# HEPATOLOGY

## Marrow SS Medicine

## Dr. Tarun S Joseph

*MBBS, MD, DM (Gastroenterology)*

Having completed his MBBS, DM and DNB in Gastroenterology and Hepatology from St. John's Medical College, Bengaluru, Dr. Tarun works as Consultant Gastroenterologist and Hepatologist in Kolkata. Alongside being a passionate educator, he has been an avid researcher throughout his academic and professional career. He earned his MD General Medicine degree from Kasturba Medical College, Manipal. He has also passed the SCE-Gastroenterology (ESEGH), UK.

# Hepatology

MARROW
Super Speciality

## Instructions

- The notes must be used in conjunction with the Marrow SS Medicine videos and should not be considered standalone material.

## Please note:

- The information in this book has been printed based on the transcript of the Marrow SS Medicine videos.
- The information contained in this book is for educational purposes only. The content provided is not intended to substitute for professional medical advice, diagnosis or treatment.
- This book cannot be sold separately. It has been made available to only select eligible users who have an active subscription to Marrow SS Medicine videos.
- The text, images, slides, and other materials used in this book have been contributed by the faculty, who are subject matter experts. We have merely reproduced them as video transcripts in this book.
- The notes have been consciously designed in a way that is concise and revisable. To ensure this, we have intentionally added only the most relevant modules and images that are needed for you.
- Reasonable care has been taken to ensure the accuracy of the information provided in this book. Neither the faculty nor Marrow takes any responsibility for any liability or damages resulting from applying the information provided in this book.
- This set contains notes of all main videos published in the app until Jan 2025. You can find notes for any additional videos published after this date within the app under the videos section.



//ME801SS-SAP

# Contents

## Special Topics in Hepatology

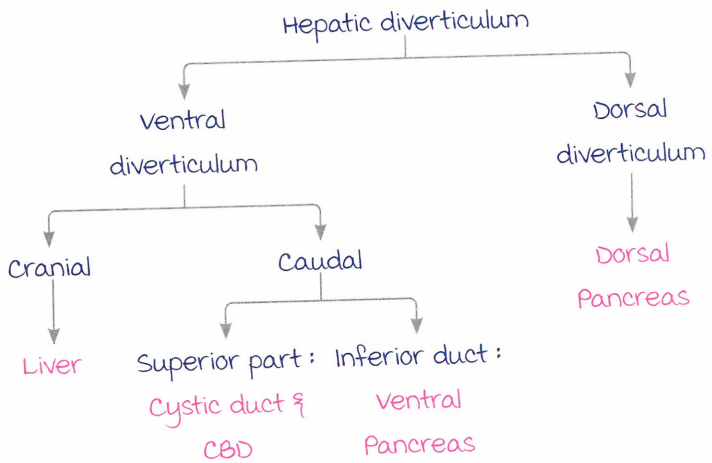
# EMBRYOLOGY OF LIVER AND BILIARY TRACT

----- Active space -----

## Development of liver

00:00:21

Development begins at 3-4 weeks of gestation.




Endodermal bud has bipotential hepatoblasts forms :

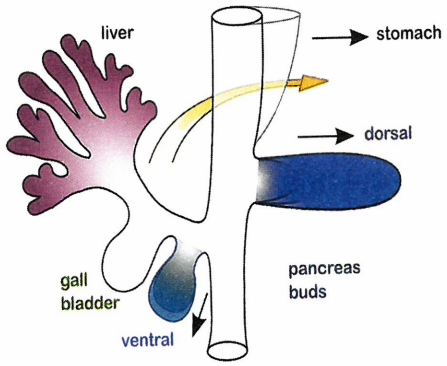
- Hepatocytes.
- Cholangiocytes.

Septum transversum forms :

- Connective tissue.
- Stellate cells.
- Capsule.

Yolk sac having resident macrophages forms : Kupffer cells.

Vitelline and umbilical veins : Forms sinusoids.




