



Kumamoto University

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*RRD Webinar
3rd of September 2026*

Clinical Experience and Applicable Guidelines for the Management of Hyperammonemia

Carglumic Acid across UCD/OA

International lecture | 45minutes

S. Matsumoto

Carbaglu®/Carglumic acid

Clinical Experience and Applicable Guidelines for the Management of Hyperammonemia

COI Disclosure

Shiro Matsumoto

Kumamoto University

The authors have no financial conflicts of interest to disclose concerning the presentation.

These all studies were supported by
Japan Ministry of Health, Labor and Welfare Research.

Outline

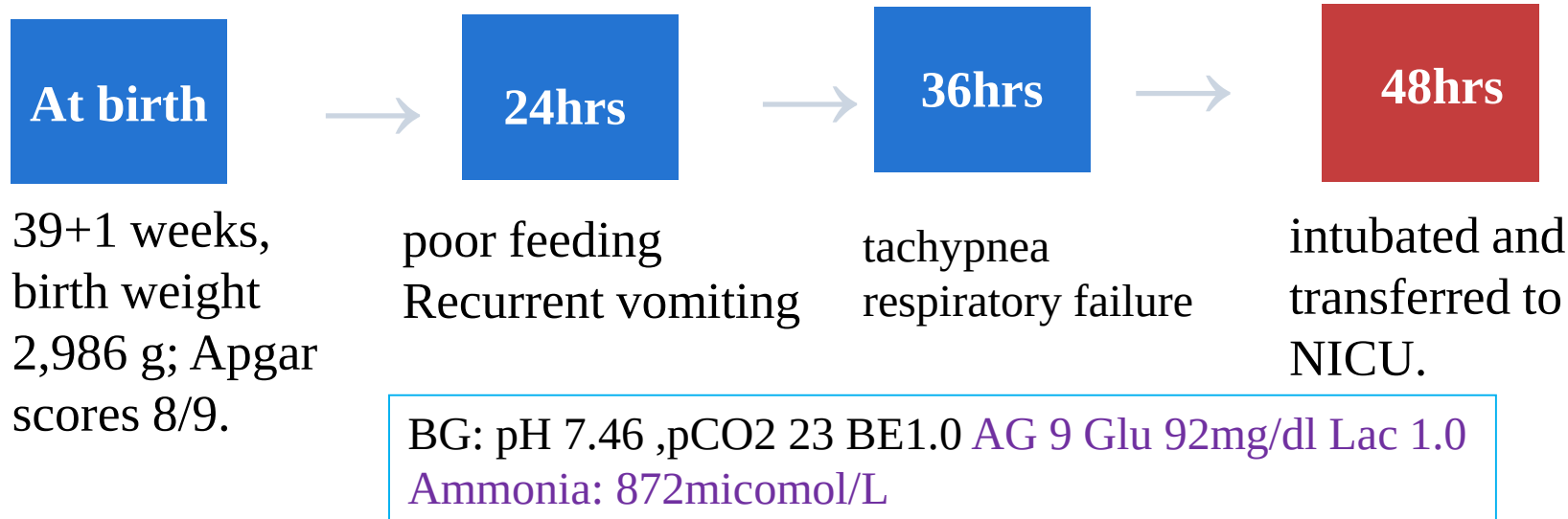
- ✓ Clinical cases of hyperammonemia
- ✓ Hyperammonemia: overview and recent advances
- ✓ Long term outcome and management
- ✓ Pathophysiology-based treatment strategies and exploratory use of Carbaglu



➤ Clinical Cases of Hyperammonemia Urea-Cycle Disorders and Organic Acidemias

Case 1: Typical neonatal-onset Hyperammonemia (CPS1D)

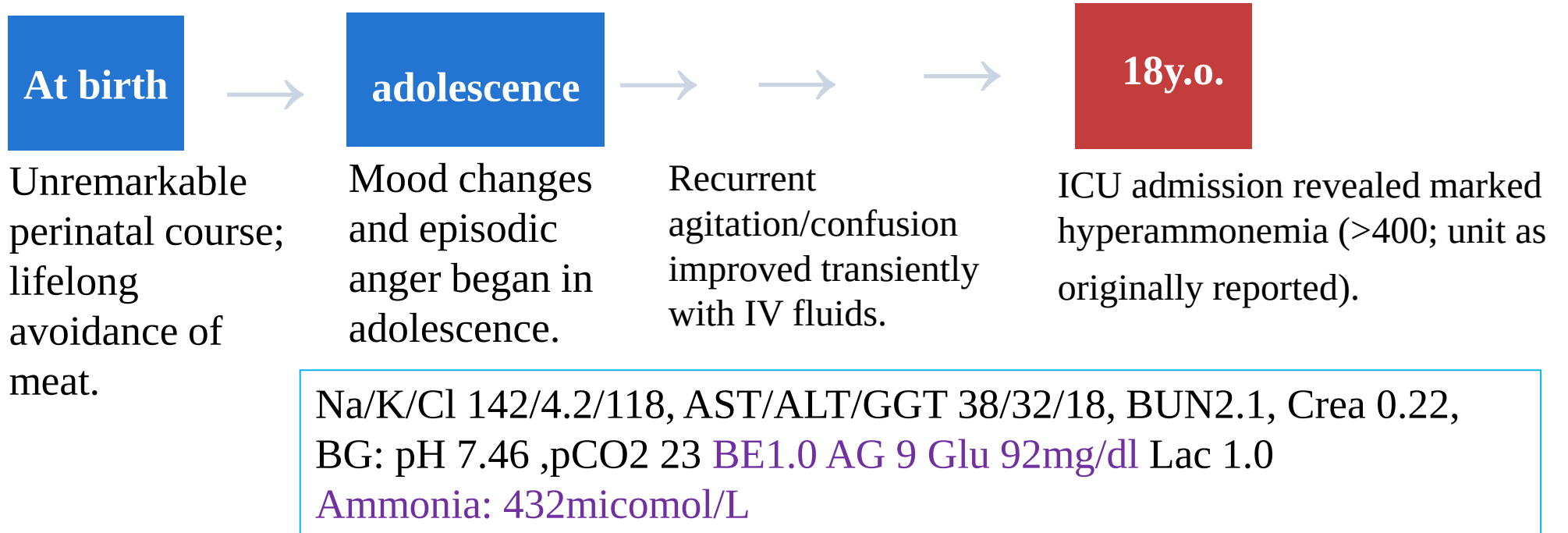
Newborn Japanese boy



Clinical trigger
Anabolic stress into an acute hyperammonemia crisis
without metabolic acidosis and hypoglycemia

Case 2: Late-onset Hyperammonemia (Female OTCD)

