UREA CYCLE DISORDERS ECHO *The Essentials*

National Urea Cycle Disorders Foundation

Project ECHO®

Welcome

Session 3

The Importance of Diet

Erin MacLeod, PhD, RD, LD

Nicholas Ah Mew, MD

Children's National Hospital

Session 4: Long-term Management

Tuesday, November 11, 5-6:30 pm ET

Laura Konczal, MD, University Hospitals Cleveland Medical Center

UREA CYCLE DISORDERS ECHO

The Essentials

Session 3: Importance of Diet

The Essentials

Session 3 : The Importance of Diet

Time	Content
5 minutes	Introductions and housekeeping
60 minutes	Didactic presentations and case studies: Nicholas Ah Mew, MD and Erin MacLeod, PhD, RD, LD, Children's National Hospital
25 minutes	Group discussion

UREA CYCLE DISORDERS ECHO

The Essentials

- If possible, please make sure to keep your camera turned on
- ECHO is intended for educational purposes only
- Presenters cannot and will not provide medical advice
- To receive CME credit, please remain in the session and complete the evaluation form using the link that will be provided after the presentation

Welcome

Introduce yourself
in the chat

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Disclosures

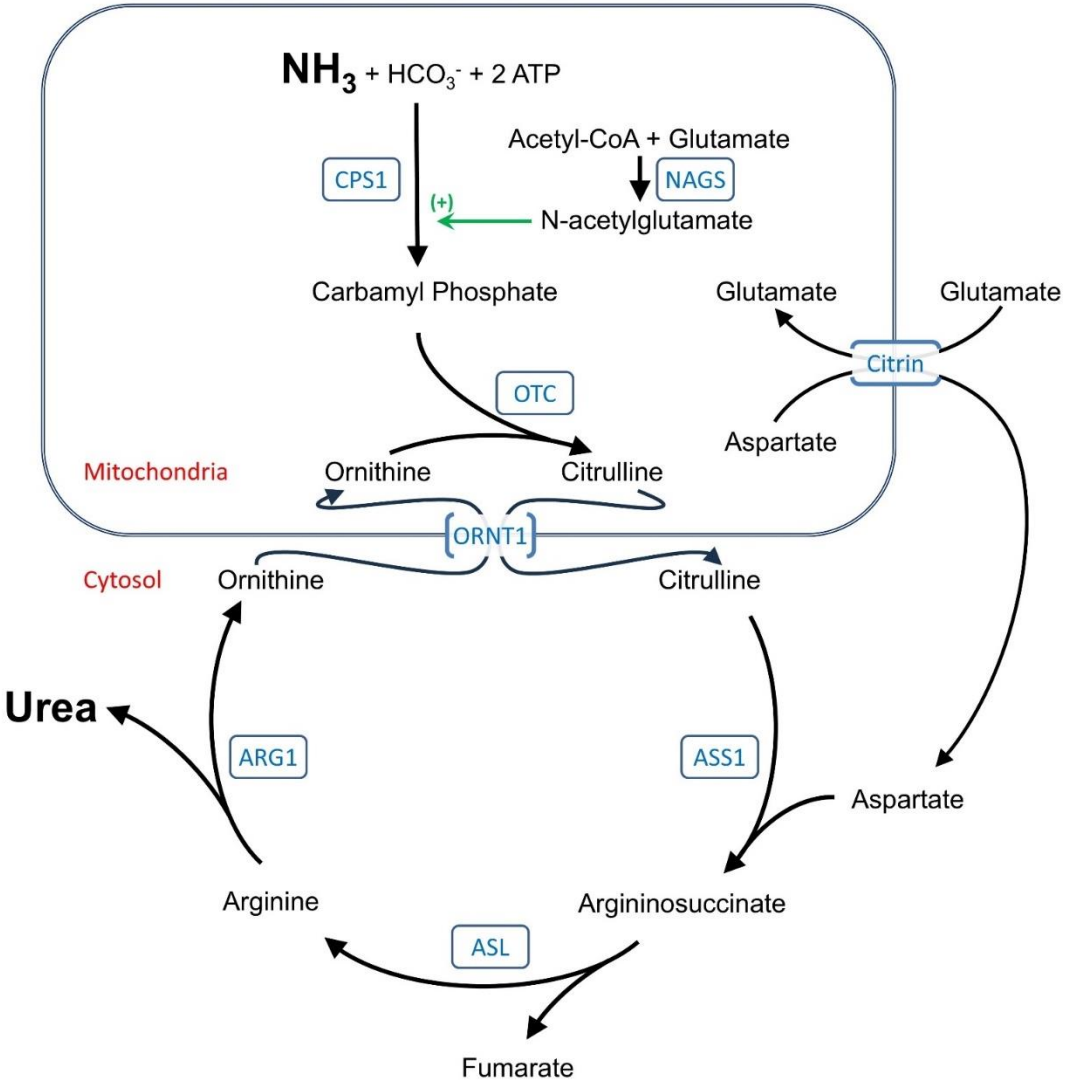
- ***Nicholas Ah Mew serves on the Data Monitoring Board of clinical trials conducted by iECURE and Arcturus, and is a consultant to Ultragenyx and Moderna***
- ***Erin MacLeod has participated in advisory boards for Amgen***

Objectives

- Understand primary principles of chronic UCD management
- Identify differences in management strategies for severe vs mild UCD cases
- Recognize differences in management between different UCD diagnoses

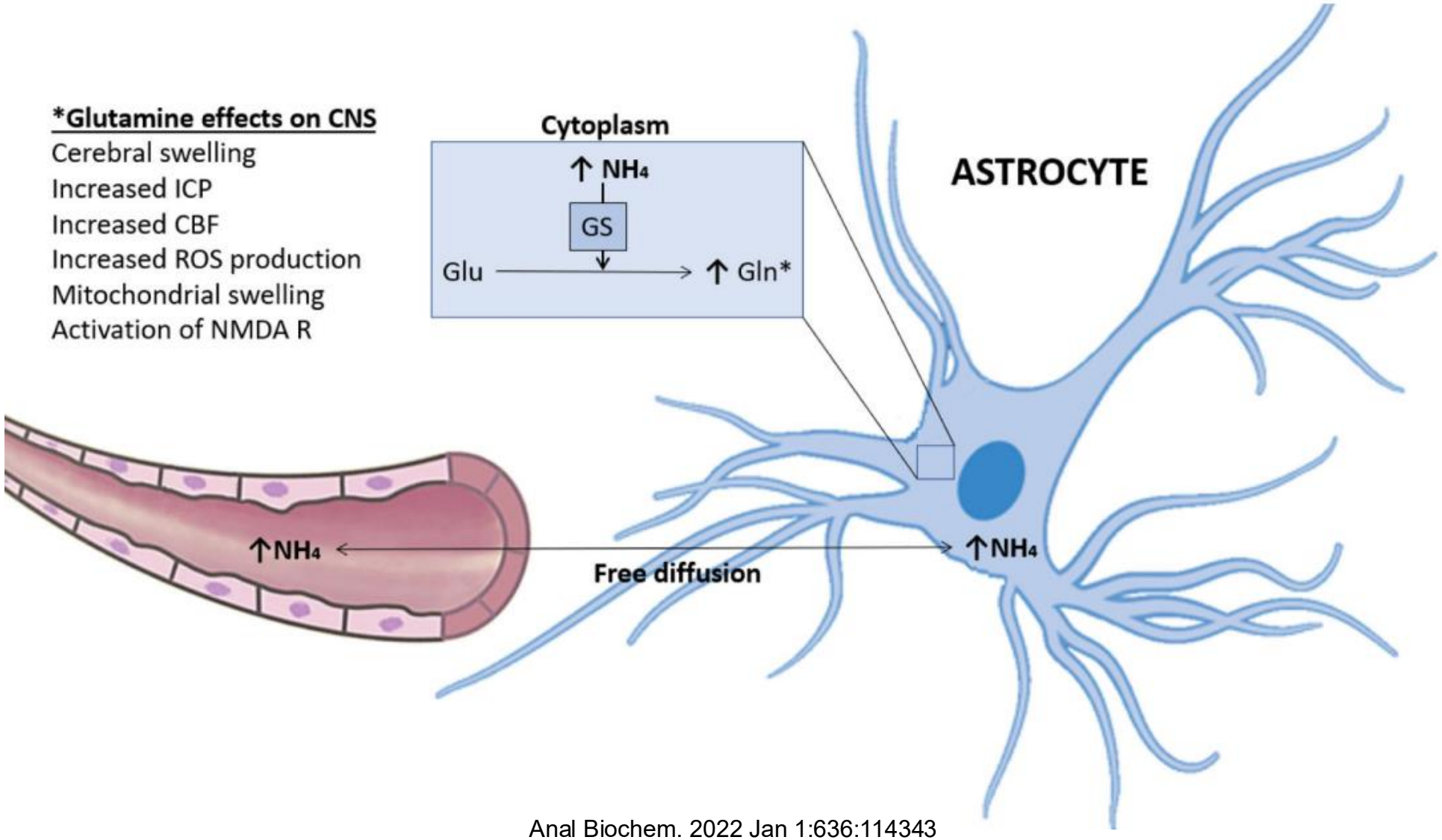
How many patients have you followed with a UCD?

The hepatic urea cycle



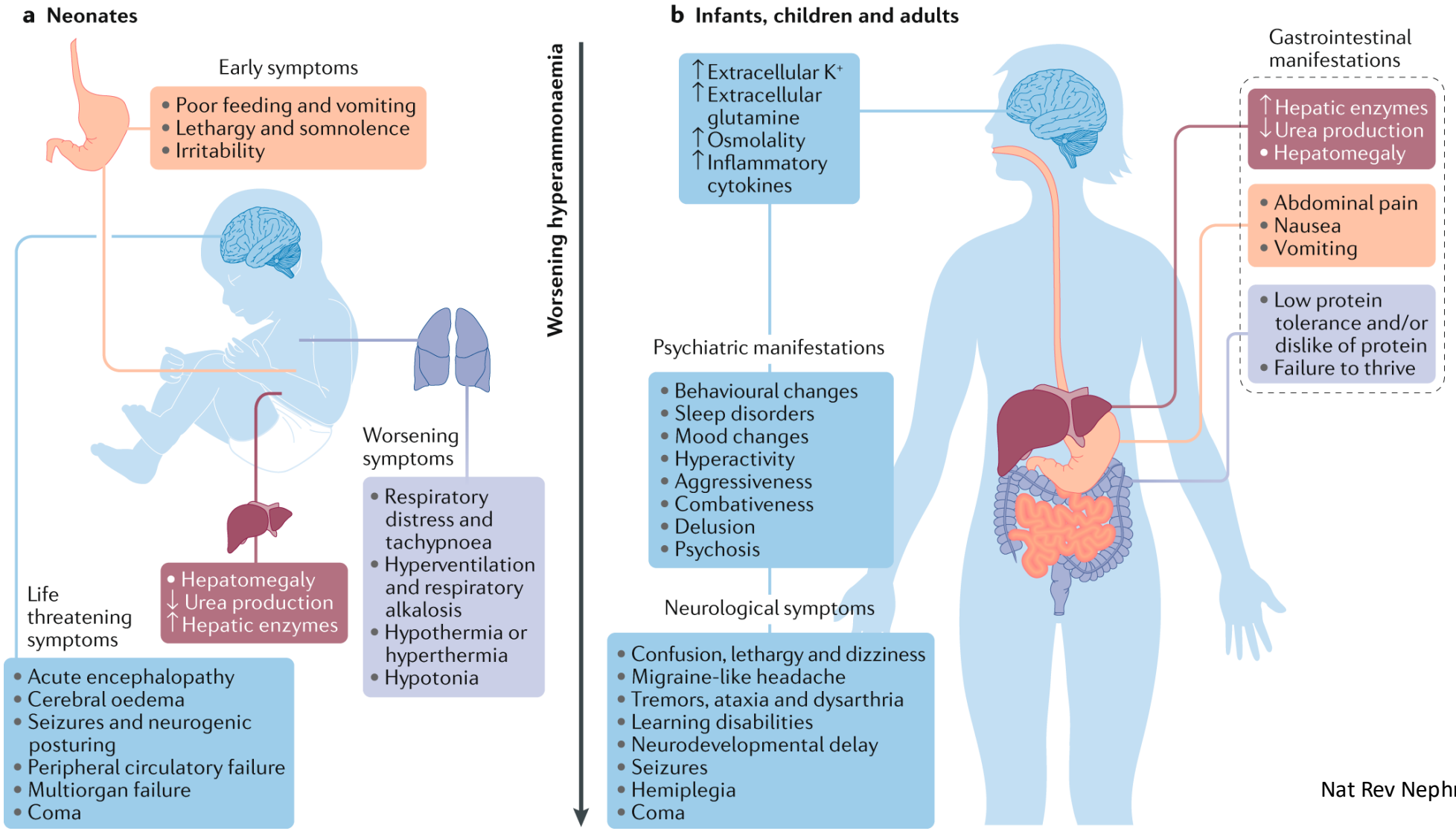
- The hepatic urea cycle converts ammonia (nitrogen) into urea
- The liver expresses all enzymes and transporters of the urea cycle
- A defect in any enzyme or transporter can cause a build up of ammonia

Hyperammonemia causes brain edema



Anal Biochem. 2022 Jan 1:636:114343

Features of acute hyperammonemia



Nat Rev Nephrol. 2020 Aug;16(8):471-482.