Embryology

### Growth signalling :

Signals from :

- Cardiogenic mesoderm : Fibroblast growth factors (FGF) 1, 2, 8.
- Septum transversum : Bone morphogenetic proteins (BMP).

FGF & BMP activates transcription factors Prox-1 & Hhex (Biliary development).

Loss of E-Cadherin → Cells delaminate from the bud and invade.

### Hepatoblasts :

They are bipotentiate cells.

Early markers : AFP & SOX-9.

Can differentiate into hepatocytes & cholangiocytes.

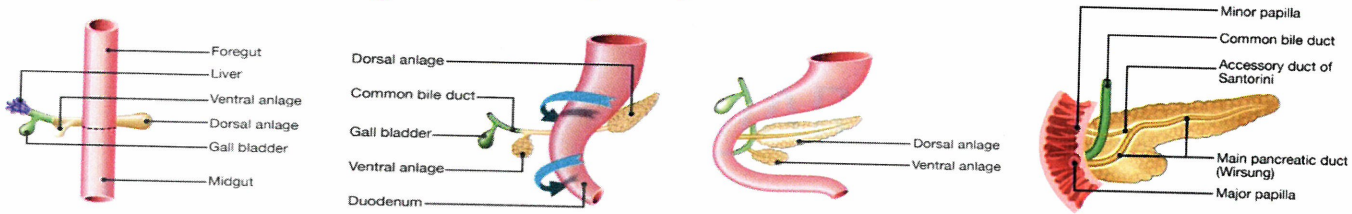
----- Active space -----

Hepatocytes :

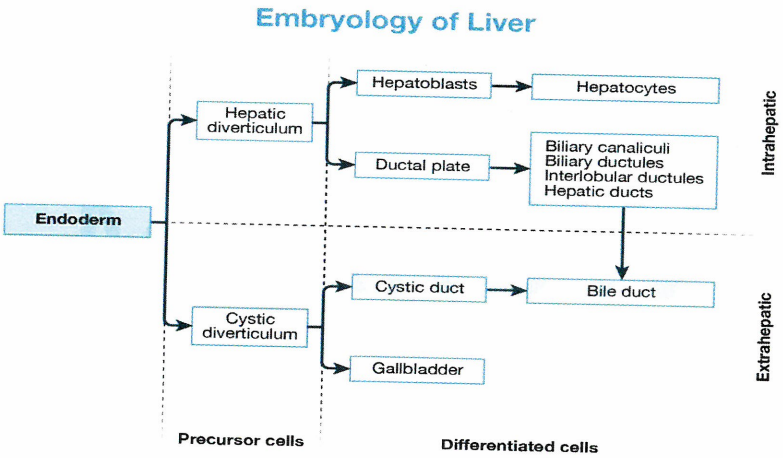
- Formed by hepatoblasts having early markers AFP.
- Contain HNF-4α.
- Gives characteristic sinusoidal appearance.
- They contain : Albumin, CK-8, CK-18.

Cholangiocytes :

- Formed by hepatoblasts having early markers SOX-9.
- It is the marker for biliary development.
- Marker is lost as they invade septum transversum but reappars again.
- They contain : CK-8, CK-18, CK-19.




Development of liver and pancreas.




## Vascular development

00:06:40

### Development of venous system :

Starts at 4th gestational week.

- Vitelline veins : Drains blood from yolk sac to heart.
- Umbilical veins : Drains blood from placenta to the heart.

Goes through primitive liver

- Both Cardinal veins : Drain blood from everywhere else to heart.
- Sinus Venosus : Future heart

Only left umbilical vein & major part of right vitelline vein persists.

----- Active space -----

Intra-viteline anastomoses :

Total 4 in number (Subhepatic 3, subdiaphragmatic 1).

Subhepatic :

- Inferior : Ventral.
- middle : Dorsal.
- Superior : Ventral.

Sub diaphragmatic : Just below sinus venosus.

Vessels grow along with liver → Future sinusoids.

Umbilical circulation :

Each side has 2 branches :

1. Branch to liver.
2. Branch to sinus venosus.

Right UV → Becomes completely fibrosed.

