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Managing Infants & Toddlers with UCDs: Rolling with the Punches

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Disclosures

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- Honorarium for educational talks accepted from Met Ed, Abbott, Nutricia, and Vitaflo
- Consulting and advisory board participation from Acer Therapeutics, Horizon Therapeutics, and PTC Therapeutics
- Faculty for Metabolic University (Met Ed)
- ***None pose any conflict of interest for this presentation***

The opinions reflected in this presentation are those of the speaker and independent of Nutricia North America

Learning Objectives

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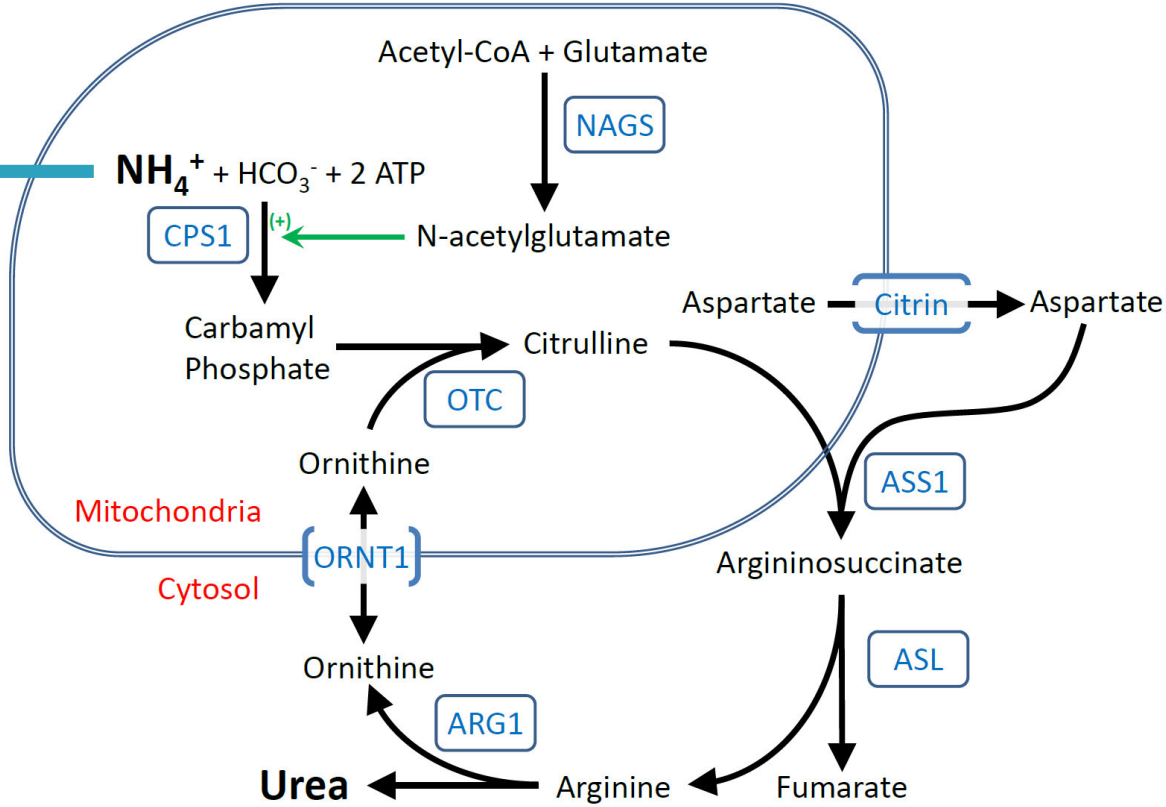
- Understand the rationale for nutrition management of UCDs in infants with different presenting symptoms.
- Compare the level of protein restriction required for different UCDs based on biochemical markers.
- Develop a transition plan for toddlers with UCDs to promote growth and optimize feeding.

