"Trastornos del ciclo de la urea"

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Early "Ornithine" Cycle

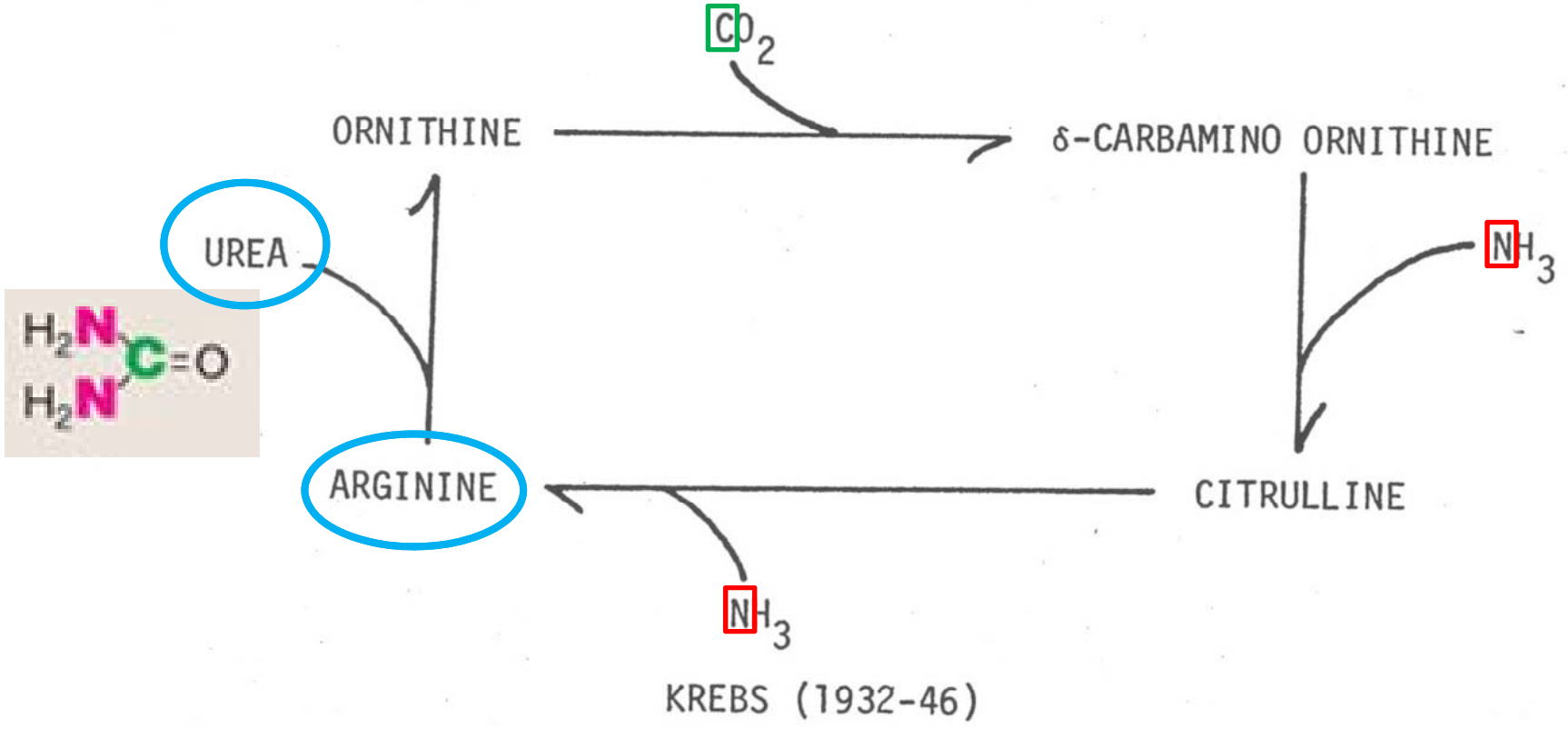

Figure 1

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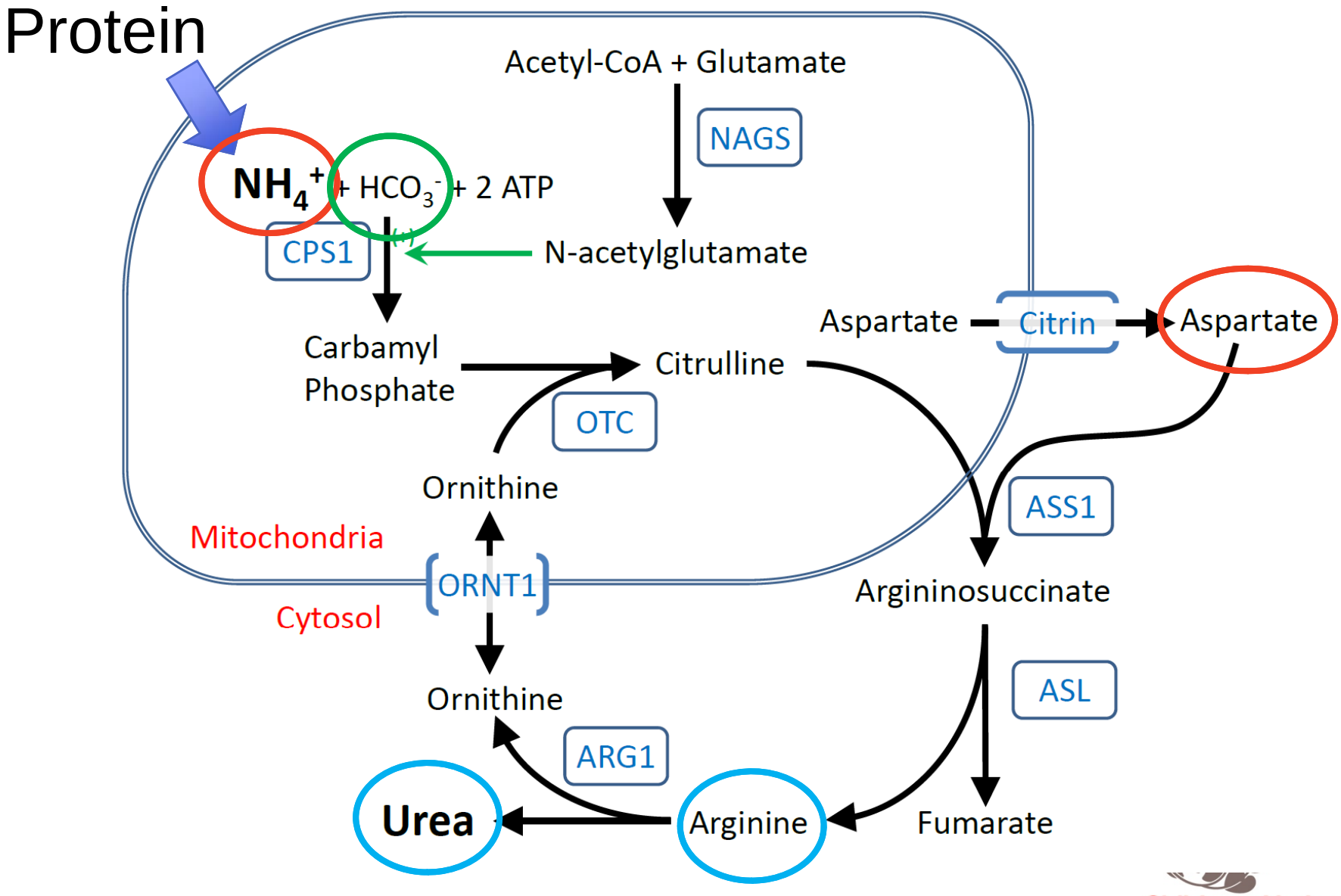
The Hepatic Urea Cycle



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Case 1 – neonate with hyperammonemia

- 3 day-old girl
- Birth Weight = 2.8 kg
- 38 week-old female born to G1 mother
  - Uncomplicated pregnancy, SVD delivery
  - Rubella Immune, RPR non-reactive, HIV negative, GBS negative
  - Discharged at 2 days of age

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At primary-care hospital

- On day 3 of life: poor feeding, lethargy, hypothermia
- Presents to primary hospital obtunded
- WBC = 12, Hgb = 19 g/dL, Plt = 318
- Na = 137, K = 4.8, Cl = 106, HCO_3 = 18
- Anion Gap = 18
- Urinalysis: 2+ Bacteria, 2+ WBC, 2+ ketones

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Metabolic differential diagnosis

With wide anion gap acidosis:

- Organic acidemia (e.g., Propionic or methylmalonic acidemia)
- Lactic acidosis (e.g., mitochondrial disorders)
- Ketosis

No acidosis:

- Hyperammonemia (Urea Cycle Disorder)
- Maple Syrup Urine Disease

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Additional investigations