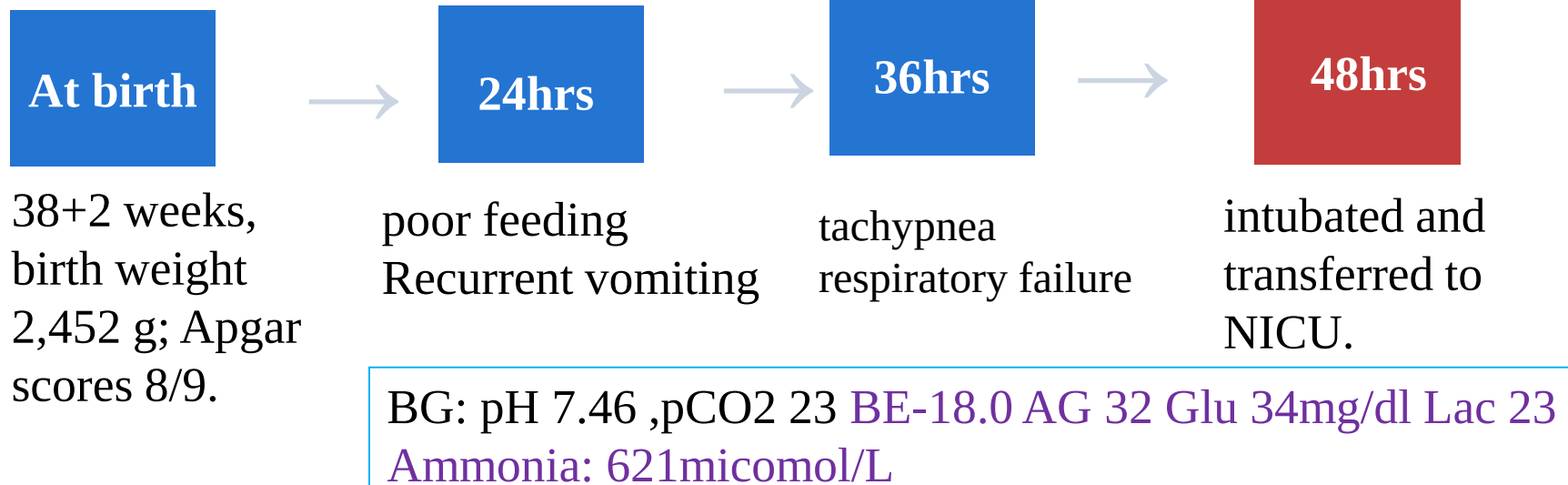
18-year-old woman



1. Avoidance of meat
2. Protein intake and Anabolic stress into recurrent hyperammonemia crisis **without** metabolic acidosis and hypoglycemia

Case 3: Typical neonatal-onset Hyperammonemia with metabolic acidosis (Organic acidemia: MMA)

Newborn Japanese boy

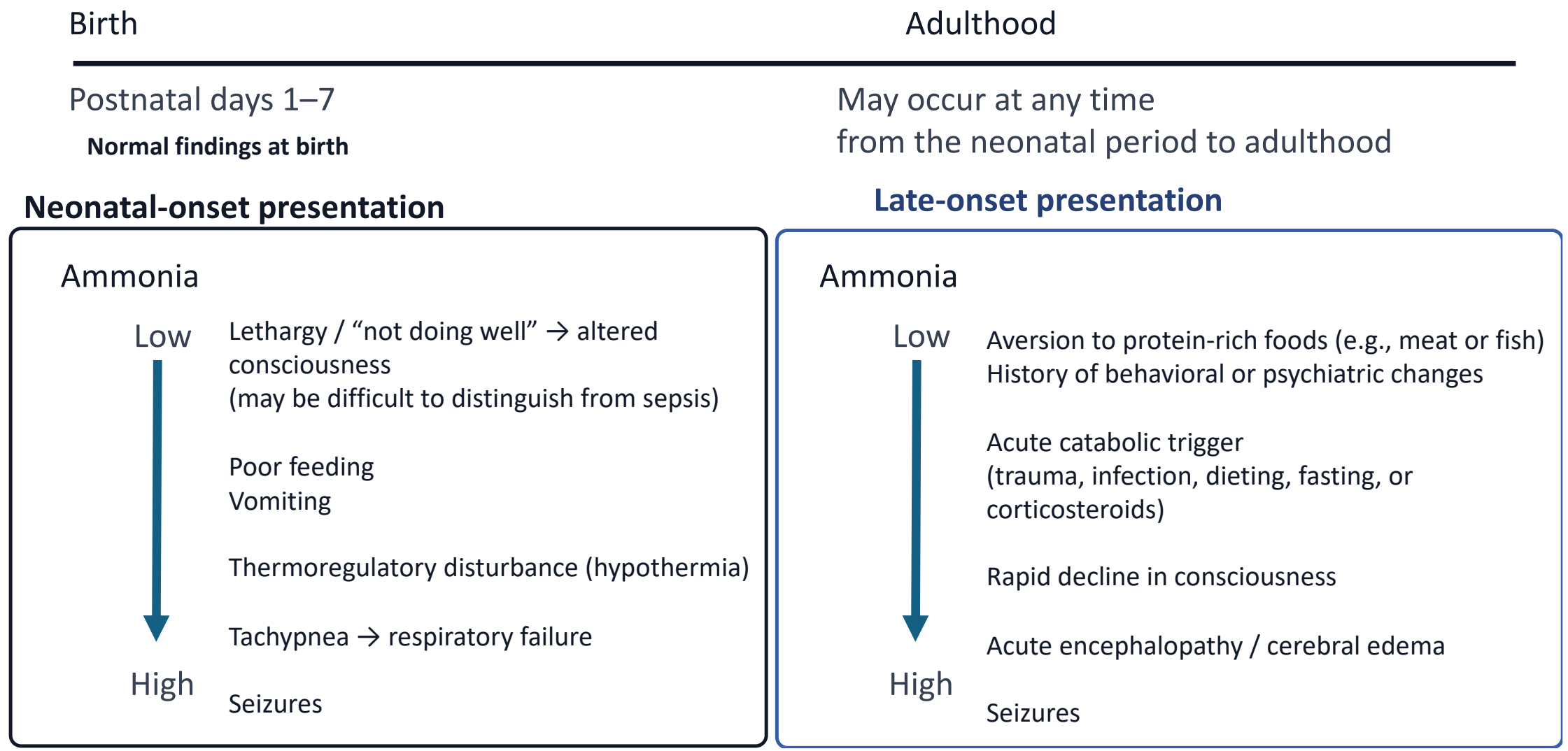


Clinical trigger
Anabolic stress into an acute hyperammonemia crisis
with metabolic acidosis and hypoglycemia

➤ Overview of Hyperammonemia Urea-Cycle Disorders and Organic Acidemias

When to suspect hyperammonemia

Figure 3. Initial Clinical Manifestations



Clinical clues to hyperammonemia

Neonates

Not doing well (Lethargy)



Severe infection
Neuromuscular disease, etc.



Metabolic disorder

Late-onset disease

Unexplained

Treatment-resistant neurological symptoms
or altered consciousness



Encephalitis/encephalopathy
Neurodegenerative disease
Toxins, etc.



Metabolic disorder

1. Maintain a high index of suspicion
2. Recognize manifestations of ammonia neurotoxicity

Causes of hyperammonemia

- Functional impairment of the urea cycle

- Genetic defects (urea-cycle disorders)

- Liver injury (e.g., acute hepatitis)

- Chemical toxicity (e.g., alcohol and organic compounds)

- Severe systemic infection

- Drug-induced

- Valproate

- Chemotherapy

- Antifungal agents

- Acetaminophen, etc.

