MEDICAL EDUCATION RESOURCE

Heme Synthesis and Breakdown

? HEME SYNTHESIS AND BREAKDOWN

Includes:
? Structure of heme
? Biosynthesis (all steps, sites, enzymes, cofactors)
? Regulation
? Porphyrias (all types, features, lab findings)

Everything will be pointwise, exam-focused, with tables in your preferred list format.

? STRUCTURE OF HEME

- Heme = **protoporphyrin IX + ferrous iron (Fe²?)**.
- Porphyrin ring = **tetrapyrrole** (four pyrrole rings linked by methenyl bridges).
- Central Fe²? binds:
  - O? (in Hb, Mb)
  - Electrons (in cytochromes)
- Side chains on protoporphyrin IX:
  - **4 methyl (–CH?)**
  - **2 vinyl (–CH=CH?)**
  - **2 propionate (–CH?–CH?–COO?)**

Function: Essential component of hemoglobin, myoglobin, cytochromes, catalase, peroxidases.

? BIOSYNTHESIS OF HEME

? Overall

- Occurs in **all nucleated cells**, most active in:
  - **Bone marrow (85%)** ? hemoglobin
  - **Liver (15%)** ? cytochromes
- Pathway takes place partly in **mitochondria** and partly in **cytosol**.

? Stepwise Synthesis (With Sites & Enzymes)

? **Step 1 – Rate-limiting step**

- **Glycine + Succinyl-CoA ? ?-ALA**
- Enzyme: **ALA synthase**
- Cofactor: **Pyridoxal phosphate (Vitamin B6)**
- Site: **Mitochondria**

? **Step 2**

- **ALA ? Porphobilinogen (PBG)**

- Enzyme: **ALA dehydratase (PBG synthase)**
- Inhibited by **lead (Pb)**
- Site: **Cytosol**

? **Step 3**

- **4 PBG ? Hydroxymethylbilane**
- Enzyme: **PBG deaminase**
- Site: **Cytosol**

? **Step 4**

- **Hydroxymethylbilane ? Uroporphyrinogen III**
- Enzyme: **Uroporphyrinogen III synthase**
- Site: **Cytosol**

? **Step 5**

- **Uroporphyrinogen III ? Coproporphyrinogen III**
- Enzyme: **Uroporphyrinogen decarboxylase**
- Site: **Cytosol**

? **Step 6**

- **Coproporphyrinogen III ? Protoporphyrinogen IX**
- Enzyme: **Coproporphyrinogen oxidase**
- Site: **Mitochondria**

? **Step 7**

- **Protoporphyrinogen IX ? Protoporphyrin IX**
- Enzyme: **Protoporphyrinogen oxidase**
- Site: **Mitochondria**

? **Step 8 — Final Step**

- **Protoporphyrin IX + $Fe^{2?}$? Heme**
- Enzyme: **Ferrochelatase**
- Inhibited by **lead (Pb)**
- Site: **Mitochondria**

? Regulation of Heme Synthesis

? 1. Rate-limiting step: ALA synthase

In liver:

- **Inhibited by heme / hemin (end-product inhibition)**

- **Upregulated by drugs** that induce cytochrome P450 (barbiturates, griseofulvin, phenytoin).

In bone marrow:

- Regulated primarily by **iron availability**.

? 2. Lead (Pb) poisoning inhibits:

- **ALA dehydratase**

- **Ferrochelatase**
  ? ? ALA, ? Protoporphyrin
  ? Anemia + neurologic symptoms

? BREAKDOWN OF HEME

Occurs mostly in **reticuloendothelial (RE) cells** of spleen, liver, bone marrow.

? Stepwise Breakdown

? 1. Heme ? Biliverdin

- Enzyme: **Heme oxygenase**

- Releases **Fe^{3}?** and **CO**

- Requires **O? + NADPH**

? 2. Biliverdin ? Bilirubin

- Enzyme: **Biliverdin reductase**

? 3. Bilirubin Transport

- Unconjugated bilirubin is **insoluble** ? binds to **albumin**.

? 4. Conjugation in Liver

- Bilirubin + UDP-glucuronic acid
- Enzyme: **UDP-glucuronyltransferase**
- Forms **bilirubin diglucuronide** (water soluble)

? 5. Excretion into Bile

? 6. Intestinal Fate

- Bilirubin ? **Urobilinogen**
- Urobilin (in urine) ? yellow
- Stercobilin (in stool) ? brown

? PORPHYRIAS

Porphyrias = inherited/acquired disorders of **heme synthesis** due to enzyme defects.

They cause accumulation of **specific intermediates** ? neurovisceral or photosensitive symptoms.

? MAJOR PORPHYRIAS (Exam Pattern)

? 1. Acute Intermittent Porphyria (AIP)

- Enzyme deficient: **PBG deaminase**
- Accumulation: **ALA, PBG**
- Features:
  - Severe abdominal pain
  - Neuropsychiatric symptoms
  - **NO photosensitivity**
  - Red wine-colored urine

? 2. Porphyria Cutanea Tarda (PCT)

- Enzyme deficient: **Uroporphyrinogen decarboxylase**
- Features:
  - **Photosensitivity**
  - Blisters on sun-exposed skin
  - Red-brown urine

- Most common porphyria.