- Blood, urine and CSF cultures sent
- CSF WBC, glucose, protein were normal
- Transported to Children's National
- On transport
  - **pH = 7.5, pO2=64, pCO2= 20.5, HCO_3 = 16.1**

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Take home point #1

Alkalemia as due to isolated respiratory alkalosis is a strong indicator of a

<u>Urea Cycle Disorder</u>

- Can observe rapid respiratory rate without retractions or evidence of respiratory distress
- Order serum/plasma **<u>ammonia level</u>**

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Additional investigations

- Blood, urine and CSF cultures sent
- CSF WBC, glucose, protein were normal
- Transported to Children's National
- On transport
  - pH = 7.5, pO2=64, pCO2= 20.5, HCO_3 = 16.1

- Ammonia **= 706 µmol/L ↑** (N: 29 - 54)
  (1202 µg/dl)

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'Metabolic' laboratory tests

- Plasma amino acid profile:
  - Glutamine = 2054 µmol/L ↑ (N:376 – 819)
  - Citrulline = 6 ↓ (N: 19 – 45)
  - Arginine = 25 (N: 6 – 120)
- Urine organic profile:
  - Ketosis
  - Elevated orotic acid
- Diagnosis: **Urea Cycle Disorder**

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Take home point #2

If ammonia is markedly elevated, consider ordering:

- Plasma amino acid profile
- Urine organic acid profile

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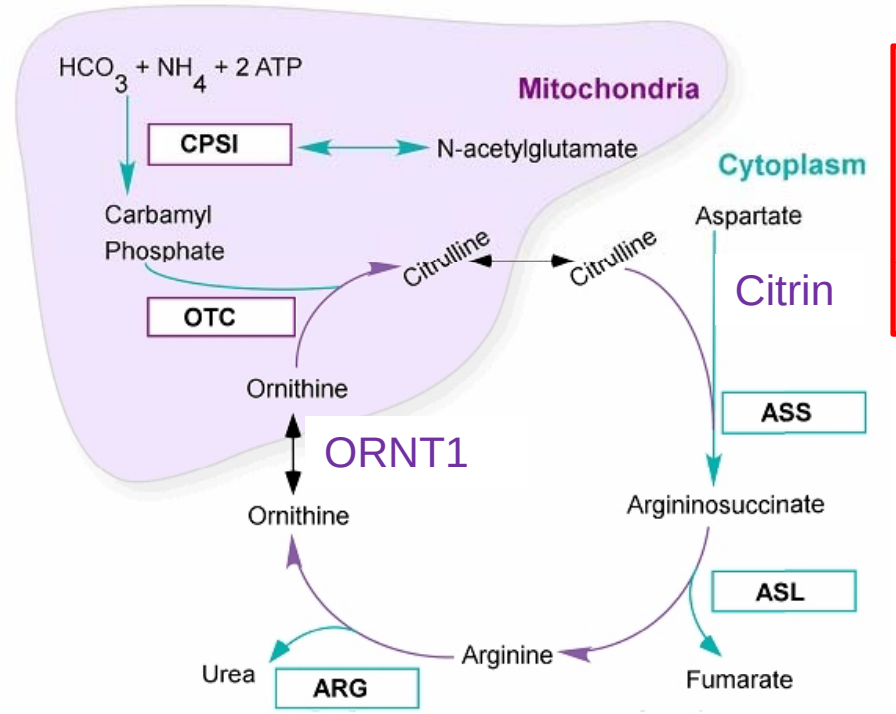
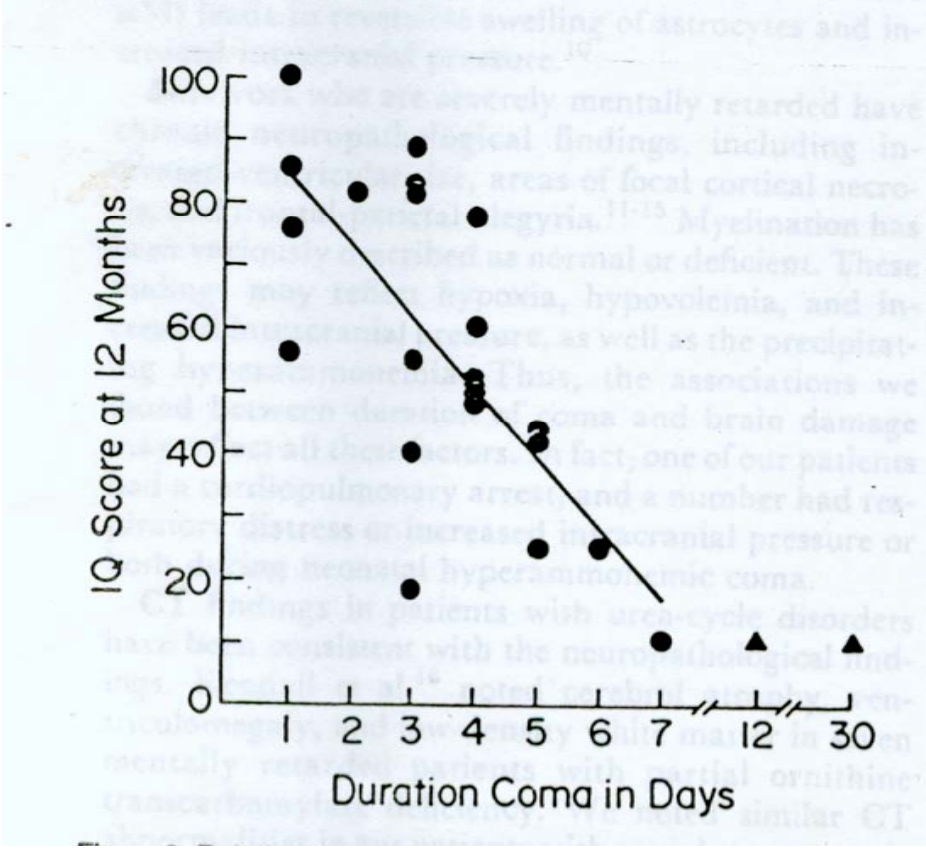
Amino acid alterations in different UCDs



Defect	Abnormal amino acids
NAGS CPS1 OTC	↓ Citrulline ↓ Arginine
ASS Citrin	↑↑↑ Citrulline ↓ Arginine
ASL	↑↑↑ Argininosuccinate ↑Citrulline ↓ Arginine
ARG	↑↑ Arginine
ORNT1	↑↑ Ornithine ↓ Citrulline

Management of Acute Hyperammonemia

Time is of the essence



Msall and Batshaw (NEJM 1984)