The Urea Cycle

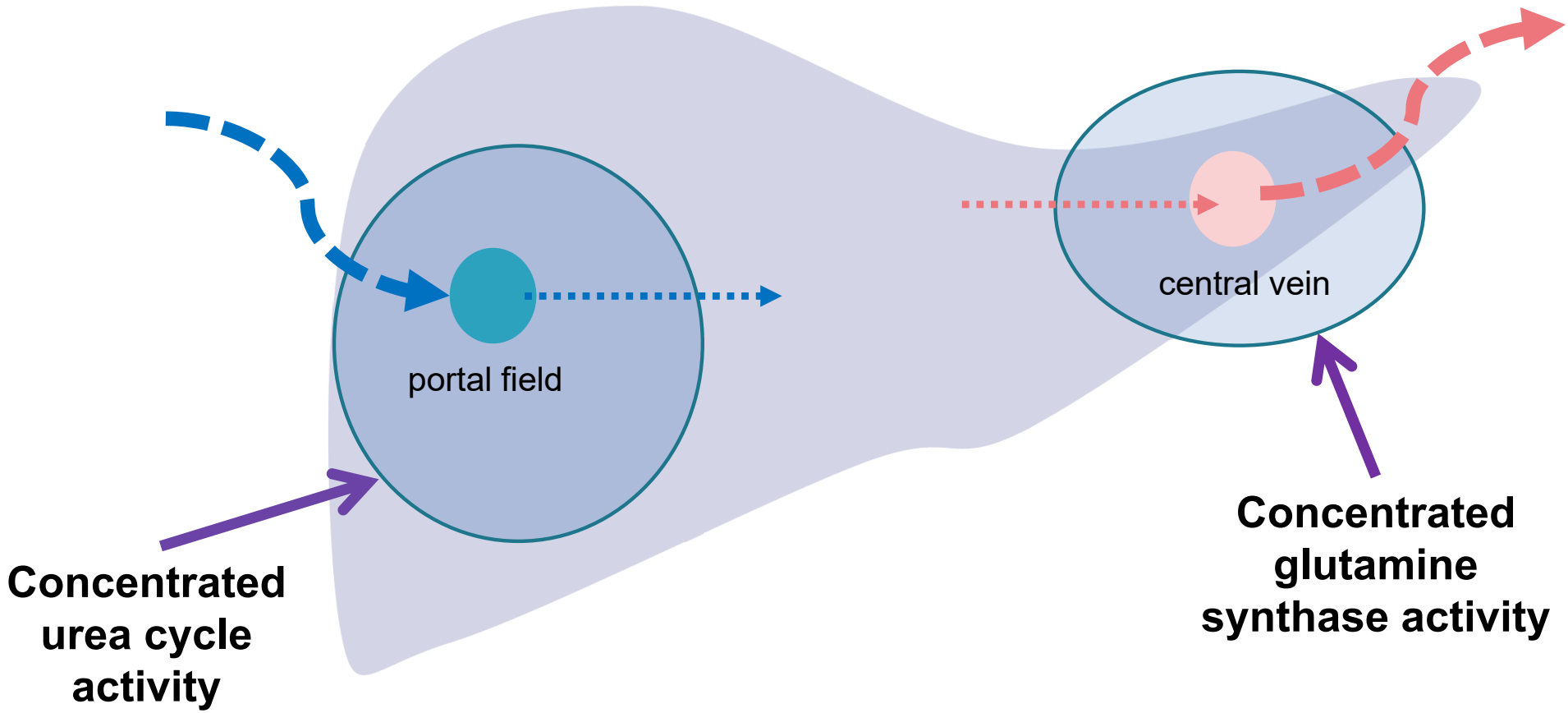
Brain Edema

- Lethargy
- Seizures
- Coma
- Death
- Intellectual disability



Ah Mew et al. Urea cycle disorders overview; GeneReviews 2017.

The role of glutamine in UCD management



Primary Urea Cycle Management

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❷ **Use a bucket to bail water out**

❶ **Turn down the faucet**

Reduce Influx
- Protein Restriction
- Anabolism

❸ **Fix the pipes**
- Carglumic acid
- Arginine/ Citrulline
- Liver Transplant
- Gene Therapy

UCD Management Overview - Supplements

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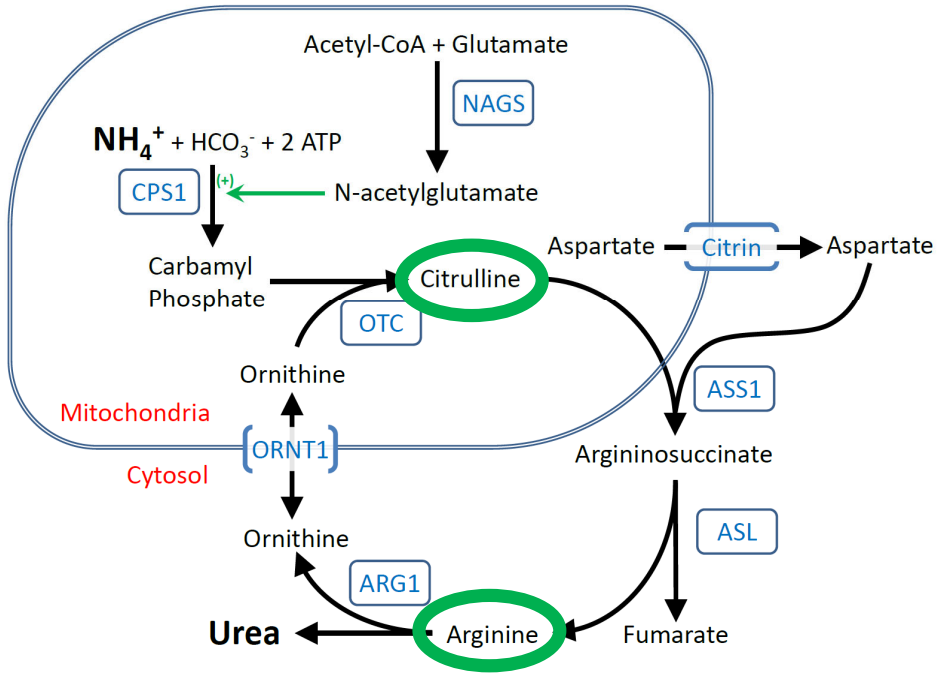
Diagnosis	Diagnosis	Supplements needed
N-acetyl glutamate synthase deficiency	NAGS	Citrulline
Carbamoyl phosphate synthase 1 deficiency	CPS1	Citrulline
Ornithine transcarbamylase deficiency	OTC	Citrulline
Argininosuccinate synthase deficiency / Citrullinemia	ASS	Arginine
Argininosuccinic aciduria / Argininosuccinate lyase deficiency	ASA / ASL	Arginine
Arginase deficiency	ARG1	None