Left UV → Forms ductus venosus.

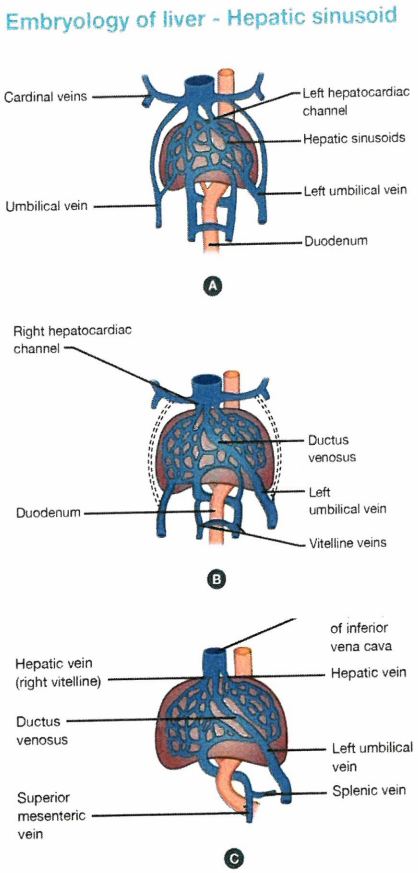
**Development of arterial system :**

more straight forward.

Hepatic artery → Formed from celiac trunk.

Sometimes, hepatic artery forms from :

- Superior mesentric artery.
- Left gastric artery.




Formation of venous system

## Intrahepatic duct (IBHD) development

00:12:34

Development starts from 6th week.

Develops from hilum → To the periphery of the liver (Following the portal vein).

At birth, intrahepatic biliary epithelium is still immature.

maturation is completed during first year of life.

**Stages of development :**

Begins with hepatocytes near PV.

Normal adult liver parenchymal cells have : CK 8 and 18.

Intrahepatic bile ducts have : CK 8,18 along with CK 7 and 19.

- Hepatoblasts near the largest portal vein → Develop CK 8, 18, 19 by 8th week.
- They form a new layer of cells by acquiring CK 7 & CK 19.
- Inner layer surrounds the portal vein branches like a sleeve. (Called ductal plate).

This is called transient asymmetry (Occurs at 8th week).

Cells closest to the portal mesenchyme maintaining a biliary phenotype.

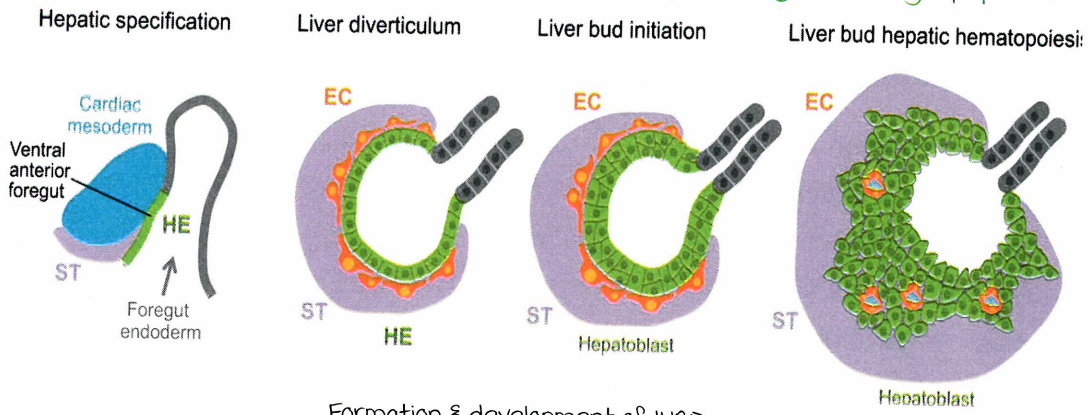
Cells closest to the parenchyma resemble hepatoblasts.

----- Active space -----

Formation of double layer :

1. Portal layer : Layer close to portal vein.
2. Lobular layer : Layer close to parenchyma.
3. Slit-like lumen forms in between.