- Metabolic disorders other than UCDs

- Organic acidemias

- Carbonic anhydrase 5A deficiency

- Lysinuric protein intolerance

- Ornithine aminotransferase deficiency

- Pyruvate dehydrogenase deficiency

- Fatty-acid oxidation disorders

- Galactosemia

- Hereditary tyrosinemia type I

- Mitochondrial disorders

- Portosystemic shunt

- Excess nitrogen load

- Multiple trauma

- Excessive parenteral nutrition

- Fasting-induced catabolism

- Postpartum stress

- Combined heart–lung transplantation

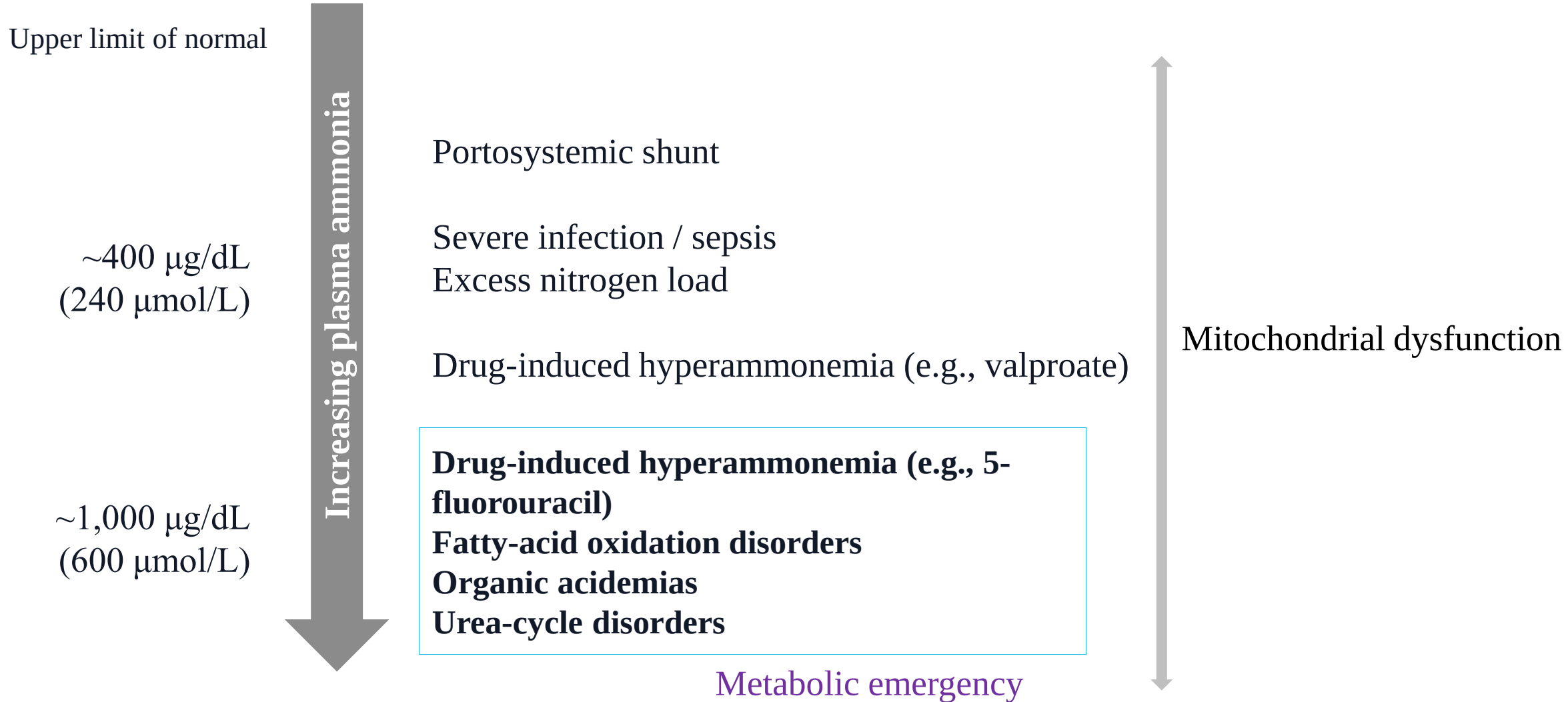
- Renal disease

- Gastrointestinal bleeding

- Other

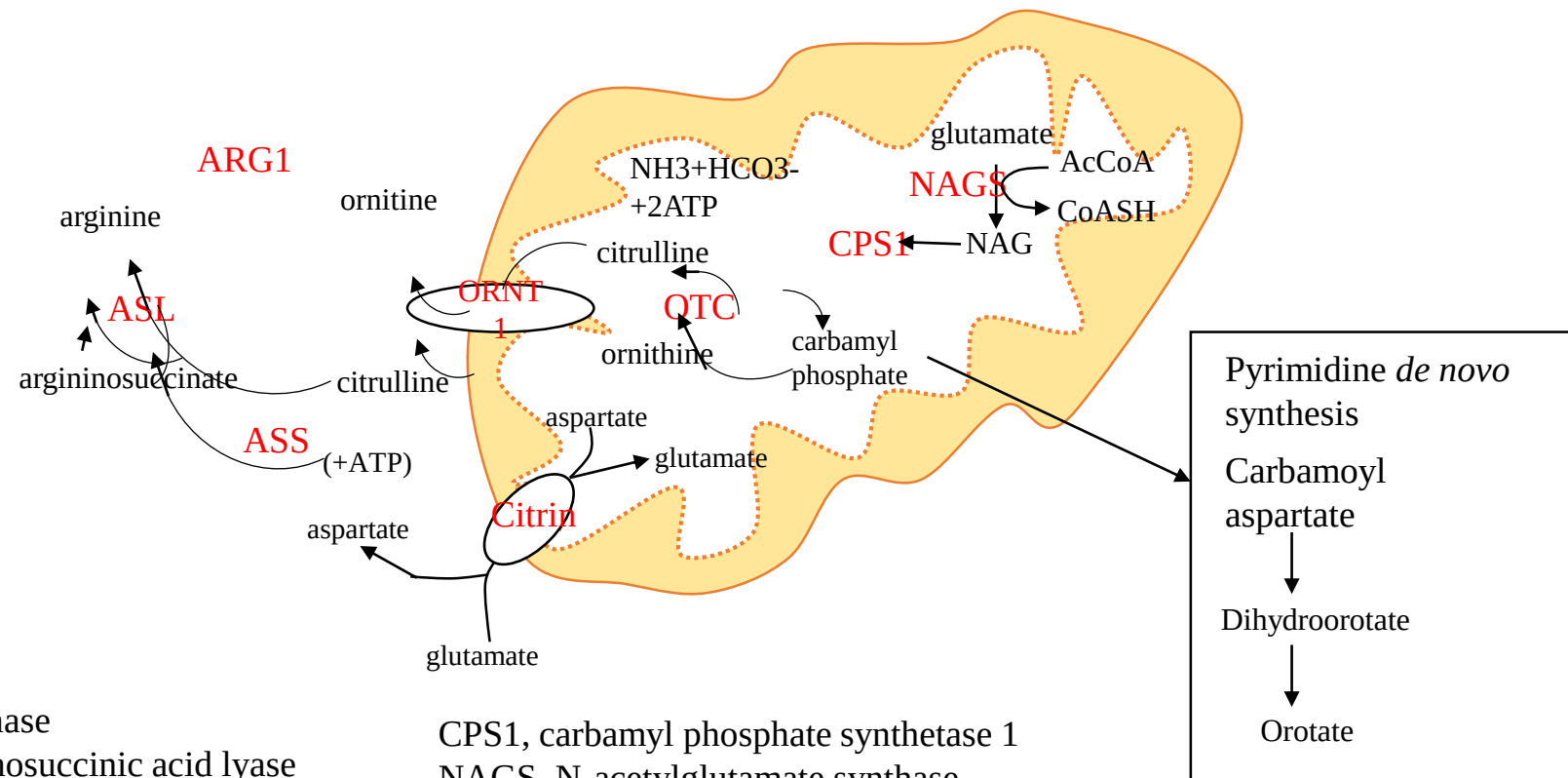
- Excessive protein restriction, etc.

