MEDICAL EDUCATION RESOURCE

General Amino Acid Metabolism (Urea Cycle, One Carbon Metabolism)

? General Amino Acid Metabolism

(Urea Cycle, One-Carbon Metabolism)

Digestion of Proteins & Absorption of Amino Acids

These notes cover the first section of the chapter:

? **Digestion of dietary proteins**

? **Absorption of amino acids & peptides**

? High-yield mechanisms and clinical points

Everything is pointwise and perfect for MBBS exam preparation.

? Digestion of Proteins

Protein digestion begins in the **stomach** and is completed in the **small intestine**.

? 1. Digestion in the Stomach

a. Hydrochloric Acid (HCl)

- Secreted by **parietal cells**
- Denatures proteins ? opens peptide bonds
- Provides pH **1–2** (optimal for pepsin)

b. Pepsin

- Chief cells secrete **pepsinogen** (inactive)
- HCl converts pepsinogen ? **pepsin**
- Pepsin is an **endopeptidase**
- Cleaves peptide bonds involving **aromatic amino acids** (Phe, Tyr, Trp)

c. Product of gastric digestion

- **Large polypeptides**
- Some free amino acids
- Stimulates **CCK** release in duodenum

? 2. Digestion in the Small Intestine

Protein digestion is mostly completed here.

a. Hormonal Regulation

- **CCK** (Cholecystokinin):
  - Stimulates pancreatic enzyme secretion
  - Slows gastric emptying
- **Secretin**:
  - Stimulates bicarbonate secretion ? neutralizes acid

? b. Pancreatic Proteases (Released as zymogens)

ZYMOGEN	ACTIVATED FORM	ACTIVATOR	FUNCTION
Trypsinogen	**Trypsin**	Enteropeptidase	Activates other proteases; cleaves Lys, Arg
Chymotrypsinogen	**Chymotrypsin**	Trypsin	Cleaves aromatic AAs
Proelastase	**Elastase**	Trypsin	Cleaves small neutral AAs
Procarboxypeptidase A/B	**Carboxypeptidase A/B**	Trypsin	Exopeptidase: removes C-terminal AA

Trypsin is the master activator of all pancreatic zymogens.

? c. Intestinal Enzymes

- **Aminopeptidases** – remove N-terminal amino acids
- **Dipeptidases & Tripeptidases** – break small peptides to amino acids
- **Enteropeptidase** – activates trypsinogen

? Products of Digestion

- Free amino acids
- Dipeptides

- Tripeptides

All are absorbable forms.

? Absorption of Amino Acids

Occurs mainly in **jejunum**.

? 1. Absorption of Free Amino Acids

a. Na?-Dependent Transporters

- Most amino acids absorbed by **secondary active transport**
- Requires:
  - Na? gradient (maintained by Na?/K? ATPase)
  - Specific carriers for:
    - Neutral AAs
    - Basic AAs
    - Acidic AAs
    - Imino acids (proline)

b. Na?-Independent Transporters

- For some neutral and basic AAs

- Facilitated diffusion at basolateral membrane releases AAs into blood

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? 2. Absorption of Dipeptides & Tripeptides

PEPT1 Transporter

- **H?-dependent cotransporter**
- High capacity
- Most dietary protein is absorbed as **di- and tripeptides**, then hydrolyzed intracellularly

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? 3. Clinical Correlations

a. Cystinuria

- Defect in transporter for **cystine, lysine, arginine, ornithine**
- Causes **kidney stones** (hexagonal cystine crystals)

b. Hartnup Disease

- Defect in absorption of **neutral amino acids**
- Causes **pellagra-like features** due to tryptophan deficiency

c. Pancreatic insufficiency

- Low trypsin/chymotrypsin

- Causes protein malabsorption ? steatorrhea

? High-Yield Summary

- HCl denatures proteins; pepsin begins hydrolysis.
- Enteropeptidase activates trypsin ? activates all pancreatic proteases.
- Aminopeptidases, dipeptidases complete digestion on brush border.
- Amino acids absorbed by **Na?-dependent active transport**.
- Dipeptides/tripeptides absorbed by **PEPT1 (H? dependent)**.
- Cystinuria involves dibasic AA transporter defect.

? Meister Cycle (?-Glutamyl Cycle)

The Meister cycle is a pathway for **transport of amino acids into cells**, especially in **kidney, intestine, and liver**.
It also regenerates **glutathione (GSH)**, a major antioxidant.

? Key Components

- **Glutathione (GSH)**
- Enzymes in **membrane & cytosol**

- Transports **neutral amino acids**

? Steps of Meister Cycle

1. ?-Glutamyl Transpeptidase (GGT) Reaction

- Located on **cell membrane**
- Transfers ?-glutamyl group from GSH to an amino acid entering the cell

GSH + Amino acid ? ?-Glutamyl amino acid (outside cell)

- Cysteinyl-glycine is released.

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2. Transport Into Cell

The ?-glutamyl amino acid is transported into cytosol.

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3. Hydrolysis Inside Cell

- ?-Glutamyl cyclotransferase removes the amino acid ? forms **5-oxoproline**.

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4. ATP-Dependent Recycling

5-oxoproline ? glutamate ? forms glutathione again.

This requires **2 ATP molecules**.

? Functions of the Meister Cycle

- Facilitates **amino acid absorption** into cells
- Regenerates **glutathione** (antioxidant)
- Maintains **redox balance**
- Important in **detoxification** (liver)

? Clinical Note

- **GGT** is a key clinical enzyme:
  - Elevated in **alcoholic liver disease**
  - Elevated with **enzyme-inducing drugs** (phenytoin, rifampicin)

? Intracellular Protein Degradation

Cells constantly degrade proteins to remove damaged, misfolded, or short-lived proteins. Two major pathways exist:

1. **Lysosomal degradation**
2. **Ubiquitin-proteasome pathway**

? 1. Lysosomal Protein Degradation

Occurs inside **lysosomes**, using acidic hydrolases.

Key Features

- Degrades **extracellular proteins**, membrane proteins, and long-lived proteins
- **ATP-independent**
- Uses **cathepsins** (lysosomal proteases)

? Cathepsins

Cathepsins are **lysosomal proteases** responsible for degrading proteins inside the lysosome.

Characteristics

- Optimum pH: **acidic (pH 5)**
- Many types: **Cathepsin B, D, L, K, etc.**
- Important for:
  - Protein turnover
  - Collagen breakdown
  - Antigen processing
  - Bone resorption (Cathepsin K)

Clinical Correlation

- **Cathepsin deficiency** ? lysosomal storage disorders

- Cathepsin overactivity ? bone diseases, cancer invasion

? 2. Ubiquitin–Proteasome Pathway (UPP)

The major pathway for degrading **short-lived, abnormal, and regulatory proteins**.

Where?

- **Cytoplasm & nucleus**

Requires ATP

? Steps in Ubiquitin–Proteasome Pathway

? 1. Activation of Ubiquitin

- Ubiquitin is activated by **E1 enzyme** (ATP-dependent).

? 2. Conjugation

- Ubiquitin is transferred to **E2 enzyme**.

? 3. Ligation

- **E3 ligase** attaches ubiquitin to Lys residues on target protein.

? 4. Polyubiquitination

- Protein is tagged with a **chain of ubiquitin molecules**.