If not involved in formation of bile duct → Ductal plate regresses by apoptosis.




Formation & development of IHBD

**Cause of development :**

Portal vein mesenchyme secretes :

- TGF-β
- Jagged 1 : Induces Notch 2 based signalling (Defective in Alagille syndrome).

TGF-β + NOTCH -2 → Stimulates differentiation of BD type cells.

## Extrahepatic duct (EBHD) development

00:17:28

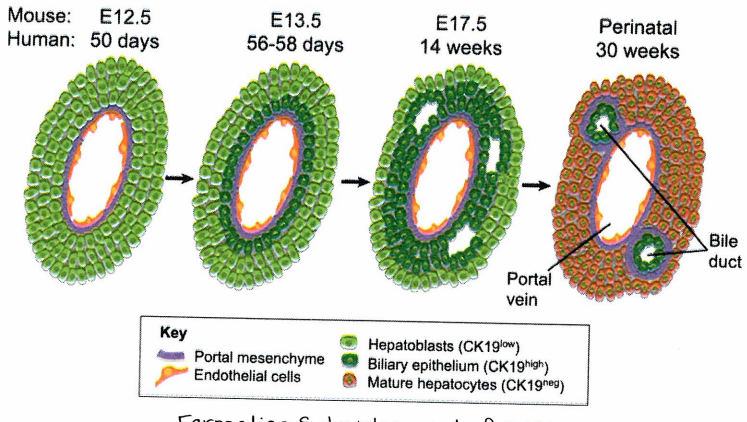
CBD, gall bladder, cystic duct : From caudal bud.

Occurs by :

- Progenitor cells expressing Pdx-1 .
- TX factor : SOX-17.

Primitive EHBD continues with IHBD and becomes whole.

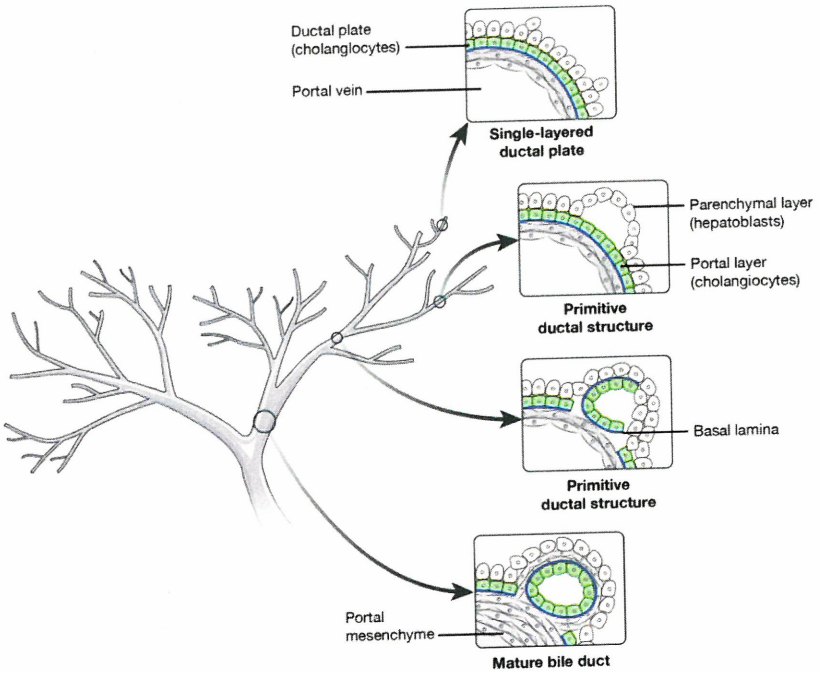
Occurs before IHBD.




