

Treatment of Hyperammonemia

An Evidence-Based and Practical Approach

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Treatment Goals

Rapid reduction

Lower plasma ammonia promptly

Brain protection

Prevent neurological injury

Restore anabolism

Stop catabolism and provide energy

Treat the cause

Address the underlying disorder

The Treatment Priorities

STOP

Catabolism / protein
temporarily

START

High-calorie IV glucose
± lipid

ENHANCE

Nitrogen disposal

REMOVE

Ammonia when
necessary

Treat immediately — diagnose simultaneously

What Should We Do Immediately?

STOP

Protein temporarily

START

High-calorie IV glucose
± lipid
Ammonia-lowering
therapy

CORRECT

Dehydration
Electrolyte abnormalities
Precipitating factors

MONITOR

Plasma ammonia
frequently

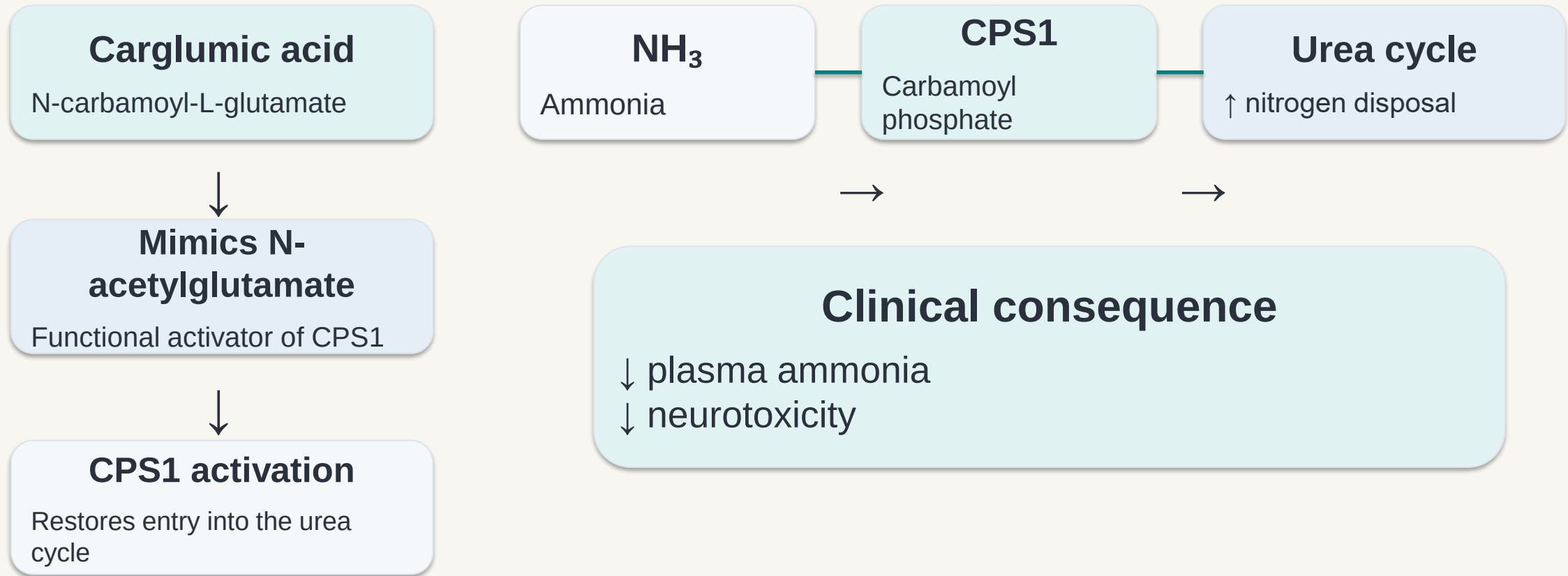
Pharmacological Treatment

Strategy	Examples
Alternative nitrogen disposal	Benzoate; phenylacetate/phenylbutyrate
Urea-cycle substrates	Arginine; citrulline
Urea-cycle activation	Carglumic acid
Adjunctive therapy	L-carnitine; cofactors

Drug mechanism

Drug	Main principle
Sodium benzoate	Glycine conjugation
Phenylacetate	Glutamine conjugation
Phenylbutyrate	Prodrug of phenylacetate
Glycerol phenylbutyrate	Alternative nitrogen disposal

How Does Carglumic Acid Work?