? 5. Degradation in Proteasome

- Polyubiquitinated protein enters the **26S proteasome**.
- Proteasome cleaves it into **small peptides**.

? Proteins Degraded by UPP

- Misfolded proteins
- Damaged proteins
- Regulatory proteins (cyclins)
- Transcription factors
- Cancer-related proteins (p53, BRCA1)

? Clinical Applications

- **Cancer therapy**:
  - **Bortezomib** inhibits proteasome ? used in multiple myeloma
- Neurodegenerative diseases:
  - Faulty UPS ? accumulation of misfolded proteins in Alzheimer’s, Parkinson’s
- HPV E6/E7 proteins cause **ubiquitin-mediated destruction** of **p53** and **Rb**

? High-Yield Quick Revision

- Meister cycle = **GSH-dependent amino acid transport + GSH regeneration**.
- GGT is a marker of **alcoholic liver disease**.
- Cathepsins = **lysosomal proteases**.
- Ubiquitin pathway = **ATP-dependent degradation of misfolded or short-lived proteins** .
- 26S proteasome = main cytosolic degradation machinery.
- Polyubiquitin tag directs proteins to **proteasome**.

? Proteasomes

Proteasomes are **large multi-enzyme complexes** that degrade **ubiquitin-tagged proteins** inside the **cytoplasm and nucleus**.

? Structure of Proteasome

- The functional unit is the **26S proteasome**.
- Composed of:
  - **20S core** (catalytic barrel; protease activity)
  - **19S regulatory caps** (recognize ubiquitin tag, unfold proteins, feed them into core)

? Functions

- Degrades:
  - Misfolded proteins
  - Oxidatively damaged proteins
  - Regulatory proteins (cyclins)
  - Transcription factors
- Maintains **protein quality control**.
- Important in **cell cycle regulation**, immune responses, cancer cell survival.

? Clinical Relevance

- **Bortezomib** & **Carfilzomib**: proteasome inhibitors used in **multiple myeloma**.
- Failure of proteasomal degradation ? **aggregation diseases**
  (Parkinson’s, Alzheimer’s, Huntington’s).

? Inter-Organ Transport of Amino Acids

Amino acids move between tissues to meet metabolic demands.
Different organs prefer specific amino acids.

? 1. Muscle

Muscle exports:

- **Alanine** (major)
- **Glutamine** (also significant)

Muscle uses amino acids for energy during fasting and exercise.

? 2. Liver

- Primary site of **urea cycle**.
- Receives **alanine** from muscle ? removes nitrogen ? converts to urea.
- Also receives **glutamine** from muscle & gut.

? 3. Intestine

- Uses **glutamine** as the preferred fuel.
- Releases **alanine** into blood after metabolizing dietary amino acids.

? 4. Kidney

- Uses **glutamine** during acidosis ? releases **NH??** for acid excretion.
- Produces **serine** via gluconeogenesis from glycine.

? 5. Brain

- Depends on glutamine ? glutamate cycling for neurotransmitter balance.

? 6. Blood

Transports:

- Free amino acids
- Alanine (main nitrogen carrier from muscle to liver)
- Glutamine (major carrier of ammonia)

? High-Yield Summary

- **Alanine ? liver** (nitrogen transport, glucose production)
- **Glutamine ? many tissues** (fuel, nitrogen donor)
- **Muscle = major exporter**
- **Liver = major receiver**

? Glucose–Alanine Cycle (Cahill Cycle)

The Glucose–Alanine cycle transfers **nitrogen from muscle to liver** and returns **glucose** to muscle.

It operates during:

- Fasting
- Prolonged exercise
- Muscle protein breakdown
- Conditions requiring glucose conservation

? Steps of the Glucose–Alanine Cycle

? 1. In Muscle

- Muscle proteolysis ? amino acids ? release **NH?**.
- NH? + pyruvate ? **alanine** (via alanine transaminase, ALT).
- Alanine is released into blood.

? 2. Transport to Liver

- Alanine travels through blood to the **liver**.

? 3. In Liver

- Alanine ? pyruvate + NH? (via ALT).

- NH? enters **urea cycle** ? converted to **urea**.
- Pyruvate enters **gluconeogenesis** ? forms **glucose**.

? 4. Glucose Returned to Muscle

- Liver releases **glucose** into blood.
- Muscle uses this glucose for **energy**.

? Functions of Glucose–Alanine Cycle

? 1. Transport of nitrogen

Carries nitrogen from muscle ? liver safely as alanine.

? 2. Removal of toxic ammonia

Ammonia converted to **urea** in liver.

? 3. Fuel supply

Provides **glucose** back to muscle during fasting/exercise.

? 4. Supports gluconeogenesis

Pyruvate ? glucose (especially during prolonged fasting).

? Clinical Importance

- Elevated **ALT** in serum indicates muscle or liver damage.

- Overactive cycle occurs in **catabolic states** (burns, sepsis).
- Important for survival during **starvation**.

? High-Yield Exam Lines

- Alanine is the **major amino acid released from muscle** during fasting.
- Muscle uses alanine to send **nitrogen ? liver**.
- Liver uses alanine for **gluconeogenesis + urea production**.
- The cycle links **protein breakdown** with **glucose homeostasis**.

? Catabolism of Amino Acids

Amino acid catabolism involves two major processes:

1. **Removal of nitrogen**
2. **Metabolism of the carbon skeleton**

These processes occur mainly in the **liver**.

? 1. Removal of Nitrogen

Amino acids first undergo one of the following:

a. Transamination

Transfer of amino group to ?-ketoglutarate ? forms **glutamate**.

b. Oxidative deamination

Glutamate releases NH? ? **free ammonia**.

c. Non-oxidative deamination

Serine, threonine ? NH? release without oxidation.

d. Decarboxylation

Produces amines (GABA, histamine, serotonin).

? 2. Fate of Carbon Skeleton

After nitrogen removal, carbon skeletons enter major metabolic pathways as:

- Pyruvate
- Acetyl-CoA / Acetoacetate
- ?-Ketoglutarate
- Succinyl-CoA
- Fumarate
- Oxaloacetate

? Glucogenic Amino Acids

Produce glucose precursors (**all except leucine and lysine**).

? Ketogenic Amino Acids

- **Leucine and Lysine (strictly ketogenic)**
- Produce **acetyl-CoA / acetoacetate**.

? Formation of Ammonia

Ammonia (NH?) is mainly formed during amino acid breakdown.
Because ammonia is **toxic**, it must be converted to **urea**.

? Sources of Ammonia

? 1. Oxidative Deamination

- Enzyme: **Glutamate dehydrogenase**
- Glutamate ? ?-ketoglutarate + **NH?**
- Occurs in **liver mitochondria**

? 2. Oxidative Deamination of Amino Acids

Dehydratases produce NH? (e.g., serine, threonine).

? 3. Intestinal Bacteria

- Urease-producing bacteria liberate NH? from urea.
- Largest **extrahepatic** source of ammonia.
- Explains high NH? in **liver failure**.

? 4. Amino Acid Oxidases

Produce NH? using FMN/FAD.

? 5. Purine and Pyrimidine Metabolism

Deamination releases NH?.

? 6. Kidney

Glutaminase releases NH? to buffer urine.