? 3. Congenital Erythropoietic Porphyria

- Enzyme deficient: **Uroporphyrinogen III synthase**
- Severe photosensitivity
- Red teeth (erythrodontia)

? 4. Hereditary Coproporphyria

- Enzyme deficient: **Coproporphyrinogen oxidase**
- Mixed: abdominal pain + photosensitivity

? 5. Variegate Porphyria

- Enzyme deficient: **Protoporphyrinogen oxidase**
- Neurovisceral + photosensitivity

? Short Summary Table (List Format)

Porphyria – Enzyme Defect ? Symptoms

- **AIP** – PBG deaminase ? abdominal pain, neuropathy, NO photosensitivity

- **PCT** – Uroporphyrinogen decarboxylase ? blistering photosensitivity
- **CEP** – Uroporphyrinogen III synthase ? severe photosensitivity, red teeth
- **HCP** – Coproporphyrinogen oxidase ? pain + photosensitivity
- **VP** – Protoporphyrinogen oxidase ? mixed symptoms

? Lead Toxicity in Heme Synthesis (Rapid Recall)

Lead inhibits:

- **ALA dehydratase**
- **Ferrochelatase**
  ? ? ALA
  ? ? Protoporphyrin
  ? Microcytic anemia

? STRUCTURE OF HEME

- Heme is a **porphyrin ring** with **iron (Fe^{2}?)** at the center.
- The ring is called **protoporphyrin IX**.
- It consists of **four pyrrole rings (A, B, C, D)** linked via **methene bridges**.
- Side chains on pyrrole rings include **methyl, vinyl, and propionate groups**.

- The **central Fe²?** binds with:
  - 4 nitrogens of the ring
  - 1 binding site for **globin**
  - 1 site for **O?, CO, NO** or other ligands (“sixth position”).
- Fe must be in **ferrous form (Fe²?)** to bind oxygen (Fe³? cannot bind O?).
- Heme is found in hemoglobin, myoglobin, cytochromes, catalase, and peroxidases.

? BIOSYNTHESIS OF HEME

Occurs in **all tissues**, mainly:

- **85% in bone marrow** (RBC formation)
- **15% in liver** (cytochrome production)

? Location of Steps

- **Mitochondria ? Cytosol ? Mitochondria**

? Step-by-Step Pathway (with key enzymes & regulation)

? 1. Condensation of Glycine + Succinyl CoA ? ?-ALA

- Enzyme: **ALA synthase (ALAS)**
- Cofactor: **Pyridoxal phosphate (Vitamin B?)**

- Rate-limiting step
- Occurs in mitochondria
- Inhibited by **heme (negative feedback)**
- Induced by many drugs in liver that increase cytochrome P450 demand ? ALAS upregulation

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? 2. Two molecules of ?-ALA ? Porphobilinogen (PBG)

- Enzyme: **ALA dehydratase (ALA-D)**
- Location: Cytosol
- **Lead inhibits ALA dehydratase**, causing ALA accumulation.

? 3. Four PBG molecules ? Hydroxymethylbilane (HMB)

- Enzyme: **PBG deaminase (HMB synthase)**
- Deficiency ? **Acute Intermittent Porphyria**

? 4. HMB ? Uroporphyrinogen III

- Enzyme: **Uroporphyrinogen III synthase**
- If enzyme deficient ? non-physiological type I porphyrins form (photosensitive).

? 5. Uroporphyrinogen III ? Coproporphyrinogen III

- Enzyme: **Uroporphyrinogen decarboxylase**
- Defect ? **Porphyria Cutanea Tarda (PCT)**
    - Most common porphyria
    - Photosensitivity

? 6. Coproporphyrinogen III ? Protoporphyrinogen IX

- Enzyme: **Coproporphyrinogen oxidase**
- Occurs in mitochondria (re-entry).

? 7. Protoporphyrinogen IX ? Protoporphyrin IX

- Enzyme: **Protoporphyrinogen oxidase**

? 8. Protoporphyrin IX + Fe^{2}? ? Heme

- Enzyme: **Ferrochelatase**
- Inhibited by **lead**, causing accumulation of **protoporphyrin IX**
- Final step in mitochondria

? Regulation of Heme Synthesis

- **Key regulatory enzyme:** ALA synthase

- Inhibited by **heme/hemin**
- Liver ALAS induced by drugs: barbiturates, alcohol, antiepileptics
- RBC heme synthesis depends on erythropoietin & iron availability

? Lead (Pb) Poisoning – Where Does It Act?

- Inhibits:
  - **ALA dehydratase**
  - **Ferrochelatase**
- Effects:
  - ? ALA
  - ? Protoporphyrin
  - ? Heme synthesis
  - Microcytic hypochromic anemia

? PORPHYRIAS

Porphyrias = **defects in heme biosynthetic enzymes** ? accumulation of intermediates.