Formation & development of EHBD

----- Active space -----

Embryology of liver - hepatic sinusoid




## Summary :

- Liver development : 4 weeks.
- Biliary development : 8 weeks.
- Pouch (Hepatic diverticulum) : Develops from foregut.
- FGF and BMP from outside the liver.
- Prox-1 and Hhex from inside the liver.
- Hepatoblasts to hepatocytes → HNF 4 alpha (Sinusoidal appearance).
- AFP : marker of hepatoblasts and not of any other cells.
- Earliest specific marker of Biliary development : SOX-19.
- Hepatocytes : CK -8 and 18.
- Cholangiocytes : CK8, 18, 19 and CK 7 (Last formed is CK).
- IHBD : TGF B and Jagged-1 (NOTCH-2 signalling).
- EHBD : Pdx-1 and SOX-17.

Ligamentum teres : Remnant of umbilical vein outside the liver.

Ligamentum venosum : Remnant of ductal venosus formed from left umbilical vein.

----- Active space -----

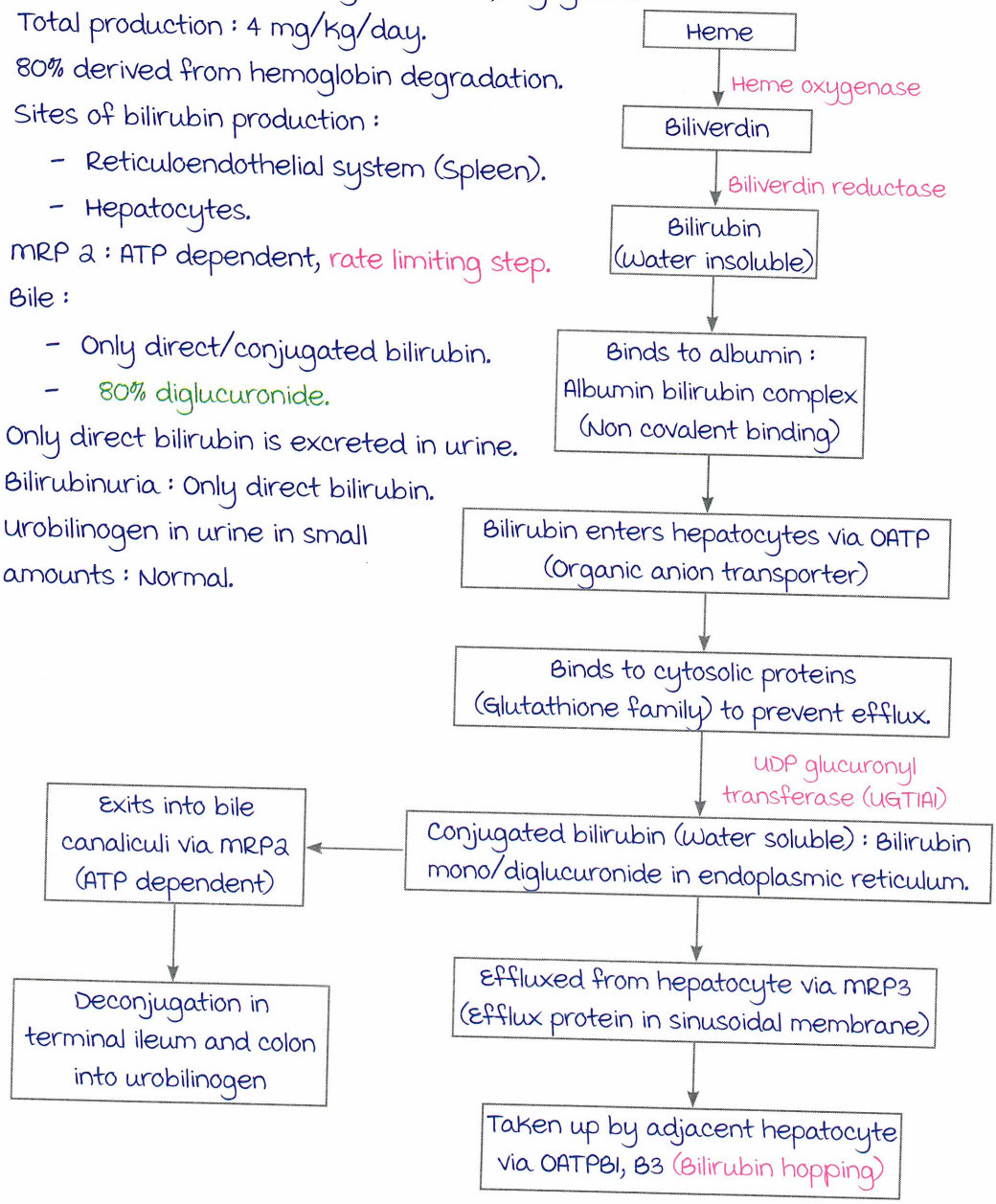
# PHYSIOLOGY AND LFT

## Bilirubin

00:00:48

### Bilirubin synthesis :

- Source of heme : RBCs, cytochromes, myoglobin.
- Total production : 4 mg/kg/day.
- 80% derived from hemoglobin degradation.
- Sites of bilirubin production :
  - Reticuloendothelial system (Spleen).
  - Hepatocytes.
- MRP 2 : ATP dependent, rate limiting step.
- Bile :
  - Only direct/conjugated bilirubin.
  - 80% diglucuronide.
- Only direct bilirubin is excreted in urine.
- Bilirubinuria : Only direct bilirubin.
- Urobilinogen in urine in small amounts : Normal.



----- Active space -----

Delta bilirubin :

- Conjugated bilirubin covalently bonded to albumin → Cannot pass through glomerular membrane.
- Conjugated hyperbilirubinemia but no bilirubinuria.

In multiorgan dysfunction :

- D/t lack of ATP, MRP2 does not function, direct bilirubin is pushed via MRP3 into bloodstream.
- Conjugated hyperbilirubinemia without obstruction.

**measurement of bilirubin :**

Van den bergh reaction :

- Diazo reaction.
