# UPDATE ON UREA CYCLE DISORDERS TREATMENT

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# Disclosure

Consultant / Independent Contractor:

- Hyperion Therapeutics

# Overview

1. Current Treatment Guidelines
    a) Acute Presentations
    b) Chronic Management
2. Ongoing Efforts to Improve Outcomes

# PRINCIPLES OF UCD TREATMENT

Supplement to
THE JOURNAL OF PEDIATRICS
January 2001 Volume 138 Number 1

## Consensus statement from a Conference for the Management of Patients With Urea Cycle Disorders

*The Urea Cycle Disorders Conference Group**

## Current strategies for the management of neonatal urea cycle disorders

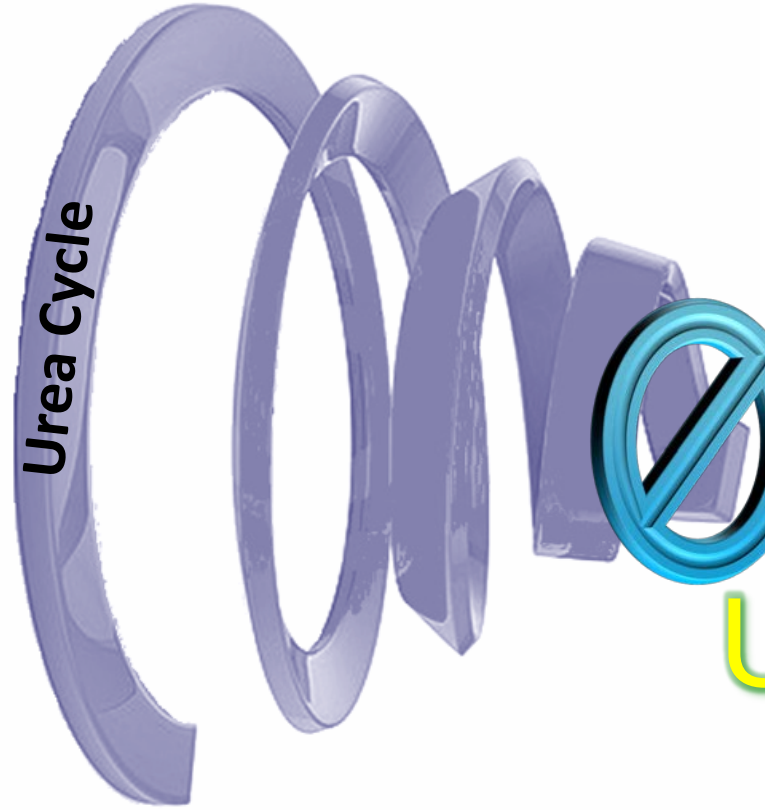
*Marshall Summar, MD*

Dietary Protein

Tissue Breakdown (Acute illness)

Nitrogen

*Ammonia*



# TREATMENT OF ACUTE HYPERAMMONEMIC CRISIS

***Table III.*** Treatment team members and roles and responsibilities

| Team member | Roles and responsibilities |
|---|---|
| Metabolic specialist | Coordinate treatment and management. |
| Pharmacy | Formulate ammonia scavenging and dialysis agents. Check dosing orders. |
| Nephrologist or dialysis team | Dialysis |
| Intensive care team | Assist with physiological support, pain management, and ventilator management. |
| Surgical team | Catheter placement for hemo- and peritoneal dialysis. Obtain biopsy sample for diagnostic testing. |
| Laboratory staff | Ammonia, amino acids, and organic acids |
| Nutritionist | Establish dietary prescription with metabolic foods and supplements. Assist with parenteral calorie management and transition to enteral feeding. |

Summar M, J Peds (2001) 138

# TREATMENT OF ACUTE HYPERAMMONEMIC CRISIS

- **Treat increased intracranial pressure**
  - Hyperventilation
  - Manage IV fluids carefully
  - Mannitol – relative contraindication
- **Reverse catabolism with high glucose infusion rate, +/-insulin, +/-IV lipid**
- **Transfer to a tertiary medical center if local expertise unavailable**
- **Ammonia detoxification**
  - Hemodialysis
  - Ammonia scavenging-medications

# TREATMENT OF ACUTE HYPERAMMONEMIC CRISIS

- **Stop protein intake (oral or IV)**
- **Maximize caloric intake: IV dextrose (10–20%, 8–10 mg/kg/min glucose infusion rate), insulin as necessary, intravenous lipids**
- **Nitrogen scavenger therapy:**
  **Sodium phenylacetate/Sodium benzoate/Arginine via central line**
  **250 mg/kg loading dose over 2 hr, then same dose over 24 hr**
- **Dialysis if initial ammonia is >500 µmol/L**
  **(Hemodialysis>peritoneal dialysis)**
- **Supply protein to prevent catabolism**

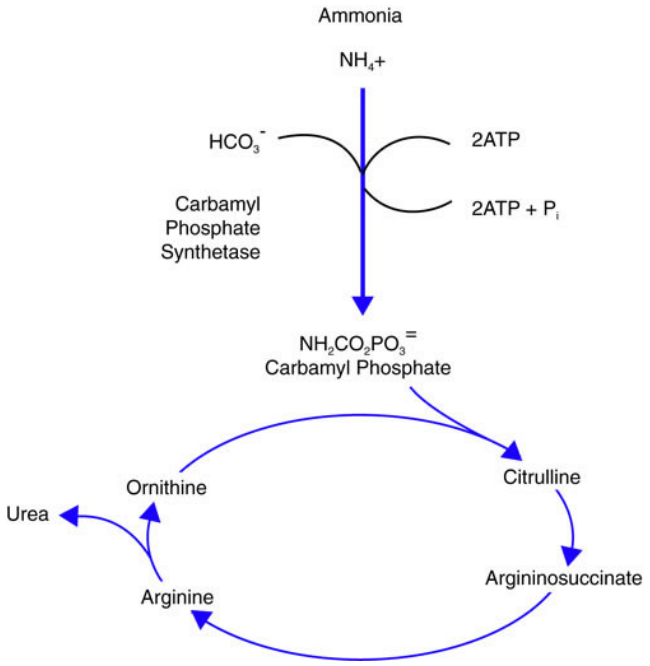
# PRINCIPLES OF UCD TREATMENT


- Restrict substrate
- Provide cofactors
- Provide product
- Provide alternate routes of elimination
- Replace enzyme
- Treat secondary effects

# PRINCIPLES OF UCD TREATMENT

Amino Acids → $NH_3$ → ~~Urea~~

- **Restrict substrate**



# NUTRITIONAL MANAGEMENT OF UCD

ELSEVIER SAUNDERS

Crit Care Clin 21 (2005) S27–S35

CRITICAL CARE CLINICS

## Nutritional Management of Urea Cycle Disorders

Rani H. Singh, PhD, RD[a,*], William J. Rhead, MD, PhD[b], Wendy Smith, MD[c,d], Brendan Lee, MD, PhD[e], Lisa Sniderman King, MSc[f], Marshall Summar, MD[g]

- **After initial reduction of ammonia, essential to avoid catabolism**
- **Prolonged periods of amino acid deficiency will result in iatrogenic hyperammonemia**
- **Chronic disease management requires attention to protein requirements to maintain positive nitrogen balance throughout life**