Classified into:

? 1. Hepatic Porphyrias

(Usually neurovisceral symptoms)

? 2. Erythropoietic Porphyrias

(Usually photosensitivity)

? Major Porphyrias — Enzyme, Accumulated Product, Key Features

? 1. Acute Intermittent Porphyria (AIP)

- Defect: **PBG deaminase**
- Accumulation: ALA, PBG
- Features:
  - Acute abdominal pain
  - Neuropsychiatric symptoms
  - Red-wine urine darkening on standing
  - **No photosensitivity**
- Triggered by drugs, starvation, alcohol
- Treatment: hemin (inhibits ALAS)

? 2. Porphyria Cutanea Tarda (PCT) – MOST COMMON

- Defect: **Uroporphyrinogen decarboxylase (UROD)**
- Accumulation: Uroporphyrin
- Features:

- Photosensitivity
- Blistering skin lesions
- Hyperpigmentation
- Elevated liver enzymes

- Associated with alcohol, estrogens, HCV infection

? 3. Congenital Erythropoietic Porphyria (CEP / Günther Disease)

- Defect: **Uroporphyrinogen III synthase**
- Accumulation: Type I porphyrins
- Features:
  - Severe photosensitivity
  - Red urine
  - Hemolytic anemia
  - Erythrodontia (red-brown teeth that fluoresce)

? 4. Hereditary Coproporphyria (HCP)

- Defect: **Coproporphyrinogen oxidase**
- Features:

- Neurovisceral attacks
- Variable photosensitivity

? 5. Variegate Porphyria

- Defect: **Protoporphyrinogen oxidase**
- Features:
  - Neurovisceral symptoms
  - Photosensitivity
  - Skin blistering
  - “Mixed” presentation

? 6. Erythropoietic Protoporphyria (EPP)

- Defect: **Ferrochelatase**
- Accumulation: Protoporphyrin IX
- Features:
  - Photosensitivity
  - Burning sensation in sunlight
  - Mild liver dysfunction possible

? Key Differentiation (Ultra-Short Clues)

- **AIP:** Abdominal pain + neuro symptoms; no photosensitivity
- **PCT:** Photosensitivity + blistering; most common
- **CEP:** Childhood onset, severe photosensitivity, red teeth
- **EPP:** Mild photosensitivity, protoporphyrin buildup
- **Variegate/HCP:** Neuro + skin symptoms both present

? CATABOLISM OF HEME

? 1. Site

- Mainly in **reticuloendothelial system (RES)**
  – Spleen
  – Liver
  – Bone marrow
- Occurs when RBCs reach end of lifespan (~120 days) or during hemolysis.

? 2. Step-by-Step Breakdown

? Step 1: Heme ? Biliverdin

- Enzyme: **Heme oxygenase**
- Requires: O? + NADPH

- Iron (Fe^{2+} ? Fe^{3+}) released and reused
- Carbon monoxide (CO) also produced

? Step 2: Biliverdin ? Bilirubin

- Enzyme: **Biliverdin reductase**
- Produces **unconjugated bilirubin (indirect)**
- Water-insoluble ? transported bound to albumin

? UNCONJUGATED BILIRUBIN TRANSPORT

- Unconjugated (“indirect”) bilirubin is **lipid-soluble**
- Strongly bound to **albumin** in blood
- Cannot be excreted in urine
- Enters hepatocytes by facilitated transport

? CONJUGATION IN LIVER

? Bilirubin + UDP-glucuronic acid ? Bilirubin diglucuronide

- Enzyme: **UDP-glucuronyl transferase (UGT1A1)**
- Water-soluble form = **conjugated bilirubin (direct)**
- Secreted into bile canaliculi ? bile ? intestine

? INTESTINAL METABOLISM

? 1. Conjugated bilirubin ? Urobilinogen

- By **gut bacteria**

? 2. Urobilinogen fate

- Some absorbed ? liver (enterohepatic circulation)
- Some filtered by kidneys ? **urobilin (yellow)**
- Most converted in colon ? **stercobilin (brown)**

This gives stool its **brown color** and urine its **yellow color**.

? PLASMA BILIRUBIN

? Types of bilirubin measured

1. **Direct bilirubin**
    - Water-soluble
    - Conjugated
    - Can appear in urine
2. **Indirect bilirubin**
    - Water-insoluble
    - Unconjugated

- Albumin-bound
- Cannot appear in urine

Total bilirubin = Direct + Indirect

? SHUNT BILIRUBIN (IMPORTANT PG TOPIC)

“Shunt bilirubin” refers to **bilirubin formed from heme precursors *other than hemoglobin* before the RBC matures.**

? Where it comes from

- Destruction of **ineffective erythroid precursors** in bone marrow
- Called **intramedullary hemolysis**

? Seen in

- Thalassemia major
- Megaloblastic anemia
- Sideroblastic anemia
- Myelodysplastic syndromes

? Effect

- Elevated **unconjugated bilirubin**
- Normal or mildly reduced hemoglobin

- Reticulocyte count may not rise proportionately

This concept explains jaundice in severe ineffective erythropoiesis without peripheral hemolysis.

? HYPERBILIRUBINEMIAS (VERY HIGH YIELD)

Classified into:

? 1. Pre-hepatic (Hemolytic) Hyperbilirubinemia

? Key features:

- ? RBC destruction
- ? Unconjugated bilirubin
- No bilirubin in urine
- ? Urobilinogen

? Causes:

- Hemolytic anemia
- Thalassemia
- G6PD deficiency
- Shunt bilirubin (ineffective erythropoiesis)

? 2. Hepatic Hyperbilirubinemia

Due to impaired uptake, conjugation, or excretion.