- Blood + diazotized sulfalinic acid (30-60 sec) → Colour change = Direct bilirubin.
- Add accelerator (Alcohol/caffeine) → (After 1 hour) = Total bilirubin.
- Total bilirubin - indirect bilirubin = Indirect bilirubin.

High performance liquid chromatography : Commonly used.

$T_{1/2}$ of bilirubin : 4 hours.

$T_{1/2}$ of delta bilirubin : 14-21 days.

## Hyperbilirubinemia

00:12:52

**Isolated hyperbilirubinemia :**

- Increased production : Hemolysis.
- Decreased uptake : OATP1B1/B3.
- Decreased conjugation.
- Decreased excretion.

**Conjugation defects :**

D/t deficiency of UDP glucuronyl transferase enzyme : UGT1A1 gene, chr 2.

Types :

- Crigler Najjar syndrome type 1.
- Crigler Najjar syndrome type 2.
- Gilbert syndrome (m/c).

Crigler Najjar syndrome type 1 :

- Complete enzyme deficiency.
- Complete absence of UGT1A1 : Exons 2, 3, 4, 5.
- Autosomal recessive.
- All races are affected.

----- Active space -----

C/F :

- Not compatible with life.
- Severe indirect hyperbilirubinemia in the absence of hemolysis.
- Presents in the first few days of life.
- Kernicterus.
- All races are affected.

Investigations :

- Bilirubin levels : 18 mg/dL to 30 mg/dL (Indirect bilirubin).
- Biopsy : Bile plugs in canaliculi and bile ducts.

Treatment :

- Phototherapy :
  - Converts into bilirubin isomers (Water soluble), excreted in bile.
  - Temporary change only.
  - Calcium supplements increase the effectiveness of phototherapy.
- Plasmapheresis.
- Orthoptic liver transplantation : Treatment of choice.

Crigler Najjar syndrome type 2 :

- Some deficiency of UDP glucuronyl transferase enzyme.
- Exons of UGT1A1 : Single amino acid substitution >> deletions.

Presentation :

- Late, before 10 year of age.
- Kernicterus is uncommon.

Serum bilirubin :

- Baseline bilirubin levels : 10 mg/dL (8-18 mg/dL).
- During periods of stress : Levels increase.
- <50% of normal bilirubin in bile.
- Proportion of monoglucuronides : Increases (30%).