**Table 2 . Recommended daily nutrient intake in urea cycle disorders**

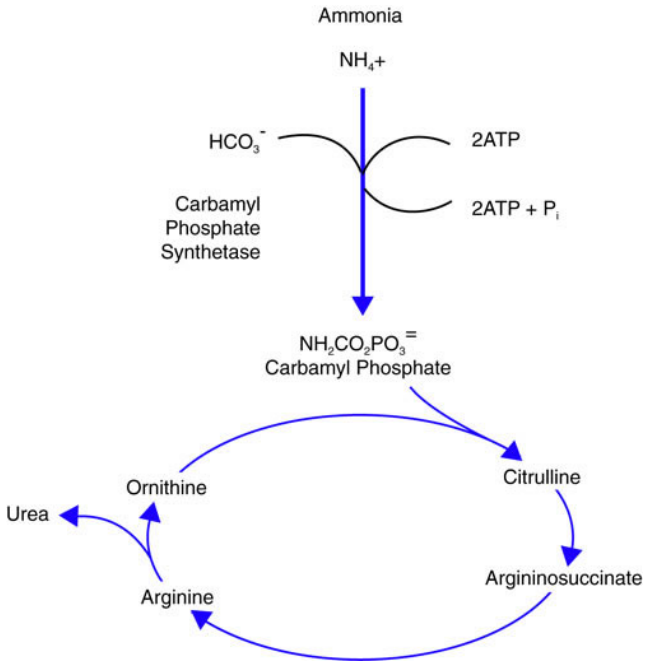
| Age | Protein (g/kg) | Patient energy intake (kcal/kg) | Energy (kcal/kg) | Fluid (mL/kg) |
|---|---|---|---|---|
| Infants | | | | |
| 0 to <3 mo | 2.20–1.25 | 150–101 | 150–125 | 160–130 |
| 3 to <6 mo | 2.00–1.15 | 100–80 | 140–120 | 160–130 |
| 9 to <12 m | 1.60–0.90 | 80–75 | 120–110 | 130–120 |
| Girls and boys | (g/day) | (kcal/day) | (kcal/day) | (mL/day) |
| 1 to <4 yr | 8–12 | 800–1040 | 945–1890 | 945–1890 |
| 4 to <7 yr | 12–15 | 1196–1435 | 1365–2415 | 1365–2445 |
| 7 to <11 yr | 14–17 | 1199–1693 | 1730–3465 | 1730–3465 |
| Women | | | | |
| 11 to <15 yr | 20–23 | | 1575–3150 | 1575–3150 |
| 15 to <19 yr | 20–23 | | 1260–3150 | 1260–3150 |
| ≥19 yr | 22–25 | | 1785–2625 | 1875–2625 |
| Men | | | | |
| 11 to <15 yr | 20–23 | | 2100–3885 | 2100–3885 |
| 15 to <19 yr | 21–24 | | 2200–4095 | 2200–4095 |
| ≥19 yr | 23–32 | | 2625–3465 | 2625–3465 |

Adapted from : Singh et al., Crit Care Clin 21 (2005) S27-S35.

# PRINCIPLES OF UCD TREATMENT

Amino Acids → $NH_3$ → Urea

- **Restrict substrate**
  - **Essential AA formulas**
- **Provide cofactors**

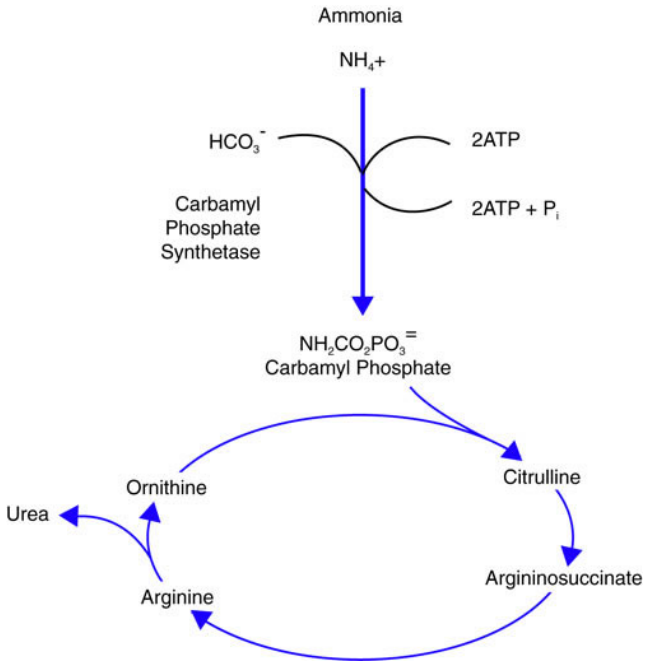


# PRINCIPLES OF UCD TREATMENT

$HCO_3$ + $NH_3$ —(CPS1, N-Acetylglutamate)→ Carbamyl Phosphate

NAGS Deficiency

- **Restrict substrate**
  - **Essential AA formulas**
- **Provide cofactors**
  - **Carglumic Acid**



# PRINCIPLES OF UCD TREATMENT

Argininosuccinate Lyase

Argininosuccinate → Arginine

- **Restrict substrate**
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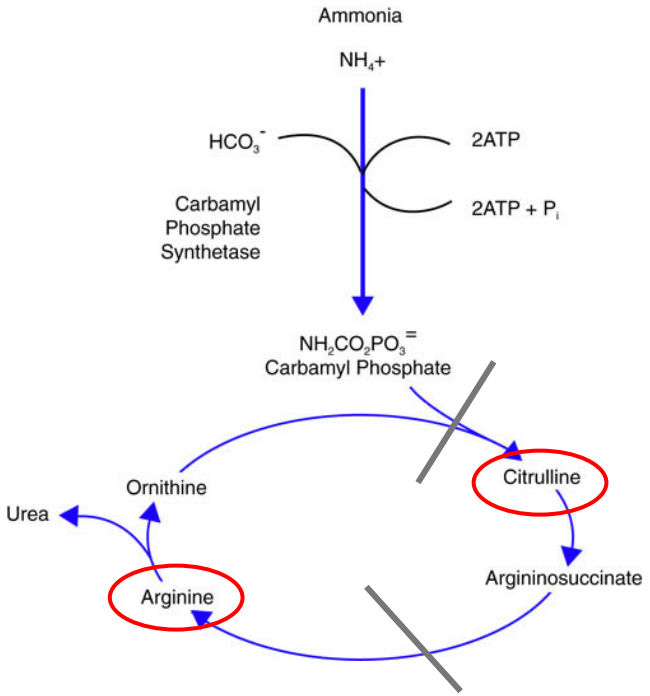
  - **Carglumic Acid**
- **Provide product**
  - **Arginine for distal defects**
  - **Citrulline for proximal defects**