? A. Impaired uptake

- Drugs (rifampicin)
- Sepsis

? B. Impaired conjugation

- **Gilbert syndrome** (mild ? UGT1A1)
- **Crigler–Najjar type I** (no UGT; severe)
- **Crigler–Najjar type II** (partial deficiency)

? C. Impaired excretion

- **Dubin–Johnson syndrome** (defective canalicular transport)
- **Rotor syndrome** (defective hepatic storage)

? 3. Post-hepatic (Obstructive) Hyperbilirubinemia

? Key features:

- ? Conjugated bilirubin
- Clay-colored stools (? stercobilin)
- Dark urine (? conjugated bilirubin)
- Pruritus (bile salts)

? Causes:

- Gallstones
- Carcinoma of head of pancreas
- Cholangiocarcinoma
- Strictures
- Primary sclerosing cholangitis

? ULTRA-SHORT DIFFERENTIATION

? Unconjugated (Indirect) bilirubin ?

- Hemolysis
- Shunt bilirubin
- Gilbert
- Crigler–Najjar
- Neonatal jaundice

? Conjugated (Direct) bilirubin ?

- Obstruction
- Dubin–Johnson
- Rotor

- Hepatitis/cholestasis

? CONGENITAL HYPERBILIRUBINEMIAS

These are inherited defects in bilirubin **conjugation** or **excretion**.

? 1. Gilbert Syndrome

- Mild ? **UGT1A1 activity**
- Slight ? unconjugated bilirubin (usually <3 mg/dL)
- Triggered by fasting, stress, infection
- Completely benign

? 2. Crigler–Najjar Syndrome Type I

- Complete absence of **UGT1A1**
- Very high unconjugated bilirubin (>20 mg/dL)
- Fatal in infancy due to kernicterus
- No response to phenobarbital

? 3. Crigler–Najjar Syndrome Type II

- Partial deficiency of UGT1A1
- Moderate unconjugated bilirubin
- Responds to **phenobarbital** (induces enzyme)

? 4. Dubin–Johnson Syndrome

- Defect in **canalicular transport protein (MRP2)**
- ? conjugated bilirubin
- Dark, **black pigmented liver**
- Benign

? 5. Rotor Syndrome

- Defect in hepatic **storage/uptake** of conjugated bilirubin
- ? conjugated bilirubin
- **Liver is not pigmented** (unlike Dubin–Johnson)
- Benign

? KEY DIFFERENCE (Ultra-Short)

DISORDER	CONJUGATION	EXCRETION	TYPE
Gilbert	?	Normal	Unconjugated
Crigler–Najjar I	Absent	Normal	Unconjugated
Crigler–Najjar II	??	Normal	Unconjugated
Dubin–Johnson	Normal	Defective	Conjugated
Rotor	Normal	Defective uptake/storage	Conjugated

? HEMOLYTIC (PRE-HEPATIC) JAUNDICE

Caused by **increased RBC breakdown** ? overproduction of bilirubin.

? Features:

- ? **Unconjugated bilirubin**
- Normal liver function
- **No bilirubin in urine** (unconjugated is water-insoluble)
- ? **Urobilinogen** (more bilirubin entering gut)
- Dark stools
- Anemia + reticulocytosis

? Causes:

- Hemolytic anemia (autoimmune, hereditary spherocytosis)
- G6PD deficiency
- Sickle cell disease
- Thalassemia
- Malaria
- Shunt bilirubin from ineffective erythropoiesis

? HEPATOCELLULAR (LIVER) JAUNDICE

Due to **damage to hepatocytes** ? impaired uptake, conjugation, and excretion.

? Features:

- ? **Both** unconjugated & conjugated bilirubin
- ? AST/ALT
- **Bilirubin in urine** (conjugated)
- Variable stool color
- ? or ? urobilinogen
- Jaundice + hepatomegaly + systemic symptoms

? Causes:

- Viral hepatitis

- Alcoholic hepatitis
- Drug-induced liver injury
- NAFLD
- Cirrhosis
- Wilson disease, hemochromatosis

? OBSTRUCTIVE (POST-HEPATIC) JAUNDICE

Due to **bile flow blockage**.

? Features:

- ? **Conjugated bilirubin**
- **Very dark urine** (conjugated bilirubin excreted in urine)
- **Clay-colored stool** (? stercobilin)
- Severe itching (bile salts in skin)
- ? ALP & GGT
- ? urobilinogen

? Causes:

- Gallstones
- Carcinoma head of pancreas

- Cholangiocarcinoma
- Primary sclerosing cholangitis
- Biliary atresia
- Strictures

? DIFFERENTIAL DIAGNOSIS OF JAUNDICE (HIGH YIELD)

Here is the **cleanest differentiation**, perfect for exams:

? 1. Hemolytic (Pre-hepatic)

- Bilirubin: **Unconjugated ?**
- Urine bilirubin: **Absent**
- Urine urobilinogen: **?**
- Stool color: Dark
- Enzymes: Normal
- Example: G6PD deficiency

? 2. Hepatocellular

- Bilirubin: Both ?

