatotoxin

TYPE B: Dose-independent hepatotoxicity ➔ divided into:

Direct cumulative dose

- Amiodarone
- Oral

Direct cumulative + Direct dose dependent hepatotoxicity

Alchohol

Methotrexate

Direct dose dependent hepatotoxicity (increased dose)

Acetaminophen

Salicylates

Statins

Hepatotoxic Drugs

Treatment

MOA of hepatotoxicity?

Non-covalent interactions:

-**Lipid peroxidation** ➔ generation of cytotoxic **oxygen radicals**

-Impairment of mitochondrial respiration

-Depletion of **GSH(glutathione)** reactions ➔ 'oxidative stress'

-Modification of sulfhydryl groups ➔ impair Ca^{2+}homostasis

-**Protein synthesis** inhibition

Covalent interactions:

-It is adduct formation between the metabolite of the drug & cellular macromolecules

-If covalent binding to **protein** ➔ immunogenic reaction

If binding to **DNA** ➔ carcinogenesis

What are the lines of treatment?

* Immediate withdrawal of any suspected drug
* No specific treatment
* Supportive;

High carbohydrate, moderate protein diet adequate in calories

* Emergency liver transplantation : for drug induced fulminant hepatic failure

Symptomatic;

- If a severe allergic reaction (not pruritus) is observed : Corticosteroids
- If pruritus : Cholestyramine which enhance bile acid excretion
- If cholestatic liver injury : Ursodeoxycholic acid (Ursodiol)
- If coagulopathy or encephalopathy develop : treat accordingly

Specific antidotes :

- N-acetylcysteine to treat acetaminophen toxicity.
- L-carnitine ➔valproate toxicity

Presenting manifestations

LATENCY PERIOD → short ,intermediate ,long

-In Direct dose-dependent Hepatotoxicity →Latency period is SHORT as it occurs after a threshold of toxicity is reached e.,g : acetaminophen (Paracetamol) (toxic dose)

-In Direct cumulative or In Indirect Immunoallergic Idiosyncratic Hepatotoxicity →Latency period is INTERMEDIATE , but may continue to evoke even after drug withdrawal e.g : amiodarone (cumulative) / phenytoin, isoniazid (idiosyncratic)

-In Indirect Metabolic Idiosyncratic Hepatotoxicity → Latency period is USUALLY LONG , Unpredictable , most problematic (it takes months to years and may cause carcinogenesis) e.g : tetracyclines, oral contraceptives

A clinical pattern or particular pathological finding

* The clinical presentation could be of variable intensity, ranging from **asymptomatic** with **increase of liver enzymes** up **to fulminant hepatic failure.**
* Some drugs just induce: **Asymptomatic** ↑ In Aminotransferases

e.g: Phenytoin, Statins, Sulfonamides,Sulfonylureas

* Other drugs induce **Symptomatic manifestations**

★ **If injury targets both hepatocytes & biliary system** : **Mixed type**

Some patterns of symptomatic drug-induced liver disease

Hepatic injury	Hepatocellular	Cholestatic	Mixed
	Flu-like, malaise, m. aches weakness, loss of appetite, GIT symptoms, diarrhea, jaundice, urine discolored,	Yellowish discoloration of skin, dark urine, rash, pruritus, stool may be light	
ALT	≥ 3 fold rise	Normal or slight	≥ 3 fold rise
ALP	Normal	≥ 2 fold rise	≥ 2 fold rise
Examples	• Acetaminophen • NSAIDs • Isoniazid • Amiodarone	• Chlorpropamide • Erythromycin • Rifamycin • Oral contraceptives	• Phenytoin • Carbamazepine • Sulfonamides • ACE Inhibitors

★ **If injury targets hepatocytes** : apoptosis or necrosis → **Hepatitis** (cytotoxic) develops : rapid onset of malaise, severe anorexia and jaundice + ↑ **in alanine aminotransferases (ALT)**

★ **If injury targets biliary system (canalicular or ductal)** : **Cholestasis** develop : jaundice ± severe **pruritis** predominate → ↑ **in alkaline phosphatase (ALP) ± hyperbilirubinaemia**