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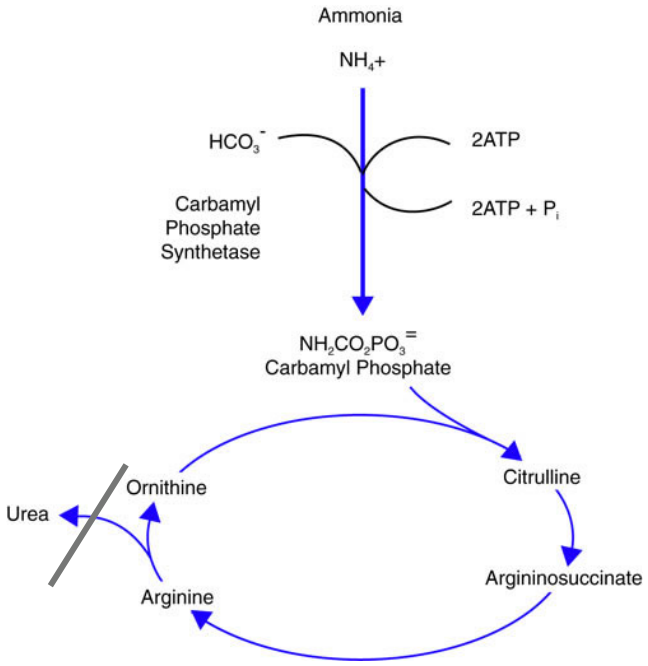
- **Provide alternate elimination routes**



# AMMONIA SCAVENGING AGENTS

December 1980
The Journal of PEDIATRICS 893

## *Treatment of hyperammonemic coma caused by inborn errors of urea synthesis*

*The relative effectiveness of exchange transfusion, peritoneal dialysis, arginine, and sodium benzoate was evaluated during 44 episodes of hyperammonemic coma in 31 patients with congenital urea cycle enzymopathies. The overall survival rate was 56%. In 15 episodes treated with EXT the fall in ammonium was 19 ± 24%, P > 0.05. In 30 episodes treated with PD, the fall in ammonium was 60 ± 9%, P < 0.001. Ten times more nitrogen was removed as glutamine than as ammonium during dialysis, suggesting that the effectiveness of PD resides in the removal of glutamine, glutamate, and alanine as well as ammonium. Prior to therapy all patients had hypoargininemia (18 ± 2 uM); they responded to arginine supplementation with a rise in plasma arginine concentration to normal. In patients with AL deficiency, arginine supplementation (4 mmol/kg/day) was associated with a fall in ammonium level from 917 ± 62 to 103 ± 18 μM within 24 hours. When sodium benzoate (250 mg/kg/day) was used during eight episodes of coma, six patients responded with a significant decrease in plasma ammonium.*

**Mark L. Batshaw, M.D., and Saul W. Brusilow, M.D.,** *Baltimore, Md.*

# AMMONIA SCAVENGING AGENTS



## TREATMENT OF INBORN ERRORS OF UREA SYNTHESIS

### Activation of Alternative Pathways of Waste Nitrogen Synthesis and Excretion

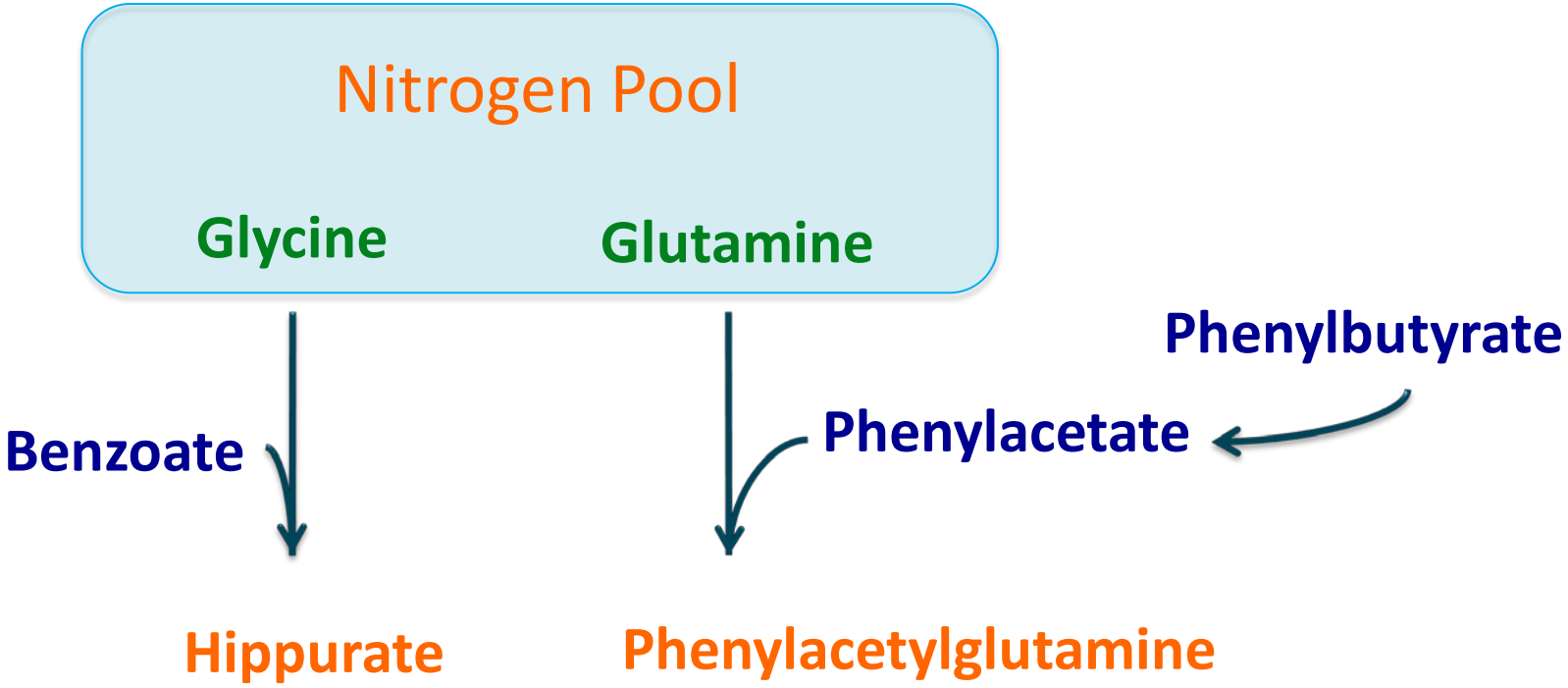
MARK L. BATSHAW, M.D., SAUL BRUSILOW, M.D., LEWIS WABER, PH.D., M.D., WIM BLOM, PH.D., ANN MARIE BRUBAKK, M.D., BARBARA K. BURTON, M.D., HOWARD M. CANN, M.D., DOUGLAS KERR, M.D., PETER MAMUNES, M.D., REUBEN MATALON, M.D., DAVID MYERBERG, M.D., AND IRWIN A. SCHAFER, M.D.

**Abstract** Children with inborn errors of urea synthesis accumulate ammonium and other nitrogenous precursors of urea, leading to episodic coma and a high mortality rate. We used alternative pathways for the excretion of waste nitrogen as substitutes for the defective ureagenic pathways in 26 infants. These pathways involve synthesis and excretion of hippurate after sodium benzoate administration, and of citrulline and argininosuccinate after arginine supplementation.

The children were treated for seven to 62 months; 22 survived. The mean plasma level of ammonium (±S.E.) was 36±2 μmol per liter, and that of benzoate was 1.5±1.0 mg per deciliter. Alternative pathways accounted for between 28 and 59 per cent of the total "effective" excretion of waste nitrogen. Nineteen infants had normal height, weight, and head circumference, and 13 had normal intellectual development.

Activation of alternative pathways of waste nitrogen excretion can prolong survival and improve clinical outcome in children with inborn errors of urea synthesis.
(N Engl J Med. 1982; 306:1387-92.)

