Navigating the promise landscape of Urea Cycle Disorder Treatment: An in-depth exploration of market dynamics and growth opportunities

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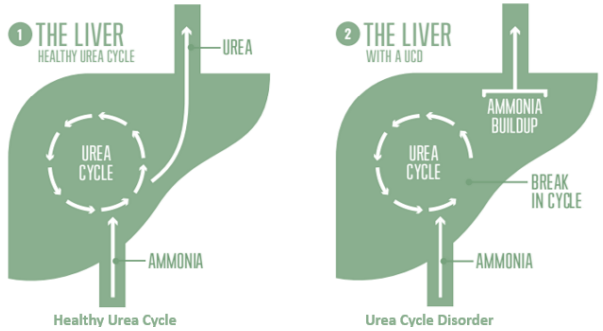
INTRODUCTION

Disease Overview[1]

- **Are rare genetic condition caused by enzyme deficiencies in the urea cycle, which is responsible for removing ammonia from the bloodstream**
- These deficiencies lead to ammonia and other nitrogenous compounds accumulating, causing Urea cycle disorder can manifest at any age, from birth to adulthood, with symptoms ranging from mild encephalopathy to severe developmental disabilities

Pathophysiology[2]



UCD → Hyperammonemia → Astrocyte Swelling → Brain Edema → Increase Intracranial pressure → Neurological Impact → Seizure , Coma

Symptoms[1]

- Lethargy or feeling tired
- Fussiness in babies
- Nausea or vomiting
- Breathing too fast or too slow

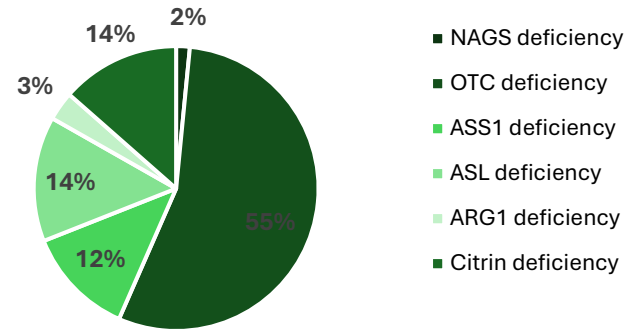
Diagnosis:

- UCD involves evaluating clinical, biochemical, and molecular data
- For detailed diagnosis please click here

Biomarker[4]	Role
Arginine	Biomarker for urea cycle disorders
ActiTest™	Marker for hepatic necroinflammation
Metabolomic profiling	Identifying new clinical biomarkers
Untargeted metabolomic analysis	Revealing novel biomarkers for UCDs
Ammonia levels	Monitoring urea cycle function
Argininosuccinic acid	Diagnostic marker for certain UCDs
Citrulline	Biomarker for urea cycle function
Ornithine	Indicator of urea cycle metabolism

