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PEARLS OF LABORATORY MEDICINE

Inherited Disorders of the Urea Cycle

Van Leung-Pineda, PhD

Children's Healthcare of Atlanta
Emory University School of Medicine

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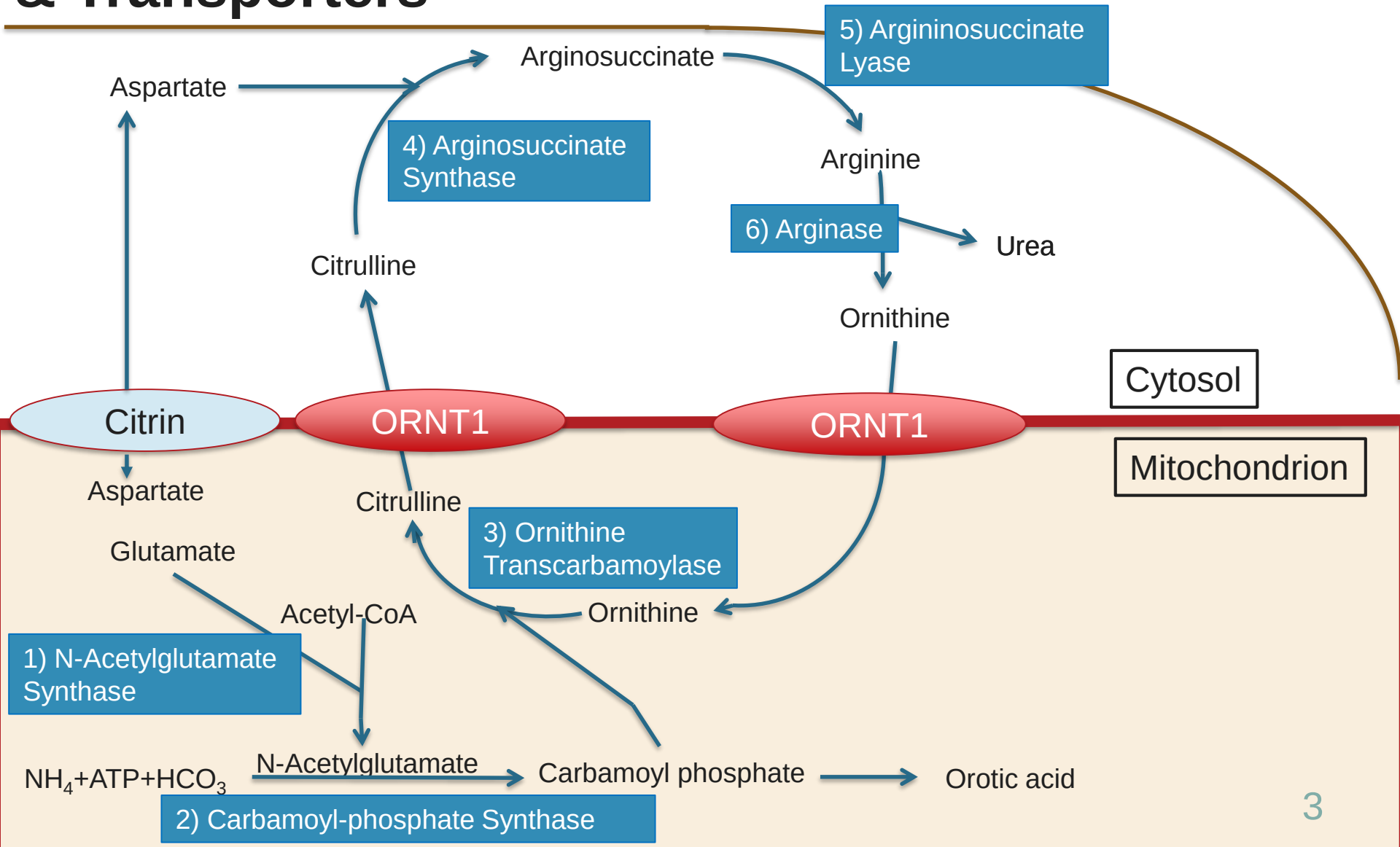
The Urea Cycle

Metabolic pathway to excrete toxic waste nitrogen

- Convert ammonia to urea
- Full functionality in the liver
- Occurs in cytosol and mitochondria
- Proper function depends on enzymes and amino acid transporters