# AMMONIA SCAVENGING AGENTS




| |
|---|
| Sodium Phenylbutyrate (oral) |
| Glycerol Phenylbutyrate (oral) |
| Sodium Phenylacetate + Sodium Benzoate ± Arginine (intravenous) |

# CLINICAL STUDIES COMPARING SODIUM PHENYLBUTYRATE AND GLYCEROL PHENYLBUTYRATE

- **Phase 1**
  - 32 Healthy Adults and 24 Hepatic Disease Patients
    *McGuire et al., *Hepatology* 2010
- **Phase 2 ( 21 UCD patients)**
  - Phase 2 Study in UCD Adults (n=10); Open Label, Fixed Sequence Switchover
    *Lee et al., *Mol Gen Metab* 2010
  - Phase 2 Study in UCD Children (n=11); Open Label, Fixed Sequence Switchover
    *Lichter et al., *Mol Gen Metab* 2011
- **Phase 3 (69 UCD patients)**
  - Pivotal Efficacy Study; 4-week, Double-Blind, Randomized, Crossover
  - Open Label 12-month Safety Studies
    *Diaz et al., *Hepatology* 2013

# Urinary phenylacetylglutamine as dosing biomarker for patients with urea cycle disorders

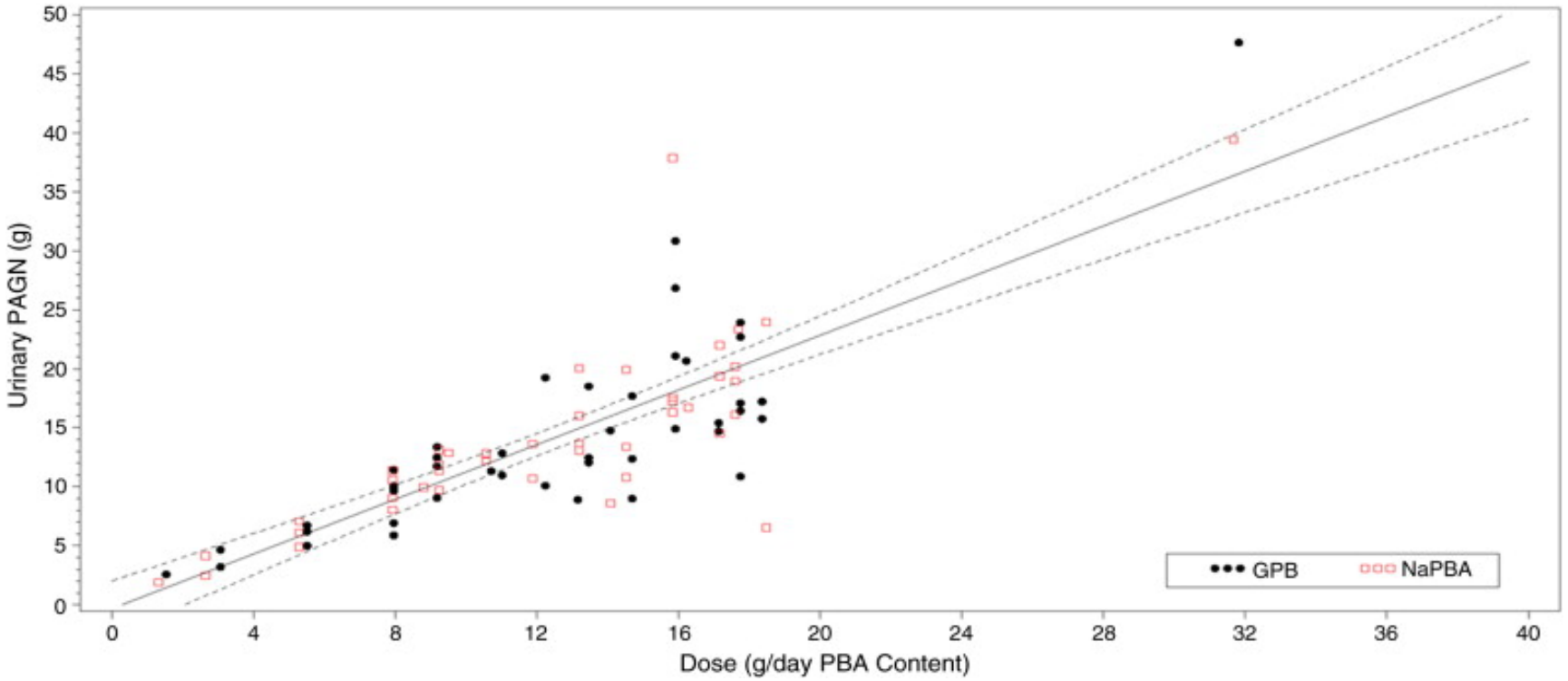


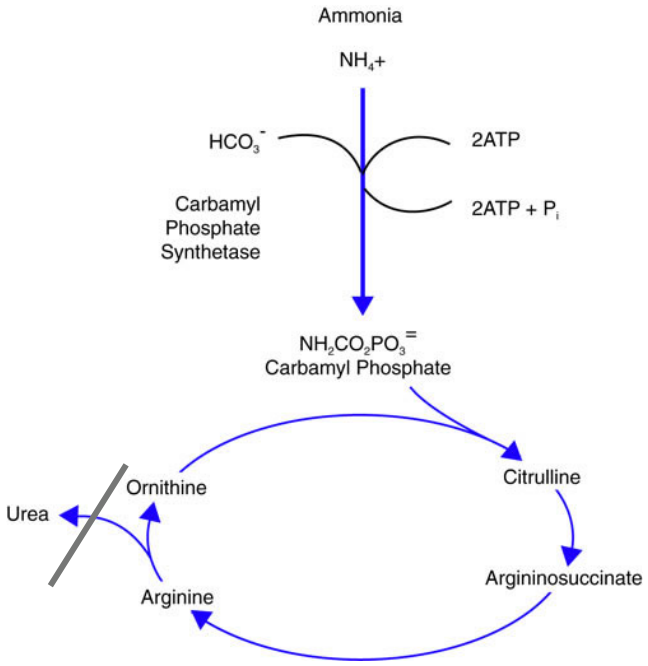

Fig.1 Urinary phenylacetylglutamine excretion versus total dose of glycerol phenylbutyrate or sodium phenylbutyrate administered.