Percentage of Ucd's Subtypes on the basis of their incidence

Incidence[1]
1 in 35,000 births
~113 new cases per year in USA



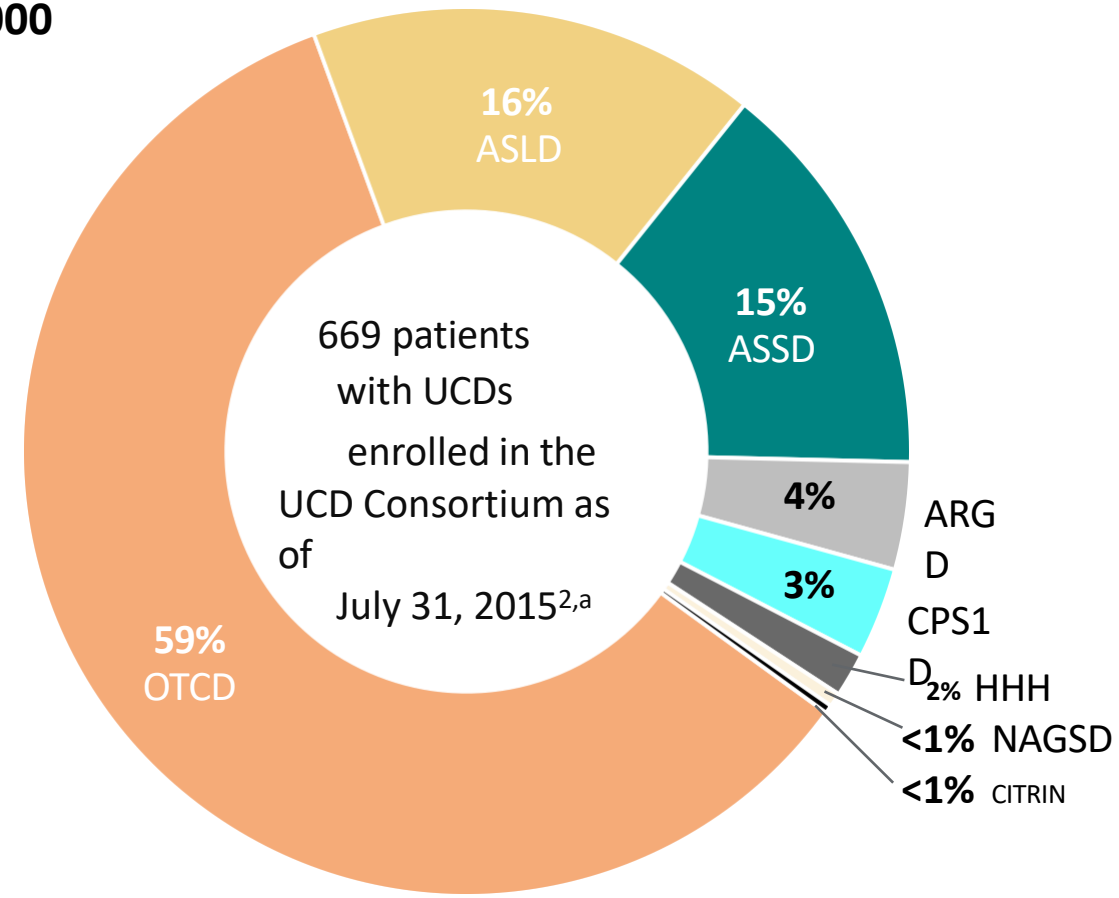
Active Ingredient	Company	Brand Name	Dosage form	Route	Strength	Approval date
Glycerol Phenylbutyrate	HORIZON	RAVICTI	Liquid	Oral	1.1 GM/ML	2013
Carglumic Acid	RECORDATI RARE DISEASES GROUP	CARBAGLU	Tablet , for Suspension	Oral	200MG	2010
Approved , yet to be commercially Available Sodium Phenylbutyrate	Acer Therapeutics / Medunik USA	OLPRUVA	For Suspension	Oral	2GM/3GM/4/GM/5GM/6GM/6.67GM Packet	2022
		PHEBURANE	Pellets	Oral	84GM / BOT	2022
	HORIZON	BUPHENYL	Powder	Oral	3GM / TEASPOONFUL	1996
			Tablet	Oral	500MG	1996
Sodium Phenylacetate &Sodium Benzoate	BAUSCH Health	AMMONUL	Injection	IV	10%/10%	2005

BACKGROUND

Estimated Overall Incidence of UCD Is 1:35,000 Births[1,2]

Incidence of UCD subtypes[1]

