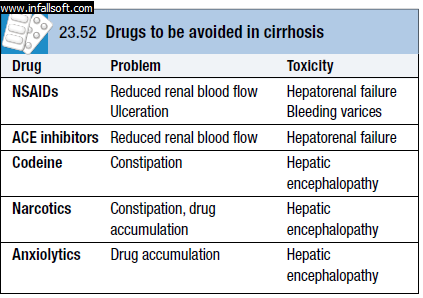
**Drugs , Toxin and the liver**

-The liver is the primary site of drug metabolism.

-Liver disease may affect the capacity of the liver to metabolise drugs

-unexpected toxicity may occur with normal doses in patients with liver disease



**Hepatotoxic drug reactions**

\*Drug toxicity should be high in the differential diagnosis of ( presentations) :

1- acute liver failure ---- ( mostly self limited )

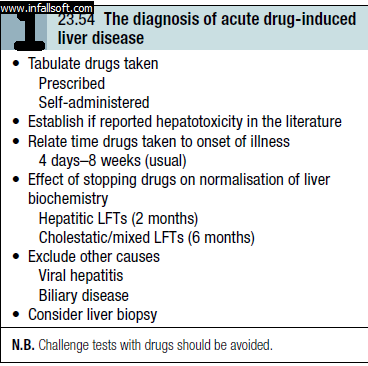
2- jaundice---------- (indicate severe liver damage )

3- abnormal L.F.T. ( drug induce toxicity)------( take weeks to return normal )

\* the most common picture is of a **mixed cholestatic hepatitis**. ----that required months to return normal .

\*The key to diagnosing **acute drug-induced liver** disease is (**detailed drug history**)

\*



**\*liver biopsy should be considered** 1-if there is suspicion of pre-existing liver disease 2- L.F.T. fail to improve when the suspect drug is withdrawn

**Types of liver injury**

1. ***Cholestasis***

-Pure cholestasis (selective interference with bile flow in the absence of liver injury) ---most commen with **oestrogens**; (50 μg/day)

-Both the **current** oral contraceptive pill and hormone replacement therapy can be safely used in **chronic liver disease**.

***2- Mixed cholestatic hepatitis : most commen, caused by:-***

1. Chlorpromazine and antibiotics ( flucloxacillin)

b-  **Co-amoxiclav** is the most common antibiotic to cause abnormal LFTs but, unlike other antibiotics, it may not produce symptoms until **10–42** days after it is stopped.

c- Anabolic steroids used by body-builders

d - NSAIDs and COX-2 inhibitors

e- statins

***3-Hepatocyte necrosis***

a- paracetamol is the best known. ---dose related

b-(an NSAID) via diclofenac

c-isoniazid (an anti- tuberculous drug). Is most serious but less commen

d-refampcin (anti-T.B.)IS most commen but less serious and is 1st one to be stop in regeim

e- allopurinol -----Granuloma in liver

f- herbal remedies --------- germander,comfrey and jin bu huan.

g-Recreational drugs-------cocaine and ecstasy

***4- Steatosis***

1. Microvesicular hepatocyte fat deposition--- tetracyclines and sodium valproate
2. Macrovesicular hepatocyte fat deposition--- tamoxifen, and amiodarone

**5- *Vascular/sinusoidal lesions***

\*alkylating agents used in oncology(busulfan), azothioprine , chronic dose of vit. A ---damage the vascular endothelium ---- lead to hepatic venous outflow obstruction----Portal HT.

***6-Hepatic fibrosis (***Methotrexate)

Risk factors for drug-induced hepatic fibrosis include:-

1. pre-existing liver disease b- high alcohol intake

Inherited Liver Disease

**Haemochromatosis**

\* is a condition in which the amount of total body iron is increased

\* the excess iron is deposited in, and causes damage to, several organs, including the liver.

\* It may be primary or secondary to other diseases .

**Hereditary (primary) haemochromatosis**

-In HHC iron is deposited throughout the body and total body iron may reach 20–60 g (normal= 4g). -The important organs involved are the **liver, pancreatic islets, endocrine glands and heart**.

***Pathophysiology or aetiology***

\*The disease is caused by increased absorption of dietary iron and is inherited as an autosomal recessive trait.

1-Approximately 90% of patients are ***homozygous for a single-point mutation***-------- resulting in a cysteine to tyrosine substitution at position 282 (C282Y) in the HFE protein -----lack of functional HFE ----- defect in uptake of transferrin-associated iron----- up-regulation of enterocyte iron-specific divalent metal transporters ----excessive iron absorption.

2- A histidine to aspartic acid mutation at position 63 (H63D) in **HFE** causes a less severe form of haemochromatosis that is most commonly found in patients who are ***compound heterozygotes***

also carrying a C282Y mutated allele

\*Iron loss in menstruation and pregnancy protects females from developing clinical manifestations

of HHC, as 90% of patients are male.

***Clinical features***

\* Symptomatic disease usually presents in MALE over 40 yrs

\* hepatic cirrhosis (hepatomegaly)

\* D.M.