Differential Diagnosis by Degree of Hyperammonemia



Ammonia detoxification through the urea cycle

1) Overall urea-cycle reaction

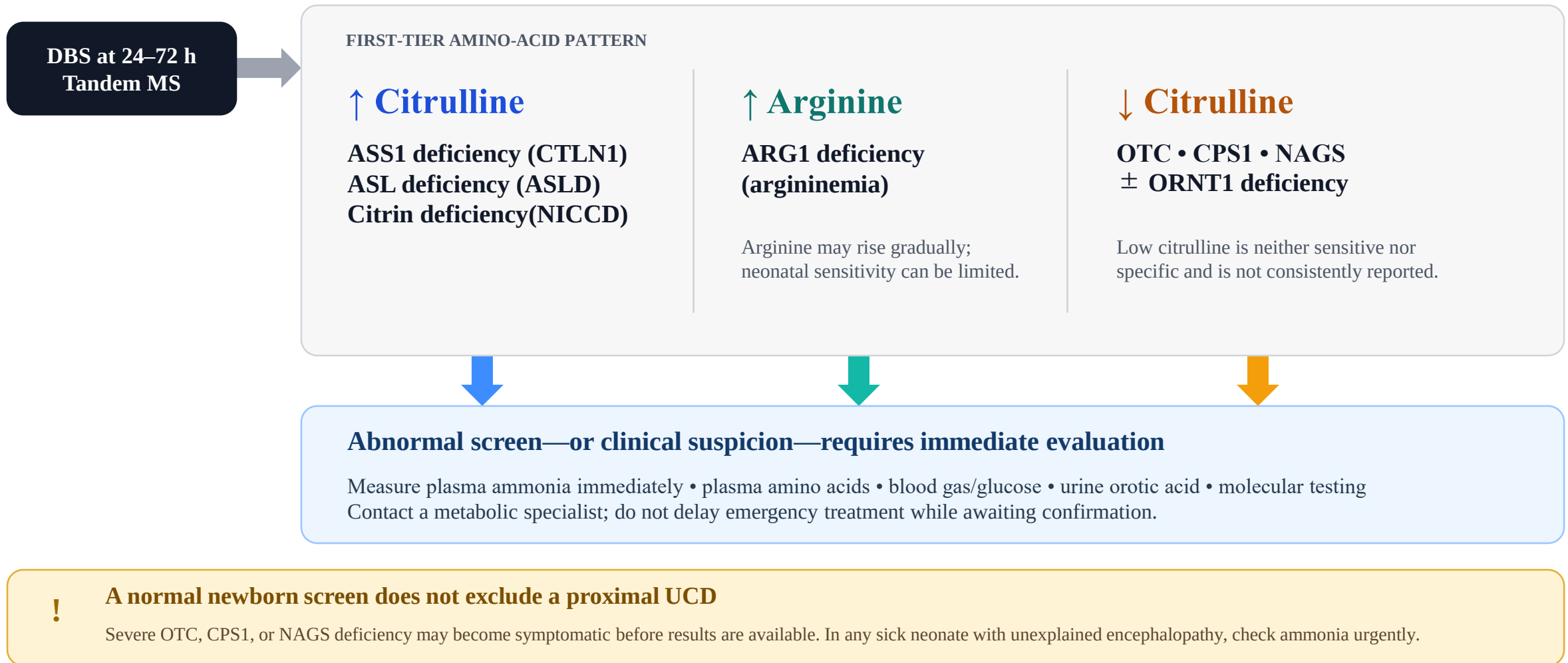


ARG1, arginase
ASL, argininosuccinic acid lyase
ASS1, argininosuccinic acid synthase
ATP, adenosine triphosphate
AcCoA, Acetyl-coenzyme A;

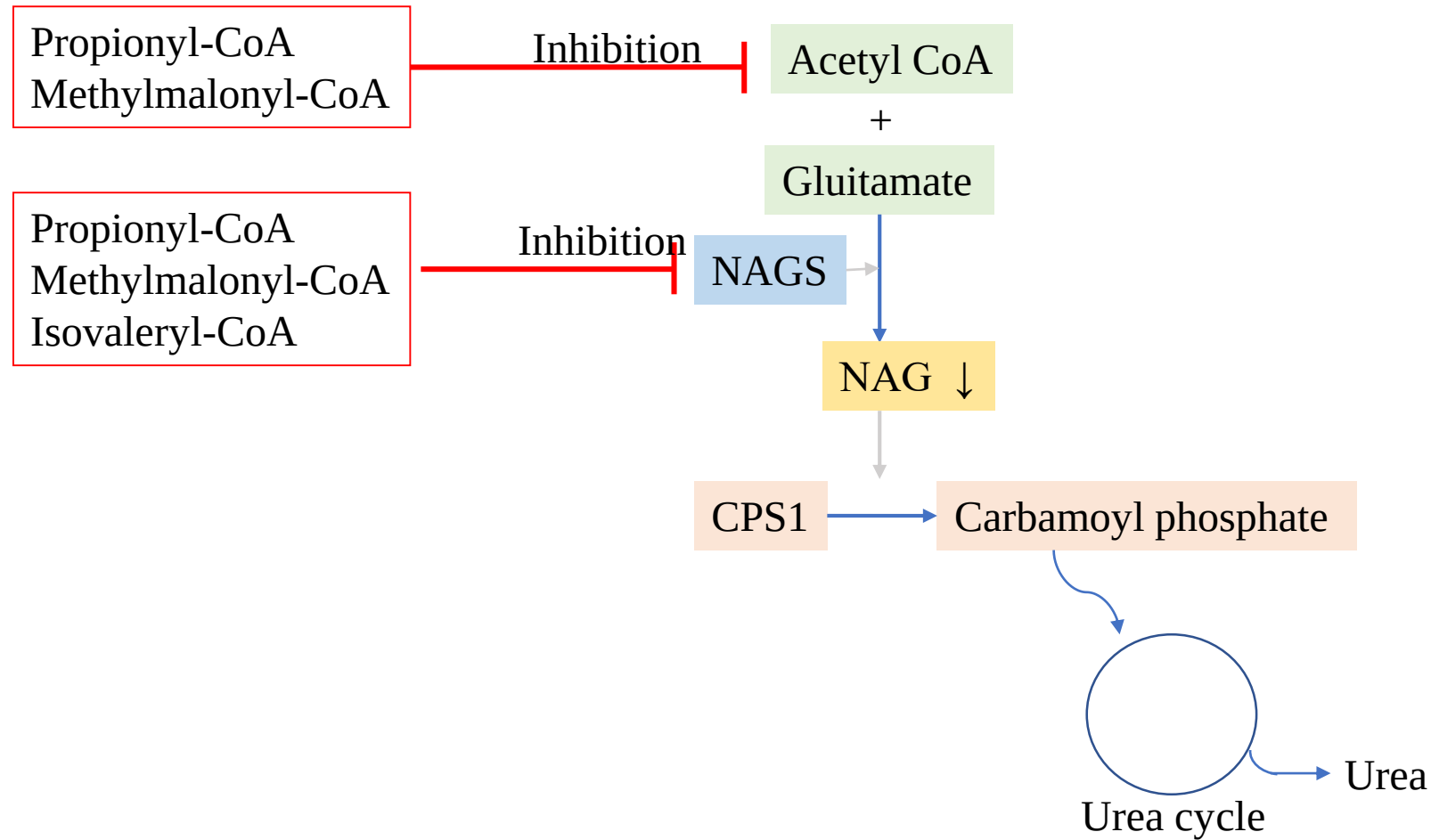
CPS1, carbamyl phosphate synthetase 1
NAGS, N-acetylglutamate synthase
ORNT1, mitochondrial ornithine transporter 1
OTC, ornithine transcarbamylase.

NBS detects distal UCDs better than proximal UCDs

Dried-blood-spot amino acids provide clues—but do not rule out a urea cycle disorder