Ammonia metabolism in the intestine

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- Enterocytes exhibit all proximal steps of the urea cycle up to citrulline production
- Ammonia is produced in enterocytes due to intestinal breakdown of glutamine[1]
- 15-30% of blood urea is broken down into ammonia by gut bacteria[2]
- Arginine production occurs in the kidney

1. Damink et al.; Hepatology 2002 36:1163-1171
2. Jackson et al.; Journal of Nutrition 1993;123:2129-36

Primary Urea Cycle Management

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❷ **Use a bucket to bail water out**

- Medications

❶**Turn down the faucet**

Reduce Influx
- Protein Restriction
- Anabolism

❸ **Fix the pipes**

- Carglumic acid
- Arginine/ Citrulline
- Liver Transplant
- Gene Therapy

Protein goals

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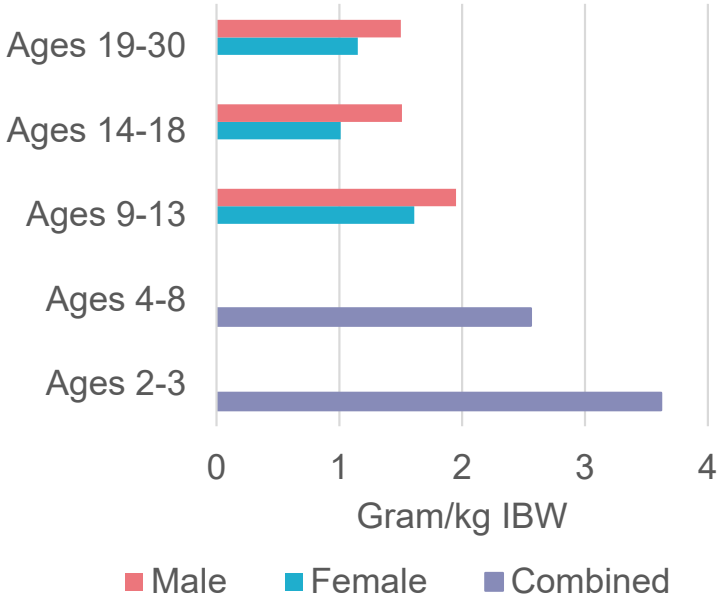
Average protein intake in America (NHANES 2013-14)



Adapted from: Am J Clin Nutr, Volume 108, Issue 2, August 2018, Pages 405-413. https://doi.org/10.1093/ajcn/nqy088

Protein goals in UCDs

Age	Natural Protein (g/kg)	EAA (g/kg)	Total Protein (g/kg)
0-1 yr	0.8-1.1	0.6-1.1	1.2-2.2
1-7 yr	0.7-0.5	0.3-0.7	1.0-1.2
7-19 yr	0.3-0.7	0.4-0.7	0.7-1.4
> 19 yr	0.6-0.7	0.2-0.5	0.5-1.0

Adapted from: Singh RH. Nutrition management of urea cycle disorders. 2014: A practical reference for clinicians and Haberle 2019

Rule Breakers

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Argininosuccinate lyase deficiency (ASA or ASL)

- Not all individuals will have hyperammonemic episodes
- Developmental delay still noted even without hyperammonemia
- At risk for hypertension and liver disease
- Is there utility for a protein restriction in the absence of hyperammonemia?

Rule Breakers

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Arginase deficiency

- Elevations in ammonia and glutamine are less common
- Management goal is to decrease arginine with primary goal to prevent movement differences
- Often difficult to achieve without significant natural protein restriction
- Consider arginine content of consumed proteins

Diagnostic Presentation Drives Management Decisions

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Positive NBS	Symptomatic Presentation	Family History
• Most distal disorders • Results at 4-7 days of life	• Age of presentation • Severity	• Prenatal diagnosis • Diagnosis of family members after NBS or symptomatically

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Newborn Screen Identification

It’s 4:30 on a Friday (always) when the state calls with a positive screen.

What do you do?

UCD Management Overview

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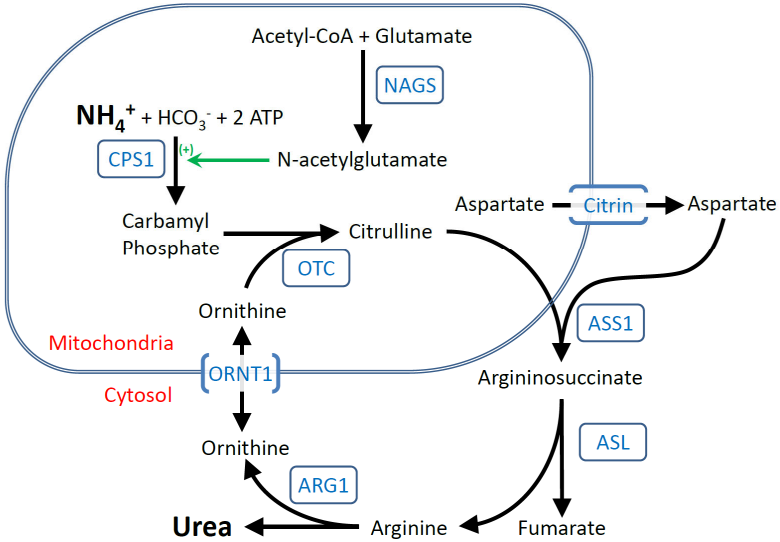
Diagnosis	Diagnosis	Supplements needed	RUSP
N-acetyl glutamate synthase deficiency	NAGS	Citrulline	No*
Carbamoyl phosphate synthase 1 deficiency	CPS1	Citrulline	No*
Ornithine transcarbamylase deficiency	OTC	Citrulline	No*
Argininosuccinate synthase deficiency / Citrullinemia	ASS	Arginine	Yes
Argininosuccinic aciduria / Argininosuccinate lyase deficiency	ASA / ASL	Arginine	Yes
Arginase deficiency	ARG1	None	Secondary