- Urine bilirubin: Present
- Urine urobilinogen: Variable
- Stool: Normal or pale
- Enzymes: AST/ALT ?
- Example: Viral hepatitis

? 3. Obstructive (Post-hepatic)

- Bilirubin: **Conjugated ?**
- Urine bilirubin: Present (very high)
- Urine urobilinogen: ?
- Stool: **Clay-colored**
- Enzymes: ALP/GGT ??
- Example: Gallstones, pancreatic cancer

? ULTRA-SHORT SUMMARY (10 seconds revision)

- **Unconjugated ?:** hemolysis, Gilbert, Crigler–Najjar
- **Conjugated ?:** obstruction, Dubin–Johnson, Rotor

- **Urine dark:** conjugated bilirubin
- **Clay stool:** obstructive jaundice
- **High urobilinogen:** hemolysis
- **Pruritus:** cholestasis

? IMPORTANT POINTS TO REMEMBER (Whole Chapter)

? Structure of Heme

- Heme = **protoporphyrin IX + Fe²?** at center.
- Consists of **four pyrrole rings** linked by methene bridges.
- Fe²? must be in **ferrous form** to bind oxygen.
- Found in hemoglobin, myoglobin, cytochromes, catalase, peroxidases.

? Heme Biosynthesis

- Occurs in **mitochondria ? cytosol ? mitochondria**.
- Major sites: **bone marrow (85%)**, liver (15%).
- **ALA synthase** is the **rate-limiting step**.
- Requires **Vitamin B6 (PLP)**.

- Inhibited by **heme (feedback)**; induced by drugs that increase cytochrome P450.

? Lead Poisoning

- Lead inhibits **ALA dehydratase** and **ferrochelatase**.
- Leads to ? ALA, ? protoporphyrin, ? heme synthesis.

? Key Steps to Remember

- Glycine + Succinyl CoA ? ALA (ALAS)
- 2 ALA ? PBG (ALA dehydratase)
- 4 PBG ? Hydroxymethylbilane (PBG deaminase)
- Uroporphyrinogen III ? Coproporphyrinogen
- Coproporphyrinogen ? Protoporphyrin
- Protoporphyrin + $Fe^{2?}$? Heme (ferrochelatase)

? Porphyrias (High Yield)

- Due to **enzyme defects in heme pathway** ? accumulation of intermediates.
- **Hepatic porphyrias** ? neurovisceral symptoms.
- **Erythropoietic porphyrias** ? photosensitivity.

? Important Types:

- **Acute Intermittent Porphyria (AIP):**
  - ? PBG deaminase
  - ? ALA & PBG
  - Abdominal pain + neuro symptoms
  - No photosensitivity
- **Porphyria Cutanea Tarda (PCT):**
  - ? Uroporphyrinogen decarboxylase
  - Photosensitivity, blistering
  - Most common porphyria
- **Congenital Erythropoietic Porphyria (CEP):**
  - ? Uroporphyrinogen III synthase
  - Severe photosensitivity, red urine, erythrodontia
- **Erythropoietic Protoporphyria (EPP):**
  - ? Ferrochelatase
  - Mild photosensitivity

? Catabolism of Heme

- Occurs in **RES** (spleen/liver/bone marrow).
- Heme ? **biliverdin** (heme oxygenase).
- Biliverdin ? **bilirubin** (biliverdin reductase).
- Unconjugated bilirubin ? albumin-bound ? liver.
- Conjugated bilirubin formed by **UGT1A1**.
- Excreted into bile ? intestine ? urobilinogen ?
    - **Urobilin (urine)**
    - **Stercobilin (stool)**

? Shunt Bilirubin

- Bilirubin produced from **ineffective erythropoiesis** (intramedullary destruction).
- Causes isolated **unconjugated hyperbilirubinemia** without hemolysis.

? Plasma Bilirubin

- **Unconjugated (indirect):**
    - Albumin-bound
    - Lipid-soluble
    - Cannot appear in urine

- **Conjugated (direct):**
  - Water-soluble
  - Appears in urine
  - Indicates intrahepatic or obstructive pathology

? Congenital Hyperbilirubinemias

? Unconjugated:

- **Gilbert:** Mild ? UGT
- **Crigler–Najjar I:** Absent UGT (fatal)
- **Crigler–Najjar II:** Marked ? UGT (responds to phenobarbital)

? Conjugated:

- **Dubin–Johnson:** MRP2 defect, black liver
- **Rotor:** Defect in hepatic uptake/storage, normal-colored liver

? Hemolytic (Pre-Hepatic) Jaundice

- ? RBC destruction ? ? unconjugated bilirubin
- No bilirubin in urine
- ? urobilinogen

- Normal liver enzymes
- Seen in hemolysis, thalassemia, G6PD deficiency, shunt bilirubin.

? Hepatocellular Jaundice

- Hepatocyte damage ? impaired uptake, conjugation, excretion
- ? both conjugated & unconjugated bilirubin
- ? AST/ALT
- Urine bilirubin present
- Variable stool/urobilinogen

? Obstructive (Post-Hepatic) Jaundice

- Blocked bile flow
- ? conjugated bilirubin
- Clay-colored stool
- Dark urine
- Pruritus (bile salts)
- ? ALP & GGT
- ? urobilinogen

? Differential Diagnosis — Quick Rule

FEATURE	HEMOLYTIC	HEPATOCELLULAR	OBSTRUCTIVE
Type of bilirubin	Unconj ?	Both ?	Conj ?
Urine bilirubin	Absent	Present	Present (high)
Urine urobilinogen	?	Variable	?
Stool color	Dark	Normal/light	Pale (clay)
Enzymes	Normal	AST/ALT ?	ALP/GGT ?