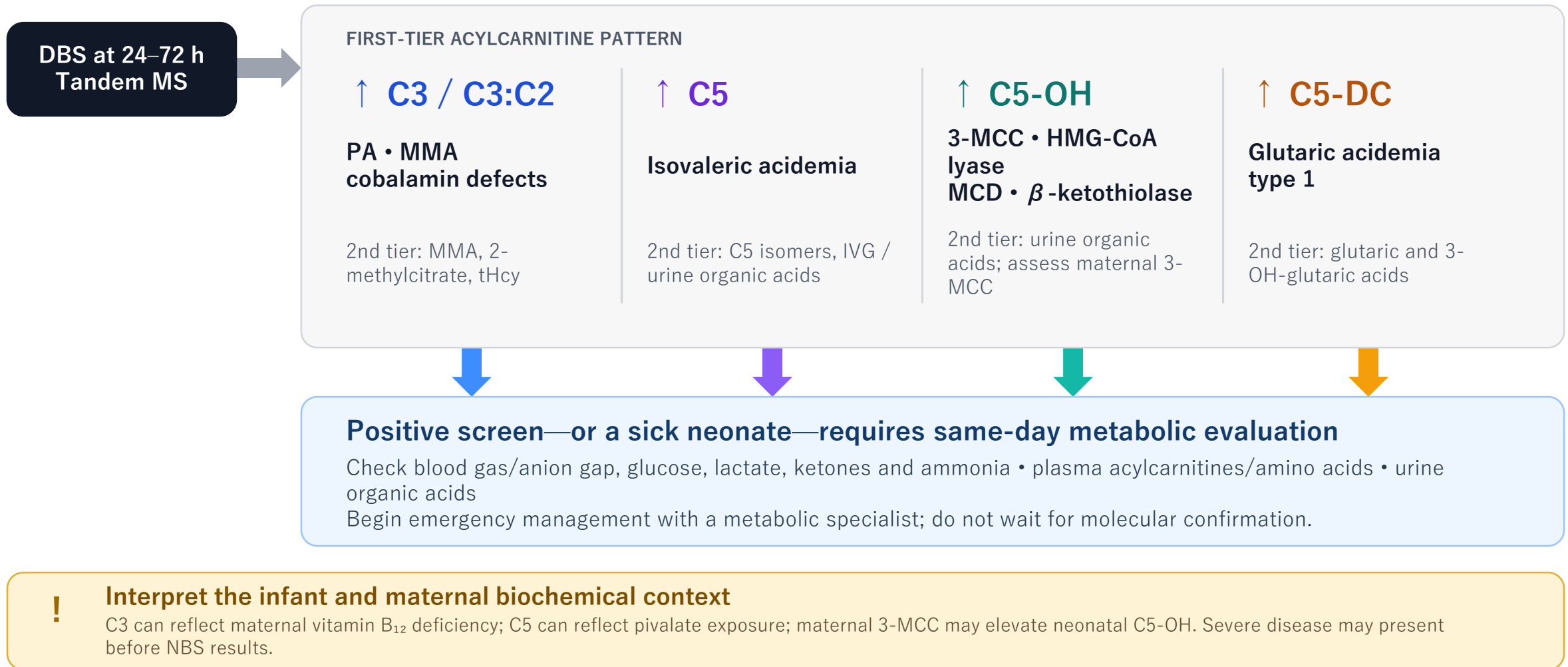


Mechanisms of hyperammonemia in organic acidemias



Acylcarnitine patterns guide—but do not establish—the diagnosis

Second-tier metabolites are essential for rapid, specific follow-up



Labo-data during metabolic crisis

Table 4 Bedside differential diagnostics of inborn errors of metabolism presenting with acute encephalopathy (modified from Haeberle et al. [14])

Parameter	Condition		β-Keto-thiolase deficiency	MSUD	β-oxidation defects	HMG CoA lyase deficiency	HIHA	Mitochondrial/PC deficiency ^e	PDH deficiency
	UCD	MMA/PA							
↑ NH ₃	++	+	-	-	+/-	+	+	+/-	-
Acidosis	+/-	+	++	-	+/-	+	-	+	+
Ketonuria ^a	-	++/+++	+++	+/++	-	-	-	+/++	-
Hypoglycemia ^b	-	+/-	-	-	+	+	++	+/-	-
↑ Lactic acid ^c	-	+	+	-	+/-	+	-	++	++
↑ AST & ALT	(+)	+/-	-	-	++	+/-	-	+/-	-
↑ CPK	-	-	-	-	++	-	-	+/-	-
↑ Uric acid	-	+	+	+	+	+	-	+/-	+/-
↓ WBC/RBC/Plt	-	+	-	-	-	-	-	+/-	-
Weight loss	-	+ ^d	+	+/-	-	-	-	+	-

Non-standard abbreviations include: MSUD, maple syrup urine disease; HMG-CoA lyase, 3-hydroxy-3-methylglutaryl-CoA lyase; HIHA, Hyperinsulinism-hyperammonemia syndrome; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase.

^aKetonuria (++ - +++) suggests OA in neonates.

^bHypoglycemia and hyperammonemia ("pseudo-Reye") are predominant in 3-HMG-CoA-lyase deficiency (more than in PC deficiency).

^cLactic acid elevation refers to a plasma lactate > 6 mmol/l; lower levels of 2-6 mM may be due to violent crying or extensive muscle activity.

^dOnly in neonates.

^eOnly type B associated with hyperammonemia but not types A and C.

Grade of recommendation: D.

Acute Management

- NICU/ICU
- Infusion therapy and alkalization
- Dialysis
- Vitamin B12
- Carnitine
- Metronidazole for selective decontamination of the digestive tract
- Diet therapy, including tube feeding
- Liver transplantation



Acute management for UCD/OA

- Blood Catheter for neonate

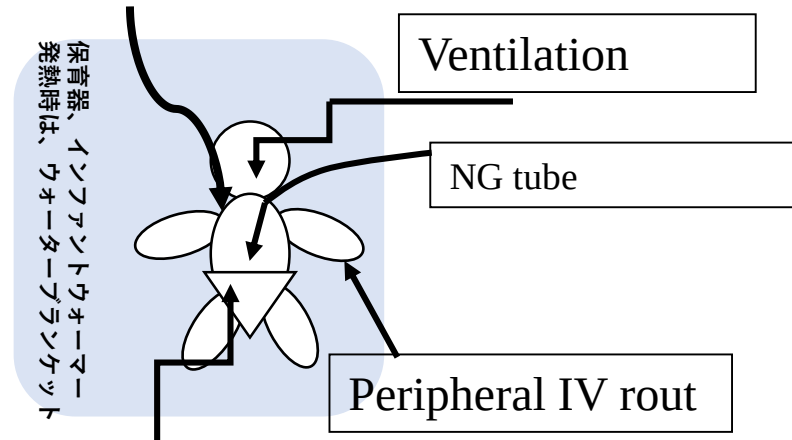


- Performed via ultrasound-guided puncture of the right internal jugular vein.
- The tip is secured near the superior vena cava or the right atrium.
- Continuous hemodiafiltration (CHDF) is used.
- Start at a QB of 15–20 (6–8 mL/kg/min)
- QD and QF are initiated at 500–1,200 mL/h (200–500 mL/kg/h) and adjusted according to the patient's condition

Mangement

Neonatal onset

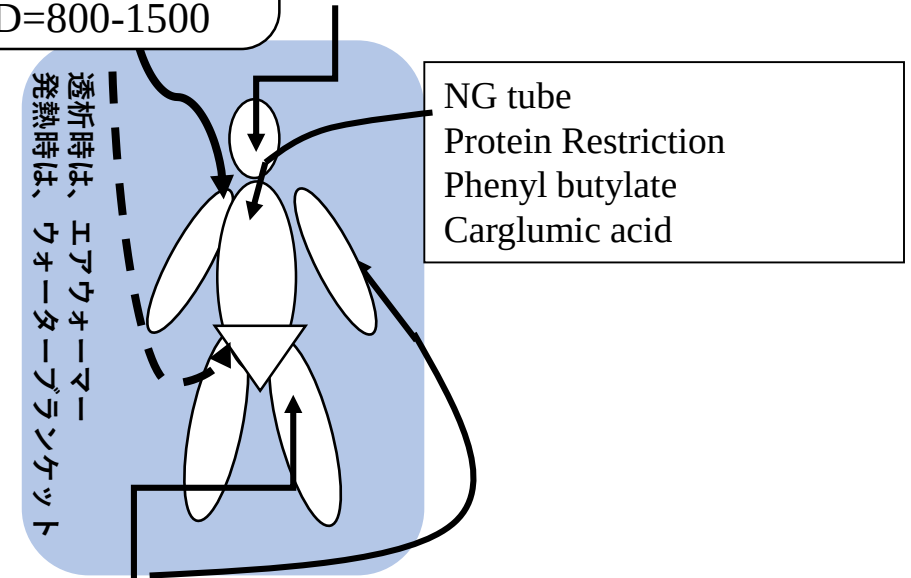
CHD(F) or high-flow CHD
QB 5-10ml/kg/min
 $Q_s/Q_F+Q_D=400-1200$