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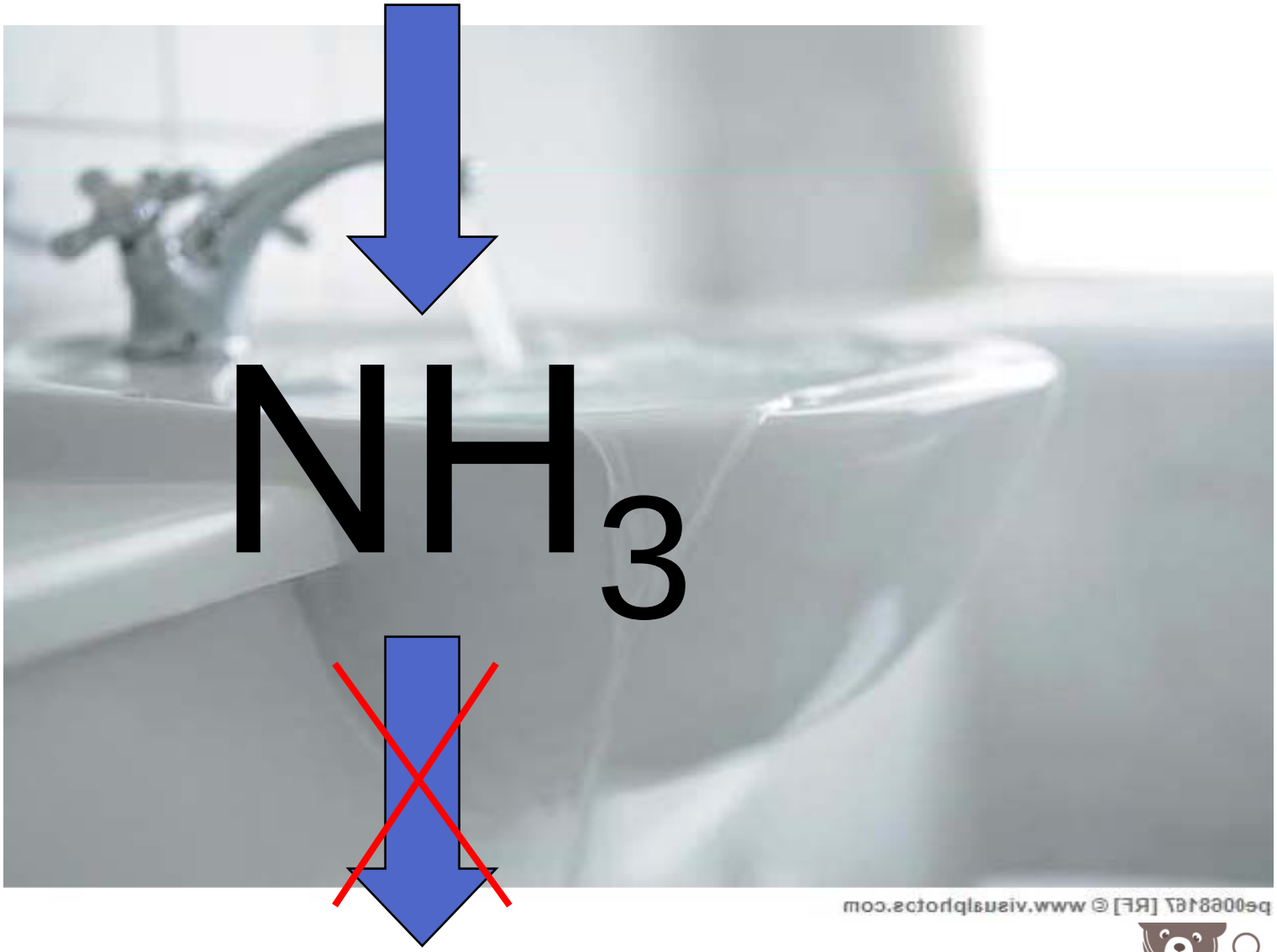

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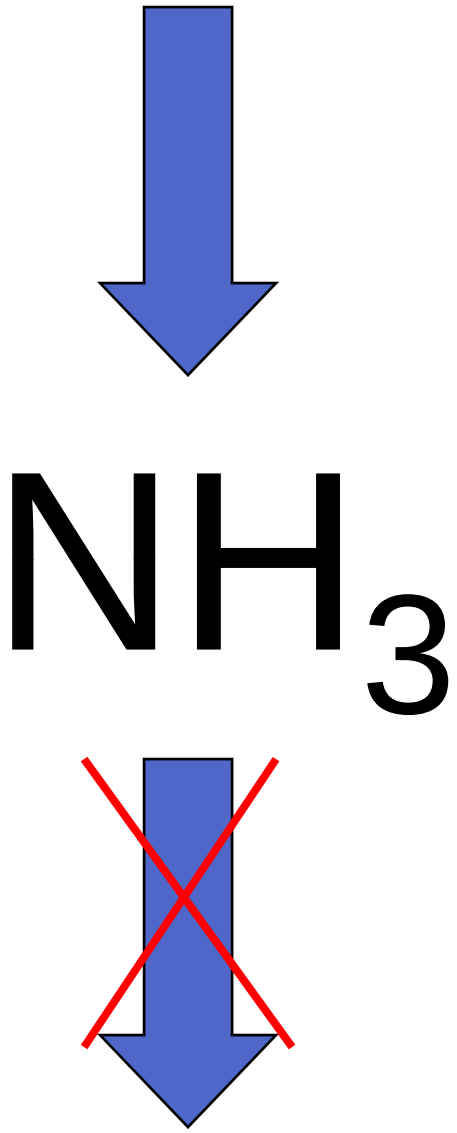