? Transport of Ammonia

Because free NH? is toxic, it moves between tissues as:

? 1. Alanine (muscle ? liver)

Via **Glucose–Alanine cycle**.

? 2. Glutamine (all tissues ? liver/kidney)

Glutamine carries **two nitrogen atoms** safely.

? Transamination

Transamination is the **first step of amino acid catabolism**.

? Definition

Transfer of an amino group from an amino acid ? ?-ketoglutarate
to form:

- A **new amino acid**

- A **new keto acid**

> **? Enzyme**

Aminotransferases / Transaminases

All require **Pyridoxal phosphate (PLP)**
? Vitamin **B6** derivative.

? Important Transamination Reactions

? 1. Alanine Transaminase (ALT)

Alanine + ?-ketoglutarate

? Pyruvate + Glutamate

ALT rises in **liver injury**.

? 2. Aspartate Transaminase (AST)

Aspartate + ?-ketoglutarate

? Oxaloacetate + Glutamate

AST rises in **cardiac + liver injury**.

? 3. Universal Amino Group Acceptor

? **?-Ketoglutarate**
Forms glutamate.

? Features of Transamination

- **Reversible**
- Does **not** release free ammonia
- Occurs in **cytosol & mitochondria**
- Not performed by:
  - **Lysine**
  - **Threonine**
  - **Proline**
  - **Hydroxyproline**

? Functions of Transamination

- Collects nitrogen as **glutamate**
- Produces keto acids for energy
- Transfers nitrogen to urea cycle via:
  - **Glutamate**
  - **Aspartate**

? Clinical Relevance

- ALT and AST are **important liver function markers**.
- Vitamin B6 deficiency ? ? transamination ? neurological problems.

? Oxidative Deamination

Oxidative deamination **removes the amino group as free ammonia (NH?)** while oxidizing the amino acid.
This is the major pathway for **liberating ammonia** in the body.

> **? Key Enzyme: Glutamate Dehydrogenase (GDH)**

Location:

- **Mitochondria** of liver and kidney

Reaction:

Glutamate + NAD?/NADP?

? ?-ketoglutarate + NH? + NADH/NADPH

Why glutamate?

Transamination reactions funnel amino groups from most amino acids onto **?-ketoglutarate**, forming **glutamate**.
Thus glutamate becomes the **central collector** of amino groups ? oxidative deamination removes them.

? Features of GDH

- Uses **either NAD? or NADP?**
- Reaction is **reversible**
- Activated by **ADP, GDP** (signals need for energy)
- Inhibited by **ATP, GTP** (energy abundance)

? Clinical Point

A defect in GDH regulation ? **hyperinsulinism-hyperammonemia syndrome**
(Excess ammonia + recurrent hypoglycemia).

? Non-Oxidative Deamination

These reactions remove ammonia **without oxidation**.

They occur mainly in amino acids containing **hydroxyl or sulfur groups**.

? Enzymes

1. **Serine dehydratase**

2. **Threonine dehydratase**
3. **Cysteine desulfhydrase**

> **? Examples of Reactions**

1. Serine ? Pyruvate + NH?

Catalyzed by **serine dehydratase**.

2. Threonine ? ?-ketobutyrate + NH?

Catalyzed by **threonine dehydratase**.

3. Cysteine ? Pyruvate + NH? + H?S

Catalyzed by **cysteine desulfhydrase**.

? Features

- PLP (Vitamin B6) dependent
- No involvement of NAD?/NADP?
- Occur mainly in **liver**

? Disposal of Ammonia

Ammonia is **highly neurotoxic**, so the body must convert it into safe, non-toxic forms.

The major routes:

1. **Urea Cycle** (primary disposal mechanism)
2. **Formation of glutamine**
3. **Formation of alanine**
4. **Excretion via kidney**

Let's summarise them.

? 1. Urea Cycle (Primary Disposal)

Occurs in **liver** (mitochondria + cytosol).

Converts NH? + CO? into **urea**, which is excreted by kidneys.

(Full urea cycle will be detailed separately in the next section.)

? 2. Formation of Glutamine — Most Important Extrahepatic Pathway

? Enzyme: Glutamine Synthetase

Glutamate + NH? + ATP ? Glutamine

? Importance

- Glutamine carries **two nitrogen atoms** safely through blood.
- Occurs in **muscle, brain, and liver (periportal)**.

? Uses of Glutamine

- Transport NH? to liver
- Fuel for **kidney & intestine**
- Detoxification in brain
- Precursor for nucleotide synthesis

? 3. Formation of Alanine — Transport from Muscle to Liver

Through **Glucose-Alanine Cycle**:

- Muscle: pyruvate + NH? ? **alanine**
- Alanine travels to liver
- Liver: alanine ? pyruvate + NH? ? urea
- Pyruvate ? glucose ? back to muscle

? 4. Renal Ammonia Excretion

In **kidneys**, ammonia traps protons to excrete acid.

? Enzyme: Glutaminase

Glutamine ? Glutamate + NH?

NH? + H? ? NH?? (excreted in urine)

? During acidosis

- Kidney produces **more ammonia**
- Helps remove excess H?
- Important in maintaining **acid–base balance**

? 5. Minor Routes

- Bacterial urease in gut produces NH?—absorbed ? detoxified by liver.
- Purine/pyrimidine metabolism releases small amounts of NH?.

? High-Yield Summary

- **Oxidative deamination** (GDH) liberates most ammonia.
- **Non-oxidative deamination**: serine, threonine, cysteine.
- Ammonia is disposed mainly via **urea cycle**, **glutamine**, and **alanine**.
- Kidney disposes NH?? especially during **acidosis**.
- Glutamine is the **major carrier** of ammonia in blood.
- Alanine carries ammonia **from muscle ? liver**.

? UREA CYCLE (Ornithine Cycle)

The urea cycle converts **toxic ammonia (NH?)** into **non-toxic urea**, which is excreted by the kidneys.

? Site

- **Liver** — only organ with complete cycle
- Steps occur in **mitochondria + cytosol**

? Purpose of the Urea Cycle

- Remove **ammonia**, a potent neurotoxin
- Convert nitrogen ? **urea**
- Regeneration of **ornithine**

? STEPS OF THE UREA CYCLE

? Step 1 (Mitochondria)

Formation of Carbamoyl Phosphate

Enzyme: **Carbamoyl Phosphate Synthetase I (CPS-I)**
Requires:

- **2 ATP**
- **NH?**
- **CO?**

- **N-acetylglutamate (NAG)** as **obligatory activator**

Product: **Carbamoyl phosphate**

? Step 2 (Mitochondria)

Carbamoyl Phosphate + Ornithine ? Citrulline

Enzyme: **Ornithine Transcarbamoylase (OTC)**
Citrulline enters **cytosol**.

? Step 3 (Cytosol)

Citrulline + Aspartate ? Argininosuccinate

Enzyme: **Argininosuccinate Synthetase**
Requires **ATP**

Aspartate provides the **second nitrogen** of urea.

? Step 4 (Cytosol)

Argininosuccinate ? Arginine + Fumarate

Enzyme: **Argininosuccinate Lyase**

Fumarate ? TCA cycle (fumarate shuttle)

? Step 5 (Cytosol)

Arginine ? Ornithine + Urea

Enzyme: **Arginase**

Urea enters blood ? excreted by kidney.
Ornithine returns to **mitochondria**.