Residual enzyme activity predicts age of onset

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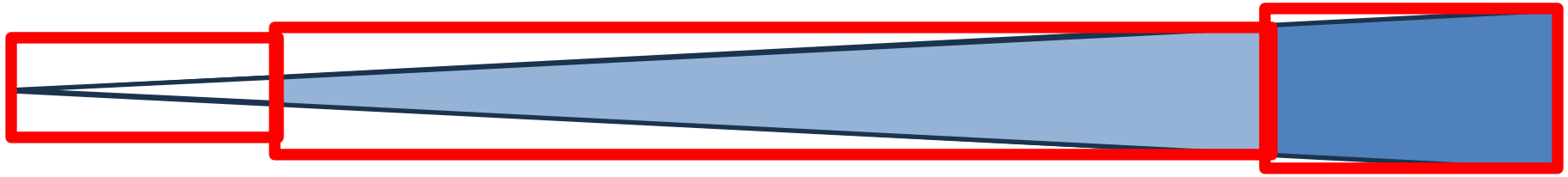
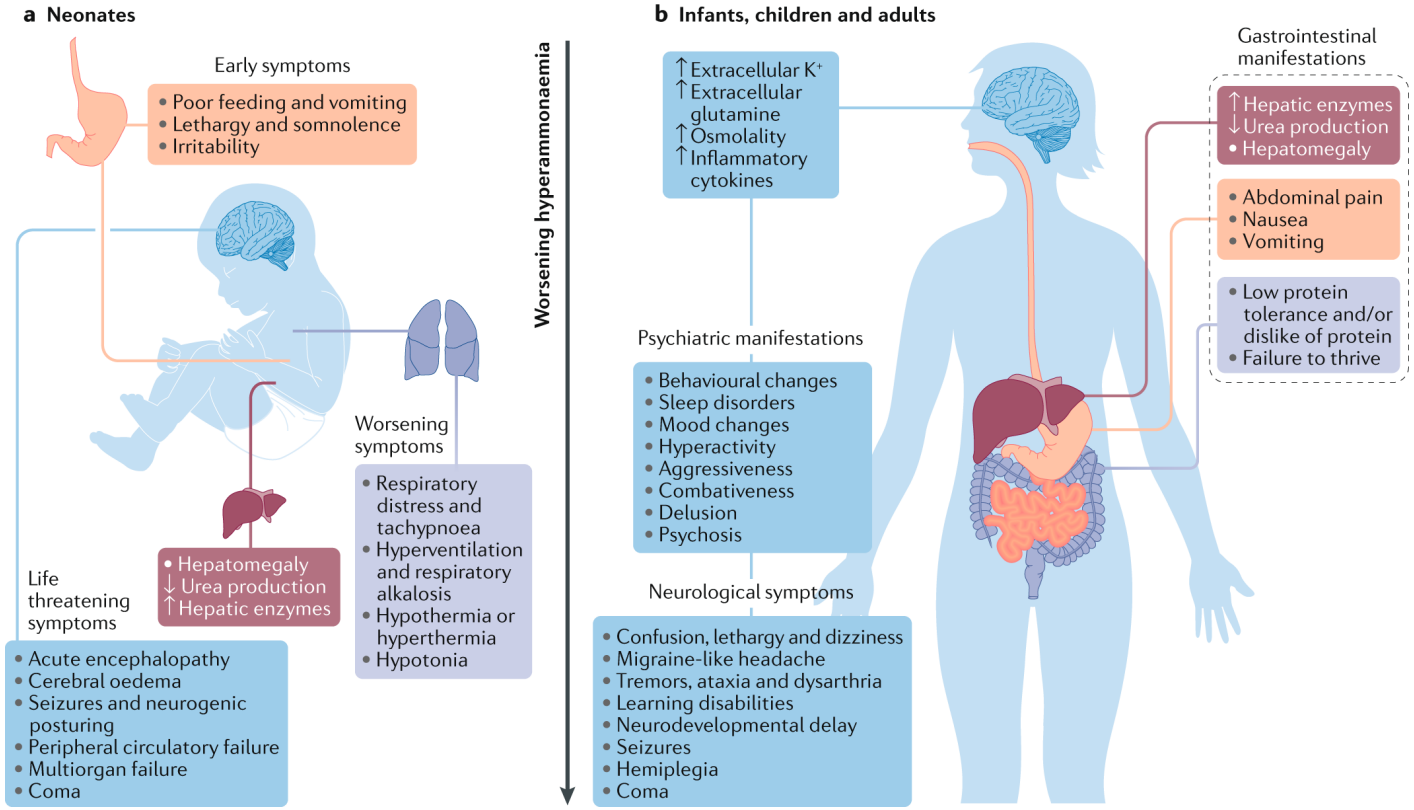
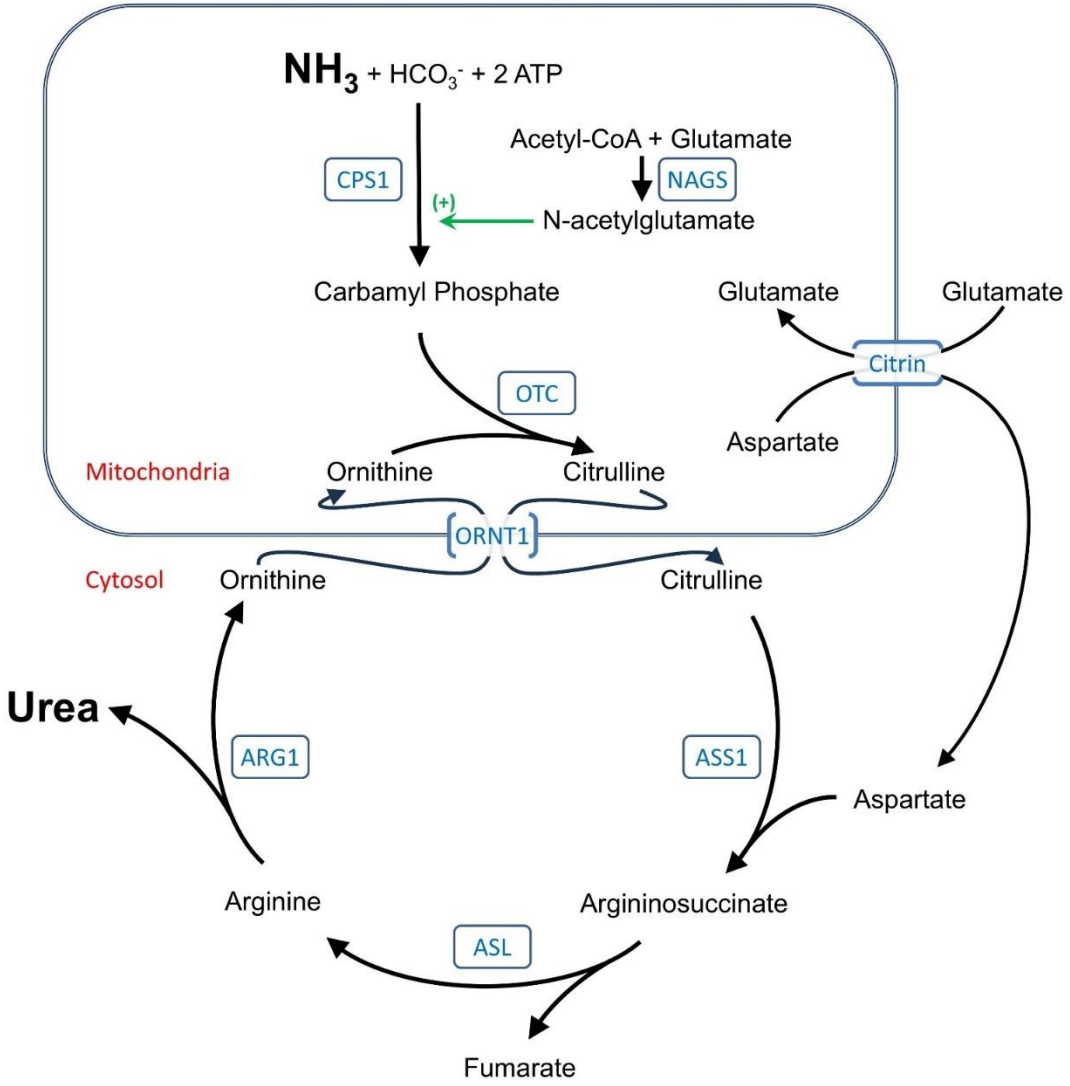
Absent urea cycle enzyme — Partial urea cycle enzyme activity — Normal enzyme activity