- Stop ammonia production
  - Recall: Ammonia comes from protein
  - Two sources of protein:
    - Exogenous: Restrict protein from food
    - Endogenous: Prevent catabolism (i.e., breakdown of muscle protein)
      - Give lots of other calories – carbohydrate & fat
- Remove ammonia
  - Ammonia scavengers
  - Extracorporeal Detoxification

- Make the urea cycle work better
  - Co-factor therapy (e.g., NCG)
  - Liver transplant
  - Gene therapy (in clinical trials)
- Treat intercurrent illness

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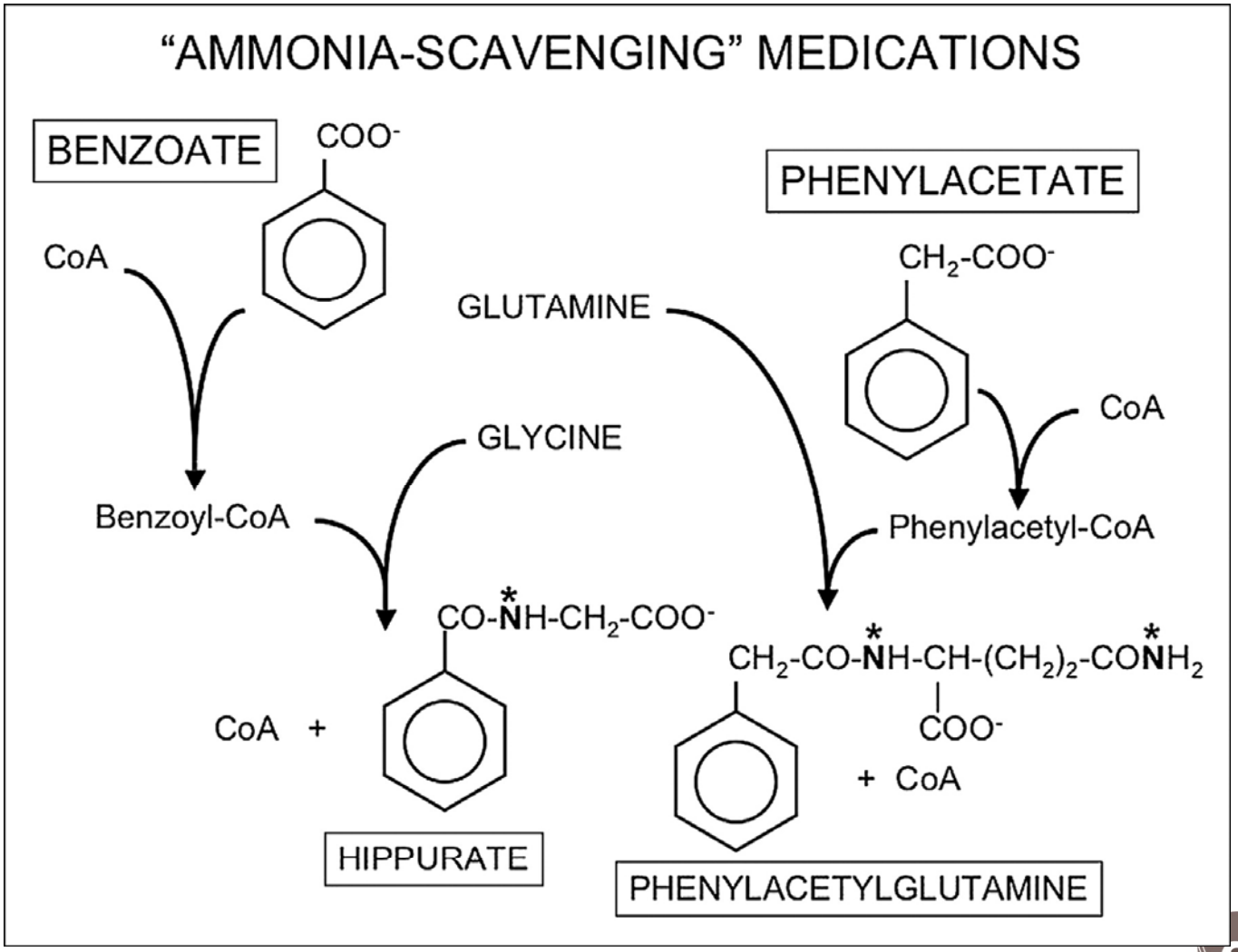
Alternative Pathway Medications



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What is a 'normal' ammonia level?