\* heart failure and arrhythemia due to iron deposition in the heart.

\* Fatigue and arthropathy , arthritis with **chondrocalcinosis** secondary to **calcium pyrophosphate deposition** are also common and early symptoms.

\* **Leaden-grey skin pigmentation due to excess melanin occurs**(not due to excess iron ) especially in exposed parts, **axillae, groins and genitalia**; hence the term ***‘bronzed diabetes’***.

\*Impotence, loss of libido, testicular atrophy .

***Investigations***

1. increased (S. iron ,S. ferritin, saturated plasma iron-binding capacity)

\*Transferrin saturation > 45%

\*Significant liver disease is unusual in patients with ferritin < 1000 μg/L.

2- Radiology:- a- C.T. SCAN ---detect iron in liver

b-MRI------------ has high specificity but poor sensitivity.

3-Liver biopsy allows assessment of fibrosis and distribution of iron and confirm DX.

4- genetic testing (C282Y and H63D mutations)

5-The Hepatic Iron Index (HII)(μmol of iron per g dry weight of liver/agein years). HII > 1.9 suggests genetic haemochromatosis

***Management***

1. weekly venesection of **500 mL** blood (**250 mg iron**) until the serum iron is normal;

this may take 2 years or more. The aim is to reduce ferritin to < 50 μg/L.

1. Genetic screening (First-degree family members)
2. Liver biopsy is only indicated in asymptomatic relatives if the LFTs are abnormal and/or the serum ferritin is greater than 1000 μg/L because these features are associated with significant fibrosis or cirrhosis.

\*Liver and cardiac problems improve after iron removal,

\* joint pain is less predictable and can improve or worsen after iron removal.

\*Diabetes mellitus does not resolve after venesection.

4- Other therapy for cirrhosis and diabetes mellitus.

***Prognosis***

1. **Pre-cirrhotic patients** with HHC have a normal life expectancy
2. cirrhotic patients have a good prognosis, compared with other forms of cirrhosis (three-quarters of patients are alive 5 years after diagnosis)because liver function is usually well preserved at diagnosis and improves with therapy.

\*Screening for hepatocellular carcinoma is mandatory affecting 1/3 of patients with cirrhosis irrespective of therapy.

\*Venesection reduces but does not abolish the risk of hepatocellular carcinoma in the presence of

cirrhosis.

**Secondary haemochromatosis ( causes )**

1- chronic haemolytic disorders, sideroblastic anaemia, requiring **multiple blood transfusion** (generally over 50 L)

2-porphyria cutanea tarda, dietary iron overload and occasionally alcoholic cirrhosis, are associated with widespread **secondary siderosis**.

3- patients are heterozygotes for the *HFE* gene may contribute to the development of iron overload.

\*\*\*\*\*The features are similar to primary haemochromatosis, but the history and clinical findings

point to the true diagnosis.

**Wilson’s disease (Hepatolenticular Degeneration)**

-important autosomal recessive disorder of copper metabolism that is caused by a variety of mutations in the *ATP7B* gene on chromosome 13.

-Total body copper is increased, excess copper deposited ,Causing damage to, several organs.

***Pathophysiology or aetiology***

-Normally, dietary copper is absorbed from the stomach and proximal small intestine and is rapidly taken into the liver, where it is stored and incorporated into caeruloplasmin, which is secreted into the blood.

-In Wilson’s disease, there is almost always a failure of synthesis of caeruloplasmin; however,

some 5% of patients have a normal circulating aeruloplasmin .

-organs most affected are the liver, basal ganglia of the brain, eyes, kidneys and skeleton.

***Clinical features***

\*Symptoms usually arise between the ages of **5 and 45** yrs.

\*Hepatic disease occurs predominantly in childhood and early adolescence, although it can present inadults in their fifties.

\*Neurological damage causes 1- **basal ganglion syndromes**  2- **dementia** ( These features can occur alone or simultaneously).

\* renal tubular damage and osteoporosis, but these are rarely presenting features.

***A- Liver disease***

1- **acute hepatitis**, sometimes recurrent, can occur, especially in **children**, and may progress to **acute fulminant** liver failure. liberation of free copper into the blood stream, causing massive haemolysis and renal tubulopathy.

2-**Chronic hepatitis** develop insidiously and present with established cirrhosis; liver failure and portal hypertension may supervene.

***B-Neurological disease***

\* extrapyramidal features, ( tremor, choreoathetosis, dystonia, parkinsonism and dementia ). \*Unusual clumsiness for age may be an early symptom.

***C- Kayser–Fleischer rings***

\* **most important single clinical clue** to the diagnosis and can be seen in **60% of adults** with Wilson’s disease (**less often in children** but ***almost always*** in ***neurological Wilson’s disease***)

-albeit sometimes only by **slit-lamp examination**.

- Kayser–Fleischer rings are characterized by greenish-brown discoloration of the corneal margin appearing first at the upper periphery AND disappear with treatment.