? Energy Requirement

- Urea cycle consumes **4 high-energy bonds (3 ATP)**
- But fumarate ? TCA produces some ATP ? net cost slightly lower

? Regulation of Urea Cycle

? 1. N-Acetylglutamate (NAG)

- Mandatory activator of **CPS-I**
- Produced from **glutamate + acetyl-CoA**
- Formation of NAG ? when amino acid catabolism ?

? 2. Enzyme induction

High protein diet or fasting increases transcription of urea cycle enzymes.

? Clinical Importance

- Urea cycle removes bulk of nitrogen
- Liver failure ? ? ammonia ? **hepatic encephalopathy**

? DISORDERS OF THE UREA CYCLE

All are **autosomal recessive**, except **OTC deficiency (X-linked)**.

All cause:

- **Hyperammonemia**
- Lethargy
- Poor feeding
- Vomiting
- Seizures
- Cerebral edema
- Respiratory alkalosis

Early presentation in newborns ? **life-threatening**.

? 1. Carbamoyl Phosphate Synthetase I (CPS-I) Deficiency

- **Type I Hyperammonemia**
- Severe ? NH?
- No carbamoyl phosphate formed

Labs:

- ? orotic acid
- ? citrulline
- Very high ammonia

? 2. Ornithine Transcarbamoylase (OTC) Deficiency

- **Most common UCD**
- **X-linked**
- Carbamoyl phosphate builds up ? enters pyrimidine pathway ? ? **orotic acid**

Labs:

- **? Orotic acid (key marker)**
- ? citrulline
- Hyperammonemia
- Normal blood glucose

? 3. Argininosuccinate Synthetase Deficiency

Disease: Citrullinemia

- Accumulation of **citrulline**

Labs:

- **? Citrulline** (very high)
- ? ammonia

? 4. Argininosuccinate Lyase Deficiency

Disease: Argininosuccinic aciduria

- Accumulation of **argininosuccinate**

Features:

- **Brittle hair (trichorrhexis nodosa)**
- ? ammonia
- ? argininosuccinate

? 5. Arginase Deficiency

Disease: Argininemia

- ? arginine
- Milder hyperammonemia
- Spasticity, tremors, ataxia

Labs:

- **Very high arginine**

? General Laboratory Pattern in UCDs

- **High ammonia**
- **Respiratory alkalosis**
- Specific amino acids elevated depending on block
- No metabolic acidosis (unlike organic acidemias)

? Treatment of Urea Cycle Disorders

? Acute Management

- Stop protein intake
- Hemodialysis (rapid ammonia removal)
- IV sodium benzoate / phenylacetate ? nitrogen scavengers
- IV arginine (except in arginase deficiency)

? Chronic Management

- Low protein diet
- Benzoate/phenylbutyrate therapy
- Oral arginine (depending on defect)

- Liver transplantation (curative)

? High-Yield Differences

Disorder	Marker	Amino Acid Elevated
CPS-I Deficiency	? orotic acid	? citrulline
OTC Deficiency	**? orotic acid**	? citrulline
Citrullinemia	Normal orotic acid	**?? citrulline**
Argininosuccinate lyase deficiency	Normal orotic acid	? argininosuccinate
Arginase deficiency	Normal orotic acid	**? arginine**

? Ultra-Short Revision

- CPS-I needs **NAG**.
- OTC deficiency ? **high orotic acid**.

- Citrullinemia ? **very high citrulline**.
- Argininosuccinic aciduria ? **hair abnormalities**.
- Arginase deficiency ? **spasticity + high arginine**.
- All cause **hyperammonemia + respiratory alkalosis**.

? HEPATIC COMA (Hepatic Encephalopathy)

Hepatic coma results from **failure of the liver to detoxify ammonia**, leading to **accumulation of NH? in blood and brain**.

This is a LIFE-THREATENING complication of liver failure.

? Causes

1. Liver failure

- Acute fulminant hepatitis
- Severe alcoholic hepatitis
- Cirrhosis with portal hypertension

2. Portosystemic shunts

- Blood bypasses liver ? ammonia remains undetoxified

3. Precipitating factors

- GI bleeding
- High protein intake
- Constipation
- Diuretics ? hypokalemia
- Infections
- Sedatives
- Renal failure

? Pathogenesis

? 1. Ammonia Accumulation

- Gut bacteria produce ammonia
- Failing liver cannot convert ammonia ? urea
- NH? crosses blood–brain barrier

? 2. Astrocyte swelling

- Ammonia + glutamate ? **glutamine**
- Osmotic swelling of astrocytes ? **cerebral edema**

? 3. Neurotransmitter abnormalities

- Increased GABAergic tone

- Altered serotonin, glutamate pathways
- “False neurotransmitters” accumulation

? Clinical Features

- Confusion, irritability
- Personality changes
- Flapping tremor (**asterixis**)
- Disorientation, slurred speech
- Drowsiness ? stupor ? **coma**
- Fetor hepaticus (sweet musty smell)
- Seizures in severe cases

? Investigations

- **Very high blood ammonia level**
- EEG: triphasic waves
- LFT abnormalities
- Precipitating factor identification (K?, infection, bleeding)

? Management

1. Reduce ammonia production

- **Lactulose**: converts NH? ? NH??, increases stool frequency
- **Rifaximin**: reduces ammonia-producing gut bacteria

2. Correct precipitating factors

- Treat GI bleed, infection, dehydration
- Stop sedatives, adjust diuretics

3. Diet

- Low protein initially
- Vegetable protein preferred later

4. Severe cases

- ICU care
- Mechanical ventilation
- Liver transplantation

? High-Yield Lines

- Ammonia accumulation is the **main cause**.
- Ammonia ? glutamine ? **astrocyte swelling** ? cerebral edema.

- **Lactulose** is the drug of choice.
- Asterixis = classic sign.

? BLOOD UREA

Urea is the **major end product of nitrogen metabolism**, produced exclusively by the **liver** through the **urea cycle**.

It is excreted mainly by the **kidneys**.

? Normal Values

- **Blood Urea Nitrogen (BUN):** 7–20 mg/dL
- **Serum urea:** 20–40 mg/dL (depending on lab standards)

? Factors Affecting Blood Urea

? 1. Increased Blood Urea

? a. Pre-renal causes (high BUN/Creatinine ratio)

- Dehydration
- Shock
- Heart failure

- High protein diet
- GI bleeding (digested blood ? amines ? urea)
- Corticosteroid therapy

? b. Renal causes

- Acute or chronic renal failure
- Glomerulonephritis
- Tubular necrosis

? c. Post-renal causes

- Obstruction (stones, prostate enlargement)

? 2. Decreased Blood Urea

- **Severe liver disease** (urea cycle suppressed)
- **Low protein intake**
- **Pregnancy** (increased plasma volume)
- **SIADH**

? Clinical Uses of Blood Urea

- Marker of **renal function**
- Assessment of **hydration status**
- Differentiates **pre-renal vs renal** azotemia
- Monitors **dialysis effectiveness**
- Elevated in **GI bleed** due to increased protein absorption

? BUN : Creatinine Ratio

? Normal: 10–15 : 1

Condition	BUN:Cr Ratio	Explanation
Pre-renal azotemia	**>20:1**	Increased urea reabsorption
Renal failure	**10–15:1 (normal)**	Both impaired
Post-renal	**Variable**	Obstruction

? High-Yield Points

- Urea depends on **liver synthesis**, creatinine does not.