Mokhtarani M et al., Molecular Genetics and Metabolism Volume 107, Issue 3 2012 308 - 314

# PRINCIPLES OF UCD TREATMENT

Amino Acids → $NH_3$ → Urea

- **Restrict substrate**
  - **Essential AA formulas**
- **Provide cofactors**
  - **Carglumic Acid**
- **Provide product**
  - **Arginine for distal defects**
  - **Citrulline for proximal defects**
- **Provide alternate elimination routes**



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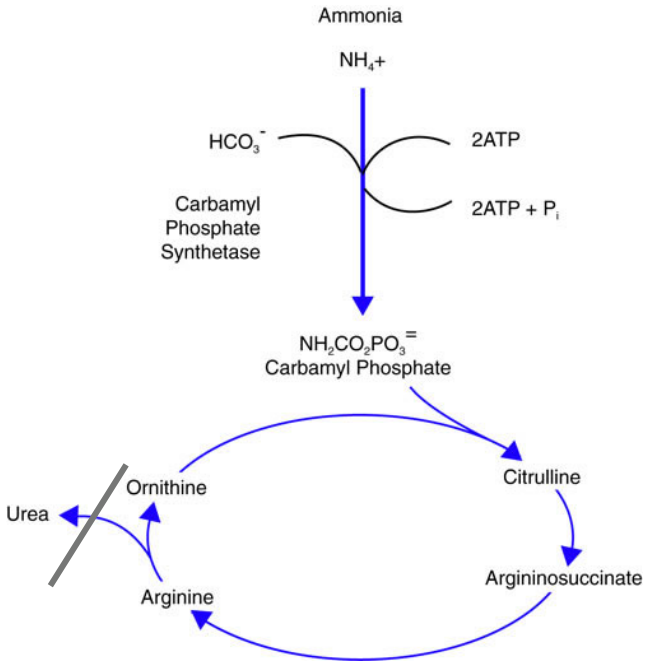
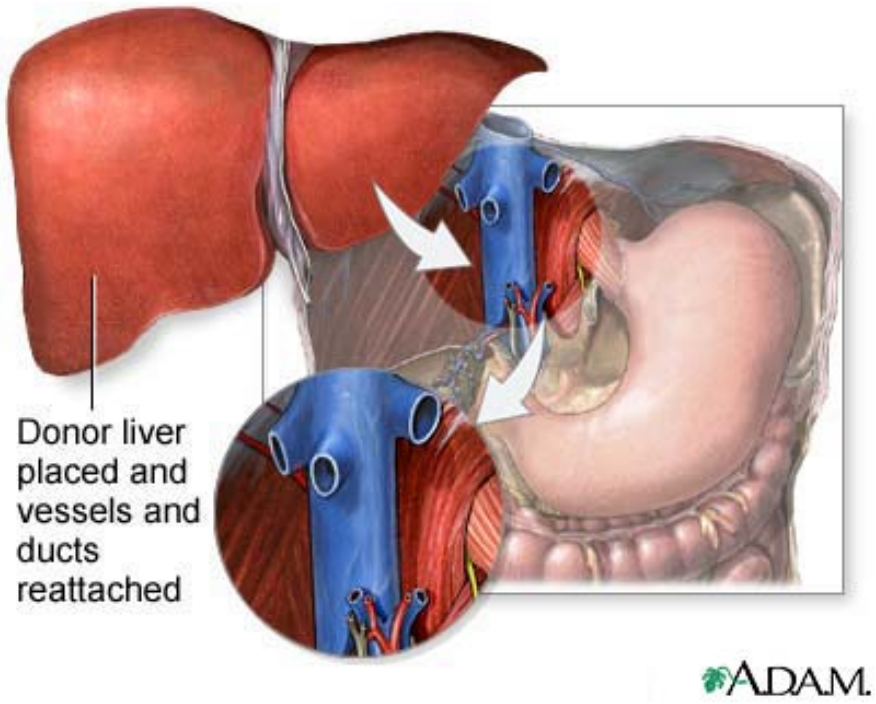
  - **Arginine for distal defects**
  - **Citrulline for proximal defects**
- **Provide alternate elimination routes**
- **Replace enzyme**
  - **Liver Transplantation**



# LIVER TRANSPLANTATION IN UCD




- Indicated For:
  - OTC Deficiency
  - CPS1 Deficiency
  - Citrullinemia type 1
- Generally Done at 6 – 12 mos.
  - Emergent Neonatal Cases
- May Consider for:
  - ASL Deficiency - Cirrhosis
  - Failure of Medical Mgmt

# Ongoing Efforts to Improve Outcomes

# FDA APPROVED TREATMENTS

- **2005 – Phenylacetate/Benzoate/Arginine**
- **2010 – Carglumic Acid**
- **2013 – Glycerol Phenylbutyrate**

- **Planned or Active Studies**

Short-term Outcome of N-Carbamylglutamate in the Treatment of Acute Hyperammonemia (PI – M. Tuchman)

- Organic Acidemias, Mild CPS1 deficiency, Partial OTC

**Can pharmacologic cofactor dosing increase flux through urea cycle in milder CPS1/OTC deficiency patients?**

# POTENTIAL FUTURE THERAPIES

- **Neurocognitive Outcomes**
  - Remain poor for a significant fraction of patients
  - Potential therapeutic targets include:

    Minimizing acute hyperammonemic damage

- **Planned or Active Studies**

Pilot Study for Hypothermia Treatment in Hyperammonemic Encephalopathy in Neonates and Very Young Infants (PI – U. Lichter-Konecki)

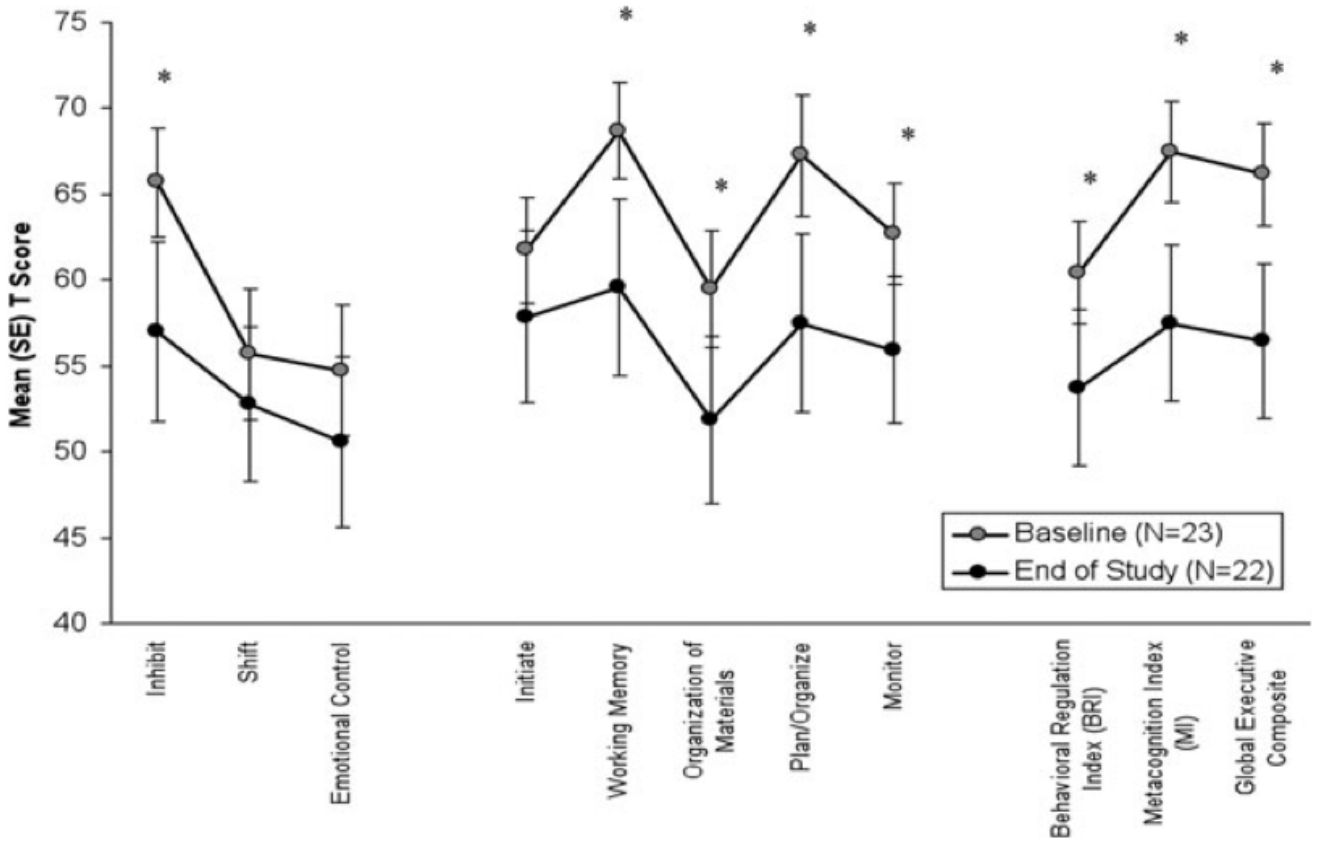
**Can hypothermia decrease ammonia production and shorten time to crisis resolution?**