CV Catheter
15% Glucose
Ammonia Scavenger

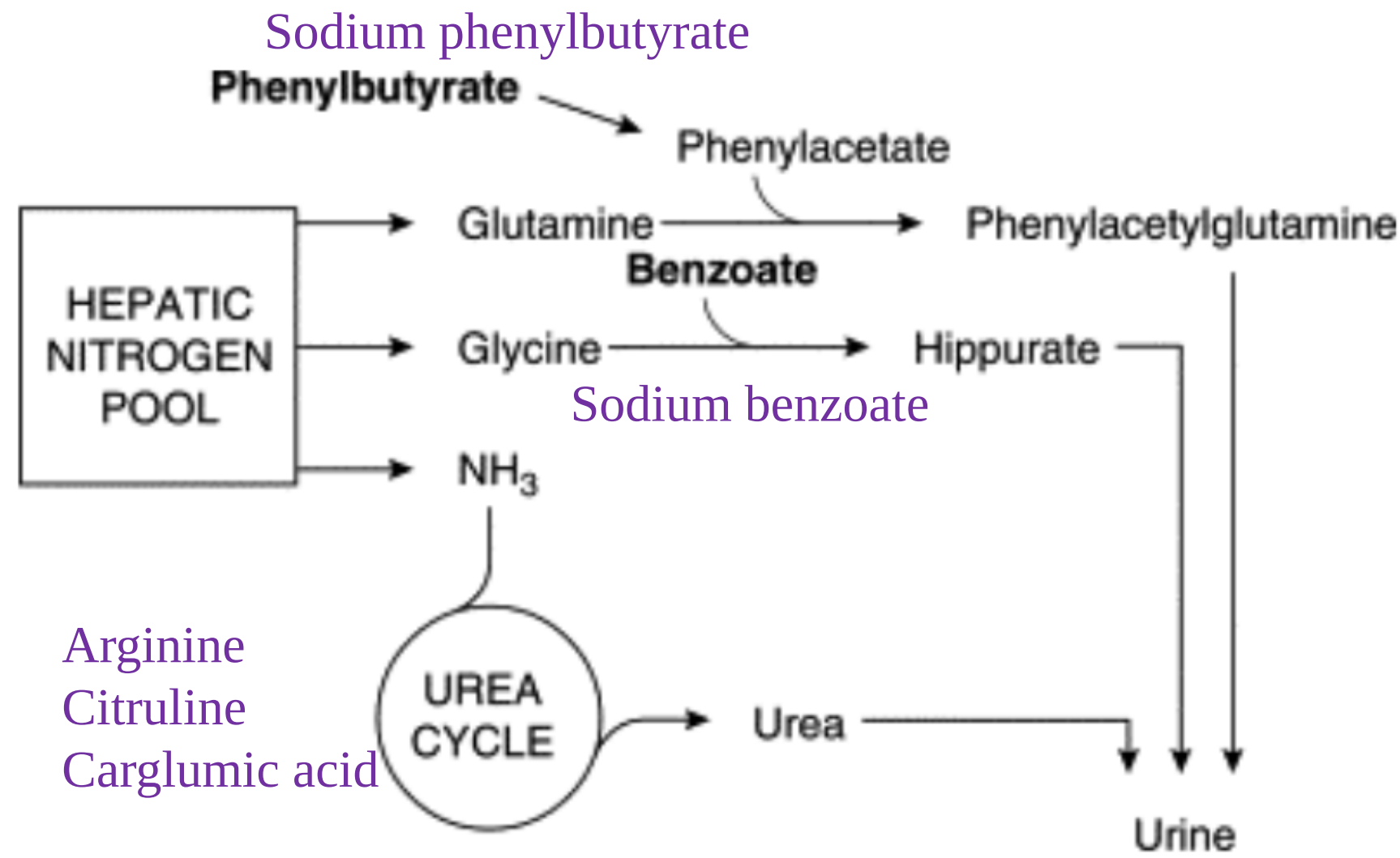
Later onset

CHD(F) or high-flow
CHD
QB 40-60ml/min
 $Q_s/Q_F+Q_D=800-1500$



CV Catheter
15-17.5% Glucose
Ammonia Scavenger

Medications

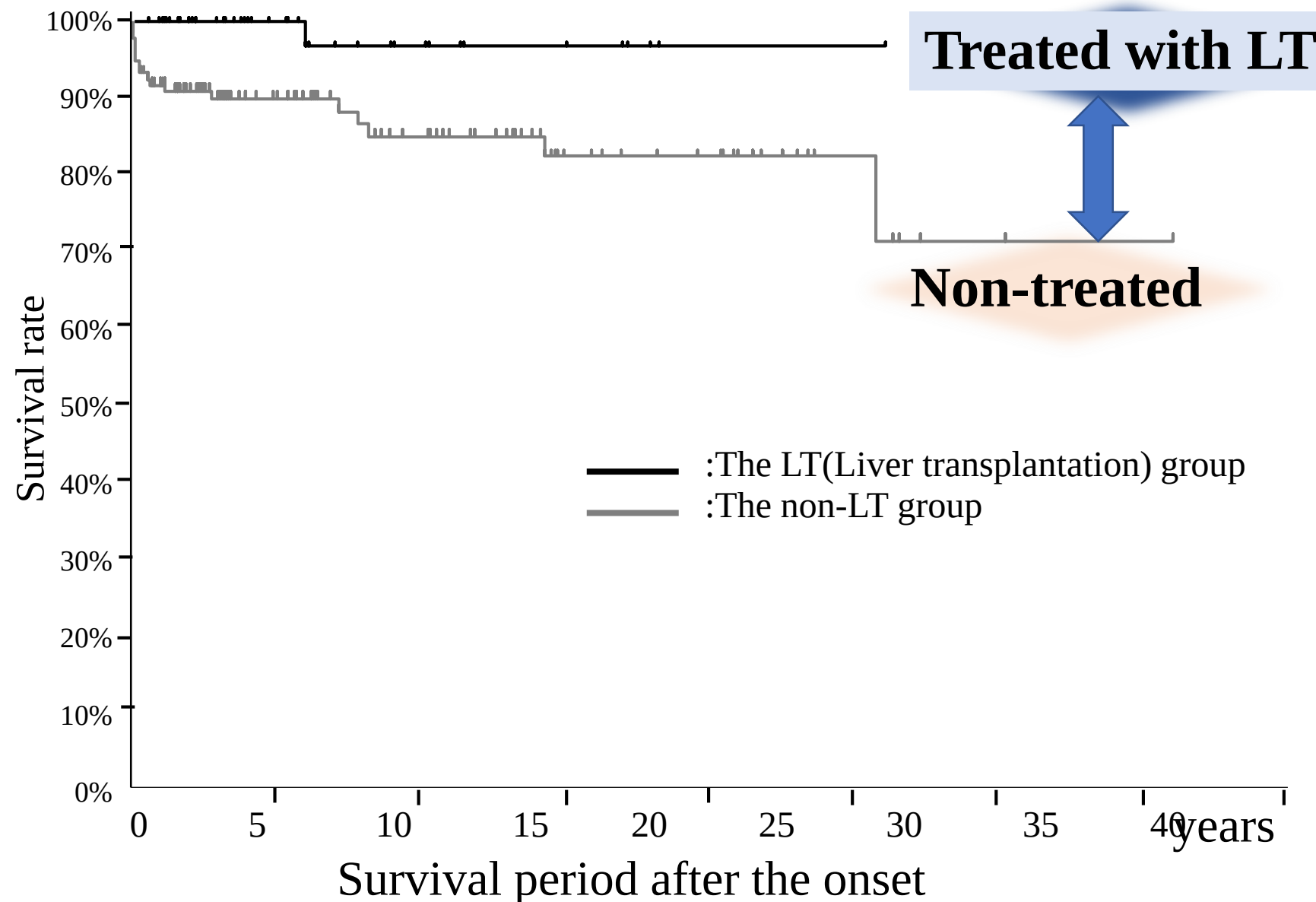


Long-term outcome : Liver transplantation for UCD



UCDs are curable with LT

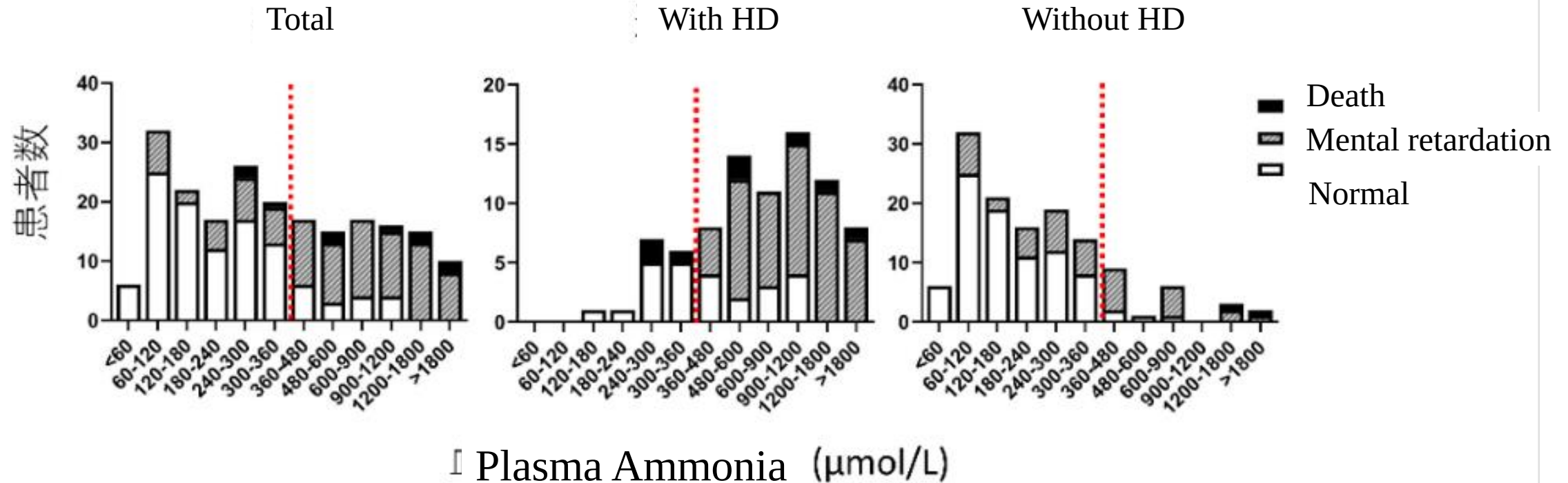
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Neurological outcome in UCDs

UCD cases in Japan

600 $\mu\text{g/dL}$ = 360 $\mu\text{mol/L}$



688 (IQR: 458-1176) $\mu\text{mol/L}$

212 (IQR: 141-294) $\mu\text{mol/L}$

Our 1st study in Japan

Clinical features and management of organic acidemias in Japan

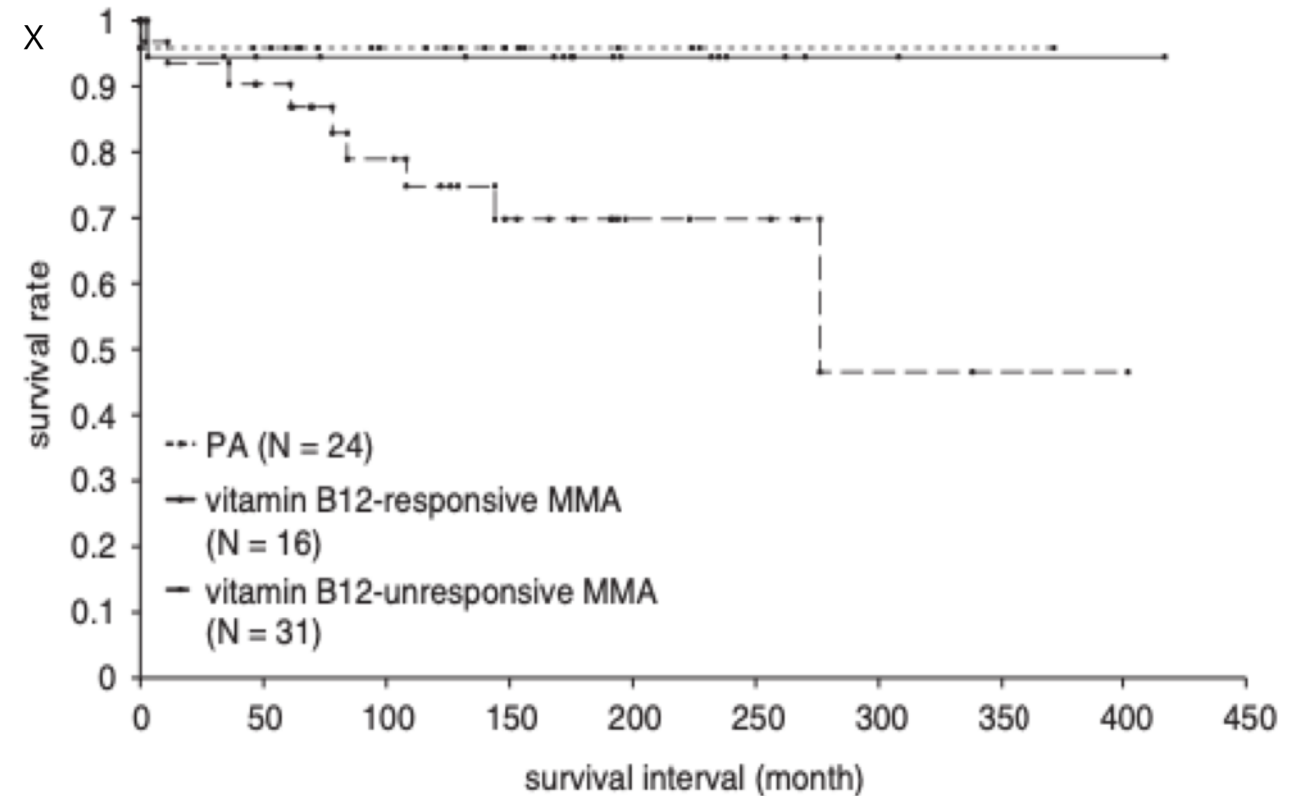
Daisuke Fujisawa¹, Kimitoshi Nakamura¹, Hiroshi Mitsubuchi¹, Toshihiro Ohura², Yosuke Shigematsu³, Tohru Yorifuji⁴, Mureo Kasahara⁵, Reiko Horikawa⁶ and Fumio Endo¹

Organic acidemias (OAs) are rare inborn errors of metabolism. The clinical presentations of methylmalonic acidemia (MMA) and propionic acidemia (PA) in Japan have not yet been examined in detail. We aimed to investigate the clinical presentations of OAs in Japan and evaluate current therapies for improving long-term outcomes, especially in MMA and PA cases. Questionnaires were sent to 928 institutions in 2009 inquiring about OAs, and secondary questionnaires were sent to those who confirmed that they had diagnosed and/or treated such cases; 119 cases were eventually included for analysis. In Japan, the majority of OAs was MMA, which was associated with a high mortality rate. The survival rates at 20 years of age in vitamin B12-unresponsive MMA, vitamin B12-responsive MMA and PA patients were 69.8%, 94.4% and 95.8%, respectively. Factors associated with mortality in MMA were failure to thrive, hypoglycemia and pancreatitis. Factors associated with mental retardation in vitamin B12-unresponsive MMA, vitamin B12-responsive MMA, and PA were seizure and liver dysfunction, seizure and failure to thrive, and failure to thrive, respectively. We advocated that avoiding failure to thrive due to too restricted protein diet, hypoglycemia and pancreatitis associated with mortality lead to improve outcome, especially in vitamin B12-unresponsive MMA patients.