- Low urea = **severe hepatic failure** or low protein intake.
- Urea cross BBB ? contributes to **encephalopathy** only when liver fails to detoxify ammonia.
- BUN rises faster in **dehydration** than creatinine.

? ONE-CARBON COMPOUNDS (One-Carbon Units)

One-carbon units are **single-carbon fragments** transferred between molecules during amino acid, nucleotide, and methylation reactions.

These 1-carbon units are carried mainly by:

? Tetrahydrofolate (THF) – the primary carrier

? S-adenosylmethionine (SAM) – the strongest methyl donor

? Vitamin B?? – accepts/transfers methyl groups in selected reactions

? Types of One-Carbon Units Carried by THF

THF carries one-carbon groups in various oxidation states:

- **Formyl (–CHO)**
- **Formimino (–CH=NH)**
- **Methylene (–CH?–)**
- **Methenyl (–CH=)**
- **Methyl (–CH?)**

- **Hydroxymethyl (–CH?OH)**

These interchangeable forms allow THF to participate in a wide range of biosynthetic reactions.

? GENERATION OF ONE-CARBON GROUPS

One-carbon units come from **amino acid metabolism**.

? 1. Serine ? Glycine

- **Major source**
- Enzyme: *Serine hydroxymethyltransferase*
- Produces: **Methylene-THF**

? 2. Glycine cleavage system

- Glycine ? CO? + NH? + 1-carbon unit
- Produces: **Methylene-THF**

? 3. Histidine metabolism

- Formiminoglutamate (FIGLU) ? Glutamate
- Produces: **Formimino-THF**

? 4. Tryptophan metabolism

- Provides formyl groups
- Produces: **Formyl-THF**

? 5. Choline metabolism

- Provides methyl groups
- Produces: **Methyl-THF**

? 6. Formaldehyde

- Detected in some metabolic reactions
- Converted ? methylene-THF

? 7. Dimethylglycine / Sarcosine

- Produce **methyl groups** during oxidation
- Contribute to methyl-THF pool

? Summary: Sources of One-Carbon Units

Source Amino Acid	One-Carbon Group Produced
Serine	Methylene-THF
Glycine	Methylene-THF
Histidine	Formimino-THF
Tryptophan	Formyl-THF
Choline	Methyl-THF

? UTILIZATION OF ONE-CARBON GROUPS

One-carbon units are used in **many essential biochemical pathways**.

? 1. Purine Synthesis

THF donates:

- **Formyl-THF** ? For C-2
- **Formyl-THF** ? For C-8

Required for synthesis of **AMP & GMP**.

? 2. Pyrimidine (Thymidine) Synthesis

- **Methylene-THF ? donates CH?** to dUMP ? **dTMP (thymidine)**
- Enzyme: **Thymidylate synthase**
- Crucial for **DNA synthesis**

? 3. Methionine Synthesis

Vitamin B?? + THF participate:

- Homocysteine + methyl-THF ? **Methionine**
- Methionine ? **SAM** (universal methyl donor)

Defects ? **homocystinuria**, megaloblastic anemia.

? 4. Methylation Reactions (via SAM)

SAM donates **methyl groups** to:

- DNA methylation
- RNA methylation
- Phospholipids (phosphatidylethanolamine ? phosphatidylcholine)
- Creatine synthesis

- Adrenaline synthesis
- Melatonin synthesis

SAM is the **most powerful methyl donor**.

? 5. Conversion Between Forms of One-Carbon Units

THF interconverts between forms:

- Methylene ? Methenyl ? Formyl
- Reversible transformations allow flexible use

Exception:
Methyl-THF ? irreversible conversion from methylene-THF
(“Methyl-folate trap” in B?? deficiency)

? 6. Detoxification and Amino Acid Metabolism

- Histidine ? glutamate (requires THF)
- Degradation of glycine & serine
- Interconversion of amino acids

? THE METHYL-FOLATE TRAP (Clinical Importance)

In **Vitamin B?? deficiency**:

- Methyl-THF cannot donate methyl group ? methionine
- THF becomes “trapped” as **methyl-THF**
- Functional folate deficiency develops
- Leads to **megaloblastic anemia**

Folate supplementation alone will NOT correct neurological symptoms.

? High-Yield Summary

- THF carries **one-carbon units** in different oxidation states.
- Major sources: **serine, glycine, histidine, tryptophan, choline**.
- Major uses: **purine synthesis, thymidine synthesis, methionine/SAM formation**.
- SAM is the **universal methyl donor**.
- B?? deficiency ? **methyl-folate trap**.

? FACTS TO REMEMBER — WHOLE CHAPTER

? Digestion & Absorption

- Pepsin is an **endopeptidase** activated by **HCl**.
- Pancreatic proteases are released as **zymogens**; **trypsin** activates all others.

- **PEPT1** absorbs **di- and tripeptides** (H?-dependent).
- Most bowel protein absorption is via **dipeptides > free amino acids**.

? Meister (?-Glutamyl) Cycle

- Uses **glutathione (GSH)** to transport amino acids into cells.
- **GGT** is the key enzyme; elevated in **alcoholic liver disease**.
- Cycle regenerates **glutathione** at the expense of **ATP**.

? Intracellular Protein Degradation

- Lysosomes degrade **long-lived proteins** ? via **cathepsins** (acidic pH).
- Ubiquitin–proteasome system degrades **short-lived / damaged proteins**.

? Ubiquitin–Proteasome Pathway

- Requires **ATP**.
- Uses three enzymes: **E1 (activation), E2 (conjugation), E3 (ligation)**.
- **Polyubiquitin tag** targets proteins for **26S proteasome**.
- Proteasome inhibitors (e.g., **Bortezomib**) used in **multiple myeloma**.

? Inter-Organ Transport of Amino Acids

- **Alanine** = major nitrogen carrier from **muscle ? liver**.
- **Glutamine** = major carrier of ammonia from tissues.
- Intestine uses **glutamine** as its main fuel.

? Glucose–Alanine Cycle

- Muscle: amino acids ? NH? ? **alanine**.
- Liver: alanine ? pyruvate + NH? ? **urea**.
- Pyruvate ? **glucose**, returned to muscle.
- Operates in **fasting & exercise**.

? Transamination

- **ALT & AST** require **PLP (vitamin B6)**.
- ?-Ketoglutarate is the **universal amino group acceptor**.
- Transamination **does not produce free ammonia**.
- Lysine, threonine, proline do **not** undergo transamination.

? Oxidative Deamination

- Major enzyme: **Glutamate dehydrogenase (GDH)**.
- Occurs in **liver mitochondria**.
- Releases **free NH?** from glutamate.
- Uses **NAD? or NADP?**.

? Non-Oxidative Deamination

- Serine & threonine undergo **dehydration** to release NH?.
- Requires **pyridoxal phosphate (PLP)**.

? Sources of Ammonia

- Oxidative deamination (glutamate ? NH?).
- Intestinal bacteria (**largest external source**).
- Amino acid oxidases.
- Purine/pyrimidine catabolism.
- Renal glutaminase.