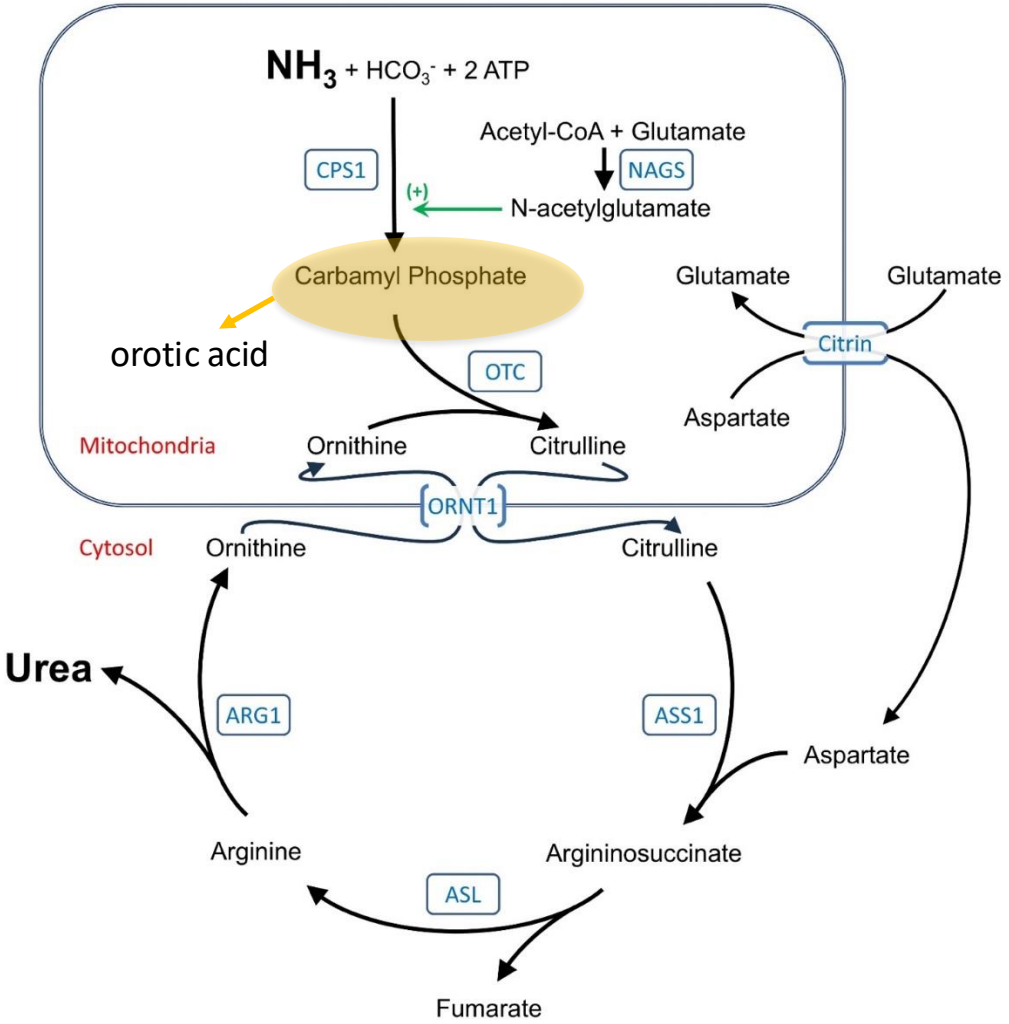


Urea Cycle Intermediates



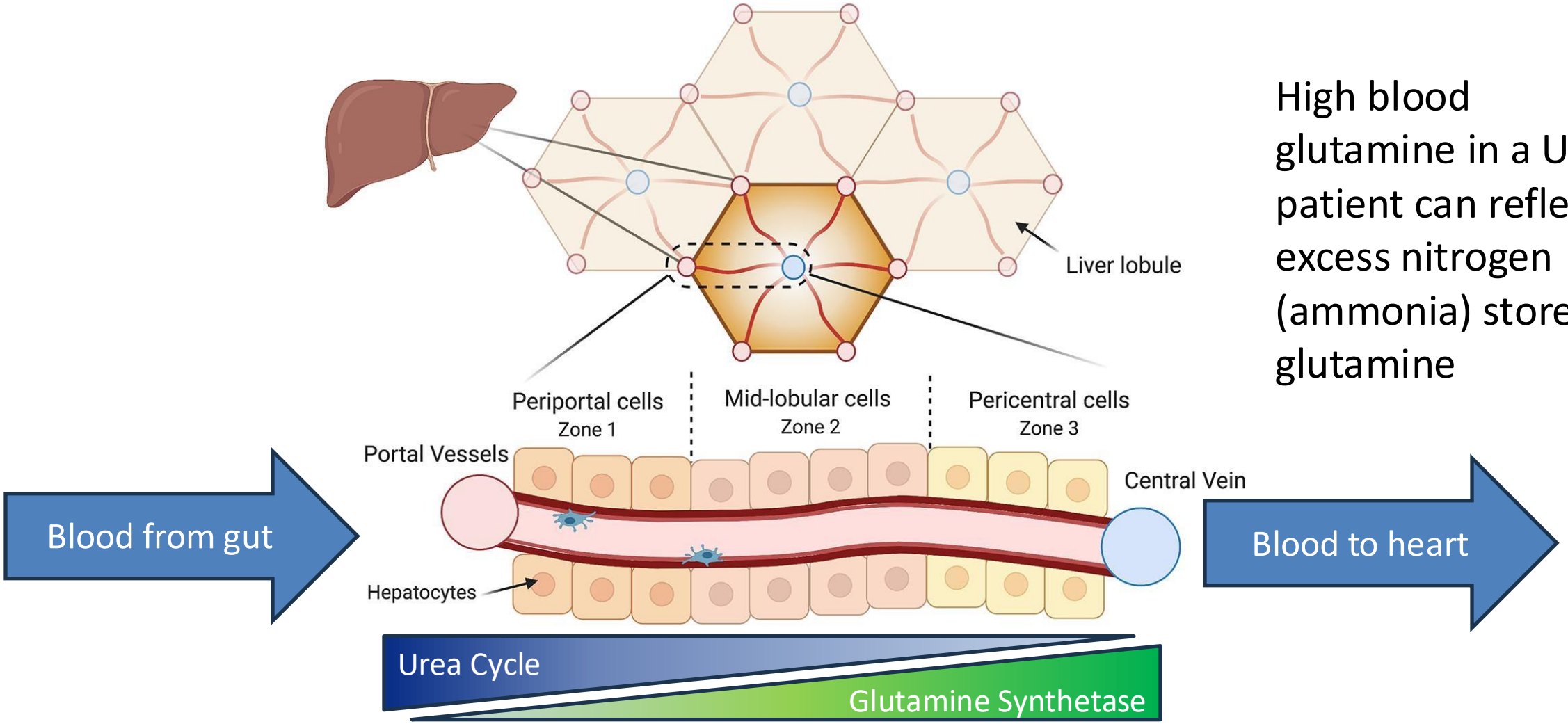
- If the hepatic urea cycle is functional, the urea cycle intermediates do not leave the hepatocyte
- If there is a urea cycle defect, metabolites upstream of the defect can leave the hepatocyte and enter the blood
- Some of these metabolites (e.g., arginine, argininosuccinate) may be toxic

Amino acid changes in UCDs



Defect	Abnormal amino acids
NAGS deficiency	↓ Citrulline ↓ Arginine
CPS1 deficiency	
OTC deficiency	
ASS1 deficiency (citrullinemia)	↑↑↑ Citrulline ↓ Arginine
Citrin deficiency	↑/**NL** Citrulline
ASL deficiency (ASA)	↑↑↑ Argininosuccinate ↑ Citrulline ↓ Arginine
ARG1 deficiency	↑↑ Arginine
ORNT1 deficiency (HHH)	↑↑ Ornithine ↓ Citrulline

Why is glutamine elevated?



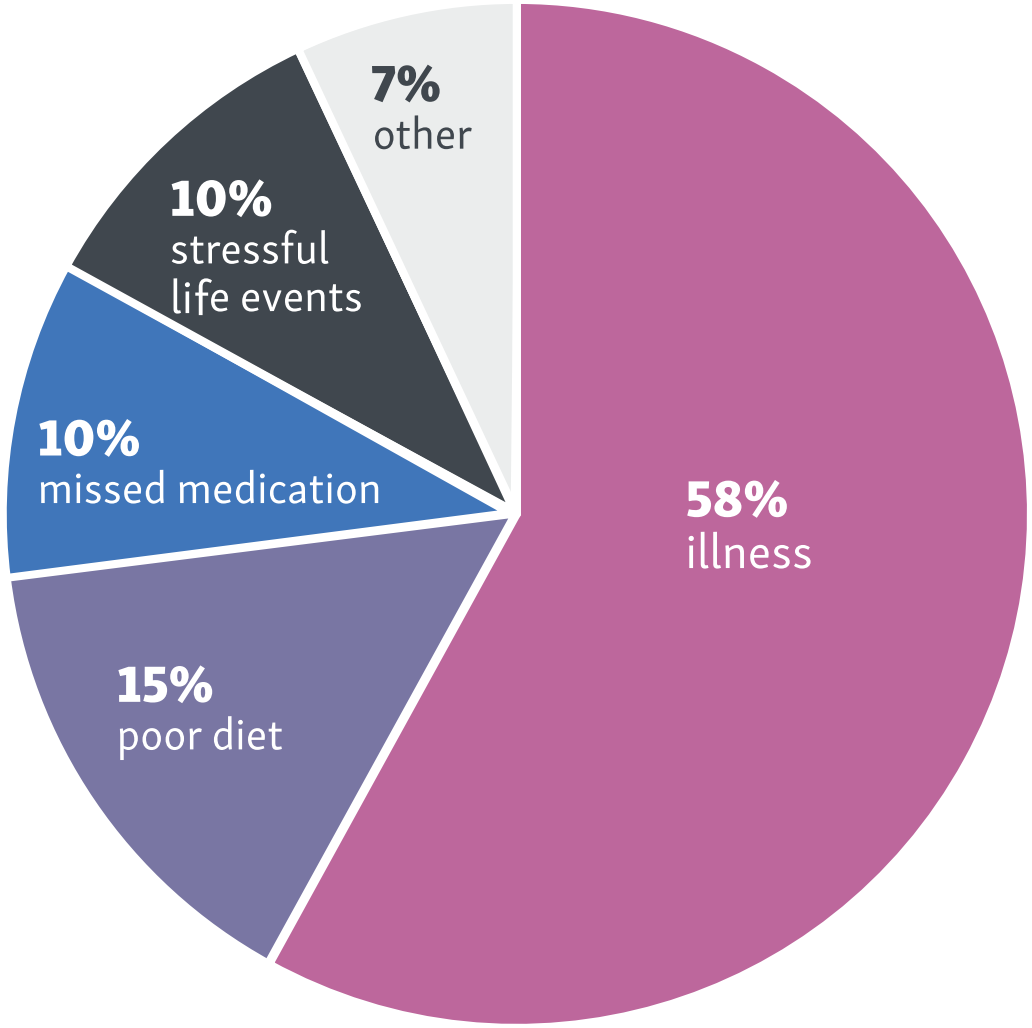
High blood glutamine in a UCD patient can reflect excess nitrogen (ammonia) stored as glutamine

Front Physiol. 2021 Sep 9:12:732929. doi: 10.3389/fphys.2021.732929

Goals of long-term management (Controlling the flow of nitrogen)

- Providing enough dietary protein for normal synthesis and growth
  - Monitoring glutamine, urea cycle intermediates and essential amino acids
- Providing enough other dietary nutrients for healthy living
  - Monitoring other essential nutrients
- Preventing episodes of acute hyperammonemia

Triggers of hyperammonemia



"Other"

- Prolonged fasting
- Surgery
- Gastric bypass
- Delivery/Postpartum
- Menses
- Medications
  - Corticosteroids
  - Valproic acid
  - Chemotherapy

https://www.highammonialevels.com/images/hyperammonemic-encephalopathy-triggers.svg

Acta Paediatr. 2008 Oct;97(10):1420-5.

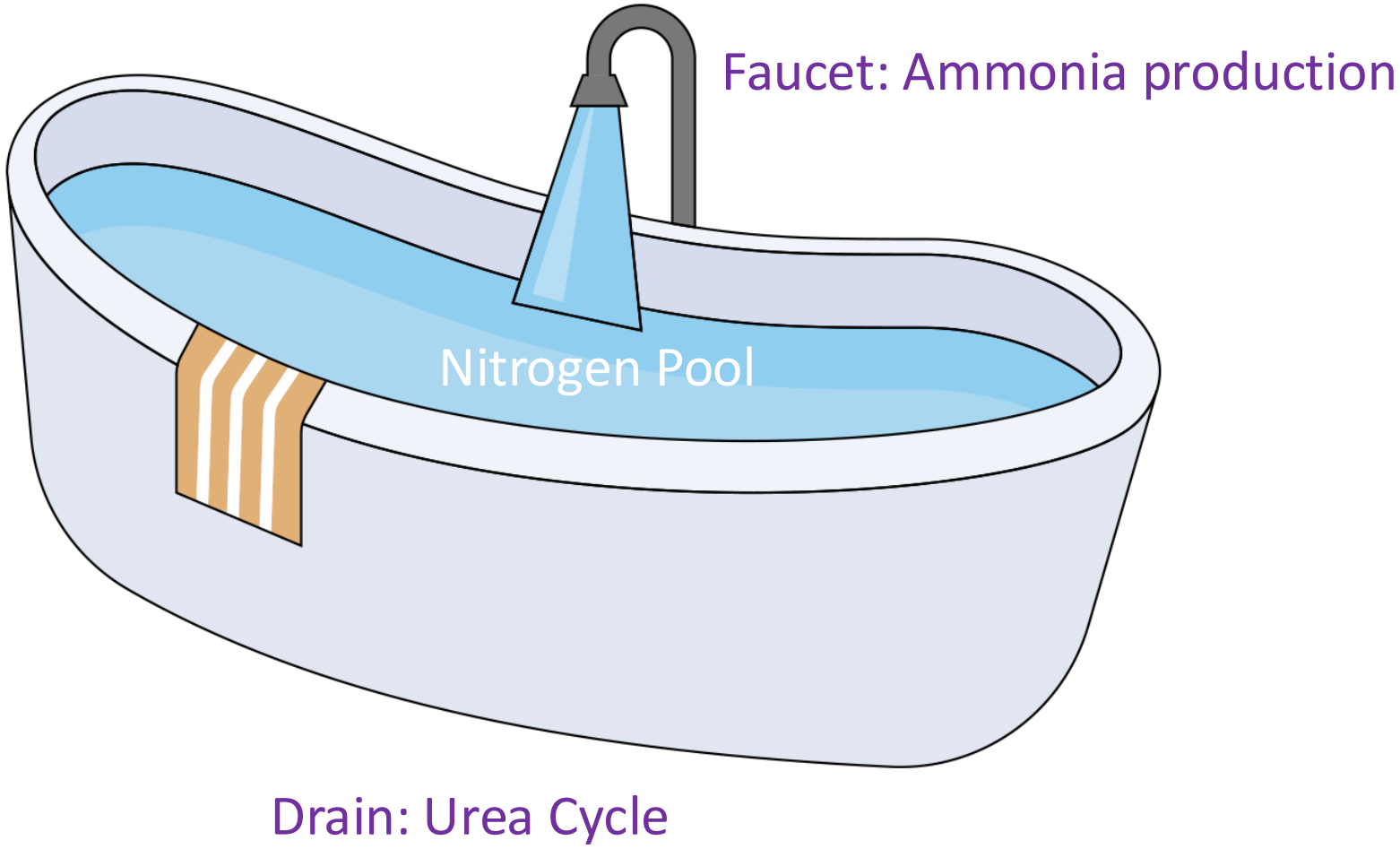
Preventing hyperammonemia

- Acute Illness:
  - ED letters – Acute management plan
  - Addition of protein-free calories (coordinated with medical team)
  - Aggressive fever management
  - Encouraging immunizations
- Avoiding fasting
  - IV fluids and preadmission for surgery or delivery
- Avoiding harmful medications
  - Medical chart alert (as allergies/reactions)
  - MedicAlert bracelet/necklace