- Newborns: ammonia ~ 100 µmol/L (~170 µg/dl)
- Sick neonate (or preemie): ~ 200 µmol/L (~340 µg/dl)
- In adults and older children: < 35 µmol/L (<60 µg/dl)

- A working guideline:
  - In neonates: ammonia >150 µmol/L bears investigation
  - Older patient: ammonia >50 µmol/L

- Maturation of liver
- Fusion of cranial sutures

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When to consider dialysis

- Follow clinical picture and ammonia progression NOT ammonia level

- Altered mental status
- Rapidly rising ammonia level
- Hyperammonemia refractory to medical therapy

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Case 2 – Older presentation of UCD

- 2 year-old girl presents with hematemesis
- Failure to thrive (75 centile → <5 centile)
- Emesis ~3 times per week
- No fever, abdominal pain, headache
- Only eats potatoes and oatmeal
- Acute hematemesis secondary to gastritis or esophagitis from chronic vomiting

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Laboratory investigations

- AST 142, ALT 175 U/L
- INR 1.5
- Albumin 3.5 mg/dl
- Bilirubin 0.3 mg/dl
- Liver ultrasound normal
- Upper endoscopy normal

- Ammonia = 132 µmol/L (↑)

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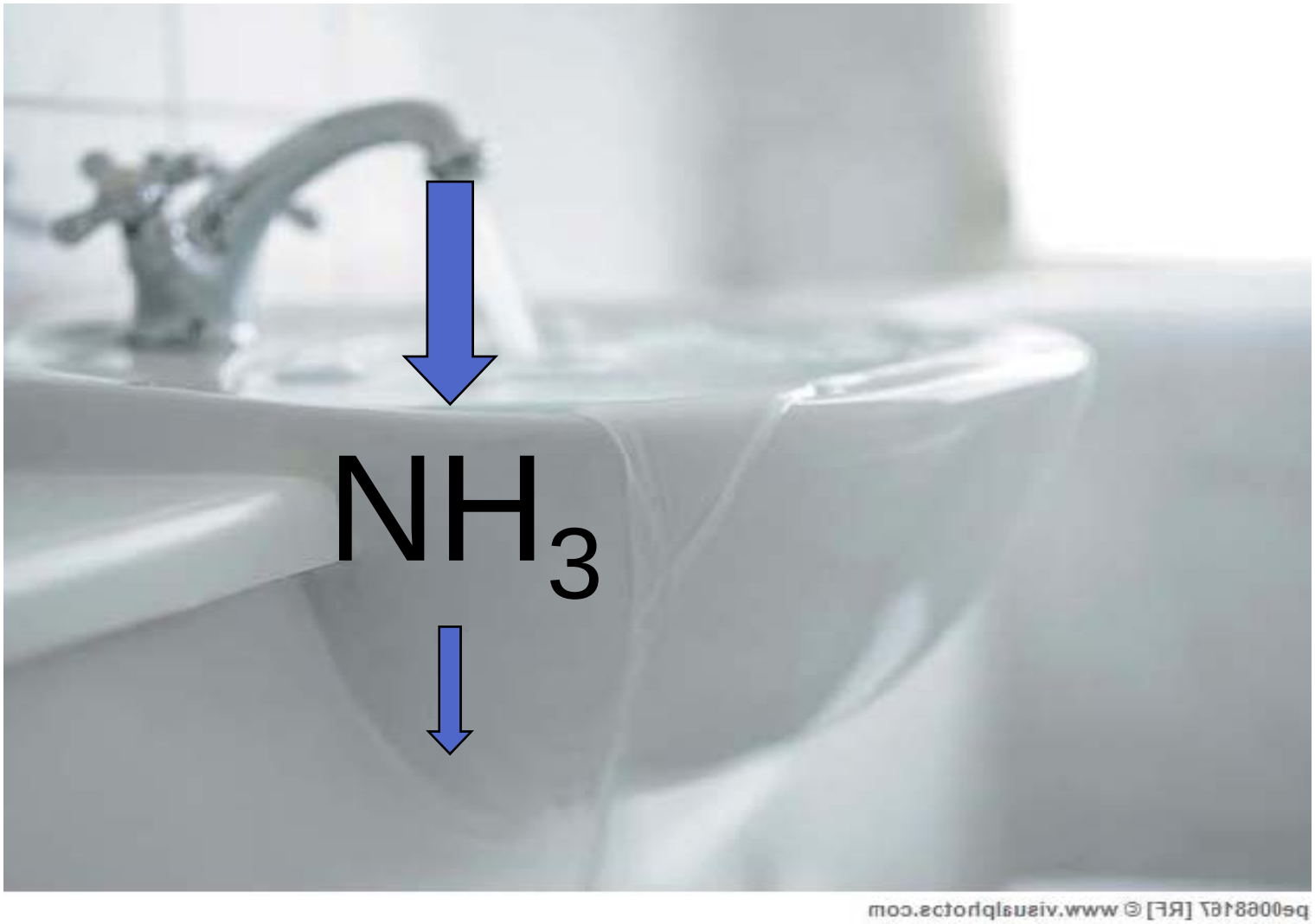

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Triggers for Decompensation in Partial Enzyme Deficiency

- Infection
- Large protein load (Enteral or Parenteral)
- GI bleeding
- Valproic acid (>5 published reports)
- Chemotherapy
- Post-partum stress (>5 published reports)
- Surgery

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Long-term management of UCD

- Dietary protein restriction (often below the RDA)
  - Protein-free formulas
  - Formulas with essential amino acids
- Daily oral ammonia scavengers
- Daily arginine (or citrulline)

- Avoidance of prolonged fasting
  - Hospitalization if patient has recurrent emesis or other illness
  - May need infused dextrose if NPO for procedures, surgery