? Ultra-Short Revision

- ALA synthase = rate-limiting; inhibited by heme.
- Lead inhibits ALA dehydratase & ferrochelatase.
- AIP = neuro symptoms, no photosensitivity.
- PCT = most common porphyria, blistering.
- Unconjugated ?: hemolysis, Gilbert, Crigler–Najjar.
- Conjugated ?: obstruction, Dubin–Johnson, Rotor.
- Clay stool + dark urine = obstructive jaundice.
- Urobilinogen ? = hemolysis.

? MCQs — Heme Synthesis, Breakdown & Jaundice (Whole Chapter)

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1. The central metal ion of heme that binds oxygen is:

A. Fe^{3}?
B. Mg^{2}?
C. Cu^{2}?
D. **Fe^{2}?**

Answer: D

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2. The rate-limiting enzyme in heme biosynthesis is:

A. Ferrochelatase
B. ALA dehydratase
C. PBG deaminase
D. **ALA synthase**

Answer: D

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3. Which vitamin is required as a cofactor for ALA synthase?

A. Vitamin C
B. Vitamin K
C. **Vitamin B6 (PLP)**
D. Vitamin A

Answer: C

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4. Lead inhibits which two enzymes in heme synthesis?

A. ALA synthase & PBG deaminase
B. **ALA dehydratase & ferrochelatase**
C. Uroporphyrinogen decarboxylase & coproporphyrinogen oxidase
D. Heme oxygenase & biliverdin reductase

Answer: B

5. A patient presents with acute abdominal pain, psychiatric symptoms, and red urine. No photosensitivity. Which porphyria is most likely?

A. PCT
B. CEP
C. Variegate porphyria
D. **Acute Intermittent Porphyria**

Answer: D

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6. Porphyria Cutanea Tarda is caused by a deficiency of:

A. PBG deaminase
B. ALA synthase
C. **Uroporphyrinogen decarboxylase**
D. Ferrochelatase

Answer: C

---

7. The porphyria associated with blistering photosensitivity and dark-colored ("tea-colored") urine is:

A. AIP
B. CEP
C. **PCT**
D. Crigler–Najjar

Answer: C

---

8. Which enzyme converts heme to biliverdin?

A. Biliverdin reductase
B. UDP-glucuronyl transferase
C. **Heme oxygenase**
D. Ferrochelatase

Answer: C

9. Unconjugated bilirubin is transported in the blood mainly bound to:

A. Hemoglobin
B. Ceruloplasmin
C. Transferrin
D. **Albumin**

Answer: D

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10. Conjugation of bilirubin requires:

A. ATP
B. Vitamin B6
C. CoA
D. **UDP-glucuronic acid**

Answer: D

---

11. Which bilirubin fraction is water-soluble and appears in urine?

A. Unconjugated
B. **Conjugated**
C. Delta bilirubin
D. Shunt bilirubin

Answer: B

---

12. Bilirubin diglucuronide is excreted through the:

A. Renal tubules
B. Blood plasma
C. **Bile canaliculi**
D. Portal vein

Answer: C

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13. The major pigment responsible for the brown color of stool is:

A. Urobilin
B. **Stercobilin**
C. Biliverdin
D. Porphobilinogen

Answer: B

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14. A 6-month-old with severe unconjugated hyperbilirubinemia not responding to phenobarbital likely has:

A. Gilbert syndrome
B. PCT
C. **Crigler–Najjar type I**
D. Dubin–Johnson syndrome

Answer: C

---

15. Dubin–Johnson syndrome is characterized by:

A. Unconjugated hyperbilirubinemia
B. **Conjugated hyperbilirubinemia + dark pigmented liver**
C. Enzyme destruction of UGT
D. Kernicterus