High Risk Life Stages

- “Honeymoon Period” : 3-4 months after stabilization.
- Toddlers: Increased illness risk + inability to explain importance of diet.
- Prepubertal Growth Spurt: Challenge consuming adequate protein for support increased growth, combined with adolescent rebellion.
- Post-Puberty Growth Slowdown: Hormonal fluctuations
- Adult Weight Loss: weight loss is a catabolic process.
- Pregnancy/ Delivery: High protein demand and delivery risks.

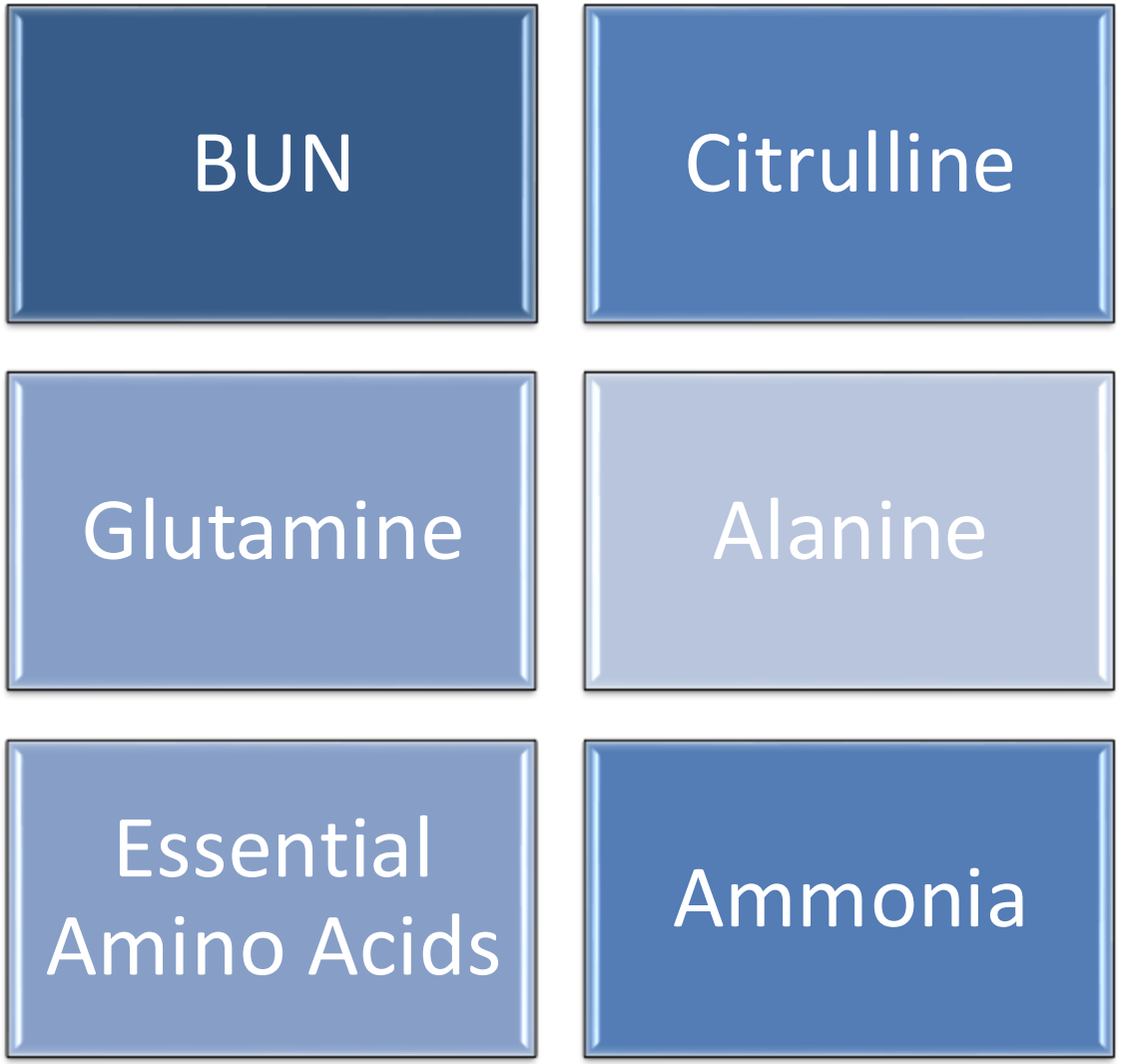
Management of UCDs- An overflowing bathtub



Adding a little Drano

- Case Example #1
  - Elevated Citrulline on NBS of 720 umol/L
    - DLO 4: Citrulline = 1,701 umol/L, Glutamine= 850 umol/L
  - Molecular testing found two mutations in ASS1, one severe one seen in neonatal and late onset citrullinemia
  - Exclusively breast fed female

Biochemical Markers to Inform Decisions

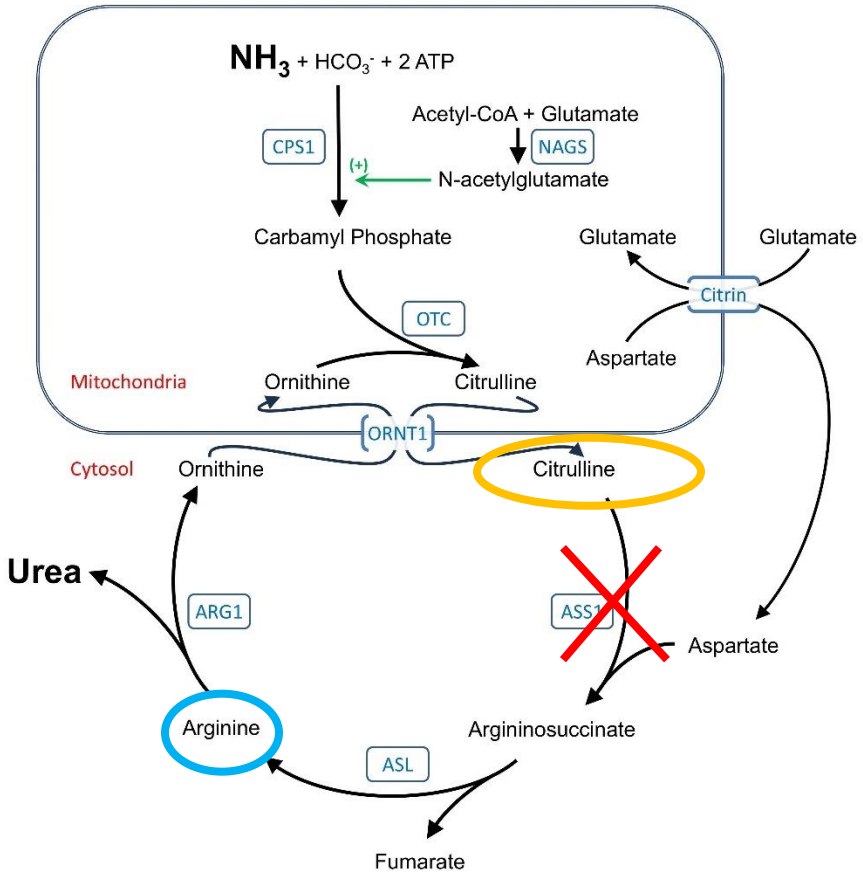


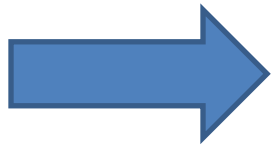
Adding a little Drano

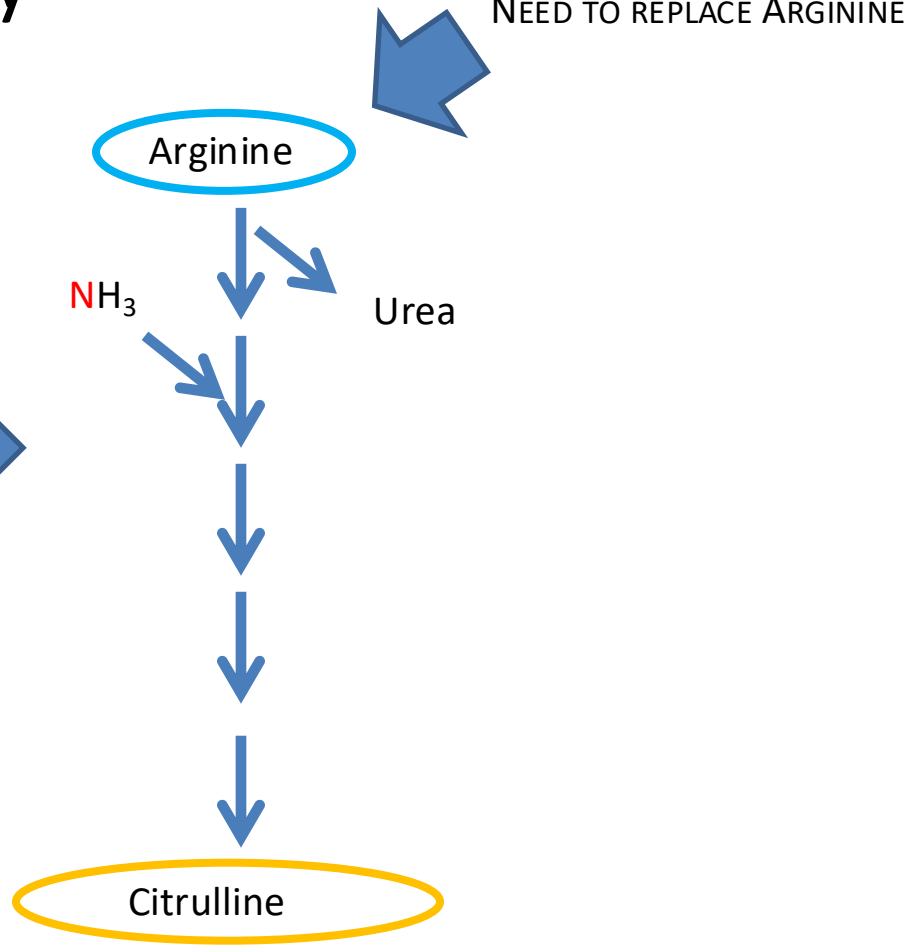
- Case Example #1
  - –Elevated Citrulline on NBS of 720 umol/L
    - DLO 4: Citrulline = 1,701 umol/L, Glutamine= 1,000 umol/L
  - – Molecular testing found two mutations in ASS1, one severe one seen in neonatal and late onset citrullinemia
  - –Exclusively breast fed female
  - – Supplemented with L-arginine (150 – 175 mg/kg)
  - – Unrestricted vegetarian diet (2.5 – 2.9 g/kg from age 18 mo – 3 y)
    - Glutamine: < 600 umol/L
    - Citrulline: 600 – 1,300 umol/L