? Transport of Ammonia

- **Glutamine** carries 2 nitrogen atoms (most important).
- **Alanine** carries nitrogen from muscle ? liver.

? Urea Cycle (Ornithine Cycle)

- Occurs in **liver** (mitochondria + cytosol).
- First step enzyme: **CPS-I** (requires **N-acetylglutamate**, NAG).
- Provides 2 nitrogen atoms:
  - One from **ammonia**
  - One from **aspartate**
- **Fumarate** links urea cycle with TCA cycle.

? Regulation

- NAG is **obligatory activator** of CPS-I.
- High protein ? increases urea cycle enzyme synthesis.

? Urea Cycle Disorders (UCDs)

- All autosomal recessive **except OTC deficiency (X-linked)**.
- All cause **hyperammonemia + respiratory alkalosis**.
- **OTC deficiency** ? ? **orotic acid** (due to pyrimidine overflow).
- **Citrullinemia** ? ? citrulline.
- **Argininosuccinic aciduria** ? ? argininosuccinate + **brittle hair**.
- **Arginase deficiency** ? ? arginine, spasticity with milder ammonia rise.
- **CPS-I deficiency** ? ? orotic acid.

? Treatment Overview

- Stop protein; give **benzoate/phenylbutyrate** (nitrogen scavengers).
- **Arginine** therapy (except in arginase deficiency).
- Dialysis for severe hyperammonemia.
- Liver transplant = curative.

? Hepatic Coma

- Caused by **ammonia accumulation** due to liver failure.
- Ammonia ? **glutamine** ? astrocyte swelling ? cerebral edema.

- Signs: asterixis, confusion, fetor hepaticus.
- Treatment: **lactulose**, rifaximin, remove precipitating factors.

? Blood Urea

- Increased in **renal failure, dehydration, GI bleed**.
- Decreased in **liver failure** (urea cycle impaired).
- High **BUN:Cr ratio (>20)** = pre-renal azotemia.

? One-Carbon Metabolism (Folate Cycle)

- THF carries **one-carbon units** ? formyl, methenyl, methylene, methyl.
- Major sources: **serine, glycine, histidine, tryptophan, choline**.
- Used for **purine synthesis**, **dTMP synthesis**, **methionine synthesis (with B12)**.
- **SAM** = strongest methyl donor.
- **B12 deficiency** ? **methyl-folate trap ? megaloblastic anemia**.

? Super-High-Yield Lines

- Glutamate is the **central amino acid** in nitrogen metabolism.
- Glutamine is the **major ammonia transport form**.

- Alanine is the **major fasting muscle export**.
- CPS-I is **mitochondrial**; CPS-II (pyrimidine synthesis) is **cytosolic**.
- Only the **liver** can produce significant quantities of **urea**.
- Hyperammonemia causes **respiratory alkalosis**, not acidosis.
- SAM donates methyl groups for **creatine, adrenaline, phosphatidylcholine**.
- FIGLU excretion ? in **folate deficiency**.

? FAQs — General Amino Acid Metabolism (Complete Chapter)

1. What is the first step in amino acid catabolism?

Transamination, where amino groups are transferred to ?-ketoglutarate to form glutamate.

2. Which vitamin is required for all transamination reactions?

Vitamin B6 (Pyridoxal phosphate, PLP).

3. Which amino acids do NOT undergo transamination?

Lysine, threonine, proline, hydroxyproline.

4. What is the main purpose of transamination?

To funnel nitrogen to **glutamate**, which can undergo oxidative deamination.

---

5. What enzyme performs oxidative deamination?

Glutamate dehydrogenase (GDH) in the **liver mitochondria**.

---

6. What is the main product of oxidative deamination?

Free ammonia (NH?) + ?-ketoglutarate.

---

7. Name important sources of ammonia in the body.

- Oxidative deamination (glutamate)
- Intestinal bacteria (urease)
- Purine/pyrimidine metabolism
- Amino acid oxidases
- Renal glutaminase

---

8. How is ammonia transported in blood?

As **glutamine** and **alanine**.

---

9. Why is ammonia toxic to the brain?

Because it forms **excess glutamine**, causing **astrocyte swelling** ? cerebral edema.

---

10. What is the major detoxification pathway for ammonia?

The **urea cycle** in the **liver**.

---

11. Which enzyme starts the urea cycle?

Carbamoyl phosphate synthetase I (CPS-I).

---

12. What is the obligatory activator of CPS-I?

N-Acetylglutamate (NAG).

---

13. Where is the urea cycle located?

Partly in **mitochondria**, partly in **cytosol**.

---

14. Which amino acid donates the second nitrogen of urea?

Aspartate.

---

15. Which step of the urea cycle is defective in OTC deficiency?

Conversion of carbamoyl phosphate + ornithine ? **citrulline**.

16. What is the biochemical hallmark of OTC deficiency?

High orotic acid in urine.

---

17. What amino acid is elevated in citrullinemia?

Citrulline (very high).

---

18. Which urea cycle disorder presents with brittle hair?

Argininosuccinic aciduria.

---

19. Which disorder shows very high arginine levels?

Arginase deficiency.

---

20. What acid–base disturbance occurs in urea cycle disorders?

Respiratory alkalosis (hyperventilation due to cerebral edema).

---

21. What is the role of glutamine synthetase?

Converts NH? + glutamate ? **glutamine**, a safe transport form.

---

22. What is the purpose of the Glucose–Alanine cycle?

To carry **muscle nitrogen ? liver**, while providing **glucose** back to muscle.

---

23. What is the major nitrogen donor in biosynthetic reactions?

Glutamine.

---

24. What is the major nitrogen acceptor in transamination?

?-Ketoglutarate ? converts to glutamate.

---

25. What is the ?-glutamyl/Meister cycle used for?

Transport of amino acids into cells using **glutathione**.

---

26. Which enzyme is elevated in alcoholic liver disease?

GGT (from Meister cycle).

---

27. What is the role of proteasomes?

Degrade **ubiquitin-tagged proteins** using ATP.

---

28. What is the difference between lysosomal & proteasomal degradation?

- Lysosomal ? long-lived + extracellular proteins
- Proteasomal ? short-lived + misfolded proteins (ATP-dependent)

---

29. What is the universal methyl donor in the body?

S-Adenosylmethionine (SAM).

---

30. Which vitamin regenerates methyl-THF?

Vitamin B12.

---

31. What happens in methyl-folate trap?

Without B12, methyl-THF cannot convert to THF ? **functional folate deficiency**.

---

32. What are the major uses of one-carbon units?

- **Purine synthesis**
- **Thymidine synthesis (dTMP)**
- **Methionine/SAM synthesis**
- **Amino acid interconversion**

33. What is FIGLU, and when is it elevated?

Formiminoglutamate ? elevated in **folate deficiency**.

---

34. What causes hepatic coma?

Failure to detoxify ammonia ? **NH? buildup ? astrocyte swelling ? coma**.

---

35. What are clinical signs of hepatic encephalopathy?

Asterixis, confusion, fetor hepaticus, altered consciousness.

---

36. What drug converts NH? ? NH?? in the intestine?

Lactulose.

---

37. What are nitrogen scavenger drugs?

Sodium benzoate, sodium phenylbutyrate.

---

38. What is the normal BUN:Creatinine ratio?

10–15 : 1.