Treatment : Phenobarbital (Enzyme inducer).

Gilbert syndrome :

- 10-12% of normal population.
- Incidental diagnosis.
- Presents in adulthood.
- Bilirubin levels :
  - ↑ Unconjugated biliubin : <3mg/dL.
  - Fluctuations : ↑ during infections, fasting, alcohol consumption (<7 mg/dL).

----- Active space -----

UGT1A1 mutation :

- UDP glucuronyl transferase levels reduced to 30%.
- Mutation in promotor region : TATAA element.

Clinical implications :

- Prolonged neonatal jaundice.
- Irinotecan : Anticancer agent, also metabolised by UGT1A1, → Severe refractory diarrhea in patients with Gilbert syndrome.
- ↓ risk of cardiac diseases : D/t antioxidant effect of indirect hyperbilirubinemia.

**Isolated conjugated/mixed hyperbilirubinemias :**

Dubin Johnson syndrome :

- Mutations of ABCC2 gene : MRP2 transporter defect.
- Upregulation of MRP3 → Conjugated bilirubin goes into plasma.
- Autosomal recessive.

C/F :

- Non hemolytic jaundice.
- Mild icterus.
- Usually diagnosed at puberty.

Bilirubin levels :

- Direct bilirubin ↑.
- Can go upto 20-40 mg/dL during intercurrent illness, pregnancy, oral contraceptives intake.
- Urine coproporphyrin I > III (Normal : Coproporphyrin III > I).

Biopsy : Black liver d/t deposition of melanin related pigment and epinephrine metabolites in lysosomes.

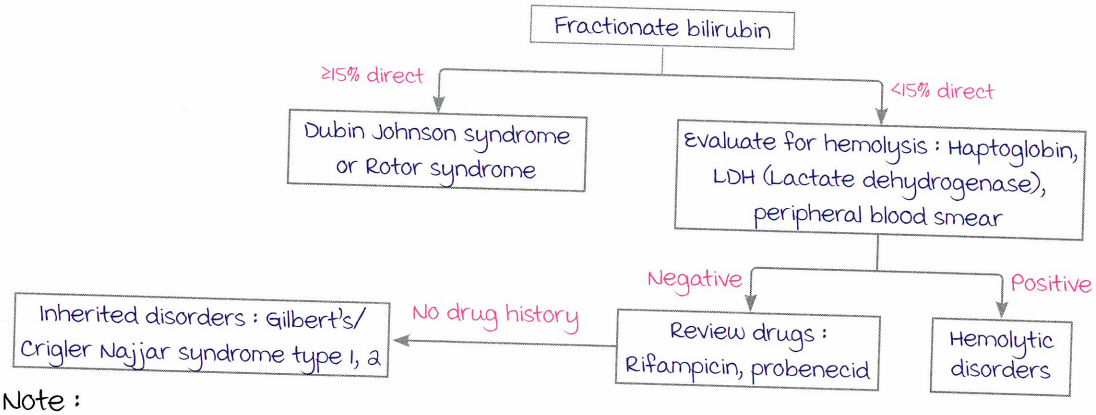
Rotor syndrome :

- Similar to Dubin Johnson syndrome.
- Autosomal recessive.
- Defective reuptake of bilirubin via OATP1B1, OATP1B3.
- SLCO1B1, SLCO1B3 : Gene mutations.
- Increased urine coproporphyrin (I > III).
- Biopsy : No liver pigmentation.
- ↑ risk of methotrexate and statin toxicity.