Arginine Supplement - Citrullinemia

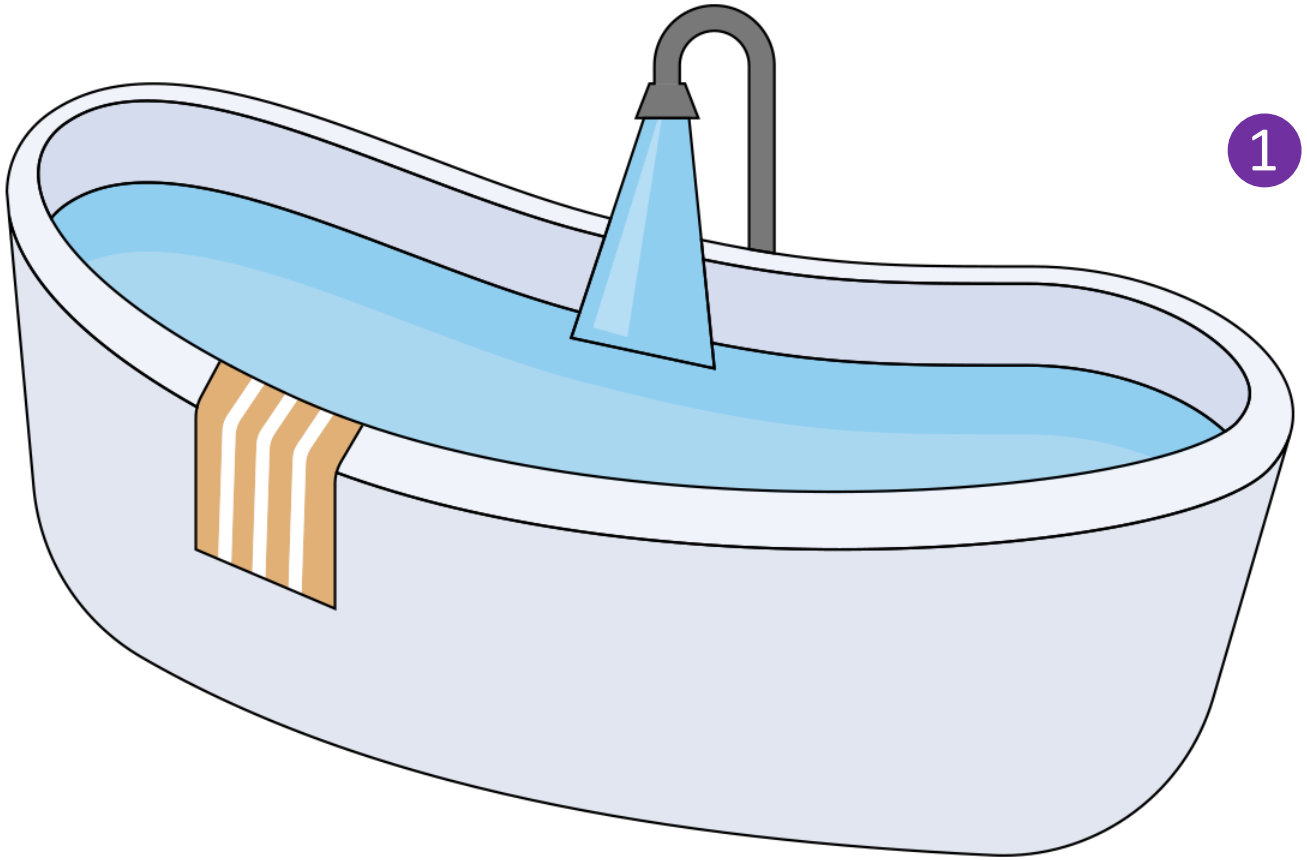
Urea cycle becomes a linear pathway







Management of UCDs- An overflowing bathtub



1. **Turn down the faucet**
   Reduce Influx
   - Protein Restriction
   - Anabolism

Turning down the faucet(s)

Exogenous proteins (i.e., diet)

Endogenous proteins
(i.e., body proteins)

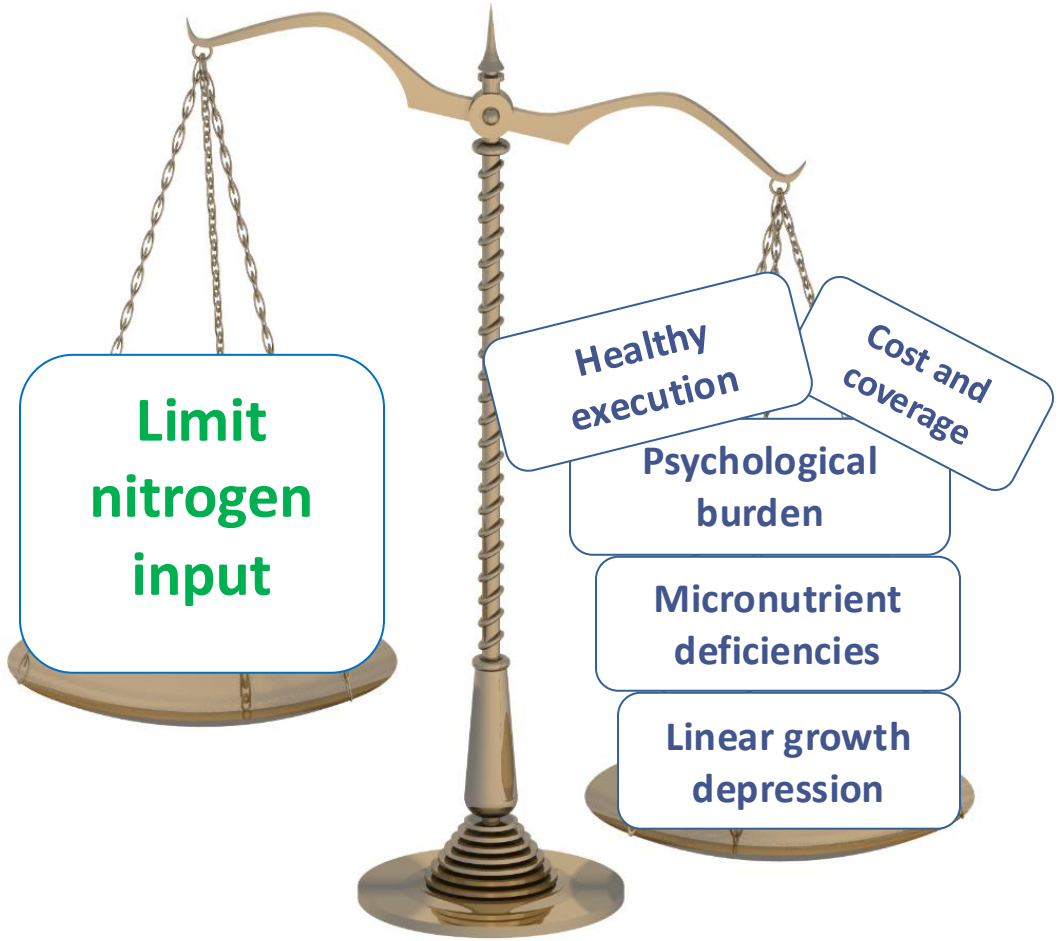
Medical Food Options

Complete EAA Formulas

Incomplete EAA Formulas

Protein Free Formulas

Diet is not without risks



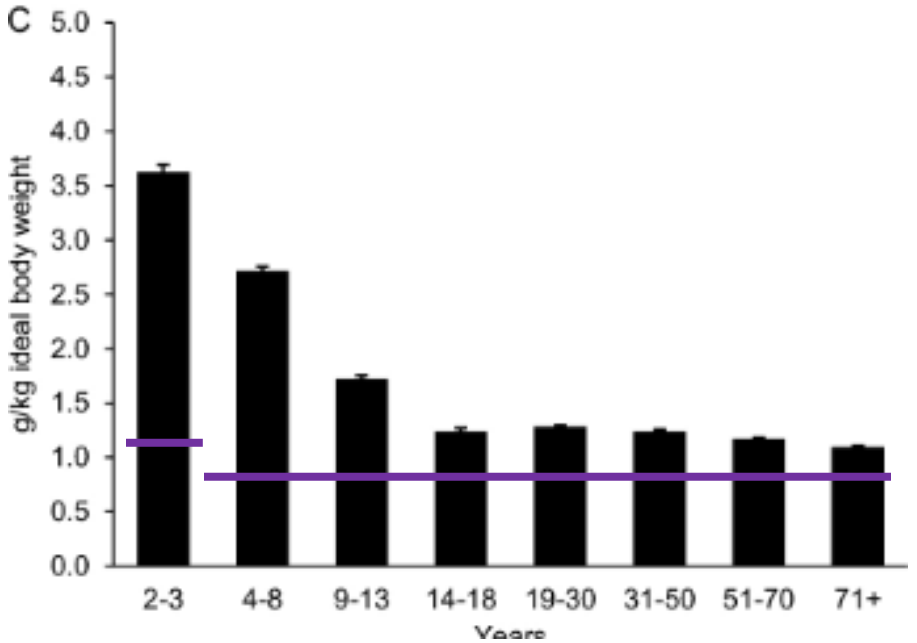
Protein Needs

40 yo F 68 kg 170 cm	WHO= 47.6 g 10%kcal = 50 g

40 yo M 80 kg 183 cm	WHO= 56 g 10%kcal = 63.5 g

Age	WHO g/kg	DRI g/kg	AMDR (% kcals)
Infants	1.1 – 1.7	1.0 – 1.5	N/A
1-3 years	0.8	0.9	5 - 20 %
4-8 years	0.7	0.8	10 - 30 %
9-13 years	0.7	0.8	10 - 30 %
14-18 years	0.7	0.7	10 - 30 %
Adults	0.7	0.7	10 - 35 %

Average protein intake in America by age is higher than WHO requirements



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

Protein Goals for 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

Consider the diagnosis

- Neonatal OTC-D/CPS1
- Arginase
- Citrullinemia *
- Late onset OTC-D
- ASL Deficiency *
- HHH
- NAGS

* Neonatal presenting ASL-D and citrullinemia will require more protein restriction than presymptomatic diagnosis

Turn down the faucet

- Case Example #2 –
  - –Elevated Citrulline on NBS of 516 umol/L
    - DLO 6: Citrulline = 1,072 umol/L, Glutamine= 899 umol/L
  - Maintained on L-arginine (100 mg/kg)
  - Protein free formula added to support calories and growth
  - Vegetarian diet to provide 1.5 - 2 g/kg protein
    - Family counted high protein foods

Protein: Quantity – QUALITY – Composition

Remember importance of quantity AND quality

- –Small French Fries + Salad
- –Fruit + 2 oz yogurt + 2 T granola
- –3 T hummus + GF pretzels + veggies + olives
- –1 T nut butter + banana

3.5 – 4.5 g protein and 150 – 200 kcals

Protein: Quantity – QUALITY – Composition

Other foods to consider:

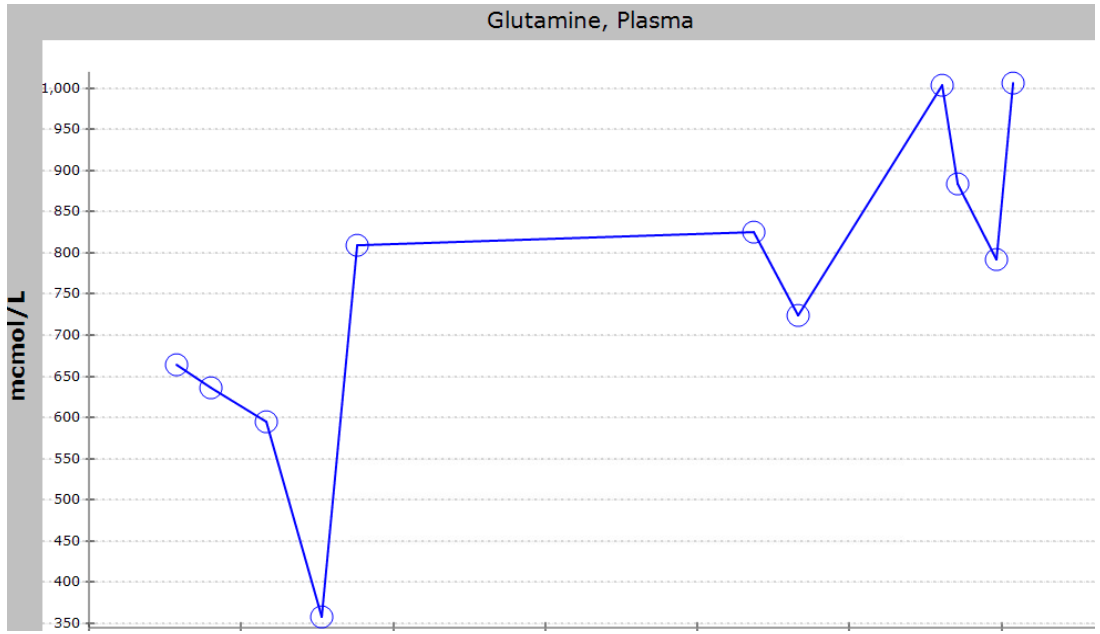
- Alternative grains
  - Barley, farro, quinoa, bulgur
- High arginine foods: grapes, peas, chickpeas
- High citrulline foods: watermelon
- Foods high in nitric oxide: beets, celery

Vegetarian Products:

- Not always a lower protein alternative

Turn down the faucet more?