Disorder	Sodium benzoate (to be given IV in glucose 10%)	Sodium PBA/Sodium phenylacetate (to be given IV in glucose 10%)	L-arginine hydrochloride (to be given IV in glucose 10%)	N-carbamylglutamate (only available as oral/enteral drug)
Undiagnosed patient ^a	250 mg/kg as bolus in 90-120 minutes, then maintenance 250-500 mg/kg/d ^c >20 kg bw: 5.5 g/m ² /d	250 mg/kg as bolus in 90-120 minutes, then maintenance: 250-500 mg/kg/d ^c	250(-400) mg/kg (1–2 mmol/kg) as bolus in 90-120 minutes, then maintenance 250 mg/kg/d (1.2 mmol/kg/d)	100 mg/kg bolus per NG tube then 25-62.5 mg/kg every 6 h
NAGSD	Same ^c	Same ^c	250 mg/kg (1.2 mmol/kg) as bolus in 90-120 minutes, then maintenance 250 mg/kg/d (1.2 mmol/kg/d)	Same
CPS1D and OTCD	Same ^c	Same ^c	Same	-
ASSD	Same ^c	Same ^c	Same	-
ASLD ^d	Same ^c	Same ^c	200-400 mg/kg (1–2 mmol/kg) as bolus in 90-120 minutes, then maintenance 200-400 mg/kg/d (1–2 mmol/kg/d)	-
ARG1D ^b	Same ^c	-	AVOID	-
HHH syndrome	Same ^c	Same ^c	250 mg/kg (1.2 mmol/kg) as bolus in 90-120 minutes, then maintenance 250 mg/kg/d (1.2 mmol/kg/d)	-

Where Does Carglumic Acid Fit?

NAGS deficiency

Specific / first-line therapy

Propionic acidemia

Hyperammonemic crisis

Methylmalonic acidemia

Hyperammonemic crisis

Isovaleric acidemia

Hyperammonemic crisis

Other causes: evidence is limited and use should be individualized.

Mechanisms of Hyperammonemia in PA and MMA

1 -Urea-cycle inhibition

Accumulation of propionyl-CoA or methylmalonyl-CoA can competitively inhibit NAGS and CPS1, impairing activation of the urea cycle.

2 -Impaired ammonia detoxification

High concentrations of 2-methylcitric acid can inhibit glutamine synthase, contributing to increased ammonia and reduced glutamine.

Evidence for Carglumic Acid

Acute decompensation

98 episodes
Carglumic acid $\pm$ scavengers

Randomized trial

38 patients
2-year follow-up

Real-world evidence

Prospective multicenter
PA / MMA

Evidence has moved beyond case reports.

Randomized Clinical Trial in PA/MMA

38 patients

Followed for 2 years

Two groups

Carglumic acid + standard
treatment
vs standard treatment

Key outcome

ER admissions for
hyperammonemia
6.31 vs 12.76
P = 0.0095

**Carglumic acid may reduce recurrent hyperammonemic
decompensations when added to standard treatment.**

**6.31 vs 12.76 ER admissions
P = 0.0095**

Carglumic Acid + Ammonia Scavengers

OR?

Carglumic acid

Urea-cycle activation

Scavenger

Alternative nitrogen
disposal

Metabolic support

Reverse catabolism

In severe crisis: think complementary

When Should I Give Carglumic Acid?