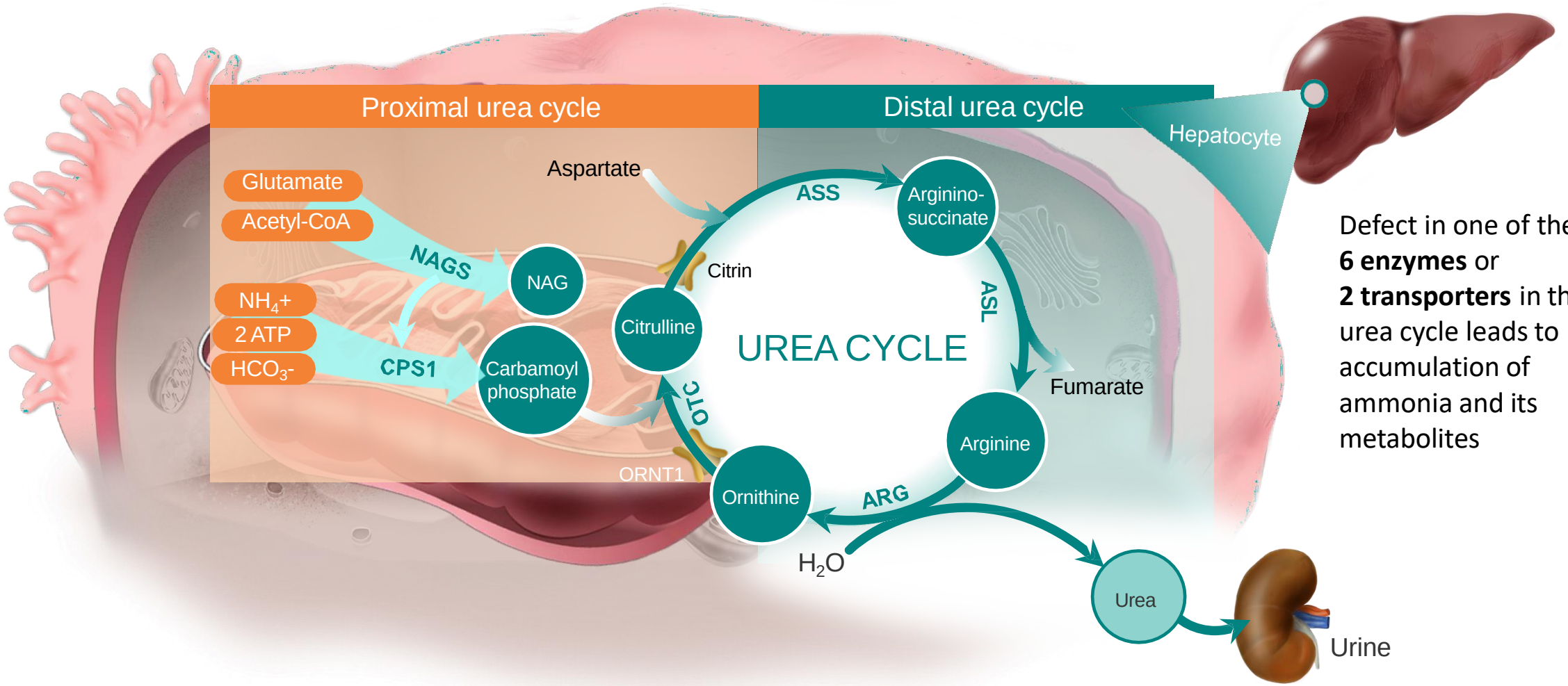
OTCD	1:56,500
ASLD	1:218,750
ASSD	1:250,000
ARGD	1:950,000
CPS1D	1:1,300,000
NAGSD	<1:2,000,000
HHH	<1:2,000,000
CITRIN	<1:2,000,000



UCDC, Urea Cycle Disorder Consortium.

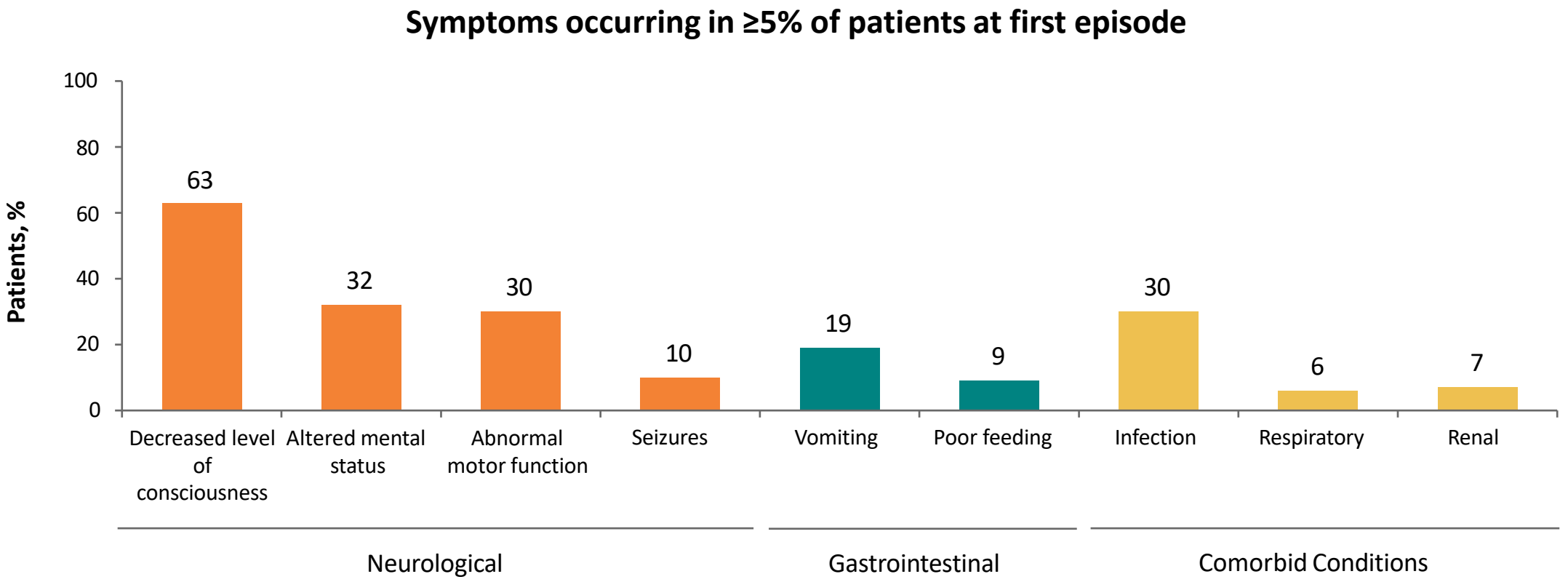
[a]As of July 31, 2015, 678 patients were accrued in the UCDC longitudinal study; data exclude 9 patients with pending diagnosis.

