PIPADOR REVISION

MRCOG Part 1 Revision Notes

Proteins: Urea Cycle

BIOCHEMISTRY • LECTURE 225

VISUAL EXAMINATION REVISION NOTES

2026 Edition

225

MRCOG PART 1 REVISION NOTES | BIOCHEMISTRY

Proteins: Urea Cycle

Ammonia production and transport, the urea cycle, hyperammonaemia (including postpartum OTC deficiency) and urea in pregnancy

Liver	2 N	OTC	↓ Urea
Only site of a complete urea cycle	Per urea (NH_3 + aspartate)	X-linked — commonest cycle defect	In normal pregnancy (N conservation)

■ **KEY FACTS: Learning objectives**

- Describe the sources of ammonia, transamination, deamination and nitrogen transport.
- Describe the steps, location, energy cost and regulation of the urea cycle.
- Describe hyperammonaemia: urea cycle disorders (including postpartum presentation), liver failure and drugs, and its management.

225.1 Nitrogen disposal

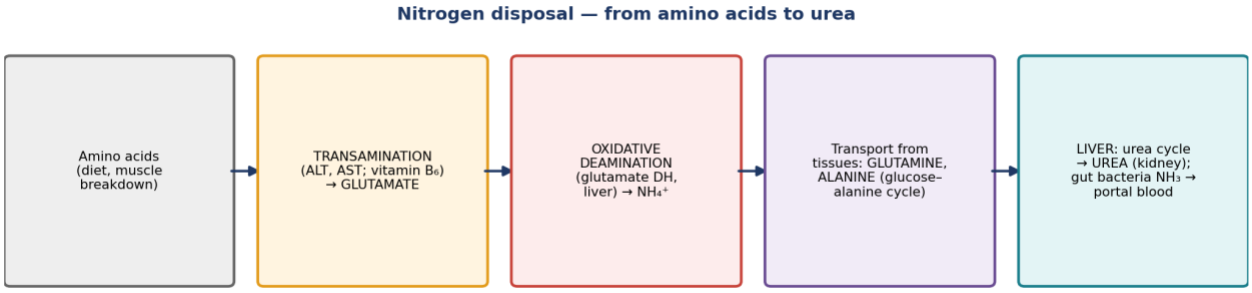


Figure 225.1 — From amino acids to urea

- **Transamination** (ALT, AST — **pyridoxal phosphate, B_6**) moves amino groups to α-ketoglutarate → **glutamate**; ALT/AST are liver function markers.
- **Oxidative deamination** of glutamate (glutamate dehydrogenase) releases **NH_4^+** in the liver.
- Ammonia is **neurotoxic** (↑ glutamine in astrocytes → cerebral oedema; depletes α-KG); peripheral tissues export N as **glutamine** and **alanine** (glucose–alanine cycle); gut bacteria produce NH_3 absorbed into portal blood.