The Urea Cycle: Enzymes & Transporters



Disorders of the Urea Cycle

- In the US about 1 in 8,200 births
- Prevalence is 1 in 35,000
- Mortality is 24% in newborn, 11% in later onset
- Occur due to mutations in enzymes or transporters
  - Most are autosomal recessive inherited
  - One is X-linked: OTC deficiency

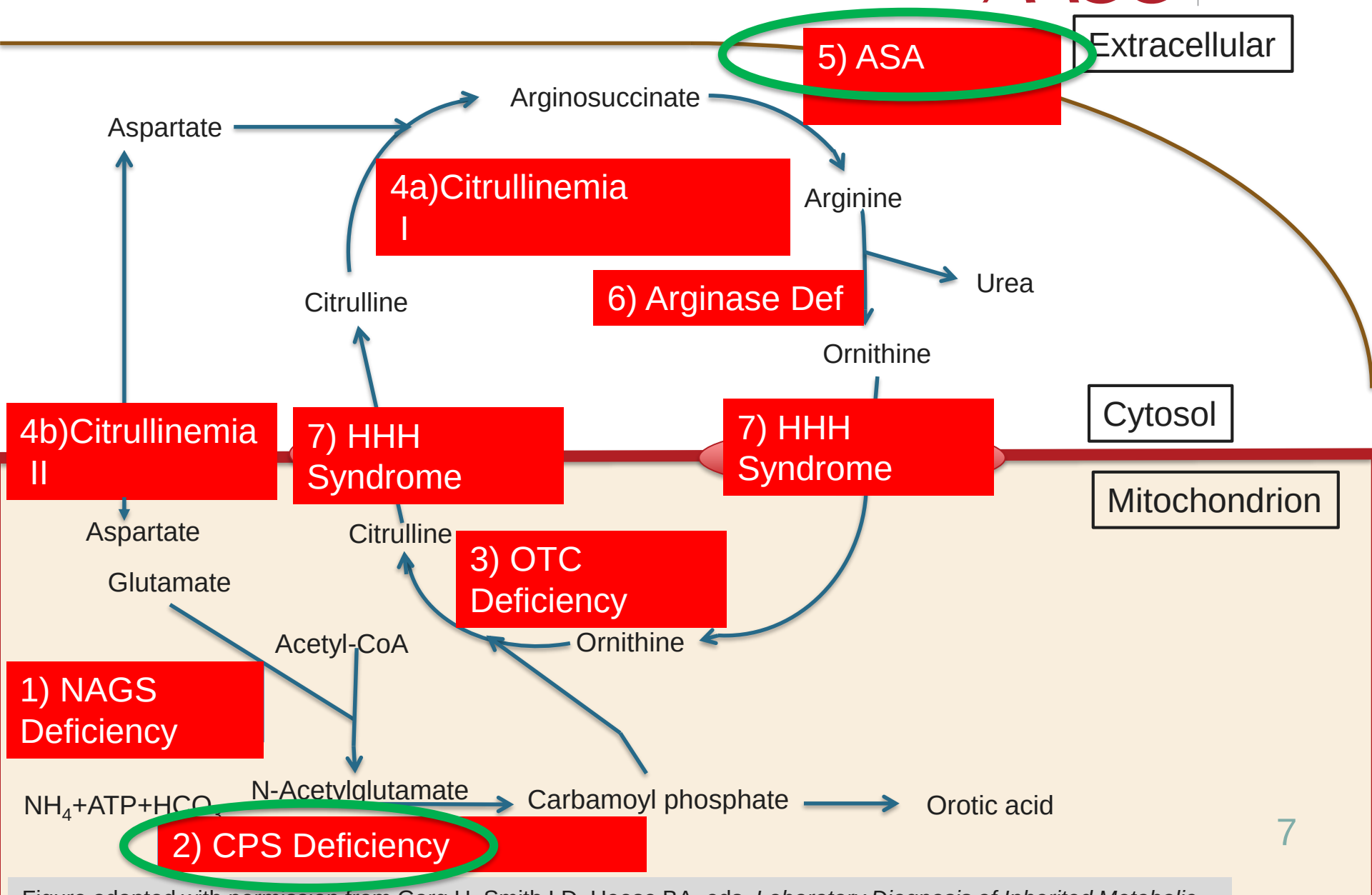
Disorders of the Urea Cycle II

- Present with **Hyperammonemia**
- Metabolic stress triggered
- Onset age can be variable
  - Neonatal
  - Infancy
  - Childhood/Adulthood