# POTENTIAL FUTURE THERAPIES

- **Neurocognitive Outcomes**
  - Remain poor for a significant fraction of patients
  - Potential therapeutic targets include:

    Minimizing chronic hyperammonemic damage

# Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate




BRIEF domain T scores in pediatric patients (6-17 years) treated with glycerol phenylbutyrate for 12 months.

Diaz GA et al., Hepatology. (2012) Sep 7. doi: 10.1002/hep.26058. [Epub ahead of print]

# PRINCIPLES OF UCD TREATMENT

**Argininosuccinate**

Argininosuccinate ——— ~~Lyase~~ ———→ Arginine

- **Restrict substrate**
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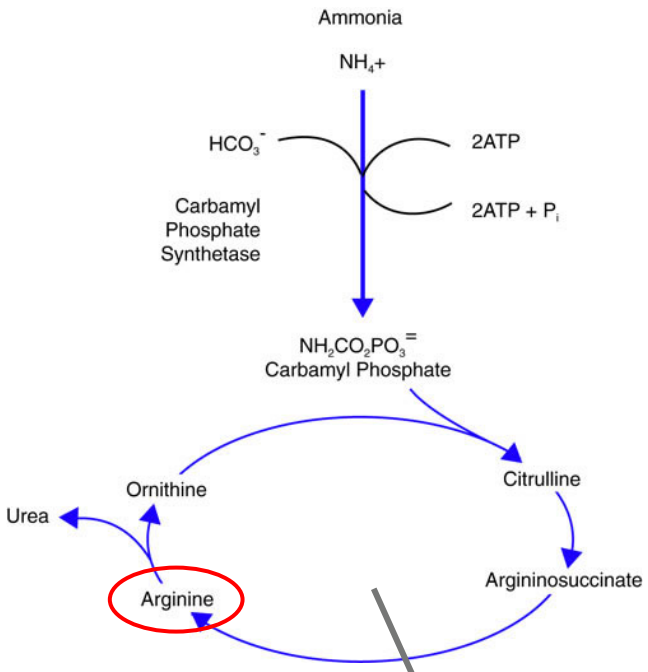
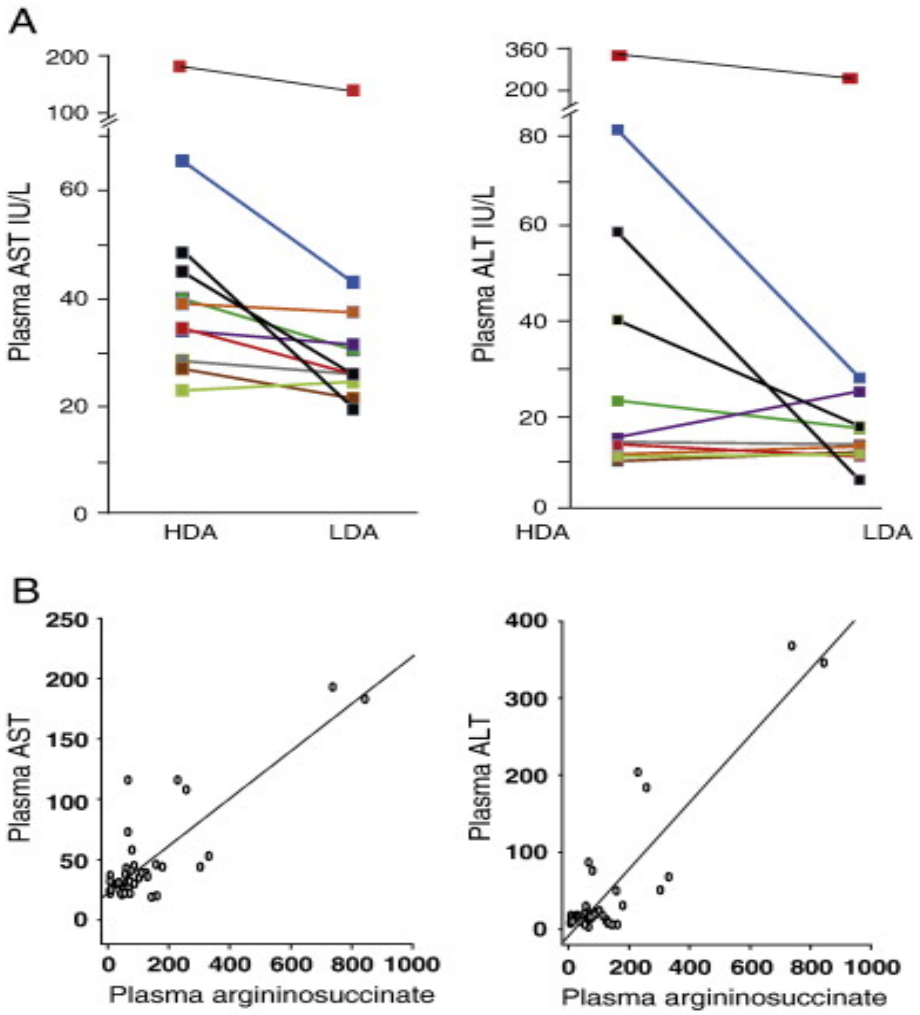
- **Provide product**
  - **Arginine for distal defects**




- **Planned or Active Studies**

Arginine and Buphenyl in Patients with Argininosuccinic Aciduria (ASA), a Urea Cycle Disorder (PI – B. Lee)