- Case Example #2
  - Continued on vegetarian diet
  - Had a preference for cheese/eggs
  - Watched portions and intake closely
  - Decreased goal to DRI for age, sampled EAA medical food



Management of UCDs – Bailing out water

1 **Turn down the faucet**

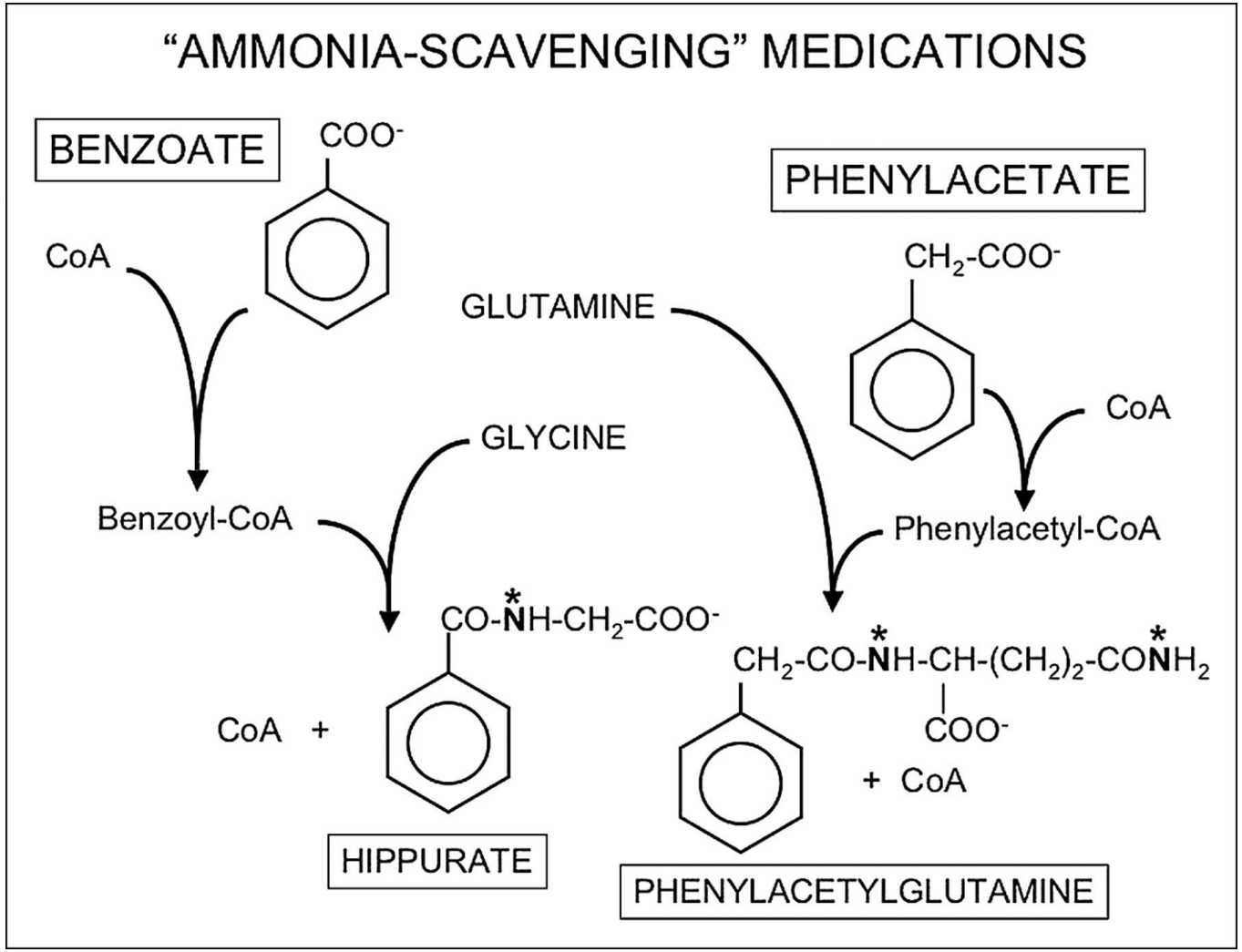
Reduce Influx

- Protein Restriction
- Anabolism

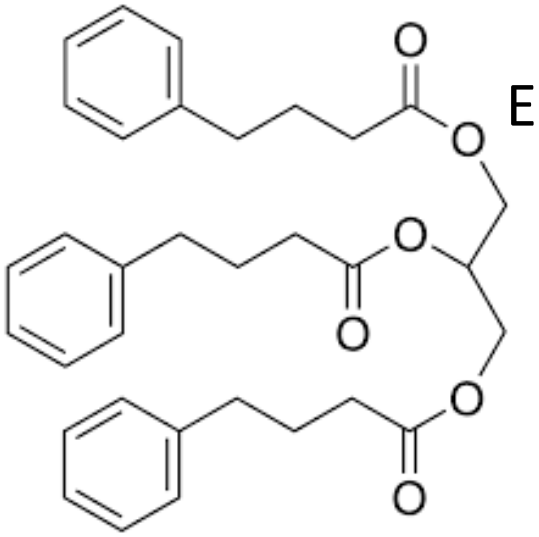
2 **Use a bucket to bail out**

- Nitrogen scavengers

Alternative Pathway Medications

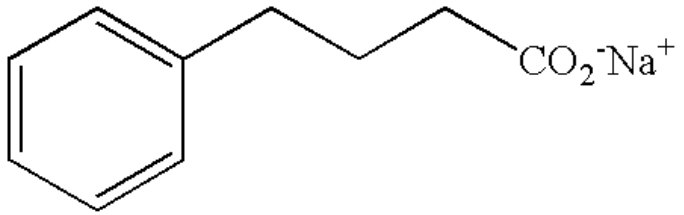


Phenylbutyrate and Glycerol Phenylbutyrate



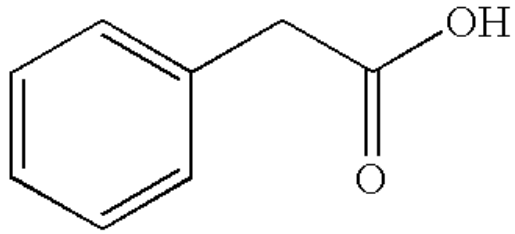
Glycerol Phenylbutyrate

Ester Hydrolysis



Phenylbutyrate

Beta Oxidation



Phenylacetic acid

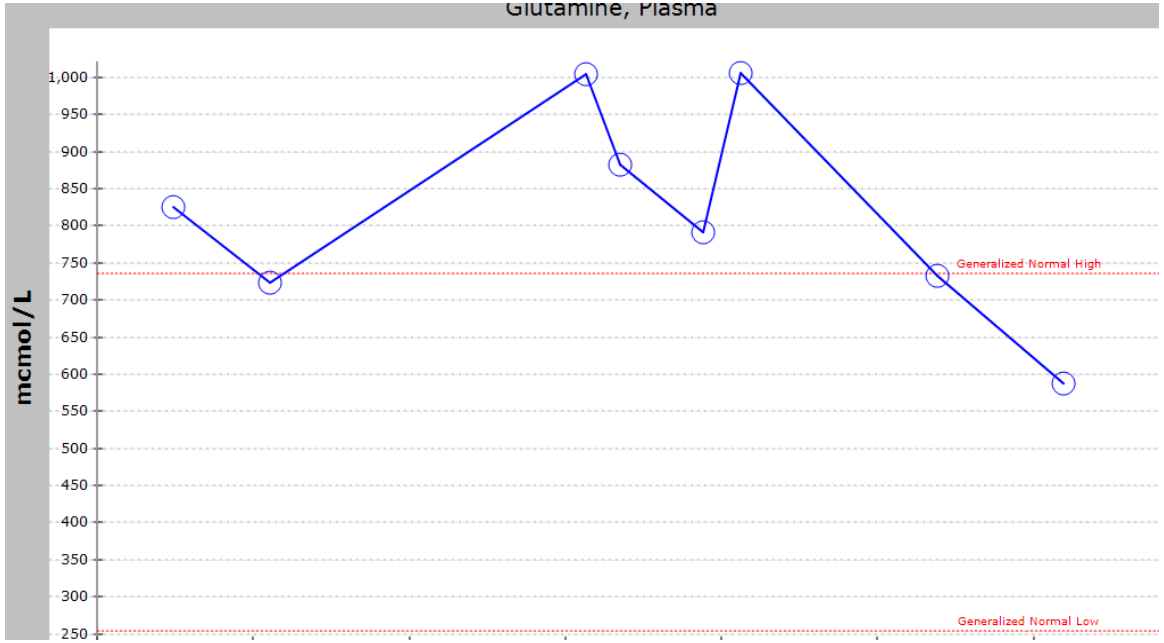
Why diet is so important!

- Scavengers work stoichiometrically: 1 mol of glycerolphenylbutyrate (GPB) optimally eliminates 6 mol of nitrogen
- GPB is 530.7 g/mol, nitrogen is 14.0 g/mol, and assuming protein is 16% nitrogen then:
- 1 ml GPB optimally eliminates the equivalent of 1.089 g of protein worth of nitrogen
- A maximum daily dose of 17.5 ml GPB = 19.1 g of protein worth of nitrogen or about:

(and most people can eat more than that)

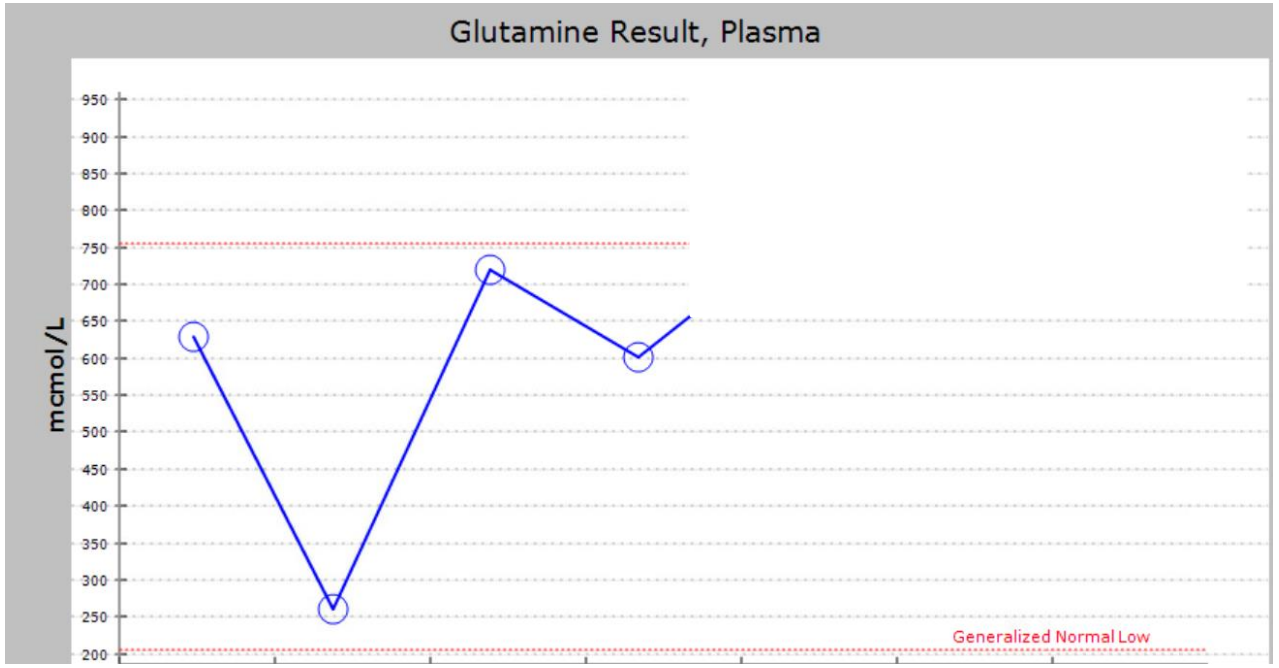
Changes in management

- Case Example #2
- Added glycerol phenylbutyrate
  - GOAL: improve glutamine, increase dietary protein tolerance