Disorders of the Urea Cycle III

Urea Cycle Disorder	Mutated Genes
1) **NAGS** deficiency (N-AcetylGlutamate Synthetase)	*NAGS*
2) **CPS** deficiency (Carbamoyl-Phosphate Synthase)	*CPS1*
3) **OTC** deficiency (Ornithine TransCarbamoylase)	*OTC*
4a) **Citrullinemia I**	*ASS1*
4b) Citrullinemia II	*SLC25A13*
5) **ASA** (Arginosuccicinc aciduria)	*ASL*
6) **Arginase** deficiency	*ARG1*
7) **HHH** syndrome (Hyperammonemia Hyperornithemia Homocitrullinuria)	*ORNT1*

The Urea Cycle Disorders



Symptoms and Presentation

- Hyperammonemia

- Neurological symptoms
  - Seizures, lethargy, altered mental status
- Gastrointestinal symptoms
  - Vomiting, food avoidance, diarrhea, nausea

- Vomiting, Protein refusal

- Neonatal-Rapid deterioration
  - Respiratory alkalosis
- Infancy-Less acute
- Childhood and later-Chronic

Symptoms and Presentation II

- Specific disorders presentations
  - Arginase deficiency-episodic hyperammonemia. Spasticity
  - HHH-universal physical and mental developmental delay
  - Citrullinemia II-neuropsychiatric defects, cholestasis and other hepatic abnormalities
- Acute encephalopathic events can occur at all stages

Laboratory Tests

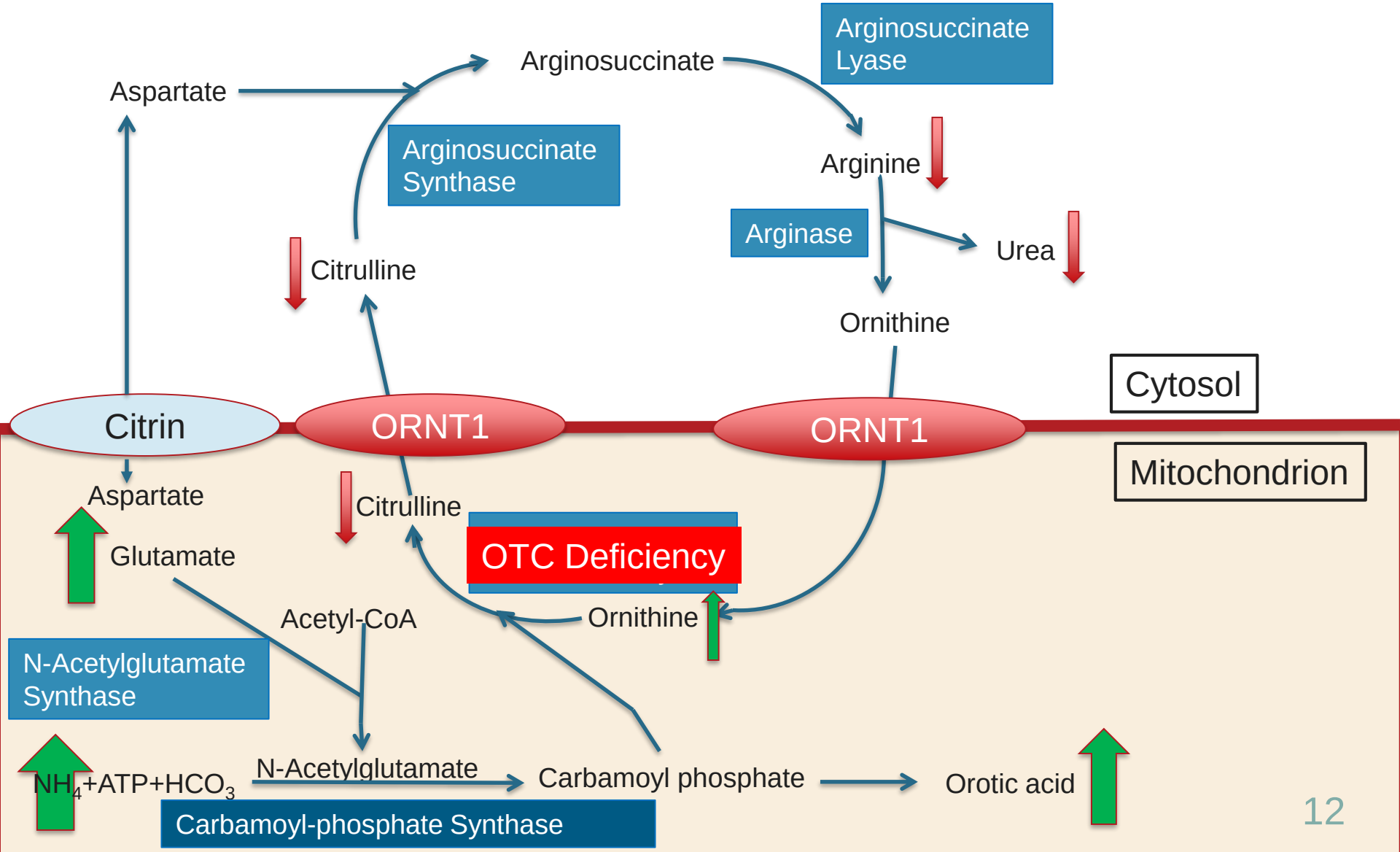
- **Chemistries**
  - **Ammonia**
  - Electrolytes and glucose
  - pH
  - BUN
  - **Blood amino acids**
  - **Urine Organic Acids (Orotic acid)**
  - Lactic acid
- **DNA testing**
- **Newborn screening**