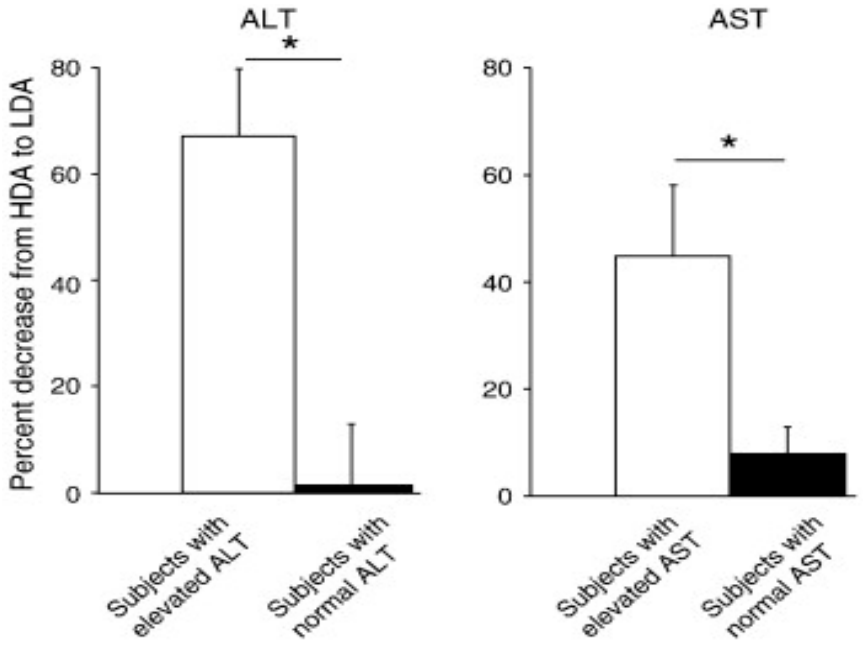
# A randomized controlled trial to evaluate the effects of high-dose versus low-dose of arginine therapy on hepatic function tests in argininosuccinic aciduria




Effect of the two treatment arms on aspartate and alanine aminotransferases.

Nagamani SCS et al., Molecular Genetics and Metabolism (2012) 107, 315 – 321.

# A randomized controlled trial to evaluate the effects of high-dose versus low-dose of arginine therapy on hepatic function tests in argininosuccinic aciduria




Stratified analysis of aminotransferase levels in subjects with elevations of AST and ALT.

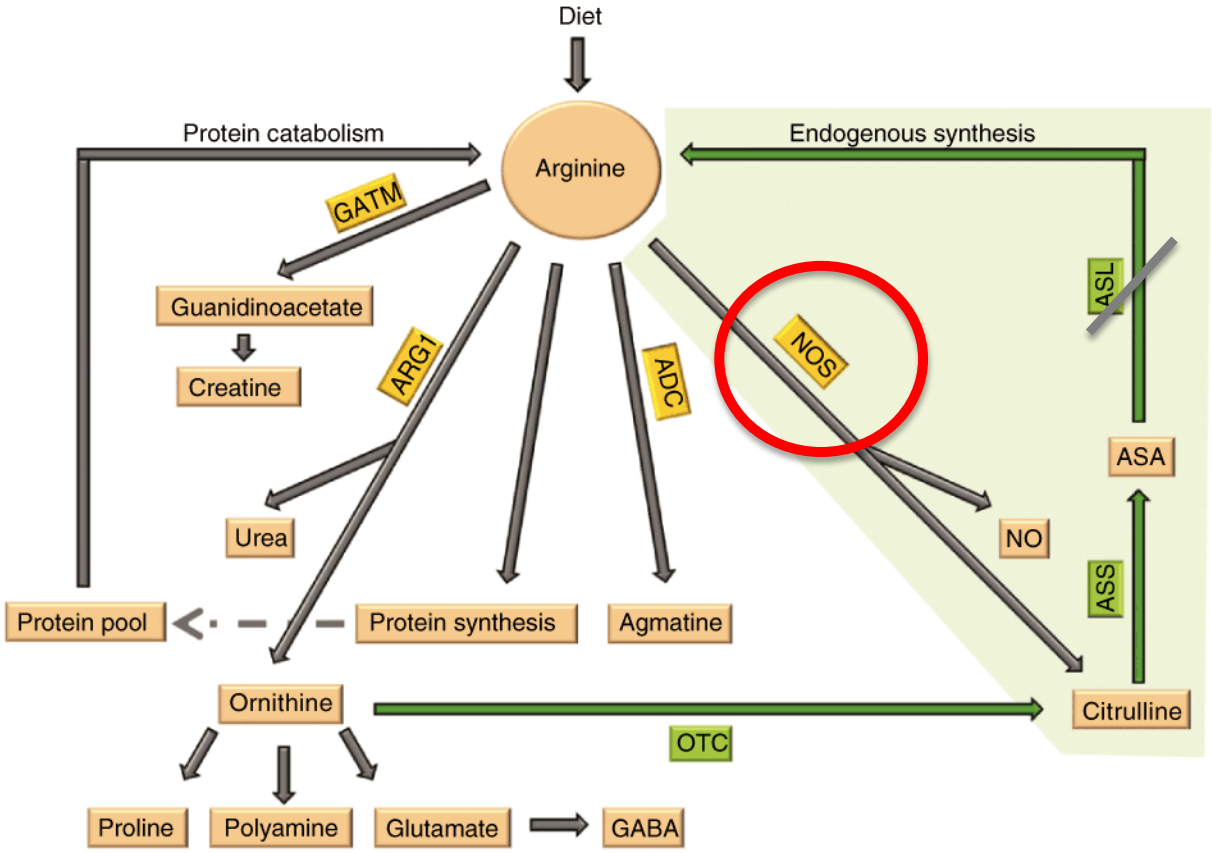
**Scavenger therapy decreased ASA flux in ASL deficiency patients and reduced transaminase elevations in patients with high levels.**

**For patients with liver dysfunction, lower Arg doses may be preferable**

Nagamani SCS et al., Molecular Genetics and Metabolism (2012) 107, 315 – 321.