---

39. What causes high BUN with normal creatinine?

Dehydration, GI bleed, high protein diet.

---

40. What causes low blood urea?

Severe liver failure (urea cycle not functioning).

? MCQs — General Amino Acid Metabolism (Whole Chapter)

---

1. The major site of amino acid catabolism is:

A. Kidney
B. Brain
C. **Liver**
D. Spleen

Answer: C
Liver contains complete machinery for transamination, deamination, and the urea cycle.

---

2. The enzyme required for all transamination reactions is:

A. FAD
B. NAD?
C. **Pyridoxal phosphate (Vitamin B6)**
D. Biotin

Answer: C

---

3. Which amino acid does NOT undergo transamination?

A. Valine
B. Isoleucine
C. Leucine
D. **Lysine**

Answer: D

---

4. The major amino acid carrying nitrogen from muscle to liver is:

A. Leucine
B. **Alanine**
C. Glutamate
D. Serine

Answer: B

---

5. The major carrier of ammonia in blood is:

A. Arginine
B. Citrulline
C. **Glutamine**
D. Lysine

Answer: C

---

6. The enzyme for oxidative deamination is located in:

A. Cytosol
B. Ribosome
C. **Mitochondria**

D. Lysosome

Answer: C
Glutamate dehydrogenase is a mitochondrial enzyme.

---

7. The product of oxidative deamination of glutamate is:

A. Pyruvate
B. **?-Ketoglutarate + NH?**
C. Aspartate
D. Urea

Answer: B

---

8. The first step of the urea cycle is catalyzed by:

A. OTC
B. Arginase
C. Argininosuccinate lyase
D. **CPS-I**

Answer: D

---

9. CPS-I is activated by:

A. ATP
B. **N-acetylglutamate (NAG)**
C. Pyridoxal phosphate
D. NAD?

Answer: B

---

10. The only X-linked urea cycle disorder is:

A. Citrullinemia
B. Argininemia
C. **OTC deficiency**
D. CPS-I deficiency

Answer: C

---

11. A newborn with hyperammonemia and very high orotic acid most likely has:

A. CPS-I deficiency
B. **OTC deficiency**
C. Arginase deficiency
D. Citrullinemia

Answer: B

---

12. Very high citrulline level indicates:

A. Arginase deficiency
B. Argininosuccinate lyase deficiency
C. CPS-I deficiency
D. **Argininosuccinate synthetase deficiency (Citrullinemia)**

Answer: D

---

13. Argininosuccinic aciduria is characterized by:

A. High citrulline
B. High orotic acid
C. **Brittle hair + high argininosuccinate**

D. High lysine

Answer: C

---

14. Which urea cycle disorder presents with high arginine and spasticity?

A. Citrullinemia
B. **Arginase deficiency**
C. OTC deficiency
D. CPS-I deficiency

Answer: B

---

15. Elevated ammonia typically causes:

A. Metabolic acidosis
B. **Respiratory alkalosis**
C. Normal ABG
D. Metabolic alkalosis

Answer: B

---

16. The brain converts ammonia into:

A. Urea
B. Alanine
C. **Glutamine**
D. Aspartate

Answer: C

---

17. Hepatic coma occurs primarily because of:

A. High glucose
B. High lactate
C. High bilirubin
D. **High ammonia**

Answer: D

---

18. Drug used to convert NH? ? NH?? in the gut:

A. Phenylbutyrate
B. Rifaximin
C. **Lactulose**
D. Ciprofloxacin

Answer: C

---

19. The glucose–alanine cycle occurs mainly between:

A. Brain and liver
B. Adipose tissue and muscle
C. **Muscle and liver**
D. Kidney and intestine

Answer: C

---

20. The function of PEPT-1 transporter is absorption of:

A. Lipids
B. Fatty acids
C. Monosaccharides

D. **Dipeptides and tripeptides**

Answer: D

---

21. GGT is a marker enzyme for:

A. Renal failure
B. Hemolysis
C. **Alcoholic liver disease**
D. Thyroid dysfunction

Answer: C

---

22. Proteins tagged with ubiquitin are degraded by:

A. Lysosomes
B. **26S proteasome**
C. Peroxisomes
D. Golgi apparatus

Answer: B

---

23. The universal methyl donor in the body is:

A. THF
B. Methionine
C. **SAM (S-adenosylmethionine)**
D. Methyl-THF

Answer: C

---

24. Methyl-folate trap occurs in deficiency of:

A. Folate only
B. Pyridoxine
C. **Vitamin B12**
D. Thiamine

Answer: C

---

25. FIGLU excretion increases in:

A. B12 deficiency only
B. **Folate deficiency**
C. Niacin deficiency
D. Riboflavin deficiency

Answer: B

? Clinical Problems — General Amino Acid Metabolism (Complete Chapter)

---

1. Newborn with vomiting, lethargy & respiratory alkalosis

A 2-day-old newborn develops poor feeding, lethargy, vomiting, and rapid breathing. Labs show:

- **Very high ammonia**
- **Low citrulline**

- **Normal orotic acid**

Diagnosis:

CPS-I deficiency

Explanation:

No carbamoyl phosphate formed ? ? citrulline + **no orotic acid buildup**.

---

2. Newborn with hyperammonemia + very high orotic acid

A male infant becomes irritable, starts vomiting, and develops seizures on day 3. Labs show:

- Very high ammonia
- Very high **orotic acid**
- Low citrulline

Diagnosis:

OTC deficiency (X-linked)

Explanation:

Excess carbamoyl phosphate enters pyrimidine pathway ? ? orotic acid.

---

3. Infant with brittle hair and high ammonia

A 4-month-old has failure to thrive, seizures, and **hair that breaks easily**. Labs:

- High ammonia

- High argininosuccinate

Diagnosis:

Argininosuccinic aciduria (Argininosuccinate lyase deficiency)

Explanation:

Brittle hair (trichorrhexis nodosa) is classic.

---

4. Child with spasticity and high arginine

A 6-year-old has progressive spasticity, tremors, and delayed development. Labs:

- High **arginine**
- Mild ammonia elevation

Diagnosis:

Arginase deficiency

---

5. Adult with confusion, asterixis & fetor hepaticus

A man with cirrhosis is brought to ER with confusion and flapping tremors. Blood ammonia is very high.

Diagnosis:

Hepatic encephalopathy (hepatic coma)

Mechanism:

Ammonia ? glutamine ? astrocyte swelling ? cerebral edema.

6. Patient with GI bleed develops severe hyperammonemia

A cirrhotic patient has hematemesis, then becomes drowsy.
Ammonia level rises sharply.

Diagnosis:

Hepatic coma precipitated by GI bleed

Mechanism:

Blood proteins ? amino acids ? gut bacteria ? **massive ammonia load**.

---

7. Alcoholic patient with high GGT

A chronic alcoholic has elevated **GGT** but near-normal ALT/AST.

Diagnosis:

Alcohol-induced enzyme induction (**Meister cycle involvement**)

Mechanism:

GGT is part of the ?-glutamyl transport system.

---

8. Patient with pellagra-like dermatitis

A young man presents with dermatitis, diarrhea & mood changes. Urine shows low tryptophan absorption.

Diagnosis:

Hartnup disease

Mechanism:

Defect in **neutral amino acid transporter** ? low tryptophan ? ? niacin ? pellagra features.