* **Note**: some state NBS programs do report out low citrulline levels

NBS Identification - Sara

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- 6 DO female
- 1.5 day NICU stay for hypoglycemia
  - Given IV fluids and standard infant formula
- D/C home exclusively breastfeeding
- NBS: Citrulline = 516 umol/L
  - Cut-off <40
- No significant family history
- Evaluated in ED with concern for urea cycle disorder
- Diagnostic evaluation
  - Glutamine: 899 umol/L
  - Citrulline: 1,072 umol/L
  - Arginine: 30 umol/L
  - No ASA present

Poll Questions:

Respond in the right-hand panel in the live event – **Click 'SUBMIT' when done**

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What would you do for initial dietary management?

A. Nothing, follow and intervene if needed later.

B. Limit protein to DRI and add protein free modular to meet calorie needs

C. Initiate a small amount of EAA medical food (<0.5 g/kg)

D. Start UCD diet of 50% protein needs met by EAA medical food

NBS Identification

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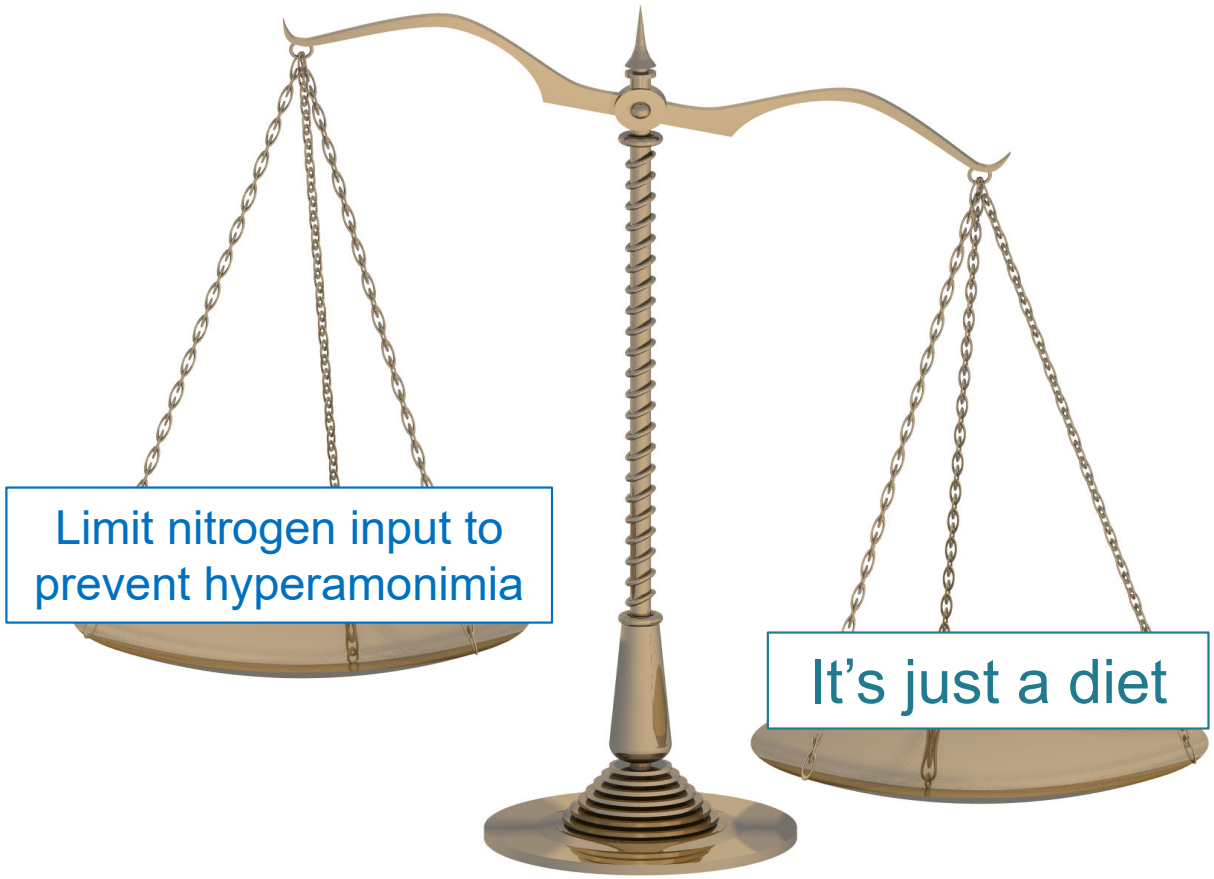
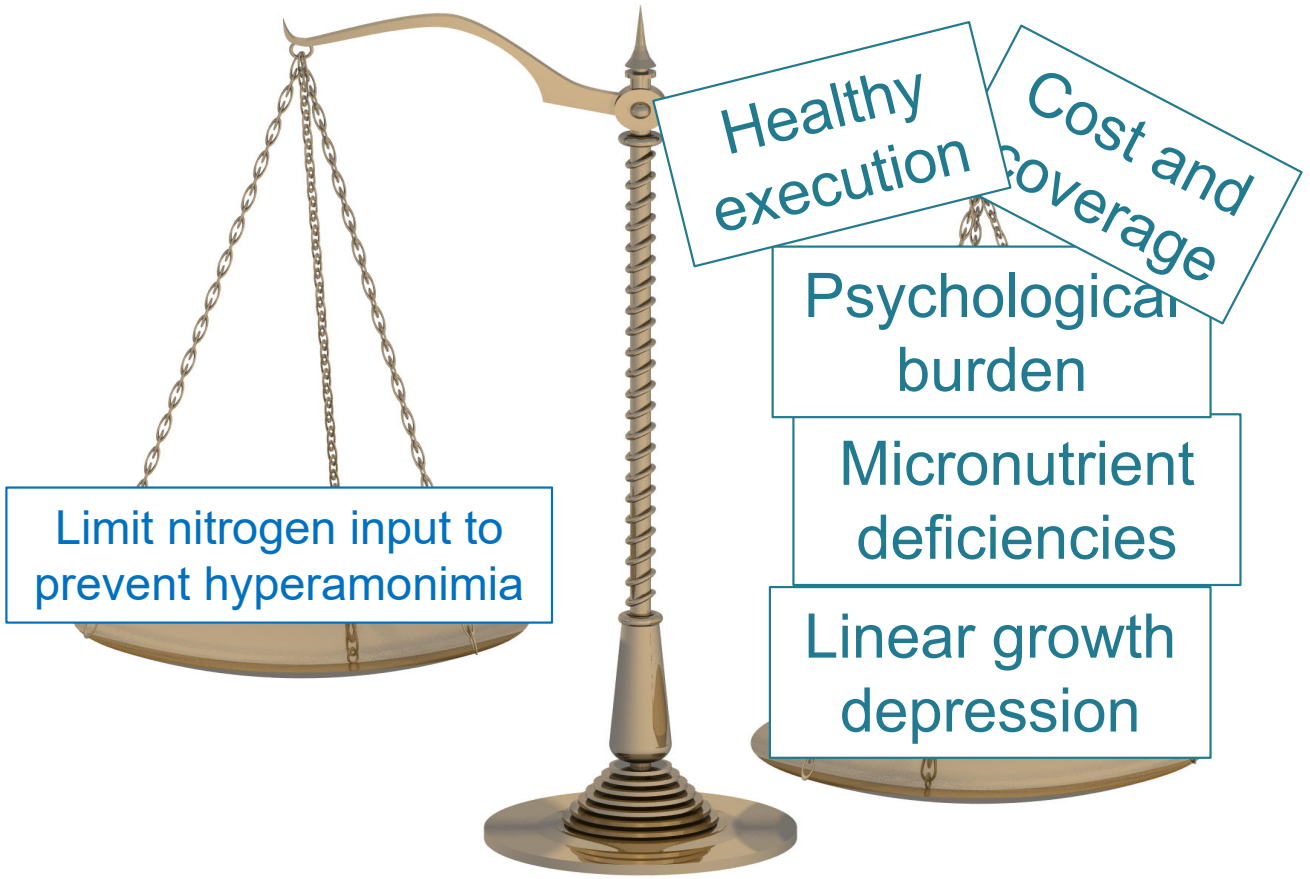
- No clear answer
  - Citrulline will never be normal in citrullinemia
  - Elevation in glutamine gives pause