The Urea Cycle Converts Nitrogen Waste Into Urea



Defect in one of the **6 enzymes** or **2 transporters** in the urea cycle leads to accumulation of ammonia and its metabolites

Presenting Signs and Symptoms at First Episode of Hyperammonemia



Data based on 260 patients with confirmed diagnosis of a UCD who were treated for 975 episodes of hospitalization between 1982 and 2003.

Characteristics of Early-Onset Versus Late-Onset UCDs

Early-onset UCDs

Gene deletions, nonsense mutations, frameshift mutations[1,2]

Complete or near-complete enzyme deficiency[1,2]

Infants develop signs and symptoms of hyperammonemia within days[3]

Late-onset UCDs

Missense mutations[1,2]

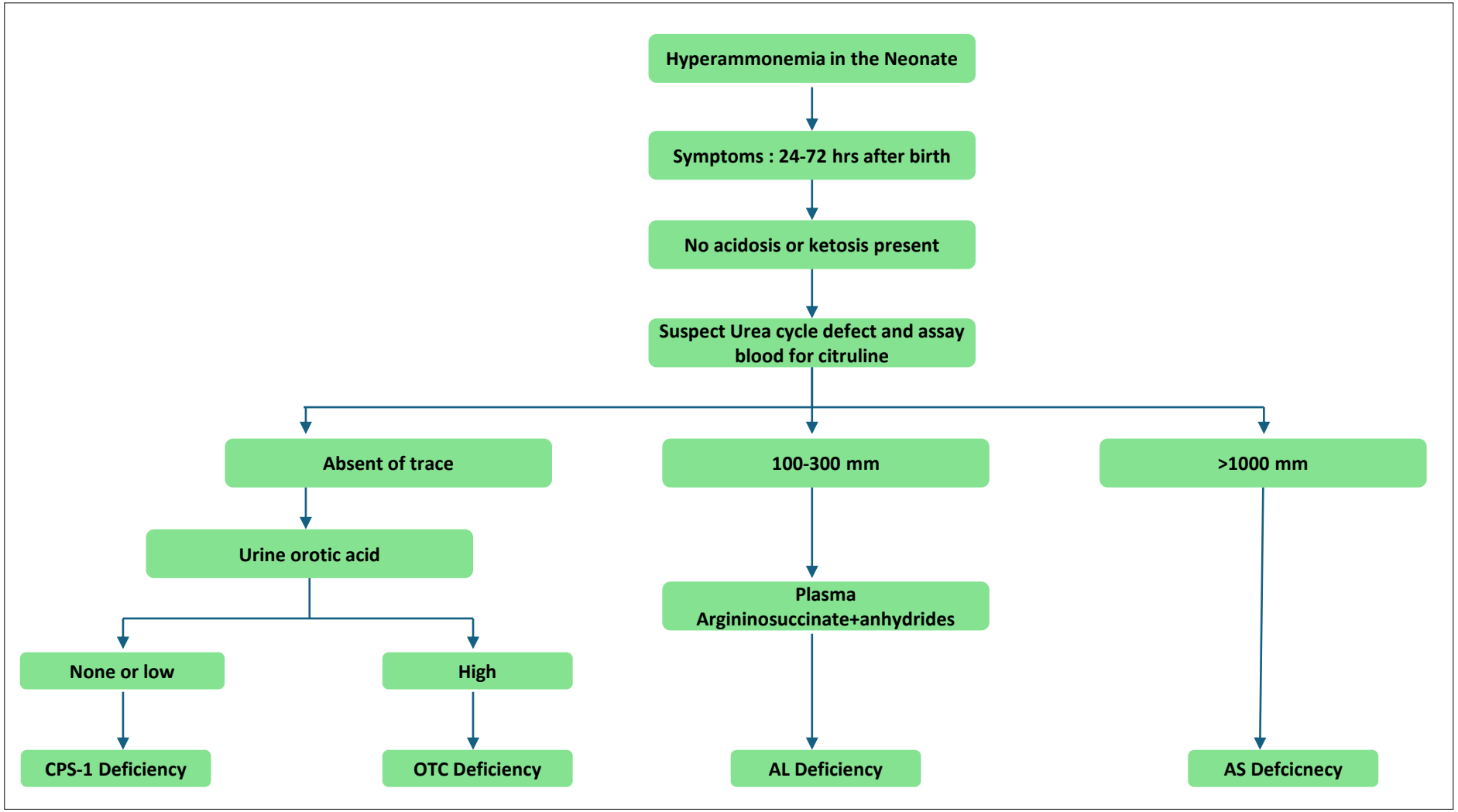
Partial enzyme deficiency[1,2]