----- Active space -----

| Congenital hyperbilirubinemia syndromes | | | | | |
|---|---|---|---|---|---|
| Features | Gilbert | Type 1 Crigler Najjar | Type 2 Crigler Najjar | Dubin Johnson | Rotor |
| Incidence | 6–12% | Very rare | Uncommon | Uncommon | Rare |
| Gene defect | UGT1A1 | UGT1A1 | UGT1A1 | MRP2 | OATP1B1, OATP1B3 |
| Metabolic defect | ↓ Bilirubin conjugation | No bilirubin conjugation | ↓↓ Bilirubin conjugation | Impaired canalicular export of conjugated bilirubin | Imapired sinusoidal |
| Plasma bilirubin | < 7 mg/dL | Very high | < 20 mg/dL | < 7 mg/dL (Conjugated) | |
| Liver histology | - | Bile plugs | - | Coarse pigment | - |
| Prognosis | Normal | Death in infancy | Usually normal | Normal | Normal |
| Treatment | None | Phototherapy as a bridge to liver transplant | Phenobarbital | Avoid estrogens | None available |

**Evaluation :**




Note :

- Rifampicin can cause hepatotoxicity.
- Rifampicin effect : Indirect hyperbilirubinemia, blocks OATP1 transporter, no need to stop drug.

## Other qualitative liver function tests

00:29:35

**Aminotransferases :**

- AST (Aspartate transaminase)/SGPT (Serum glutamate pyruvate transminase).

----- Active space -----

- ALT (Alanine transaminase)/SGOT (Serum glutamate oxaloacetate transaminase).

| | AST | ALT |
|---|---|---|
| Site of synthesis | Mitochondria > cytosol. | Cytosol |
| Organs | Liver > heart > muscle > Kidney> brain> pancreas> lung > leukocytes, erythrocytes | Liver > other organs |
| Clearance | Reticuloendothelial system, liver | Liver |
| Special feature | Macro AST : Bound to immunoglobulins. Stays in blood for a longer time. Asymptomatic. | |
| | ↓ In hemodialysis patients | |

ALT :

- More specific to liver diseases than AST except in alcohol + toxin mediated hepatitis and muscle related disorders.
- Normal levels : 30 IU/mL in males, 20 IU/mL in females.

AST :

- Rises more in non hepatic diseases.
- < 300 IU/mL : Non specific.

Alcoholic hepatitis :

- AST/ALT >2 : Alcoholic liver disease.
- AST/ALT >3 : Highly suggestive of alcoholic liver disease.
- Both enzymes require pyridoxal 5'phosphate (ALT > AST) cofactor for their production.
- Alcoholics have pyridoxal (Vitamin B6) deficiency.
- Serum enzyme levels : <400 IU/mL.

Alcohol + toxin related hepatitis :

- AST, ALT raised beyond 400 IU/mL (upto 1000).
- AST/ALT ratio is maintained.
- AST higher than ALT.

Muscles related disorders :

- AST/ALT is 3 : 1 but AST decreases (Shorter $T_{1/2}$).
- AST higher than ALT.

----- Active space -----

Chronic mild elevation of ALT > AST :
<150 U/L or 5x upper limit of normal.

Hepatic causes :

- Chronic viral hepatitis (B, C and D).
- Hemochromatosis.
- Wilson's disease.
- α1 antitrypsin deficiency.
- Autoimmune hepatitis.

Non hepatic causes :

- Celiac disease : Can also lead to chronic liver disease.
- Hyperthyroidism.

Severe acute elevations :

- ALT >AST (>1000 U/L or >20-25x upper limit of normal).
- Acute Budd Chiari syndrome : Hepatic venous occlusion (2/3 veins blocked).
- Acute viral hepatitis.
- Autoimmune hepatitis.
- Drugs and toxins.
- Hepatic artery ligation.
- Ischaemic hepatitis.
- Wilson's disease : Age < 40 years, can present in any form.

Severe acute elevations :

- AST >ALT (>1000 U/L or >20-25x upper limit of normal).
- Hepatic : medications or toxins in a patient with underlying alcohol associated liver injury.
- Non hepatic : Acute rhabdomyolysis.

Chronic mild elevation :

- AST >ALT (<150 U/L, <5X upper limit of normal).
- Hepatic :
  - Alcohol associated liver injury.
  - Cirrhosis.

Non hepatic :

- Hypothyroidism.
- Macro-AST.
- Myopathy.