Urea Cycle Defects

Disorder	Enzyme Blockade	Accumulated Substrate(s)	Presentation	Treatment
Citrullinemia	Arginosuccinate synthetase (citrulline + aspartate → argininosuccinate)	Same as OTC def but with elevated **citrulline**	Similar to OTC def, but can be in boys or girls as is AR inheritance All states include on	As above, alongside: arginine, glycerol phenylbutyrate, NO citrulline
Arginosuccinic aciduria	Arginosuccinate lyase (arginosucc → fumarate + arginine)	Same as OTC def but with elevated **citrulline** and **arginosuccinate**	Similar to citrullinemia All states include on NBS	Same as for citrullinemia
Carbamoyl phosphate synthetase (CPS) I deficiency **&** **NAGS deficiency**	CPS I (NH_3 + bicarb + Phos → CPS) NAGS is cofactor for CPSI	Same as OTC def but **without** elevated orotic acid in the urine	Similar to OTC deficiency **NOT** always evident on NBS, may flag for low citrulline	Same as for OTC deficiency

Mitochondrial Disorders / Primary Lactic Acidemias

Biochemical Defect	Disorders of **Krebs cycle** and **oxidative phosphorylation**; transmission via mitochondrial genes → defects vary / not all organs are affected equally
Presentation	Indolent, **progressive neurologic deterioration**, +/- poor feeding, vomiting, CMP, myopathy, liver failure, seizures, strokes, blindness, deafness, and nephropathy
Diagnosis	Definitive dx from enzyme assay or DNA testing; labs often show **+AG metabolic acidosis** and **primary lactic acidosis** +/- hypoglycemia w/ ketosis, liver dysfxn

Disorder	Enzyme Blockade	Accumulated Substrate(s)	Presentation	Treatment
Pyruvate Dehydrogenase Complex Deficiency	Pyruvate dehydrogenase (Pyruvate → Acetyl CoA + CO_2)	Pyruvate → **lactate**	Lactic acidosis, intellectual disability, hypotonia, seizures, exacerbated by ingestion of carbohydrates	Supplement with carnitine, thiamine, and lipoic acid (cofactors for pyruvate DH complex), high fat / low carb diet or ketogenic diet
Pyruvate Carboxylase Deficiency	Pyruvate carboxylase (pyruvate + CO_2 → oxaloacetate)	Pyruvate → **lactate** NH_3 (as Asp cannot be formed from OAA)	Severe lactic acidosis, hypothermia, hypotonia, hypoglycemia, hyperammonemia, lethargy, vomiting, often death as neonate or w/in 1 year for Type B; Types A & C are milder	High carb and protein diet; Treat metabolic crisis with 10% dex-containing IVF, avoid fasting, $NaHCO_3$ for acidosis, possible liver transplant