Family History of OTC (Case #3)

- Uncle presented at age 60 with a metabolic crisis
- Original biochemical workup was normal
- CIT 15 – 24 umol/L (ARG 40 – 60 umol/L)
- Diet analyzed yearly, never excessive in protein intake
- A second uncle passed away due to metabolic crisis
- Followed glutamine yearly



Why not always scavengers:

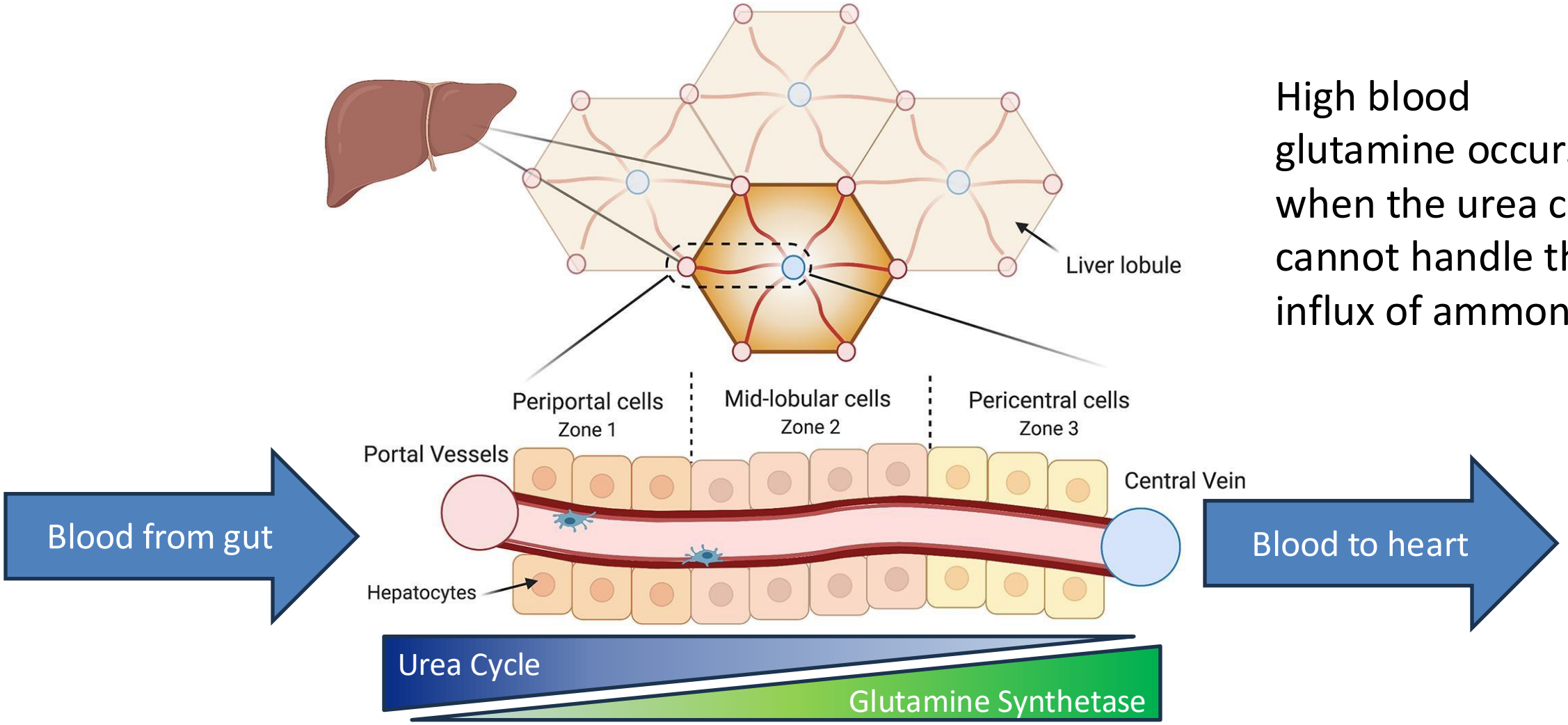
When scavengers were given to healthy adults (1914) or individuals with renal failure (1982), urinary urea went **down**!

Why?

This makes sense: in an individual in neutral nitrogen homeostasis, elimination of nitrogen via an alternative pathway must result in compensatory reduction in urea production

J Biol Chem. 1914;18:2
J Pharmacol Exp Ther. 1982 Sep;222(3):572-5

Remember:



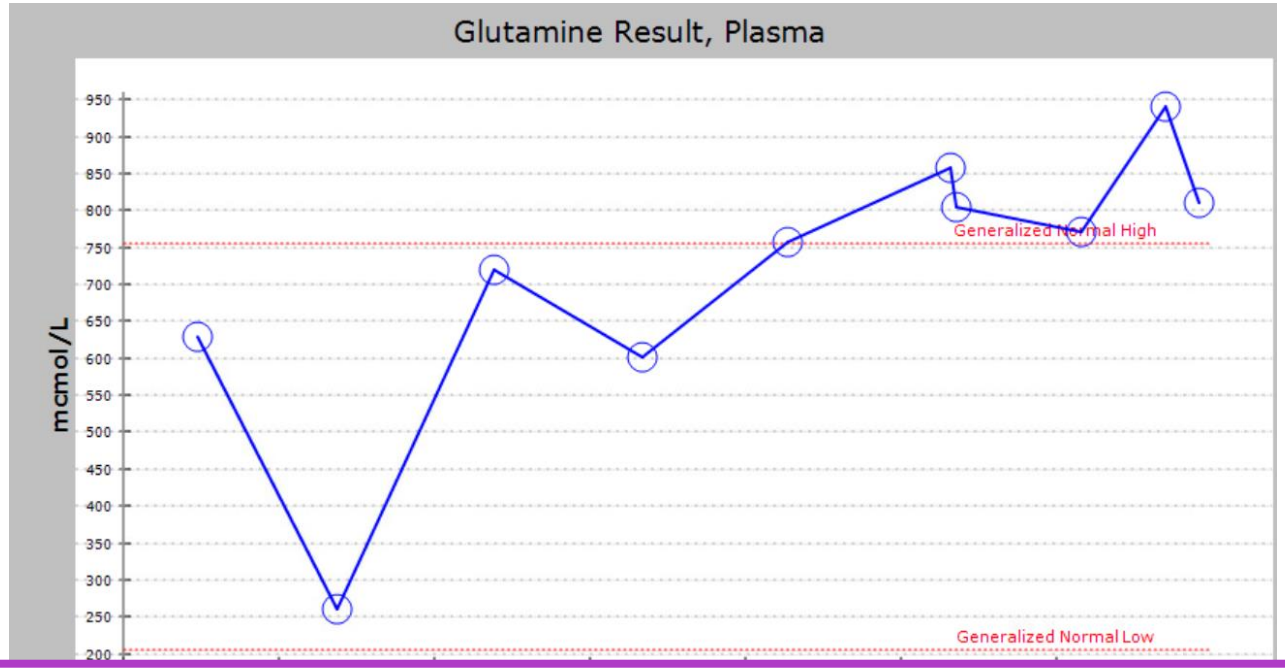
High blood glutamine occurs when the urea cycle cannot handle the influx of ammonia

Front Physiol. 2021 Sep 9:12:732929. doi: 10.3389/fphys.2021.732929

Family History of OTC (Case #3)

- Uncle presented at age 60 with a metabolic crisis
- Original biochemical workup was normal
- CIT 15 – 24 umol/L (ARG 40 – 60 umol/L)
- Diet analyzed yearly, never excessive in protein intake
- A second uncle passed away due to metabolic crisis
- Followed glutamine yearly and saw trending upward values

Increasing Plasma Glutamine over 6 years



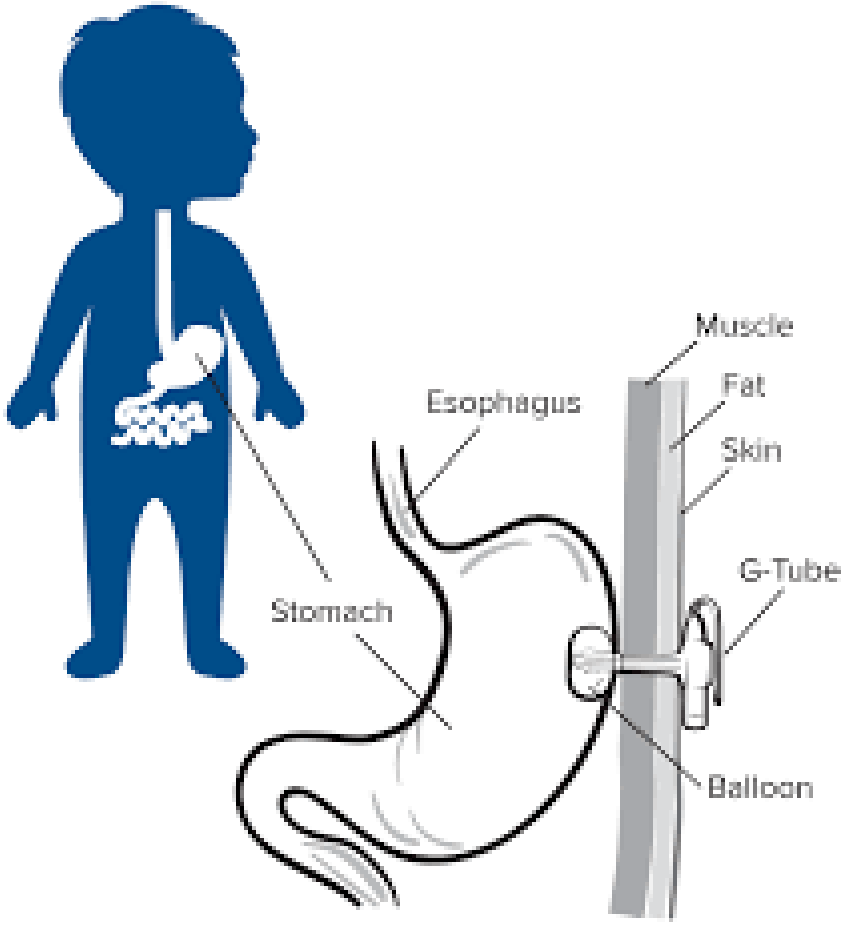
Started on Glycerol Phenylbutyrate

Call in the plumber – Case #4

- Presented on DOL 4 to an outside ED
  - Lethargic, hypothermic
  - Initial ammonia >925 mcmol/L
- Biochemical presentation
  - Peak ammonia 1677 mcmol/L
  - Glutamine 3,989 mcmol/L
  - Citrulline Undetectable
  - Arginine 14 mcmol/L
  - Orotic Acid 0 mg/g UCr
  - BUN 4 -> 1 mg/dL

- Diagnosed with presumptive NAGS/CPS1
- Following initial stabilization with dialysis, IV ammonul, carglumic acid, started on PO sodium phenylbutyrate
- Initially given IV arginine, transitioned to PO citrulline
- Started on NG / PO feeds with 0.84 g/kg protein from EAA and 0.85 g/kg natural protein (pumped breastmilk)
- Diagnosed with CPS1 deficiency, carglumic acid discontinued
- Gastrostomy tube placed

Gastrostomy Tube



- Permits consistent and adequate administration of diet and medications
  - This may prevent one or more hospital visits
- Can be easily removed when no longer used