- Started on medical food with essential amino acids
  - 0.7 g/kg protein EAA
  - 1.1 g/kg protein from breastmilk
    - Giving pumped breastmilk due to fear
    - Transitioned to feeding at the breast
- Following mutation analysis, illness without hyperammonemia, and stabilized glutamine, she was taken off EAA medical food and transitioned to vegetarian diet at 18 months

Dietary Intervention



Dietary Intervention



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Symptomatic Presentation

Newborn with hyperammonemia is transferred to your hospital.

Now what?

UCD Management Overview

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Diagnosis	Diagnosis	Supplements needed	RUSP	Degree of dietary restriction
N-acetyl glutamate synthase deficiency	NAGS	Citrulline	No*	None ◊
Carbamoyl phosphate synthase 1 deficiency	CPS1	Citrulline	No*	High
Ornithine transcarbamylase deficiency	OTC	Citrulline	No*	High
Argininosuccinate synthase deficiency / Citrullinemia	ASS	Arginine	Yes	High
Argininosuccinic aciduria / Argininosuccinate lyase deficiency	ASA / ASL	Arginine	Yes	Moderate
Arginase deficiency	ARG1	None	Secondary	High

* **Note**: some state NBS programs do report out low citrulline levels
◊**Note**: NAGS does not require protein restriction when managed with carglumic acid