Ammonia Testing

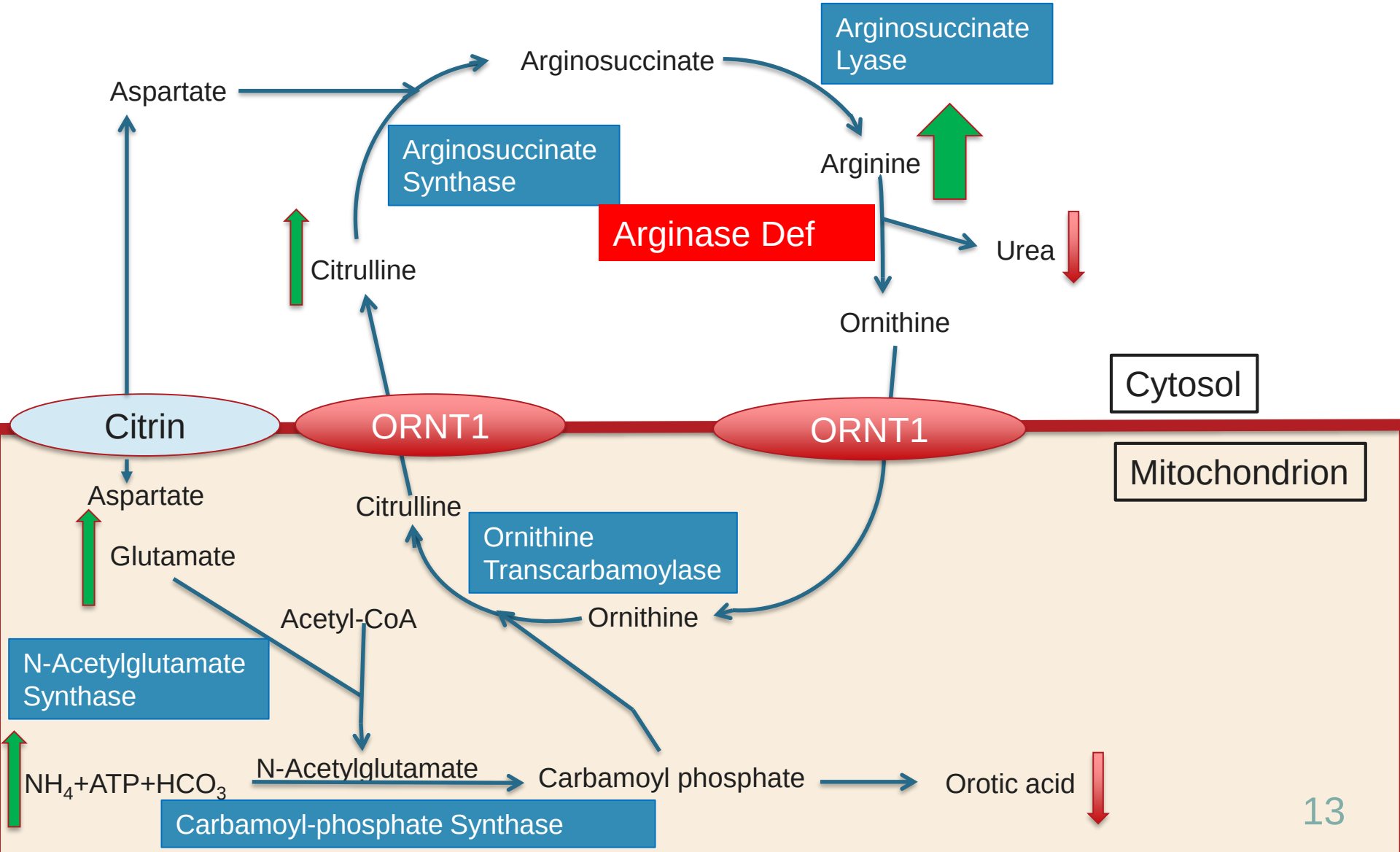
Variables that can affect interpretation