Known NAGS deficiency

→ Start

PA / MMA / IVA + hyperammonemia

→ Start

Other severe hyperammonemia

→ Individualized decision

Carglumic Acid: Acute Dosing

100 mg/kg/day

Initial dose



**Up to 250 mg/kg/day if
necessary**

Adjust according to

Plasma ammonia response

**CARBAGLU®
200 mg**



Maintenance therapy

10–100 mg/kg/day

Individualize according to metabolic control and plasma ammonia response

Carglumic acid responsiveness test

- In a comatose child, start with a dose of 100 to 250 mg/kg/day and measure ammonia plasma concentration at least before each administration
- It should normalise within a few hours after starting Carbaglu

Administration

200-mg tablets

Dispersible formulation

Prepare

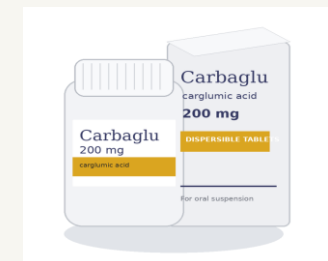
Disperse in water

Route

Oral or nasogastric administration

Dosing schedule

Divide total daily dose into 2–4 doses before meals/feedings



Monitoring and Escalation

1. START

Carglumic acid
+ metabolic support
+ ammonia-lowering
therapy

2. REASSESS

Serial ammonia
Clinical status

3. ESCALATE

If ammonia remains high
or neurological status
worsens

Clinical response determines the next step.

When Is Medical Therapy Not Enough?

Escalate early

- Severe hyperammonemia
- Rapidly increasing ammonia
- Neurological deterioration
- Inadequate response to medical therapy
- Severe ongoing metabolic decompensation

Extracorporeal removal

HEMODIALYSIS

Rapid ammonia clearance

CRRT when continuous control is needed

Do not delay urgent ammonia clearance while waiting for drug response.

Clinical Case: What Would You Do First?

8-year-old with PA

Known propionic acidemia
Weight: 22 kg
Vomiting + lethargy
pH 7.19
 HCO_3^- 10 mmol/L
Ammonia 420 $\mu\text{mol/L}$
Lactate 4.1 mmol/L

First 60 minutes

1. Stop protein temporarily
2. Start high-calorie IV glucose
3. Treat precipitating factor
4. Start ammonia-lowering therapy
5. Add carnitine
6. Send urgent metabolic samples
7. Repeat ammonia frequently

Then ask...

Ammonia remains 390 $\mu\text{mol/L}$ after initial therapy

Neurological status worsens

→ Would you continue waiting?

→ Or initiate extracorporeal ammonia removal?

Escalation should be driven by ammonia trajectory + neurological status, not a single number alone.

Disease-Specific Treatment

Underlying disorder	Main treatment strategy
NAGS deficiency	Carglumatic acid
OTC / other UCDs	Scavengers + arginine/citrulline ± dialysis
PA / MMA	Metabolic therapy + scavengers + carglumatic acid
IVA	Metabolic therapy + carglumatic acid
FAO disorders	Stop catabolism + high-energy therapy
Liver failure / drug-induced	Cause-specific treatment + supportive care

Take-Home Messages

1. Hyperammonemia is a medical emergency — treat immediately.
2. Stop catabolism and restore anabolism.
3. **Carglumic acid is specific therapy for NAGS deficiency and is used during hyperammonemic crises in PA, MMA and IVA.**
4. Carglumic acid can complement, rather than replace, other ammonia-lowering strategies.
5. Monitor ammonia and clinical status closely.
6. Do not delay extracorporeal ammonia removal when rapid clearance is required.

Key References

1. Häberle J, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. J Inherit Metab Dis. 2019.
2. Chakrapani A, et al. Carglumic acid $\pm$ ammonia scavengers in acute decompensation of organic acidurias. 2018.
3. Alfadhel M, et al. Long-term effectiveness of carglumic acid in PA/MMA: randomized clinical trial. 2021.
4. PROTECT Study. Real-world evidence of carglumic acid in PA/MMA.
5. EMA. Carbaglu (carglumic acid) — Product Information / EPAR.

Thank you for your attention