First recognized clinical episode can be delayed for months or years[3]

Ammonia accumulation may be triggered by acute illness or stress at any time of life[3]

Hyperammonemia is less severe and symptoms more subtle[3]

Diagnosis of UCD



Genetics, Clinical and Biochemical Presentation, and Diagnostic Tests for UCDs

UCD Subtype	Inheritance	Casual Gene	Clinical Manifestations	Biochemical Markers	Diagnostic Test
NAGSD	Autosomal recessive	NAGS	Encephalopathy, neurobehavioral	HA, plasma glutamine, low citrulline	DNA
CPS1D	Autosomal recessive	CPS1	Encephalopathy, neurobehavioral	HA, plasma glutamine, low citrulline	Liver enzyme analysis; DNA
OTCD	X-linked	OTC	Encephalopathy, neurobehavioral, liver disease (infrequently)	HA, plasma glutamine, low citrulline, urine orotic acid	DNA, liver enzyme analysis
ASSD	Autosomal recessive	ASS1	Encephalopathy, neurobehavioral	HA, plasma citrulline	Fibroblast enzyme analysis, DNA
ASLD	Autosomal recessive	ASL	Encephalopathy, neurobehavioral, liver disease (frequently), trichorrhexis nodosa	HA, plasma citrulline, and argininosuccinic acid	Fibroblast enzyme analysis, DNA
ARGD	Autosomal recessive	ARG1	Spastic diplegia, neurobehavioral	Increased plasma arginine, t urine orotic acid	Red blood cell enzyme analysis
HHH	Autosomal recessive	SLC25A15	Encephalopathy, neurobehavioral, spastic diplegia, retinal disease	HA, plasma ornithine, t urine homocitrulline, urine orotic acid	Fibroblast incorporation assay, DNA
CITRIN	Autosomal recessive	SLC25A13	Neuropsychiatric, neonatal cholestatic hepatitis	HA, plasma citrulline, and arginine	DNA

OBJECTIVE

- To extract information available for the marketed and available drugs for Urea Cycle Disorder
- To assess the potential of Ammonia Scavengers for Urea cycle disorder in US market
- To assess inline and pipeline drugs in US market

METHODOLOGY

- Type of Research: Secondary Research
- Duration of study: 3 Months
- Secondary Data was extracted from ct.gov website

RESULTS AND FINDINGS

- Treatment for urea cycle disorders are expected to grow at a compound annual CAGR of 3.56% in the United States between 2023 and 2030, reaching a value of US$ 510.0 million in 2023.
- Market growth is anticipated to be fueled by an increasing number of products in the pipeline and product approvals for urea cycle disorders.
- Additionally, major players in the Urea Cycle Disorders Treatment market are anticipated to fuel the market's expansion in the United States during the forecast period due to regulatory agencies' growing acceptance of inorganic growth strategies.

FDA Approved and Marketed drugs for Urea Cycle Disorder

Active Ingredient	Company	Brand Name	Dosage form	Route	Strength	Approval date
Glycerol Phenylbutyrate	Horizon	RAVICTI	Liquid	Oral	1.1 GM/ML	2013
Carglumic Acid	Recordarti Rare Diseases	CARBAGLU	Tablet, for Suspension	Oral	200MG	2010
Sodium Phenylbutyrate	Acer Therapeutics	OLPRUVA	For Suspension	Oral	2GM/3GM/4/GM/5GM/6GM/6.67GM Packet	2022
	Medunik USA	PHEBURANE	Pellets	Oral	84GM / BOT	2022
	Horizon	BUPHENYL	Powder	Oral	3GM / TEASPOONFUL	1996
			Tablet	Oral	500MG	1996
Sodium Phenylacetate &Sodium Benzoate	Bausch Health	AMMONUL	Injection	IV	10%/10%	2005

Oral Nitrogen Scavengers Available for Long-term Therapy

OLPRUVA™

Indication:

- Adjunctive therapy in the chronic management of adult and pediatric patients weighing 20 kg or greater and with a BSA of 1.2 m^2 or greater, with UCDs involving deficiencies of CPS, OTC, or AS