Neonatal Presentation - Patty

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- Full term female admitted DOL 3 for poor feeding and inability to wake
  - Initial ammonia = 706, rose to 965
  - Glutamine 2000= umol/L; Citrulline= 6 umol/L
  - Elevated orotic acid
- Enteral nutrition support needed from the beginning
  - Initial protein: 0.8 g/kg from EAA medical food and 0.8 g/kg from pumped breast milk

Everyone gets a honeymoon

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- Stabilization in first 4 - 6 months
- Goal: promote appropriate growth while preventing hyperammonemia
- Follow glutamine and EAAs for guidance in protein prescription goals.
  - WHO protein requirement for < 6 months= 1.52 g/kg
  - May tolerate and require more after initial presentation and stabilization for growth

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Family History

Let the story guide you

Family History can Drive Management

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Liam

- NBS showed elevated ASA
- Initial PAA showed elevated GLN but ASA was not present
- Repeat urine AAs showed presence of ASA
- Older siblings tested, one found to be positive for ASA with normal development at age 5

Charlotte

- NBS showed elevated ASA
- Follow up PAA showed elevated GLN, citrulline and ASA
- Older siblings tested, one found to also have ASA.
- Sibling reported to have poor sleep, signs of hyperactivity, and differences from other siblings

Family History can Drive Management

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Liam

- Exclusively breastfed
- Started on 100 mg/kg arginine
- Followed closely during illness
- At age 11 GLN has remained normal on normal diet

Charlotte

- Exclusively breastfed
- Started on 100 mg/kg arginine + 250 mg/kg glycerol phenylbuterate
- Protein restricted to meet DRI
- Transitioned to vegetarian diet

UCD Management Overview

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Diagnosis	RUSP	Supplements needed	Presentation	Degree of dietary restriction
CPS1	No*	Citrulline	neonatal	High
			Late-onset/ NBS	Moderate
OTC	No*	Citrulline	neonatal	High
			Late-onset/ NBS	Moderate – low
ASS	Yes	Arginine	neonatal	High – moderate
			Late-onset/ NBS	Moderate – low
ASA / ASL	Yes	Arginine	neonatal	High
			Late-onset/ NBS	Moderate – low
ARG1	Secondary	None	neonatal	High
			Late-onset/ NBS	Moderate - high

* **Note**: some state NBS programs do report out low citrulline levels

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Babies don’t stay babies long!

Starting solids

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Considerations during toddler transition