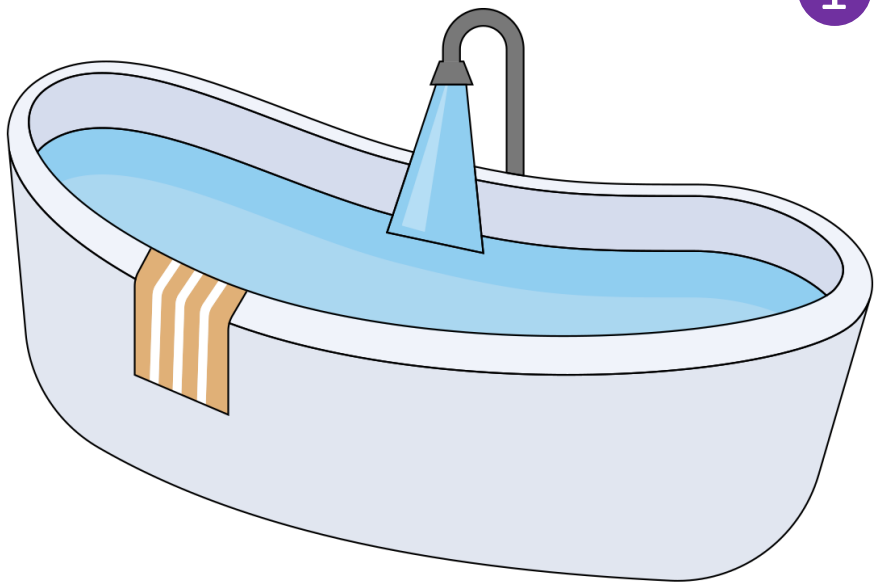
Call in the plumber – Case #4

- Labile ammonia during hospitalization
- Referred for liver transplant evaluation
- Several attempts to discharge home resulted in hyperammonemia (150-300 mcmol/L)
- Ultimately kept hospitalized until liver transplant

Management of UCDs- An overflowing bathtub

1 **Turn down the faucet**

Reduce Influx
- Protein Restriction
- Anabolism



2 **Use a bucket to bail out**

- Nitrogen scavengers

3 **Fix the drain - maximize urea cycle function**

- **Liver Transplant**
- Carglumic Acid
- Arginine/Citrulline
- Gene Therapy

Call in the plumber – Case #5

- Presented on DOL 3 to an outside ED
  - Had been difficult to wake in hospital prior to discharge ad DOL 2
  - At home parents unable to wake on DOL 3
  - Initial ammonia 706 mcmol/L
- Biochemical presentation
  - Peak ammonia 956 mcmol/L
  - Glutamine 2,054 mcmol/L
  - Citrulline 6 mcmol/L
  - Arginine 25 mcmol/L
  - Orotic Acid 27.3 mg/g UCr
  - BUN 19 -> 3 mg/dL
- Diagnosed with presumptive OTC deficiency
- Following initial stabilization with dialysis and IV ammonul, started on PO sodium phenylbutyrate
- Initially given IV arginine, transitioned to PO citrulline
- Started on NG / PO feeds with 0.8 g/kg protein from EAA and 0.8 g/kg protein from pumped breastmilk
- Discharged home after 28 days

Toddler challenges

- Following initial admission now admissions until 14 months old
- Introduction of solids went well
- Had multiple admissions at 2 yo with decreasing PO tolerance
  - First refused solids / picky with textures
  - Began to have decreased formula tolerance following admission at 2.75 yo
- Initially refused recommendation for g-tube placement
- Ultimately agreed just before turning 3 yo

Case #5 – Early Childhood

- From age 3 to 6 had 4 admissions
- Continued feeding therapy but made little progress with PO
- Admission frequency increased at 6 yo due to social changes, illness, frequent emesis
- Option of liver transplant discussed frequently with family
  - Concerns regarding operation and post transplant care
  - **Liver transplant declined**

Case #5 - Puberty

- Seen in endocrinology for precocious puberty at age 9
- 7 Hospitalizations in year leading up to menarche
- Regular menarche began at age 10.5 years
- Discussed hormonal supplementation to suppress and/or regulate cycle and promote metabolic stability
- Diet adjustment made to account for increased caloric needs with menarche
  - 100 kcal increase in week leading up to start of menstrual cycle

Case #5 - Puberty

- Regular hospitalizations continued
- Sodium benzoate added to daily management (2.5 g/m2/day)
- Stopped additional calories due to increasing weight
- No admissions since starting sodium benzoate 1.5 years ago
- Now doing regular cheerleading

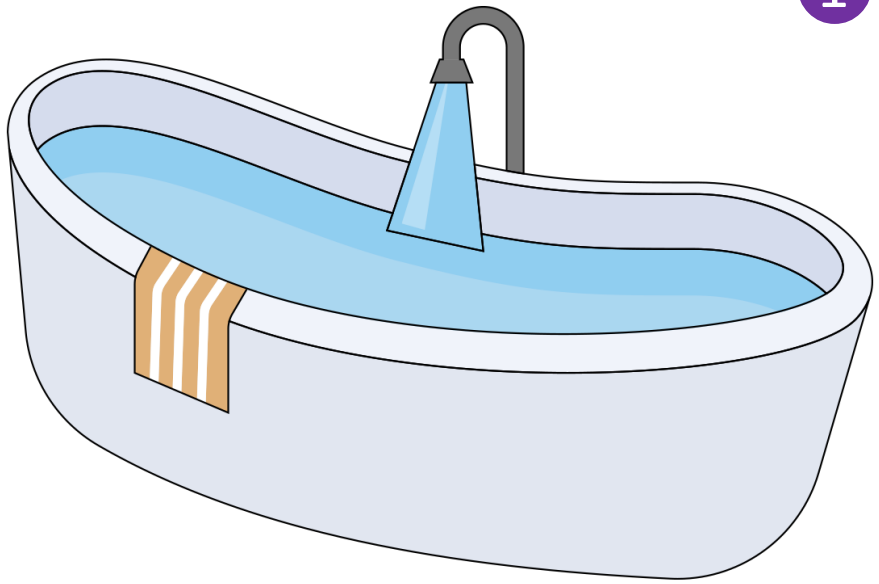
Reminder: High Risk Life Stages

- "Honeymoon Period" : 3-4 months after stabilization.
- Toddlers: Increased illness risk + inability to explain importance of diet.
- Prepubertal Growth Spurt: Challenge consuming adequate protein for support increased growth, combined with adolescent rebellion.
- Post-Puberty Growth Slowdown: Hormonal fluctuations
- Adult Weight Loss: weight loss is a catabolic process.
- Pregnancy/ Delivery: High protein demand and delivery risks.

Review: Management of UCDs

1 **Turn down the faucet**

Reduce Influx
- Protein Restriction
- Promote Anabolism



2 **Use a bucket to bail out**

-Nitrogen scavengers

3 **Fix the drain - maximize urea cycle function**

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

Rule Breakers

Citrin Deficiency

- Presentation differs by age:
  - –Neonates: Intrahepatic Cholestasis
  - –Juvenile: Failure to Thrive, dyslipidemia
  - –Adolescent or adulthood: Recurrent hyperammonemia ("Citrullinemia type II")
- Common in Asian populations: Carrier rate: 1:50-100
- Treatment
  - –Unlike UCDs: High protein, High fat, low carbohydrate diet

J Inherit Metab Dis. 2024b;47:1144-56

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?

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

Final Considerations

Food intake is not the only factor

- Remember, you need protein to build protein
- Activity Goals
  - General public: Recommendations 30 minutes of moderate exercise 5 or more days per week or 20 minutes of vigorous exercise 3 days or more per week.
  - Persons with disabilities: aerobic exercise 30-60 minutes 3-5 days per week at moderate intensity and resistance training 1-2 sets of 8 to 12 reps 2 to 3 times weekly
- Outcome benefit
  - Improved/stabilized metabolic control
  - Increased energy/ functional fitness
  - Improved protein tolerance

Hydration

- Water is necessary for optimal enzymatic processes
- Urine eliminates ammonium ions and product of nitrogen scavengers (hippurate and phenylacetylglutamine)
- Watch patient BUN relative to their individual norm
  - A BUN in the normal range may indicate dehydration

Resources

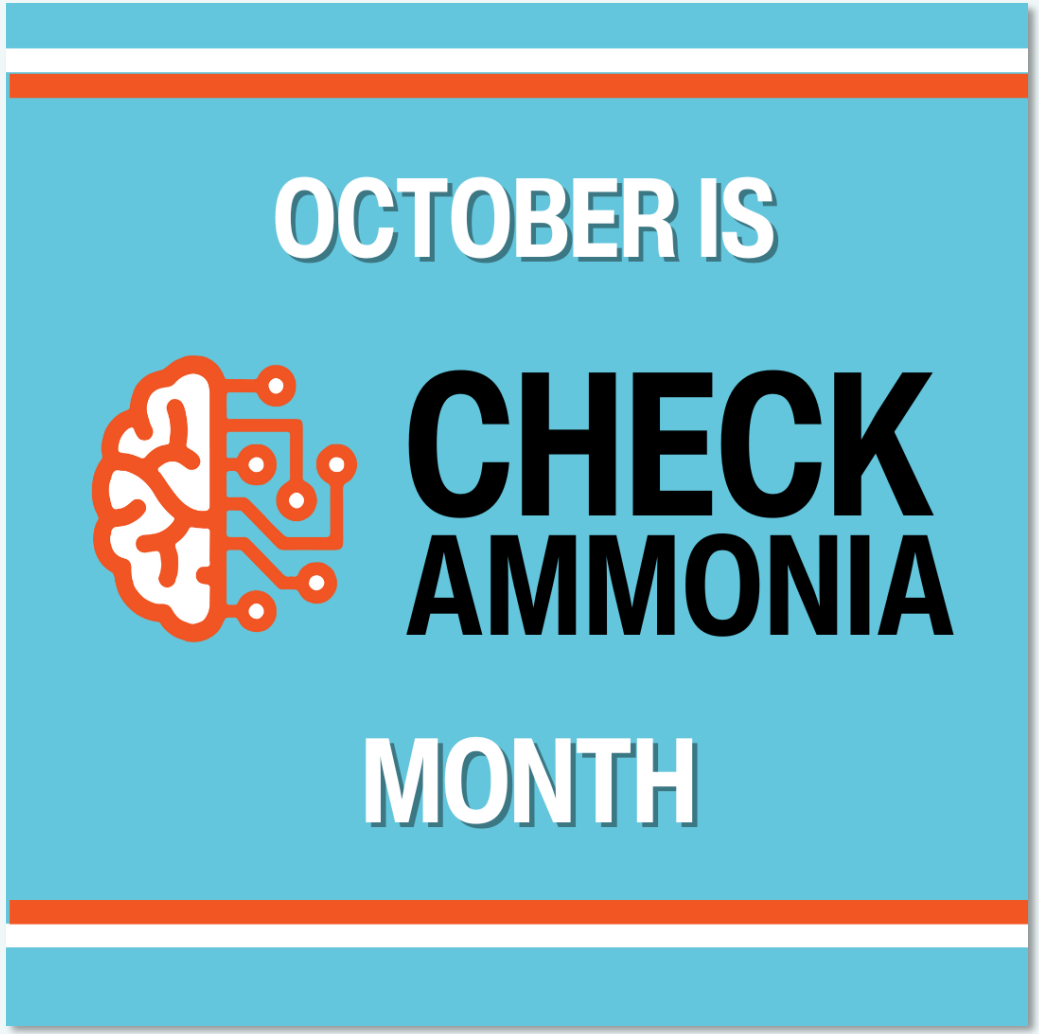
- National Urea Cycle Disorders Foundation http://www.nucdf.org/
- Urea Cycle Disorders Consortium: https://ucdc.rarediseasesnetwork.org/
- Genetic Metabolic Dietitians International: https://www.gmdi.org/
- GeneReviews
  - Urea Cycle Disorders https://www.ncbi.nlm.nih.gov/books/NBK1217/
  - Also available for individual conditions
- Haeberle et al, 2019: Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision https://pubmed.ncbi.nlm.nih.gov/30982989/

- **Coming soon GMDI/MNT4P UCD Nutrition Guidelines!**

Case Discussion

UREA CYCLE DISORDERS ECHO

The Essentials



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UREA CYCLE DISORDERS ECHO

The Essentials

Thank You

Session 4: Long-term Management

Tuesday, November 11, 5-6:30 pm ET

Laura Konczal, MD,
University Hospitals Cleveland Medical Center

Evaluation link / QR code