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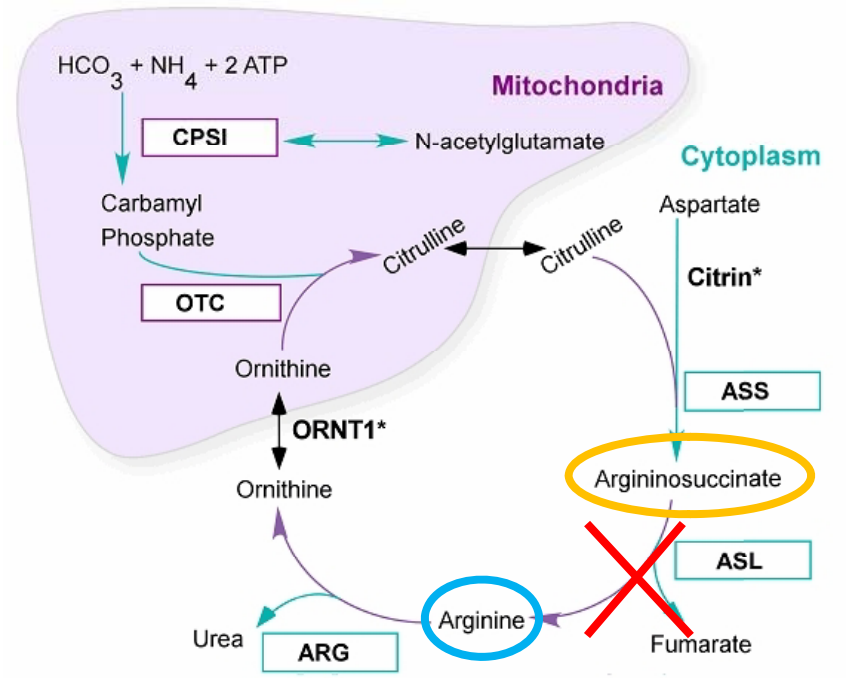
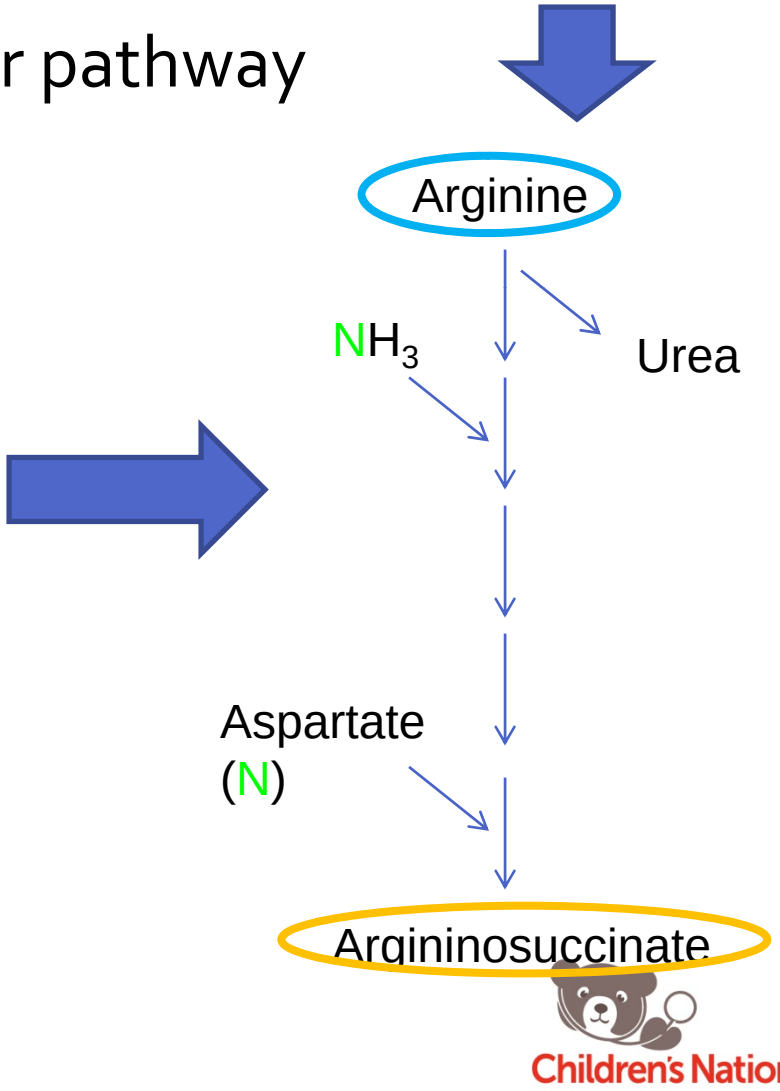
Replacement of Arginine - ASL deficiency