Answer: B

---

16. Which congenital disorder shows conjugated hyperbilirubinemia without liver pigmentation?

A. AIP
B. Gilbert
C. Dubin–Johnson
D. **Rotor syndrome**

Answer: D

---

17. In hemolytic jaundice, you expect:

A. ? Conjugated bilirubin
B. **? Unconjugated bilirubin**
C. ? ALP
D. Clay-colored stool

Answer: B

---

18. Which type of jaundice has increased urobilinogen in urine?

A. Obstructive
B. Hepatocellular
C. **Hemolytic**
D. Congenital conjugated jaundice

Answer: C

---

19. A patient presents with severe pruritus, dark urine, and clay-colored stools. Most likely diagnosis?

A. Hemolysis
B. Hepatitis
C. **Obstructive jaundice**
D. Gilbert syndrome

Answer: C

---

20. In obstructive jaundice, urine bilirubin is:

A. Absent
B. Normal
C. **Markedly elevated**
D. Increased urobilinogen

Answer: C

---

21. Which liver enzyme is MOST elevated in obstructive jaundice?

A. AST
B. ALT
C. LDH
D. **ALP**

Answer: D

---

22. Which condition shows both conjugated and unconjugated bilirubin elevation?

A. Obstruction
B. Hemolysis
C. **Hepatocellular jaundice**
D. Gilbert syndrome

Answer: C

---

23. Shunt bilirubin arises from destruction of:

A. Reticulocytes in spleen
B. Mature RBCs
C. **Ineffective erythroid precursors in bone marrow**
D. Kupffer cells

Answer: C

---

24. Which porphyria shows severe photosensitivity, hemolysis, and red fluorescent teeth?

A. PCT
B. AIP
C. **CEP (Günther disease)**
D. EPP

Answer: C

---

25. A patient develops abdominal pain and red urine after barbiturate use. Which enzyme is deficient?

A. ALA synthase
B. **PBG deaminase**
C. Ferrochelatase
D. Heme oxygenase

Answer: B

? CLINICAL CASE–BASED QUESTIONS (Whole Chapter)

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1. A 20-year-old woman presents with severe abdominal pain, confusion, and psychiatric symptoms. Her urine darkens on standing. She has no photosensitivity. Symptoms started after taking anti-epileptic medication.

Diagnosis: Acute Intermittent Porphyria
Mechanism: ? PBG deaminase ? ? ALA & PBG ? neurotoxicity
Trigger: Drugs inducing ALA synthase (cytochrome P450 inducers)

---

2. A middle-aged alcoholic man presents with blistering lesions on sun-exposed areas and hyperpigmentation. Urine shows increased uroporphyrins. Liver enzymes mildly elevated.

Diagnosis: Porphyria Cutanea Tarda
Mechanism: ? Uroporphyrinogen decarboxylase ? photosensitivity

---

3. A child has severe photosensitivity, red urine, hemolytic anemia, and red-brown teeth that fluoresce under UV light.

Diagnosis: Congenital Erythropoietic Porphyria (CEP)
Mechanism: ? Uroporphyrinogen III synthase ? Type I porphyrins accumulate

---

4. A young adult develops burning pain and swelling of the skin within minutes of sunlight exposure. Mild elevation of protoporphyrin is noted. Liver function is normal.

Diagnosis: Erythropoietic Protoporphyria
Mechanism: ? Ferrochelatase ? ? Protoporphyrin IX ? photosensitivity

---

5. A worker in a battery factory develops microcytic anemia, abdominal pain, and irritability. Labs show increased ALA, increased free erythrocyte protoporphyrins, and normal ferritin.

Diagnosis: Lead poisoning
Mechanism: Lead inhibits ALA dehydratase & ferrochelatase ? ? heme synthesis

---

6. A 15-day-old neonate has jaundice with very high unconjugated bilirubin. Kernicterus signs are present. No response to phenobarbital therapy.

Diagnosis: Crigler–Najjar Syndrome Type I
Mechanism: Complete absence of UGT1A1 ? severe unconjugated bilirubin

---

7. A teenager develops mild jaundice during fasting, illness, or stress. Unconjugated bilirubin is slightly elevated; all liver enzymes normal.

Diagnosis: Gilbert Syndrome
Mechanism: Mild ? UGT1A1 activity

---

8. A child has moderate unconjugated jaundice that improves significantly with phenobarbital.

Diagnosis: Crigler–Najjar Syndrome Type II
Mechanism: Partial UGT deficiency

---

9. A young adult presents with persistent conjugated hyperbilirubinemia. The liver is darkly pigmented on biopsy. No pruritus, normal LFTs.

Diagnosis: Dubin–Johnson Syndrome
Mechanism: Defective canalicular excretion pump (MRP2)

10. Another adult presents with conjugated hyperbilirubinemia but biopsy shows a normal-colored liver.

Diagnosis: Rotor Syndrome
Mechanism: Defective uptake/storage of conjugated bilirubin

---

11. A patient with G6PD deficiency develops jaundice after taking antimalarial drugs. Labs show ? unconjugated bilirubin, anemia, reticulocytosis. No bilirubin in urine.

Diagnosis: Hemolytic jaundice
Mechanism: RBC destruction ? ? heme breakdown ? ? unconjugated bilirubin

---

12. A patient with viral hepatitis shows jaundice, elevated AST/ALT, bilirubin in urine, and normal stool color.

Diagnosis: Hepatocellular jaundice
Mechanism: Impaired uptake, conjugation, and excretion

---

13. A patient has severe pruritus, dark urine, clay-colored stools, and very high ALP levels.

Diagnosis: Obstructive jaundice
Mechanism: Blocked bile flow ? ? conjugated bilirubin

---

14. A 2-year-old child with thalassemia major has jaundice despite no significant hemolysis. Reticulocyte count normal.

Diagnosis: Shunt bilirubin
Mechanism: Ineffective erythropoiesis ? intramedullary destruction ? ? unconjugated bilirubin

---

15. After thrombolysis for myocardial infarction, a patient develops worsening chest pain and rising troponin again. ROS markers are elevated.