# POTENTIAL FUTURE THERAPIES

- **ASL Deficiency**




**NOS-ASL Enzyme Complex**

**Important for Arg channeling**

**NOS defect in ASL KO mice**

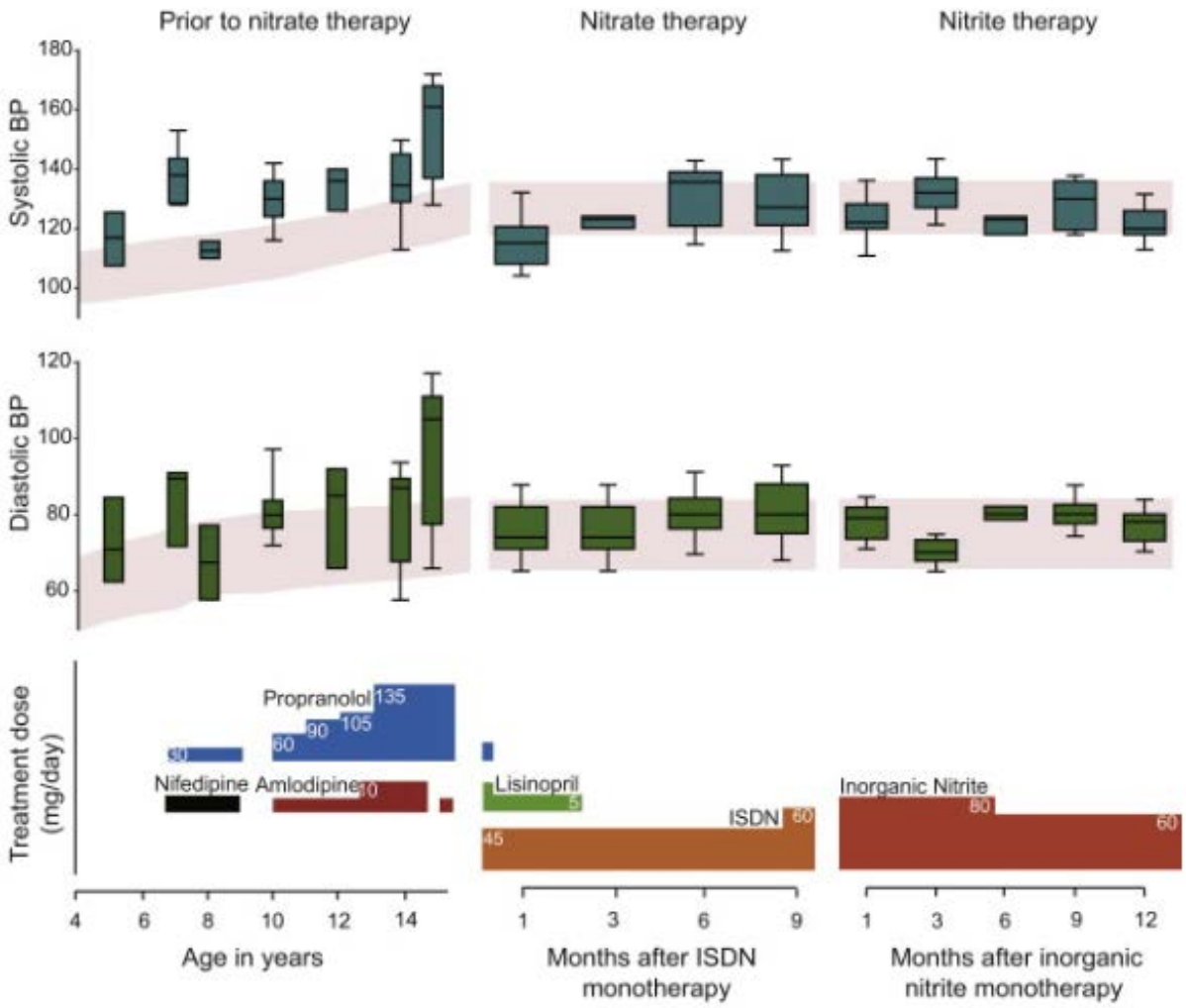
**NOS defect may explain non-ammonia related ASL phenotypes**

Nagamani SCS et al., Genetics in Medicine (2012) 14, 501–507.

# POTENTIAL FUTURE THERAPIES

- **ASL Deficiency**

Clinical Treatment with NO Supplements Corrects Hypertension in a Subject with ASA.



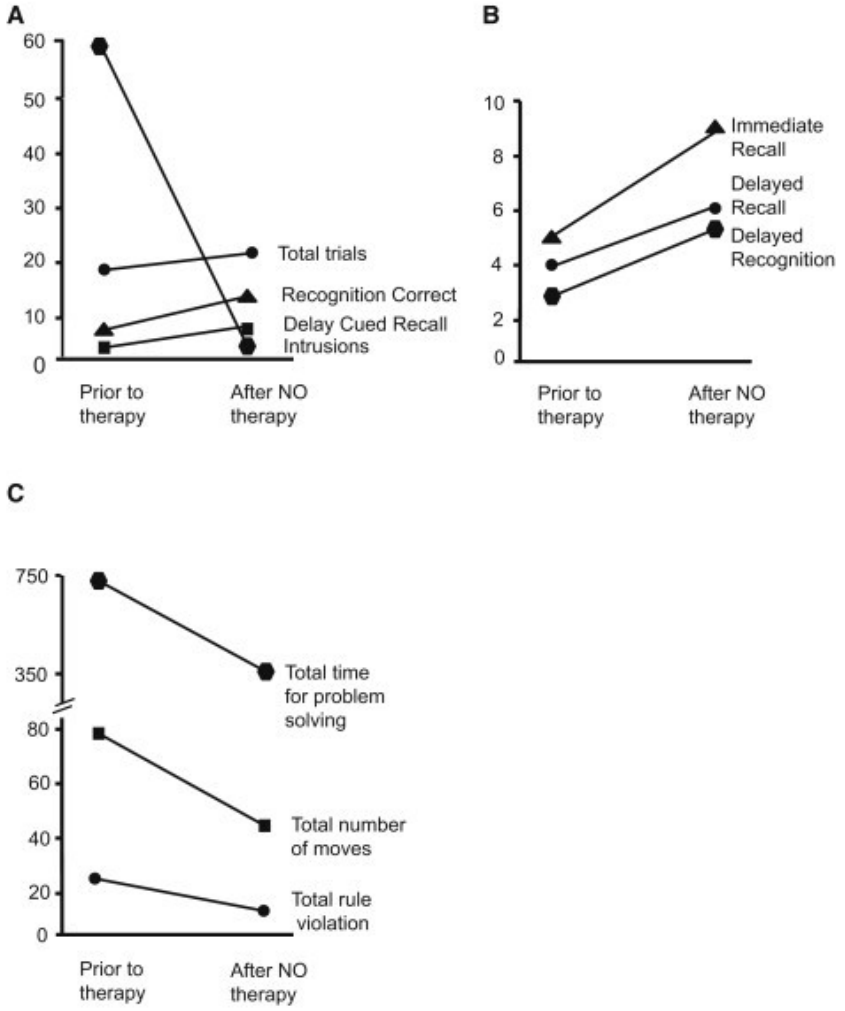

Nagamani SCS et al., Am J Hum Genet (2012) 90, 836-46.

# POTENTIAL FUTURE THERAPIES

- **ASL Deficiency**

Neuropsychological Testing Results before and after NO Supplementation.

a) California Verbal Learning Test
b) Children's Memory Scale
c) Tower of London – Drexel University

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Argininosuccinate → (Argininosuccinate Lyase) → Arginine

- **Restrict substrate**
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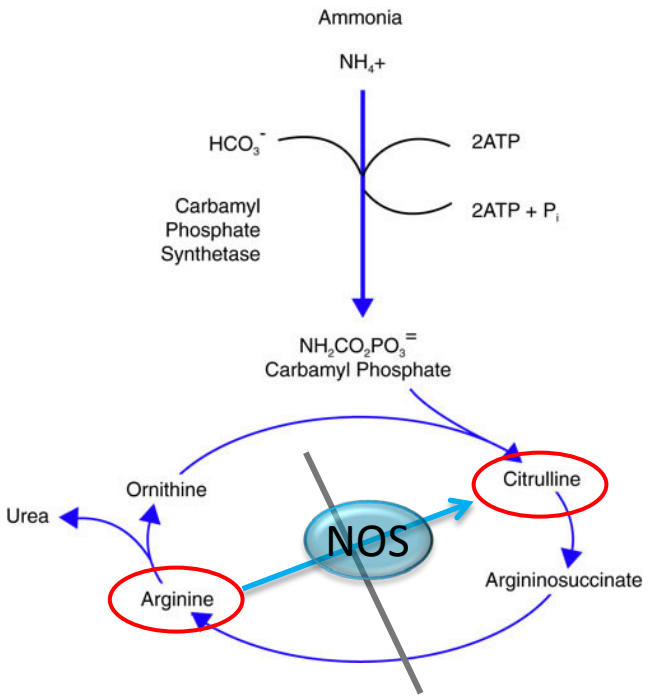
  - **Arginine for distal defects**
  - **Nitrites for NOS defect?**



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Thomas and Mary Alice O'Malley Foundation

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All of the Medical Genetics Residents

Department of Pediatrics – PICU, NICU, Renal teams

# ACKNOWLEDGEMENTS

Questions?