- Urea cycle becomes a linear pathway





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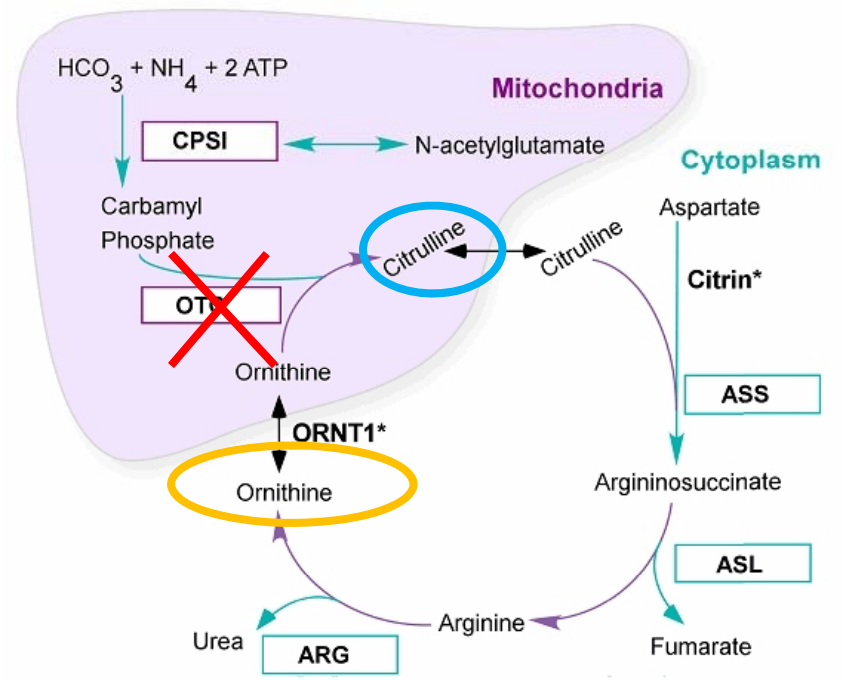
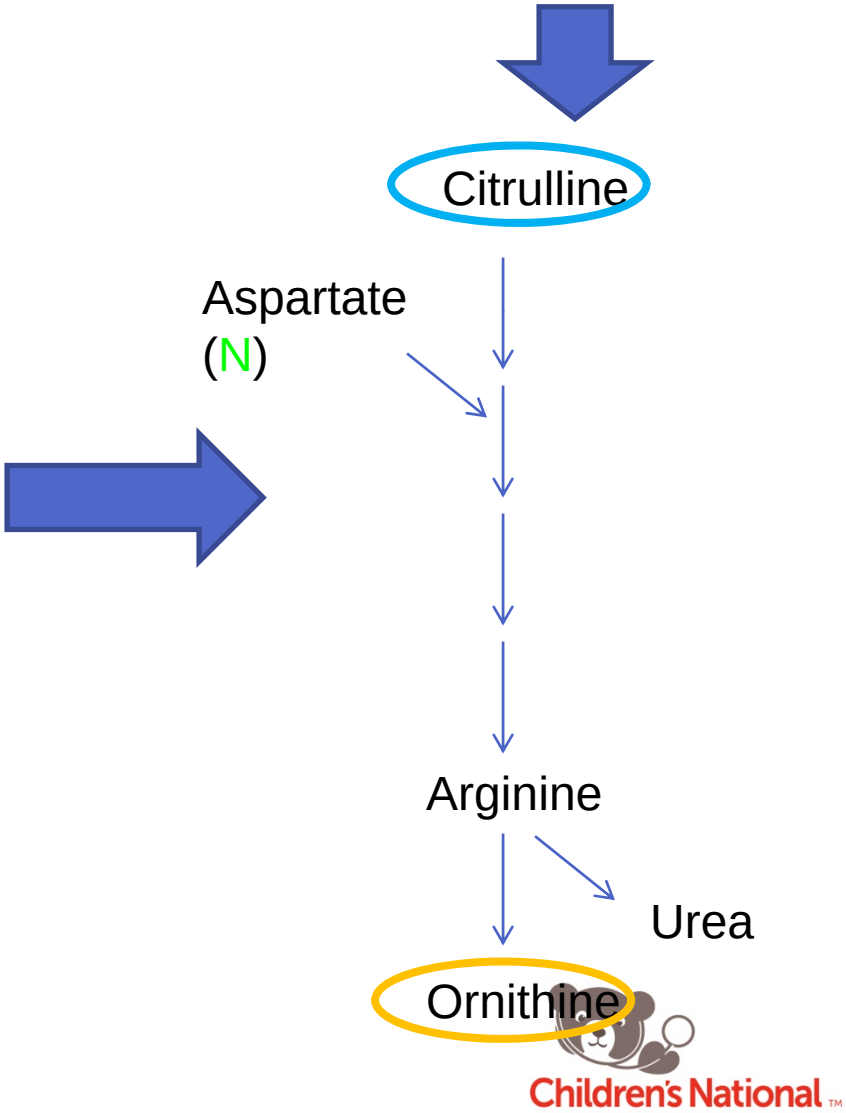
Replacement of Arginine: OTC deficiency





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Genetics and Inheritance of Urea Cycle Disorders

- All disorders are autosomal recessive except for OTC deficiency (X-linked)
- Unlikely to have a family history of affected individuals
- Common mutation for Citrullinemia in San Luis Province
  - Incidence ~ 1:2,500

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Take home points

- Alkalemia due to respiratory alkalosis → ammonia
- hyperammonia → plasma amino acids, urine organic acids

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Thank you!

Questions?

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Additional Resources

- National Urea Cycle Disorders Foundation: http://www.nucdf.org/ucd.htm
- Gene Reviews https://www.ncbi.nlm.nih.gov/books/NBK1217/
- Urea Cycle Disorders Consortium https://www.rarediseasesnetwork.org/cms/UCDC
- Genetics Home Reference (search by disorder) https://ghr.nlm.nih.gov/

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