- Timing
- Arterial or venous sample
- Temperature
- Handling
- Different units

Example: OTC deficiency



Example: Arginase deficiency



Laboratory Abnormalities

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Disorder	NH_4	BUN	Amino Acid Results	Organic Acid Results
CPS	↑-↑↑	↓	↓-N Arg, Citr, / ↑ Ala, Gln	↓ orotic
OTC	N-↑↑	↓	↑ Ala, Gln, Orn ↓ Arg ↓-N Citr	↑-↑↑ orotic
Citr I	↑↑	↓	↑↑↑ Citr(P/U)/ ↑ Ala, Gln ↓↓ Arg	↑-↑↑ orotic
Citr II	↑		↑ Gln,Citr N-↑ Arg	
ASA	↑-↑↑	↓	↑↑↑ ASA / N-↑ Ala, Gln, Citr ↓ Arg	↑↑ orotic
Arginase	N-↑↑	↓	↑↑↑ Arg ↑Ala, Gln, Citr	↑-↑↑ orotic
NAGS	↑-↑↑	↓	↓↓ Arg (P)/↓-N Citr/ ↑ Ala, Gln	↓orotic
HHH	↑-↑↑		↑↑ Homocitrulline/↑ Orn, Gln (P),	↑ orotic

Table adapted with permission from Garg U, Smith LD, Heese BA, eds. *Laboratory Diagnosis of Inherited Metabolic Diseases*. Washington, DC: AACC; 2012:55–64. © AACC.

Treatment

- Acute treatment
  1. Ammonia reduction
     – Administer nitrogen scavenger (Ammonul)
     – Hemodialysis
  2. Reverse catabolic state
     – Fluid management
     – Stop/restrict protein intake
     – IV L-arginine

  3. Reduce risk of neurologic damage

Treatment II

- Extended management
  - Nutritional control
  - Prophylaxis to viral infection
  - Disease specific treatments, including liver transplant

Summary

- The Urea Cycle is the metabolic pathway by which ammonia is detoxified and excreted as urea
- Genetic defects in the enzymes that catalyze the urea cycle can result in the pathological accumulation of ammonia
- Ammonia is the key test for suspicion of UCDs, be aware of testing pitfalls
- Biochemical genetic tests can help identify the specific disorder and monitor treatment

References

1. Smith LD, Garg U. The Urea Cycle Disorders and Hyperammonemias. In: Garg U, Smith LD, Heese BA, editors. Laboratory Diagnosis of Inherited Metabolic Diseases. Washington, DC: AACC Press; 2012 p. 55–64.

2. an Haack K, Bennett MJ. Genetic Metabolic Disorders.In: Dietzen DJ, Bennett MJ, Wong ECC, editors. Biochemical and Molecular Basis of Pediatric Disease. 4th Ed. Washington, DC:AACC Press; 2010 p. 235-260.

3. UpToDate. Urea Cycle Disorders: Clinical Features and Diagnosis. https://www.uptodate.com/contents/urea-cycle-disorders-clinical-features-and-diagnosis?search=urea%20cycle%20disorder&source=search_result&selectedTitle=1~54&usage_type=default&display_rank=1 (Accessed November 2018).

4. UpToDate. Urea Cycle Disorders: Management. https://www.uptodate.com/contents/urea-cycle-disorders-management?search=urea%20cycle%20disorder&source=search_result&selectedTitle=2~54&usage_type=default&display_rank=2 (Accessed November 2018).

5. Brusilow SW, Maestri NE. Urea cycle disorders: diagnosis, pathophysiology and therapy. Adv Pediatr 1996; 43:127-70.

6. Batshaw ML, Tuchman M, Summar M, Seminara J, Members of the Urea Cycle DisordersConsortium. A longitudinal study of urea cycle disorders. Mol Genet Metab 2014; 113:127-30.

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