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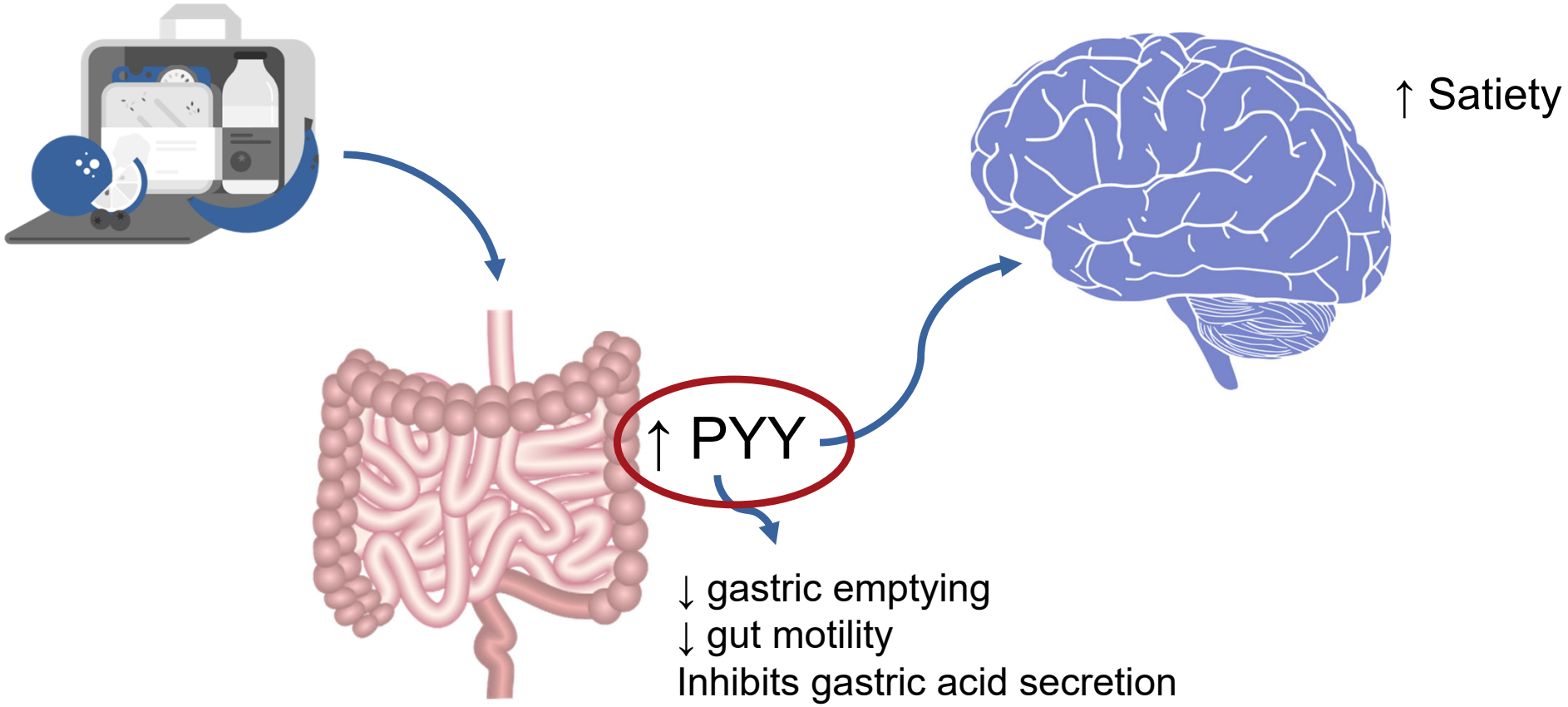
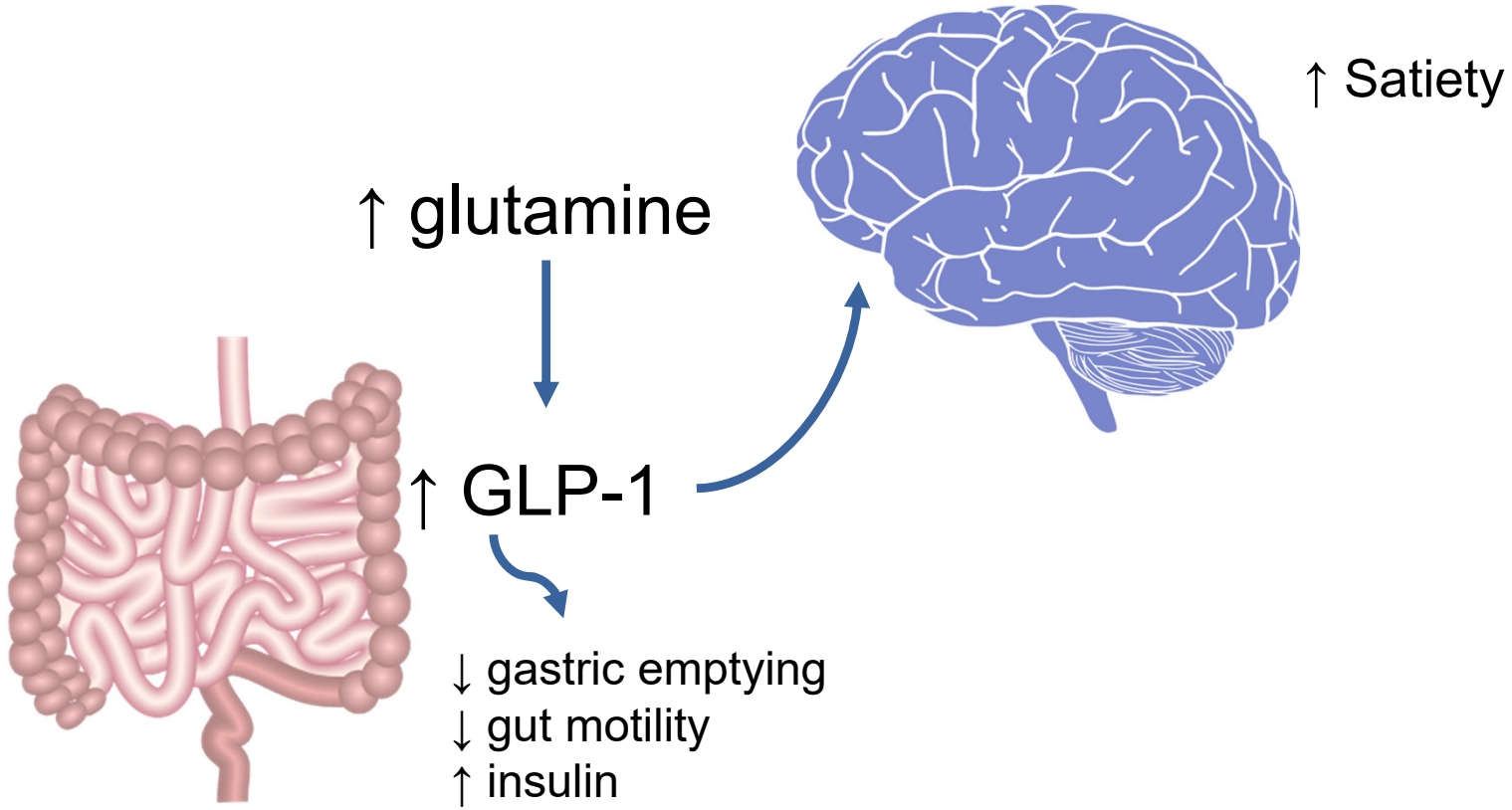
- Diagnosis and presentation
- Episodic history
- Current feeding status
- Set realistic goals and expectations
- “If they are hungry, they will eat” may not always work

Altered hunger/satiety signaling in UCDs



Mitchell S, et al; Mol Genet Metab. 2012 May;106(1):39-42

Altered hunger/satiety signaling in UCDs



Anderson, et al; Diabetes 2018;67:372-384

Toddler Transition of Protein

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- Sara (NBS identified)
  - Started with fruits and vegetables
  - Introduced high biologic value protein mindfully
  - Continued protein counting for first two years
  - Continues to be mindful of dairy and avoids other high protein foods