***Investigations***

1. low serum caeruloplasmin is the best single laboratory clue to the diagnosis.
2. high free serum copper concentration
3. high urine copper excretion of greater than 0.6 μmol/24 hrs

\*Measuring 24-hour urinary copper excretion whilst giving D-penicillamine is a useful confirmatory test; more than 25 μmol/24 hrs is considered diagnostic of Wilson’s disease.

4- Genetic testing may be useful in screening families

***Management***

1. The copper-binding agent, **penicillamine**, is the drug of choice.

\* dose must be sufficient to produce cupriuresis ,require 1.5 g/day (range 1–4 g).

\*The dose can be reduced once the disease is in remission but ***treatment must continue for life***, ***even through pregnancy***.

\*Abrupt discontinuation of treatment must be **avoided** because may precipitate ***acute liver failure***. \*Toxic effects :- 1/3 of patients ( rashes, protein-losing nephropathy, lupus-like syndrome

and bone marrow depression). If these do occur,

2-Alternative Rx. trientine dihydrochloride and zinc .

3-Liver transplantation is indicated for fulminant liver failure or for advanced cirrhosis with liver failure.

***Prognosis***

-The value of liver transplantation in severe neurological Wilson’s disease is highly controversial.

-The prognosis is excellent, provided treatment is started before there is irreversible damage.

-Screening Siblings and children of patients with Wilson’s disease must be investigated

and treatment should be given to all affected individuals, even if they are asymptomatic.

**Autoimmune Liver Disease**

**Autoimmune hepatitis**

**\*Autoimmune hepatitis is a liver disease is characterized by:-**

1- unknown aetiology

2- strong association with other autoimmune diseases

3-high levels of serum immunoglobulins (hypergammaglobulinaemia)

1. autoantibodies in the serum.
2. commen in women, particularly in the second and third decades of life, but may develop in either sex at any age.

***Pathophysiology***

• ***Classical (type I) autoimmune hepatitis***is characterised

1. high frequency of other autoimmune disorders, such as Graves’ disease.
2. is associated with HLA-DR3 and DR4, particularly HLA-DRB3\*0101 and HLA-DRB1\*0401.
3. high titres of ANA and anti-smooth muscle antibodies
4. none of these antibodies is cytotoxic.
5. Caused or influenced by viral, genetic and environmental factors.
6. aberrant expression on the hepatocyte of HLA antigen

**• *Type II autoimmune hepatitis* is characterised by the**

1. presence of anti-LKM (liver-kidney microsomal) antibodies
2. lack of ANA and anti-smooth muscle antibodies.

**• *Type III autoimmune hepatitis* is characterised**

1. elevated serum immunoglobulin levels.
2. antibodies described above are absent.
3. antibodies against soluble liver antigen are present.

\*The histopathological features of all forms of autoimmune hepatitis are **similar**.

***Clinical features*** \*The onset is usually insidious ***\*female***

\***fatigue, anorexia** ,**fever, arthralgia, vitiligo and epistaxis** AND **jaundice**(Moderate or absent ).

\*1/3 of patients the onset is acute, resembling viral hepatitis, but resolution does not occur. This acute presentation can lead to extensive liver necrosis and liver failure.

\****Amenorrhoea is the rule but general health may be good***.

**O/E :-**

\***signs of chronic liver disease**,**spider naevi** and **hepatosplenomegaly**, are usually present.

\*Some patients have a ‘**Cushingoid’ face** with **acne**, **hirsutism** and **pink cutaneous striae,**

**especially on the thighs and abdomen.**

\*Approximately 2/3 of patients have associated autoimmune disease such as **Hashimoto’s thyroiditis, RTA** and **rheumatoid arthritis**.

***Investigations***

1. **Serological tests** for **SPECIFIC** **autoantibodies** are often positive +Elevated S .IgG invariable and are an **important diagnostic feature**.
2. **liver biopsy** shows interface hepatitis, with or without cirrhosis.

***Management***

1. corticosteroids is life-saving in autoimmune hepatitis, particularly during exacerbations of

active and symptomatic disease. Initially, **prednisolone** **40 mg/day** is given orally; the dose is then gradually reduced as the patient and LFTs improve.

\*Maintenance therapy is required for ***at least 2 years after LFTs have returned to normal***. \*withdrawal of treatment should not be considered unless a liver biopsy is also normal.

2- Most individuals require long-term immunosuppression. **Azathioprine** 1.0–1.5 mg/kg/day orally may allow the dose of prednisolone to be reduced .

\*Azathioprine can also be used as the **sole maintenance** immunosuppressive agent.

\**Corticosteroids treat acute exacerbations but do not prevent cirrhosis; they are therefore less important in mild asymptomatic autoimmune hepatitis.*

**Prognosis**

\*The disease is characterised by exacerbations and remissions

\***most patients** eventually develop cirrhosis and its complications.

\***Hepatocellular carcinoma is uncommon**.