Dosing: Usual daily dose

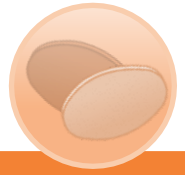
- 20 kg or greater and with a BSA of 1.2 m^2 or greater: 9.9-13 g/m^2/day

Formulation:

- Oral suspension 2g, 3g, 4g, 5g, 6g, or 6.67g of NaPB

Administration:

- 3-6 divided doses with food
- Each dose packaged in dosage envelope containing 1-2 packets of NaPB for oral suspension and a suspending agent packet.
- Must be mixed with the prepared Mix-Aid suspension in 4 oz water, drink the entire suspension within 5 minutes to minimize dissolution of coating and follow with additional rinse with 4 oz of water
- Administration via gastrostomy or nasogastric tubes has not been evaluated



BUPHENYL®

Indication:

- Adjunctive therapy in the chronic management of patients with UCDs involving deficiencies of CPS, OTC, or AS.
- All patients with neonatal-onset disease who have a history of hyperammonemic encephalopathy.
- Must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation

Dosing: Usual daily dose

- Patients <20kg: 450-600 mg/kg/day
- Patients ≥ 20kg: 9.9-13.0 g/m^2/day

Formulation:

- Tablets (500 mg)
- Powder (3000 mg/tsp)

Administration:

- 3-6 equally divided doses with each mean or feeding
- Powder indicated for oral use (via mouth, gastrostomy, or nasogastric tube) only

RAVICTI®

Indication:

- Chronic management of patients with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone
- Must be used with dietary protein restriction and, in some cases, dietary supplements

Dosing: Initial dosing

- Phenylbutyrate-naïve patients 4.5-11.2 g/m^2/day to 12.4 g/m^2/day, not to exceed total daily dosage of 17.5 ml

Formulation:

- Liquid (1100 mg/ml)

Administration

- 3 (or more for patients aged <2 years) equally divided doses with food or formula
- Administer directly into the mouth via oral syringe
- Nasogastric tube or gastrostomy tube may be used

PHEBURANE®

Indication:

- Adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients with urea cycle disorders (UCDs), involving deficiencies of CPS, OTC, or AS

Dosing: Usual daily Dose

- Patients weighing < 20 kg: 450–600 mg/kg/day of sodium phenylbutyrate..
- Patients weighing ≥ 20 kg: 9.9–13.0 g/m^2/day of sodium phenylbutyrate

Formulation:

- Oral pellets: 84 g of NAPB.

Administration:

- Schedule PHEBURANE dosages at the same time as food consumption
- Use the calibrated dosing spoon to measure PHEBURANE oral pellets Swallow the coated oral pellets with a drink or sprinkle onto spoonful of apple sauce or carrot puree.
- Do not chew PHEBURANE.
- Swallow immediately to minimize dissolution of coating

Pipeline for Urea Cycle Disorder

Drugs in Pipeline	Molecule Name	Company	MOA	Development phase	Type of Molecule	ROA
DTX301	Avalotcagene ontaparvovec	Ultragenyx Pharmaceutical Inc	Gene transference; Ornithine carbamoyl transferase replacements	Phase 3	Large molecule	IV
AEB-1102	Pegzilarginase	Spyre Therapeutics	Arginase replacements	Pre-registration	Large molecule	IV
ARCT-810		Arcturus Therapeutics	Ornithine carbamoyl transferase expression stimulants	Phase 2	Large molecule	IV

Principles of Long-Term Management of UCDs[1-3]

Minimize nitrogen load
on the urea cycle

- Ensure sufficient energy intake
- Avoid triggering events
- Supplement-deficient UC intermediates

Prevent protein catabolism

Avoid dehydration

Avoid medications such as valproic acids and steroids

Avoid hyperammonemia

Acute Treatment of UCDs[1]

Physical removal of ammonia

- Hemodialysis (or hemodiafiltration) is the most efficient treatment for reducing the plasma ammonia concentration[2]

