UREA CYCLE DISORDERS -
The What, Why, How and When

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Disclosure

Nothing to disclose.
Overview

- Basic Review – What are the UCDs?
- Clinical Biochemistry – Why are particular patterns of analytes observed in specific UCDs?
- Current Management Principles – How do we treat them?
- Usual and Unusual Presentations – When might symptoms manifest?
NITROGEN METABOLISM

Amino Acid \(\rightarrow\) \(\alpha\)-ketoglutarate \(\rightarrow\) NADH + \(\text{NH}_4^+\)

Transaminase

\(\alpha\)-keto acid \(\rightarrow\) Glutamate \(\rightarrow\) NAD\(^+\) + \(\text{H}_2\text{O}\)

Glutamate Dehydrogenase
NITROGEN METABOLISM
THE UREA CYCLE

N-Acetylglutamate Synthase
Carbamyl Phosphate Synthase
Ornithine Transcarbamylase
(Proximal Disorders)

THE UREA CYCLE

Argininosuccinate Synthase
Argininosuccinate Lyase
Arginase

Citrullinemia Type 2:
- ↑ NH3
- ↑ Citrulline
- Neonatal Intrahepatic Cholestasis
- Adult-Onset
  Citrullinemia type 2

H-H-H Syndrome:
- ↑ NH3
- ↑ Ornithine
- Homocitrullinuria

Clinical Biochemistry –
Why are particular patterns of analytes observed in specific UCDs?
UREA CYCLE DEFECTS
LABORATORY ABNORMALITIES

▶ Elevated Plasma NH$_3$
  – >300 µmol/L associated with neurological injury, chronic elevations at lower levels also damaging

▶ No Metabolic Acidosis
  – Possible respiratory alkalosis

▶ Abnormal Liver Function Tests

▶ Elevated Plasma Glutamine
PRESUMPTIVE UCD

Repeat NH$_3$
Urine Orotic Acid
Plasma Amino Acids
Unusual presentations have been described with atypical biochemical analytes. Molecular confirmation is important.
Newborn Screening for UCD

- **Analyte: Citrulline**
  - Argininosuccinic acidemia
  - Citrullinemia (type 1 or type 2)

- **Analyte: Arginine**
  - Argininemia

No Robust Analyte Currently for NAGS, CPS-1, OTC though California, Connecticut, Massachusetts screen for OTCD by citrulline ratios
Current Management Principles – How do we treat UCDs?
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
PRINCIPLES OF UCD TREATMENT

Suggested guidelines for the diagnosis and management of urea cycle disorders

Johannes Häberle¹*, Nathalie Boddaert², Alberto Burlina³, Anupam Chakrapani⁴, Marjorie Dixon⁵, Martina Huemer⁶, Daniela Karall⁷, Diego Martinelli⁸, Pablo Sanjurjo Crespo⁹, René Santer¹⁰, Aude Servais¹¹, Vassili Valayannopoulos¹², Martin Lindner¹³*, Vicente Rubio¹⁴* and Carlo Dionisi-Vici¹⁸*
TREATMENT OF ACUTE HYPERAMMONEMIA

- **Ammonia Disposal**
  - Exchange transfusion NH$_3$ clearance nil
  - Peritoneal dialysis NH$_3$ clearance 3-5 ml/min
  - Hemodialysis/filtration NH$_3$ clearance 20-30 ml/min
  - ECMOHD NH$_3$ clearance 170 ml/min
TREATMENT OF ACUTE HYPERAMMONEMIA

- **Ammonia Disposal**
  - Extracorporeal detoxification
  - Nitrogen scavenging-medications

- **Promote Anabolism**
  - High glucose infusion rate
  - +/- Intralipids
  - +/- Insulin
  - Reinitiate protein within 24-48 hours

- **Nitrogen Scavenger Medication**
  - Intravenous sodium phenylbutyrate/benzoate + arginine
  - Transition to oral medications when stable
PRINCIPLES OF UCD TREATMENT

- Restrict substrate
- Provide cofactors
- Provide product
- Provide alternate routes of elimination
- Replace enzyme
- Treat secondary effects
PRINCIPLES OF UCD TREATMENT

- Restrict substrate

Amino Acids $\rightarrow$ NH$_3$ $\rightarrow$ Urea

Diagram showing the conversion of ammonia to urea involving substrates and enzymes such as Carbamyl Phosphate Synthetase and Argininosuccinate.
Nutritional Management of Urea Cycle Disorders

Rani H. Singh, PhD, RD, William J. Rhead, MD, PhD, Wendy Smith, MD, Brendan Lee, MD, PhD, Lisa Sniderman King, MSc, Marshall Summar, MD

- 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
PRINCIPLES OF UCD TREATMENT

- Restrict substrate
  - Essential AA formulas
- Provide cofactors
**PRINCIPLES OF UCD TREATMENT**

- **HCO₃⁻ + NH₃** → Carbamyl Phosphate
  - N-Acetylglutamate
  - CPS1
  - NAGS Deficiency