Toddler Transition of Protein - Patty

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8 months old

100% orally fed
4 -6 oz bottles

Takes additional protein free modular after 24 hour supply of formula

Solids
2 Tbs puree twice a day
Fruits and vegetables only

17 months old

3 years old

Toddler Transition of Protein - Patty

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8 months old

Formula – 23 oz

- EAA Infant Medical food
- Standard Infant formula
- Canola oil
- Sodium phenyl butyrate
- Citrulline

Provides

96% kcal needs in formula

1.3 g/kg total protein

- 0.7 g/kg EAA protein
- 0.5 g/kg protein (infant formula)
- 0.1 g/kg protein from food

17 months old

3 years old

Toddler Transition of Protein - Patty

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8 months old

Formula – 23 oz
- EAA Infant Medical food
- Standard Infant formula
- Canola oil
- Sodium phenyl butyrate
- Citrulline

Provides
96% kcal needs in formula
1.3 g/kg total protein
- 0.7 g/kg EAA protein
- 0.5 g/kg protein (infant formula)
- 0.1 g/kg protein from food

17 months old

100% orally fed
4 -6 oz bottles of formula

Solids
Prescribed 4-5 grams protein
Actual = 2 grams
Little interest in solids
1-2 T portions + ¼ cup grains

3 years old

Toddler Transition of Protein - Patty

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8 months old

Formula – 23 oz
- EAA Infant Medical food
- Standard Infant formula
- Canola oil
- Sodium phenyl butyrate
- Citrulline

Provides
96% kcal needs in formula
1.3 g/kg total protein
- 0.7 g/kg EAA protein
- 0.5 g/kg protein (infant formula)
- 0.1 g/kg protein from food

17 months old

Formula – 20 oz
- EAA Medical food
- 2.5 oz Whole Milk
- Protein free modular
- Sodium phenyl butyrate
- Citrulline

Provides
70% kcal needs in formula
1.3 g/kg total protein
- 0.6 g/kg EAA protein
- 0.3 g/kg protein (infant formula)
- 0.4 g/kg protein from food

3 years old

Toddler Transition of Protein - Patty

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8 months old

Formula – 23 oz
- EAA Infant Medical food
- Standard Infant formula
- Canola oil
- Sodium phenyl butyrate
- Citrulline

Provides
96% kcal needs in formula
1.3 g/kg total protein
- 0.7 g/kg EAA protein
- 0.5 g/kg protein (infant formula)
- 0.1 g/kg protein from food

17 months old

Formula – 20 oz
- EAA Medical food
- 2.5 oz Whole Milk
- Protein free modular
- Sodium phenyl butyrate
- Citrulline

Provides
70% kcal needs in formula
1.3 g/kg total protein
- 0.6 g/kg EAA protein
- 0.3 g/kg protein (infant formula)
- 0.4 g/kg protein from food

3 years old

G-tube placed
Formula by mouth with g-tube for backup
G-tube placement has greatly reduced stress around feeding
Started feeding therapy

Solids
Prescribed 3 grams protein
Eats a few pieces of crunchy snacks
Meets protein goal with smoothie drinks

Toddler Transition of Protein - Patty

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8 months old

Formula – 23 oz
- EAA Infant Medical food
- Standard Infant formula
- Canola oil
- Sodium phenyl butyrate
- Citrulline

Provides
96% kcal needs in formula
1.3 g/kg total protein
- 0.7 g/kg EAA protein
- 0.5 g/kg protein (infant formula)
- 0.1 g/kg protein from food

17 months old

Formula – 20 oz
- EAA Medical food
- 2.5 oz Whole Milk
- Protein free modular
- Sodium phenyl butyrate
- Citrulline

Provides
70% kcal needs in formula
1.3 g/kg total protein
- 0.6 g/kg EAA protein
- 0.3 g/kg protein (infant formula)
- 0.4 g/kg protein from food

3 years old

Formula – 26 oz
- EAA Medical food
- 4 oz Whole Milk
- Protein free modular
- Citrulline

Provides
75% kcal needs in formula
1.15 g/kg total protein
- 0.6 g/kg EAA protein
- 0.3 g/kg protein (milk)
- 0.2 g/kg protein from food

Quantity and Quality matter

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- Individuals with UCDs have been found to have a less diverse microbiome than those with PKU and controls[1]
- Avoidance of protein is common[2]

- Potatoes are not the most complete protein
- Encourage diversity within protein goals
  - Small French fries + salad
  - 3 T hummus + GF pretzels + veggies + olives
- Think outside the box
  - Varied grains
  - High arginine foods: grapes, peas, chickpeas
  - High citrulline foods: watermelon

1. Timmer C, et al.; Mol Genet Metab Rep.; 2021 Sep 8;29:100794
2. MacLeod E. (2020) In Bernstein LE, Rohr F, vanCalcar S (Eds) Nutrition Management of Inherited Metabolic Diseases (Chapter 16) Springer

References

- Ah Mew et al. Urea cycle disorders overview; GeneReviews 2017.
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- Haberle J, et al; J Inherit Metab Dis. 2019 Nov;42(6):1192-1230
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- MacLeod E. (2020) In Bernstein LE, Rohr F, vanCalcar S (Eds) *Nutrition Management of Inherited Metabolic Diseases* (Chapter 16) Springer

National Urea Cycle Disorders Foundation: **nucdf.org** -> Research App

Thank you!

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Thank you!

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Make sure you select 'All Panelists'

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access the survey at:
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