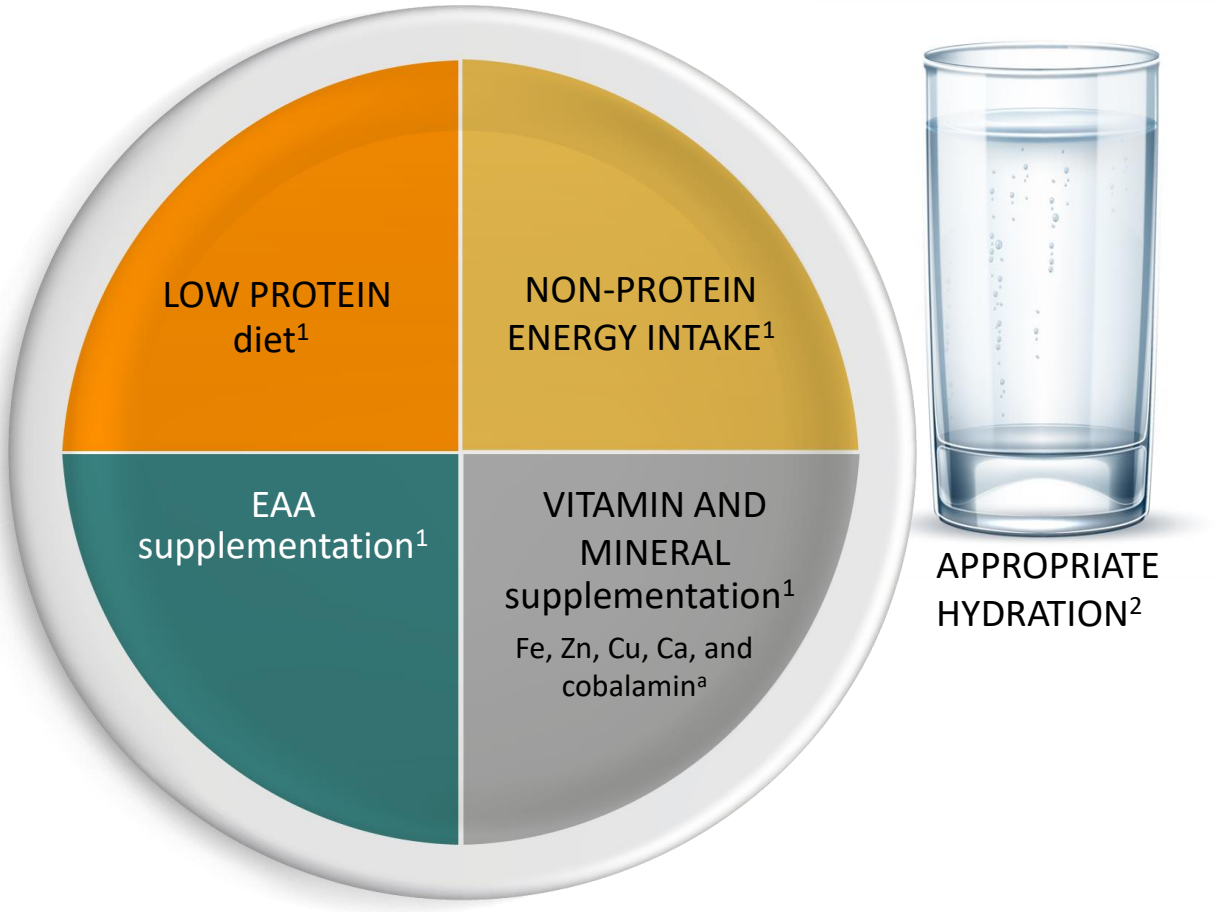
Reversal of Catabolic stage

- IV fluids (if needed)[1]
- Caloric supplementation (dextrose, IV lipid emulsion)[1]
- Stop all protein intake (initially)[1,2]
- IV L-arginine hydrochloride[2]

Pharmacological treatment

- IV nitrogen-removing agents (eg, sodium phenylacetate, sodium benzoate)[1]
- Carglumic acid[3,4]

Principles of Nutrition Management in UCD



Dietary treatment of UCDs significantly impairs patients' HRQoL[3]

~15% of hospitalizations secondary to metabolic deteriorations[b] are the result of nonadherence to prescribed diet[4]

Ca, calcium; Cu, copper; Fe, iron; HRQoL, health-related quality of life; Zn, zinc.

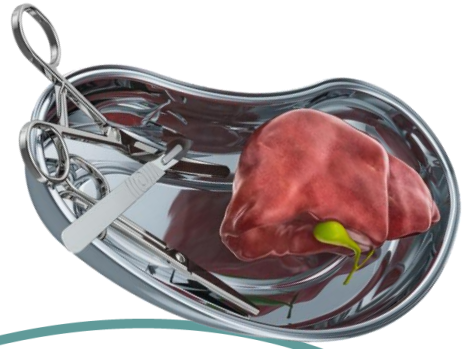
[a]Patients with UCD on low protein diets are at particular risk of Fe, Zn, Cu, Ca, and cobalamin deficiency.[1]

[b]In a study of 260 patients with UCD hospitalized 975 times during the study period of February 1982 through May 2003.