- **Restrict substrate**
  - Essential AA formulas

- **Provide cofactors**
  - Carglumic Acid
PRINCIPLES OF UCD TREATMENT

Argininosuccinate Lyase

Argininosuccinate → Arginine

- Restrict substrate
  - Essential AA formulas
- Provide cofactors
  - Carglumic Acid
- Provide product
  - Arginine for distal defects
  - Citrulline for proximal defects
PRINCIPLES OF UCD TREATMENT

- **Restrict substrate**
  - Essential AA formulas

- **Provide cofactors**
  - Carglumic Acid

- **Provide product**
  - Arginine for distal defects
  - Citrulline for proximal defects

- **Provide alternate elimination routes**

![Ammonia to Urea pathway diagram]
Treatment of hyperammonemic coma caused by inborn errors of urea synthesis

Mark L. Batshaw, M.D., and Saul W. Brusilow, M.D., Baltimore, Md.
AMMONIA SCAVENGING AGENTS

Nitrogen Pool

- Glycine
- Glutamine

- Benzoate → Hippurate
- Phenylacetate → Phenylacetylglutamine
- Phenylbutyrate
FDA APPROVED TREATMENTS

- 1996 – Sodium Phenylbutyrate (oral)
- 2005 – Phenylacetate/Benzoate/Arginine (Intravenous)
- 2010 – Carglumic Acid (oral)
- 2013 – Glycerol Phenylbutyrate (oral)
PRINCIPLES OF UCD TREATMENT

Amino Acids → NH₃ → Urea

- **Restrict substrate**
  - Essential AA formulas

- **Provide cofactors**
  - Carglumic Acid

- **Provide product**
  - Arginine for distal defects
  - Citrulline for proximal defects

- **Provide alternate elimination routes**
PRINCIPLES OF UCD TREATMENT

Amino Acids → \( \text{NH}_3 \) → Urea

- **Restrict substrate**
  - Essential AA formulas
- **Provide cofactors**
  - Carglumic Acid
- **Provide product**
  - Arginine for distal defects
  - Citrulline for proximal defects
- **Provide alternate elimination routes**
- **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 of any disorder
Morioka et al. *Liver Transp* 11, 2005

- Meta-analysis of 51 patients
- 40 currently surviving with satisfactory quality of life
- Neurological impairments in 5 surviving patients
- Cumulative patient survival rates > 90% at 5 years
SUMMARY: UCD TREATMENT

- **Day to Day:**
  - Protein restriction
  - Essential amino acid formulas
  - Ammonia detoxification medications
  - Monitor growth, developmental, and biochemical parameters

- **Emergency:**
  - Prevent catabolism
  - Ammonia detoxification medications
  - Hemodialysis

- **Long-term:**
  - Liver transplantation
Usual and Unusual Presentations – When might symptoms manifest?
UREA CYCLE DEFECTS
CLINICAL PRESENTATIONS

Early-Onset Hyperammonemonia
- Age of onset: >24 hours of age
- Lethargy
- Poor feeding
- Vomiting
- Seizures
- Bleeding
- Hyperventilation
- Coma
- Death

Differential diagnosis of lethargic newborn:
- Infection
- Congenital defect (heart, brain)
- Inborn error of metabolism (Organic acidemia, FAO)
Later-Onset Hyperammonemia

- **Age of onset:** > 4 weeks to Adulthood
- Lethargy
- Poor feeding
- Vomiting
- Seizures
- Bleeding
- Hyperventilation
- Coma
- Death
Later presentation of proximal disorders usually associated with less severe mutations (residual enzyme activity), OTC manifesting females (lyonization)

Signs And Symptoms Suggestive Of Late Onset UCD:

- Developmental delay / MR
- Recurrent vomiting
- Failure to thrive
- Recurrent encephalopathy
- History of protein aversion
- Elevated liver function tests
DECOMPENSATION TRIGGERS

▶ Catabolic Stress
- Infection
- Surgery/Anesthesia
- Post-partum

▶ Nutritional Imbalance
- Inadequate calories
- Inadequate or excess protein

▶ Medications
- Valproate, L-Asparaginase, Corticosteroids, others
CC: 30 year old male with no significant past medical history developed encephalopathy after ankle fracture

HPI:
- First day on job as taxi driver
- First passenger of day carjacked him at gunpoint and put him in trunk
- Escaped from moving vehicle on highway and suffered fractured malleolus – open surgical reduction
- Post-operatively, given high protein formula and became encephalopathic – found to be hyperammonemonic

PMH:
- Unremarkable prenatal, childhood hx by report
- No hospitalizations

Labs:
- High ammonia, low plasma citrulline, low urine orotic acid, Sequencing consistent with NAGS deficiency
UCD DIAGNOSIS SUMMARY

- Suspect UCD in Unexplained Encephalopathy
  - GI symptoms, Protein Aversion, Development

- Initial Labs When a Late-Onset UCD is Suspected:
  - Same as for neonatal case
  - Plasma ammonia (free-flowing on ice)
  - Blood gas, electrolytes, blood sugar, liver function, urine organic acid/orotic acid, acylcarnitine profile
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  All of the Pediatrics Residents
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Questions?