Diagnosis: Reperfusion injury
Mechanism: Sudden oxygen ? massive ROS ? further injury, contracture bands

---

16. A man presents with jaundice and increased urobilinogen in urine; no bilirubin in urine; stool is dark.

Diagnosis: Hemolytic jaundice
Mechanism: High bilirubin load ? more urobilinogen

---

17. A patient with gallstones has extreme itching, conjugated bilirubin in urine, and pale stools.

Diagnosis: Extrahepatic biliary obstruction
Mechanism: No bilirubin enters intestine ? ? stercobilin

---

18. A newborn with jaundice responds promptly to phototherapy.

Diagnosis: Neonatal physiological jaundice
Mechanism: Low UGT activity at birth

---

19. An alcoholic man with ascites has elevated conjugated and unconjugated bilirubin, high AST/ALT, and peripheral stigmata of chronic liver disease.

Diagnosis: Hepatocellular jaundice from alcoholic hepatitis/cirrhosis
Mechanism: Hepatocyte dysfunction

---

20. A patient's stool is dark brown and urine yellow, but serum bilirubin is mildly raised and unconjugated. Liver enzymes normal.

Diagnosis: Mild hemolysis
Mechanism: Excess RBC destruction with intact liver function

? VIVA VOCE — Heme Synthesis, Breakdown & Jaundice (Whole Chapter)

---

1. What is the basic structure of heme?

Heme is **protoporphyrin IX with Fe²?** at its center.

---

2. Why must iron be in the ferrous state ($Fe^{2?}$)?

Because only $Fe^{2?}$ can bind oxygen.

---

3. Where does heme synthesis occur?

Partly in **mitochondria** and partly in **cytosol**.

---

4. What is the rate-limiting enzyme in heme synthesis?

ALA synthase.

---

5. Which vitamin is required for ALA synthase?

Vitamin B6 (pyridoxal phosphate).

---

6. Which step of heme synthesis is inhibited by heme?

ALA synthase (feedback inhibition).

---

7. Name the two enzymes inhibited by lead.

ALA dehydratase and **ferrochelatase.**

---

8. Which porphyria presents without photosensitivity?

Acute Intermittent Porphyria (AIP).

---

9. Why is AIP neurotoxic?

Accumulation of **ALA & PBG** causes neuronal dysfunction.

---

10. Which porphyria is the most common?

Porphyria Cutanea Tarda (PCT).

---

11. Which enzyme is deficient in PCT?

Uroporphyrinogen decarboxylase.

---

12. Which porphyria shows red-brown teeth and severe photosensitivity?

Congenital Erythropoietic Porphyria (CEP).

---

13. What is the final step of heme formation?

Insertion of $Fe^{2?}$ into protoporphyrin IX by **ferrochelatase.**

---

14. Where is heme breakdown initiated?

In the **reticuloendothelial system (RES)**—mainly spleen.

---

15. What enzyme converts heme to biliverdin?

Heme oxygenase.

---

16. What enzyme converts biliverdin to bilirubin?

Biliverdin reductase.

---

17. What form of bilirubin is bound to albumin in plasma?

Unconjugated (indirect) bilirubin.

---

18. Which bilirubin fraction appears in urine?

Conjugated bilirubin.

---

19. What enzyme conjugates bilirubin in the liver?

UDP-glucuronyl transferase (UGT1A1).

---

20. What happens to conjugated bilirubin in the intestine?

Converted to **urobilinogen** by gut bacteria.

---

21. What gives urine its yellow color?

Urobilin.

---

22. What gives stool its brown color?

Stercobilin.

---

23. What is shunt bilirubin?

Unconjugated bilirubin formed from **ineffective erythropoiesis** (intramedullary destruction).

---

24. Which congenital disorder has complete absence of UGT?

Crigler–Najjar Syndrome Type I.

---

25. Which congenital disorder shows mild unconjugated jaundice during stress?

Gilbert syndrome.

---

26. Which congenital disorder has conjugated hyperbilirubinemia with a black liver?

Dubin–Johnson syndrome.

---

27. Which shows conjugated hyperbilirubinemia without liver pigmentation?

Rotor syndrome.

---

28. What is the main feature of hemolytic jaundice?

Unconjugated hyperbilirubinemia with **no bilirubin in urine**.

---

29. What is the hallmark of obstructive jaundice?

Clay-colored stools, **dark urine**, and **pruritus**.

---

30. Which jaundice type shows ? ALP and ? GGT?

Obstructive (post-hepatic) jaundice.

---

31. Why does hepatocellular jaundice show both conjugated and unconjugated bilirubin elevation?

Because hepatocyte **uptake, conjugation, and excretion** are impaired.

---

32. Which type of jaundice shows increased urobilinogen in urine?

Hemolytic jaundice.

---

33. Which type shows decreased urobilinogen?

Obstructive jaundice.

---

34. What causes clay-colored stools in obstruction?

Lack of bilirubin reaching the intestine ? no stercobilin.

---

35. What causes dark urine in obstructive jaundice?

Excess **conjugated bilirubin** excreted by kidneys.

---

36. What does phenobarbital do in Crigler–Najjar Type II?

Induces **UGT1A1**, lowering bilirubin.

---

37. What is the significance of carbon monoxide in heme breakdown?

It is a byproduct of **heme oxygenase** activity.

---

38. What does ferrochelatase insert into protoporphyrin IX?

$Fe^{2?}$.

---

39. Which bilirubin fraction rises first in viral hepatitis?

Conjugated bilirubin (due to impaired excretion).

---

40. What is the most important lab test to differentiate obstructive from hepatocellular jaundice?

ALP and GGT levels (high in obstruction).