Considerations for Liver Transplantation in UCD

Tipping point in decision influenced by multiple factors[1]

Disease severity
Disease stability
Burden on child/family
Physician approach
Consideration for child's independence



No statistically significant benefits for patient mortality, QOL, or neuropsychological outcomes vs medical management[4]

Benefits[1-3]

- Potentially "curative"
- Normalizes ammonia levels
- Improves QoL
- Allows for normal diet

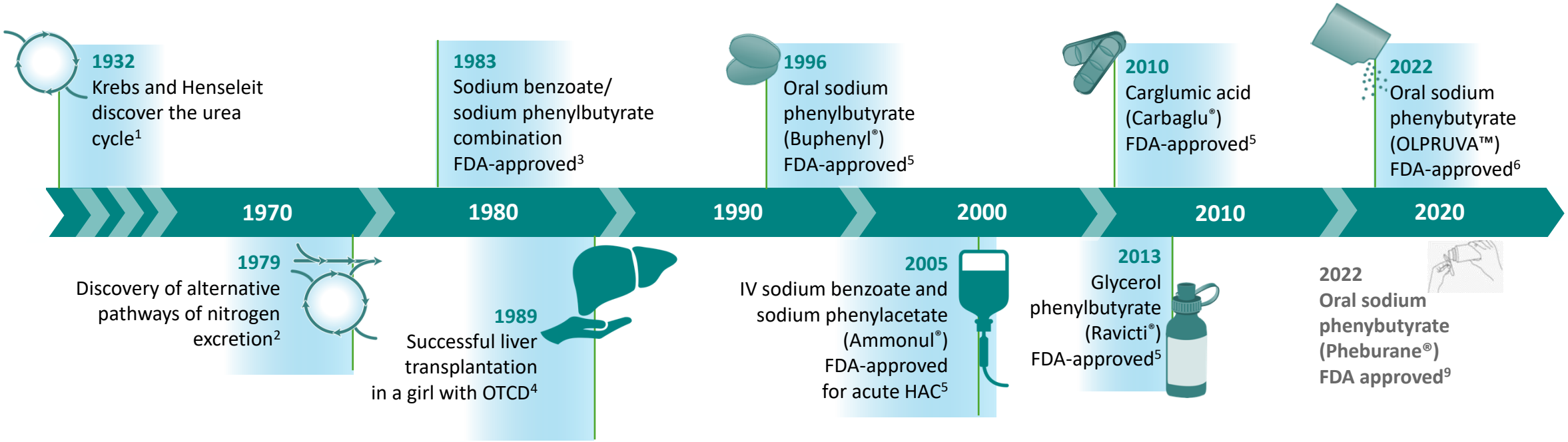
Limitations[1-4]

- Does not reverse neurological damage
- Risk of morbidity and mortality
- Life-long immunosuppression
- Defective enzymes remain in other organs

Multiple Factors Influence Protein Restriction Considerations

- Specific enzyme defect
- Age-related growth rate
- Current health status
- Level of physical activity
- Free amino acids administered
- Energy intake
- Residual urea cycle function
- Family lifestyle
- Medications
- Eating behaviors

UCD Treatments: Historical Timeline



Key Challenges for the Management of UCDs in Adults

Poor compliance with dietary and medical treatment

Severe neurological dysfunction

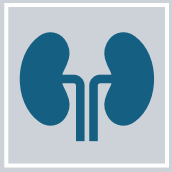
Management of the pregnancy and postpartum period

Access to multidisciplinary care perioperatively

CONCLUSION

Ammonia scavenger drugs are commonly used to treat urea cycle disorder and have other therapeutic uses as well. Between 2023 and 2030, the United State treatment market for urea cycle disorders is projected to expand at a compound annual growth rate (CAGR) of 3.56%, reaching a value of US$ 510.0 million in 2023. A rising number of medications in the pipeline and product approvals for urea cycle diseases are expected to drive market expansion. Furthermore, because regulatory bodies are beginning to allow inorganic growth techniques, key players in the Urea Cycle Disorders Treatment market are expected to drive the market's rise in the United States throughout the forecast period.

Urea cycle disorder affects approximately 1 in 35000 people of the population and is expected to become more common in future as the world population increases and people live longer. The highest prevalence of urea cycle disorders (UCDs) is seen in late-onset cases, which account for 69% of patients



The global market offers various drugs for treatment of UC, including ammonia scavengers but there are certain key unmet needs in UCD treatment which needs to be addressed that includes high costs, poor patient adherence due to side effects, lack of therapies for negative and cognitive symptoms, delayed diagnosis, and limitations of liver transplantation