225.2 The urea cycle

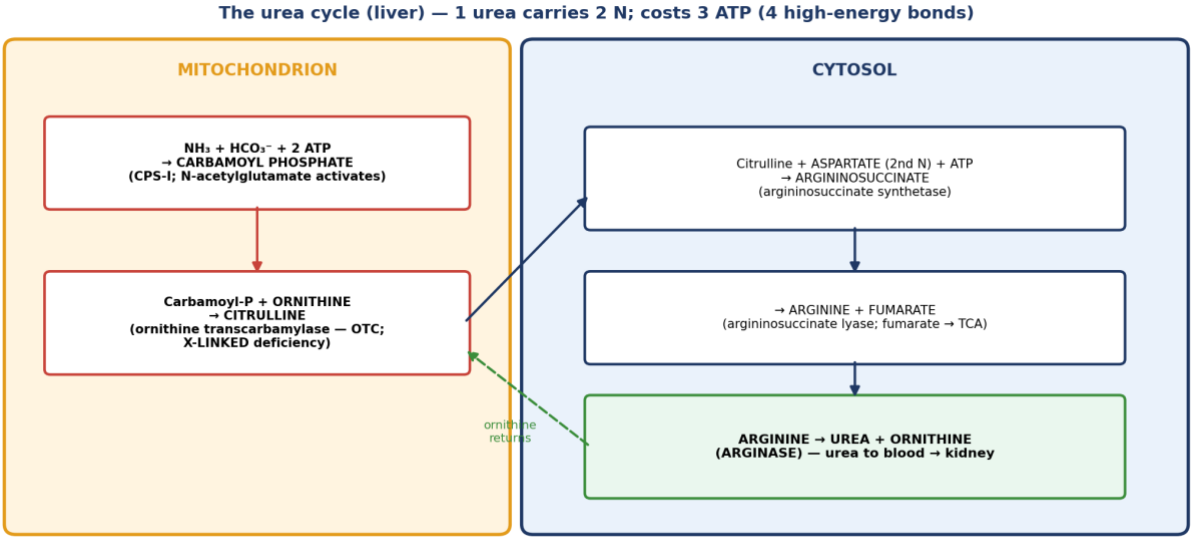


Figure 225.2 — The urea cycle

Feature	Details
Location	Liver periportal hepatocytes: first two steps in mitochondria, rest in cytosol
Nitrogen sources	1st N from NH_3 (carbamoyl phosphate); 2nd N from aspartate
Energy	3 ATP (4 high-energy phosphate bonds) per urea
Rate-limiting	Carbamoyl phosphate synthetase I — requires N-acetylglutamate (allosteric activator; ↑ by arginine, protein intake)
Link to TCA	Fumarate → malate → oxaloacetate → aspartate ('Krebs bicycle')
Output	Urea (≈ 25–30 g/day) → blood → kidney (filtered; partly reabsorbed — medullary concentrating gradient)

225.3 Hyperammonaemia

Cause	Examples
Urea cycle disorders	OTC deficiency (X-linked) — commonest; CPS-I, ASS (citrullinaemia), ASL (argininosuccinic aciduria), arginase deficiency; N-acetylglutamate synthase deficiency
Liver failure	Acute fatty liver of pregnancy, HELLP, viral hepatitis, paracetamol overdose, cirrhosis/portosystemic shunting
Drugs	Valproate (inhibits CPS-I), chemotherapy, carbamazepine
Other	Organic acidaemias, fatty acid oxidation defects, GI bleed (protein load), TPN, urinary diversion with infection

■ RED FLAGS

- **OTC deficiency in women**: heterozygous **female carriers** (skewed X-inactivation) can present for the first time **postpartum** — catabolic stress, involution of the uterus (protein breakdown) and high protein intake → **hyperammonaemic encephalopathy** (vomiting, confusion, seizures, coma) — easily mistaken for eclampsia, psychosis or sepsis. **Check ammonia** in unexplained postpartum encephalopathy.
- Management: **stop protein**, high-calorie **IV glucose** (± lipid) to stop catabolism, **sodium benzoate / sodium phenylbutyrate** (alternative N excretion), **arginine**, **haemofiltration** if severe; metabolic team; plan delivery with IV glucose and early protein reintroduction for known carriers.

225.4 Urea in pregnancy and the fetus

- **Plasma urea falls** in pregnancy (≈ 2.0–4.5 mmol/L) — ↑ GFR, ↓ urea synthesis (amino acids conserved for growth — positive nitrogen balance) and haemodilution (Lecture 152).
- A raised urea suggests dehydration (hyperemesis), haemorrhage, renal impairment (pre-eclampsia, AKI) or high protein catabolism.
- The fetus produces urea, which is **cleared across the placenta**; fetal urea cycle enzymes are relatively low — neonates with urea cycle defects become unwell after birth when placental clearance stops and protein feeding begins (days 1–3).

225.5 Must-know summary

■ **EXAM TIP**

- Transamination (B_6) → glutamate → deamination → NH_4^+; glutamine/alanine carry N from tissues.
- Urea cycle in **liver**: mitochondria (CPS-I, OTC) → cytosol (ASS, ASL, arginase); 2 N (NH_3 + aspartate); 3 ATP.
- CPS-I needs **N-acetylglutamate**; fumarate links to TCA.
- **OTC deficiency** (X-linked) — carrier women can present **postpartum**; check ammonia; treat with glucose, benzoate/phenylbutyrate, dialysis.
- Pregnancy: urea falls; AFLP and valproate cause hyperammonaemia.

■ **MNEMONIC / MEMORY AID**

Urea cycle in one line: Ornithine + Carbamoyl-P → Citrulline → (+ Aspartate) Argininosuccinate → (− Fumarate) Arginine → Urea + Ornithine. **'Mitochondria start it (CPS-I, OTC), cytosol finishes it'**.