---

9. Patient with recurrent kidney stones; hexagonal crystals

Urinalysis reveals hexagonal crystals. Amino acid quantification shows low cystine, lysine, arginine reabsorption.

Diagnosis:

Cystinuria

Mechanism:

Defective transporter for **dibasic amino acids**.

---

10. Child with severe protein malabsorption

A child with chronic pancreatitis has foul-smelling stools and poor growth.

Diagnosis:

Pancreatic insufficiency

Mechanism:

No trypsin/chymotrypsin ? protein malabsorption.

---

11. Muscle wasting with elevated ALT

A fasting individual shows muscle breakdown and elevated ALT.

Diagnosis:

Increased **Glucose–Alanine cycle** activity

Mechanism:

Muscle uses alanine to send nitrogen to liver during fasting.

---

12. Acidosis with high urinary NH??

A patient with metabolic acidosis has increased ammonia excretion via kidneys.

Diagnosis:

Renal glutaminase activation

Mechanism:

Glutamine ? glutamate + NH? ? NH?? traps H?.

---

13. B12 deficiency with megaloblastic anemia & high homocysteine

A strict vegan complains of tingling feet and fatigue.
Labs show macrocytic anemia, ? homocysteine, normal methylmalonic acid.

Diagnosis:

Folate trap due to B12 deficiency

Mechanism:

Methyl-THF cannot convert to THF ? functional folate deficiency.

---

14. Multiple myeloma patient on proteasome inhibitor

A patient treated with bortezomib shows decreased plasma cells.

Diagnosis:

Intentional inhibition of **26S proteasome**

Mechanism:

Blocks degradation of pro-apoptotic factors ? kills myeloma cells.

---

15. Acute hyperammonemia with metabolic confusion

A patient collapses after valproate overdose.
Ammonia is markedly elevated.

Diagnosis:

Drug-induced hyperammonemia

Mechanism:

Valproate inhibits **CPS-I** by reducing NAG.

---

16. Child with FIGLU in urine

A 5-year-old with anemia and weakness shows high urinary FIGLU after histidine load.

Diagnosis:

Folate deficiency

Mechanism:

FIGLU ? fails to convert to glutamate without folate.

---

17. Patient with severe lethargy after high-protein meal

A teenager collapses 3 hours after eating a meat-heavy dinner.
Ammonia level shoots up but orotic acid is normal.

Diagnosis:

CPS-I deficiency

Mechanism:

Protein load ? sudden ammonia surge.

---

18. Premature stoppage of lactulose worsens symptoms

A cirrhotic patient stops taking lactulose and becomes drowsy.

Diagnosis:

Worsening of **hepatic encephalopathy**

Mechanism:

Less NH?? trapping ? more NH? absorption.

---

19. High urea but normal creatinine

A dehydrated patient shows:

- BUN: 60 mg/dL
- Creatinine: normal

Diagnosis:

Pre-renal azotemia

Mechanism:

Water reabsorption increases urea reabsorption, creatinine unchanged.

---

20. Low urea with high bilirubin

A patient with chronic liver disease has:

- Very low serum urea
- Elevated ammonia
- High bilirubin

Diagnosis:

Liver failure

Mechanism:

Urea cycle is impaired ? low urea + high ammonia.

? Viva Voce — General Amino Acid Metabolism

1. What is the first step in amino acid catabolism?

Transamination.

2. Name the coenzyme required for transamination.

Pyridoxal phosphate (Vitamin B6).

3. Which amino acids do NOT undergo transamination?

Lysine, threonine, proline, hydroxyproline.

---

4. What is the main acceptor of amino groups in transamination?

?-Ketoglutarate.

---

5. What enzyme catalyzes oxidative deamination?

Glutamate dehydrogenase (GDH).

---

6. Where does oxidative deamination occur?

Mitochondria (mainly liver).

---

7. What are the products of oxidative deamination of glutamate?

?-Ketoglutarate and free ammonia (NH?).

---

8. Name the major carriers of ammonia in blood.

Glutamine and alanine.

---

9. Why is ammonia toxic?

It forms excess **glutamine** in the brain ? **astrocyte swelling** ? cerebral edema.

10. Where does the urea cycle occur?

In the **liver** — partly mitochondria, partly cytosol.

---

11. What is the rate-limiting enzyme of the urea cycle?

Carbamoyl phosphate synthetase I (CPS-I).

---

12. What activates CPS-I?

N-acetylglutamate (NAG).

---

13. What are the two nitrogen sources of urea?

Ammonia and **aspartate**.

---

14. Which urea cycle disorder is X-linked?

Ornithine Transcarbamoylase (OTC) deficiency.

---

15. What is the biochemical hallmark of OTC deficiency?

High orotic acid in urine.

---

16. What is the hallmark of citrullinemia?

Very high citrulline in blood.

---

17. What is the hallmark of argininosuccinic aciduria?

High argininosuccinate + **brittle hair**.

---

18. What is the hallmark of arginase deficiency?

High arginine + spasticity with mild hyperammonemia.

---

19. What acid–base disturbance occurs in hyperammonemia?

Respiratory alkalosis.

---

20. What is the treatment of hepatic encephalopathy?

Lactulose + rifaximin + treat precipitating causes.

---

21. What is the Glucose–Alanine cycle?

Alanine carries nitrogen **from muscle to liver**, where it is converted to urea; pyruvate returns as glucose.

---

22. What is the role of glutamine synthetase?

Converts NH? to **glutamine** for safe transport.

---

23. What is the role of glutaminase in kidney?

Produces ammonia to **excrete H? as NH??**, especially during acidosis.

---

24. What is GGT, and what does it indicate clinically?

A ?-glutamyl enzyme; elevated in **alcoholic liver disease**.

---

25. What is the function of the proteasome?

Degrades **ubiquitin-tagged proteins** using ATP.

---

26. What is the universal methyl donor?

S-adenosylmethionine (SAM).

---

27. Which enzyme regenerates methionine from homocysteine?

Methionine synthase (requires Vitamin B12).

---

28. What is the methyl-folate trap?

In B12 deficiency, methyl-THF cannot convert to THF ? **functional folate deficiency**.

29. What is FIGLU, and what does it indicate?

Formiminoglutamate. Increased excretion indicates **folate deficiency**.

---

30. What is the role of THF?

Carrier of **one-carbon units** in various oxidation states.

---

31. What are the major one-carbon donors?

Serine, glycine, histidine, tryptophan, choline.

---

32. What is the major use of methylene-THF?

Conversion of **dUMP ? dTMP (thymidine)**.

---

33. Why does liver failure cause low urea?

Urea cycle does not function ? **decreased urea synthesis**.

---

34. What is the normal BUN:Creatinine ratio?

10–15 : 1.

---

35. What causes a high BUN:Cr ratio?

Pre-renal causes like dehydration, GI bleed.

---

36. What are the effects of valproate on ammonia metabolism?

Inhibits CPS-I ? **hyperammonemia**.

---

37. Name the two main sites of amino acid absorption.

Jejunum and ileum.

---

38. Which peptide transporter absorbs di- and tripeptides?

PEPT-1 (H?-dependent).

---

39. What are cathepsins?

Lysosomal proteases for degrading **long-lived proteins**.

---

40. Which organ uses glutamine as a major fuel source?

Intestine.