Journal of Human Genetics (2013) 58, 769–774. doi:10.1038/jhg.2013.97. published online 26 September 2013

Table 1 Characteristic of affected individuals

	N (%)	Death case (%)
<i>Methylmalonic acidemia</i>		
Vitamin B12-unresponsive	42 (35.2)	10 (58.8)
Vitamin B12-responsive	20 (16.8)	2 (11.8)
Unidentified on response to vitamin B12	3 (2.51)	1 (5.9)
Propionic acidemia	30 (25.1)	2 (11.8)
Holocarboxylase synthetase (HCS) deficiency	6 (5.0)	—
Glutaric aciduria type II	5 (4.0)	1 (5.9)
Isovalericacidemia	3 (2.5)	—
3-Methylcrotonyl-CoA carboxylase (3MCC) deficiency	3 (2.5)	1 (5.9)
Glutaric aciduria type I	2 (1.7)	—
Multiple carboxylase deficiency	2 (1.7)	—
Ethylmalonic aciduria	1 (0.8)	—
β-Ketotiolase deficiency	1 (0.8)	—
3-Hydroxy-3-methylglutaric aciduria	1 (0.8)	—
Total	119	17



2nd trial: We decided to treat severe type of OAs with LT



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2nd study in Japan: Liver transplantation for IMDs

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ORIGINAL ARTICLE

WILEY

Improvement in the prognosis and development of patients with methylmalonic acidemia after living donor liver transplant

Preoperative characteristics and outcome of patients with MMA – emia who underwent LDLT

LDLT can prevent metabolic crisis and improve growth

Rieko Sakamoto¹ | Kimitoshi Nakamura¹ | Jun Kido¹ | Shiro Matsumoto¹ | Hiroshi Mitsubuchi² | Yukihiro Inomata³ | Fumio Endo¹

Haemodialysis can be undertaken in neonates > 600g

Virtual exp
11th of February 202

Liver transplantation can be undertaken in neonates > 2.6kg in our c

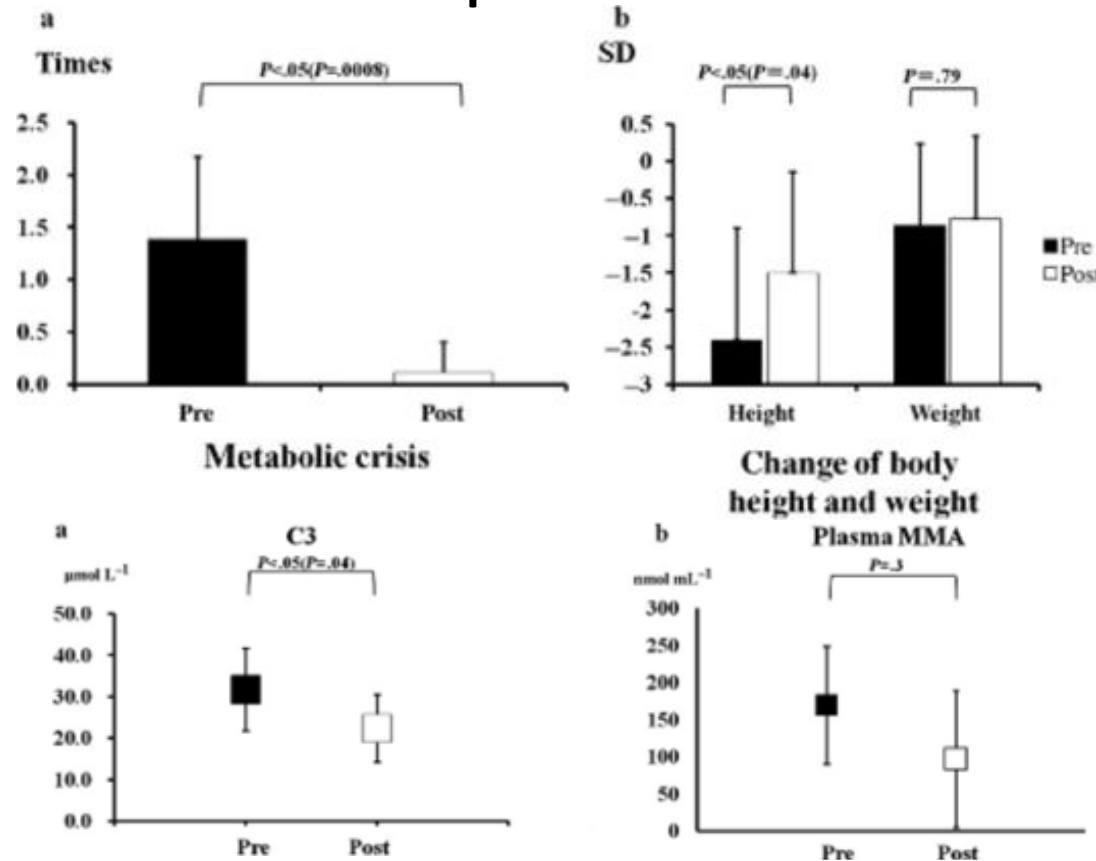
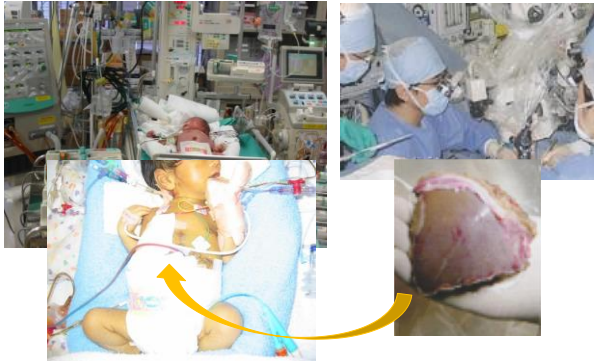


TABLE 3 Renal function and complication of post-LDLT

Case	Cre (mg/dL) Pre/Post	Post-transplant complications
1	0.34/0.47	None
2	0.60/0.70	None
3	0.20/0.28	None
4	0.16/0.31	None
5	0.13/0.33	Adhesive intestinal obstruction (→operation)
6	0.17/0.46	None
7	0.2/0.38	Strangulation ileus (→operation)
8	0.17/0.41	None
9	0.23/0.45	None
10	0.15/0.23	Bile duct stenosis (→operation)
11	0.66/0.80	Bile duct stenosis (→operation), pancreatitis after ERCP, acute renal failure
12	0.21/0.23	Convulsion
13	0.24/0.5	Portal vein stenosis, sepsis, cholangitis, infection (adenovirus, Clostridium difficile)



Living-donor liver transplantation at our center

Case (year)	Disease	Sex	Age at surgery	Donor	Graft
1 (2001)	Primary hyperoxaluria	M	15	Mother	Left lobe
2 (2003)	Wilson disease	F	11	Father	Left lobe
3 (2004)	Wilson disease	M	7	Father	Lateral segment
4 (2006)	Wilson disease	M	15	Mother	Right lobe
5 (2006)	Wilson disease	F	15	Grandmother	Right lobe
6 (2007)	Mitochondrial DNA depletion syndrome	M	0 (9 months)	Mother	Monosegment
7 (2007)	Methylmalonic acidemia	F	0 (11 months)	Mother	Lateral segment
8 (2008)	Methylmalonic acidemia	F	0 (10 months)	Mother	Lateral segment
9 (2008)	Glycogen storage disease type IV	M	0 (10 months)	Mother	Lateral segment
10 (2008)	Methylmalonic acidemia	F	1 (12 months)	Mother	Lateral segment
11 (2009)	Propionic acidemia	M	0 (7 months)	Father	Lateral segment
12 (2010)	Neonatal hemochromatosis	M	0 (13 days)	Father	Monosegment
13 (2011)	Glycogen storage disease type IV	M	0 (5 months)	Father	Lateral segment
14 (2011)	CPS1 deficiency	M	0 (6 months)	Father	Lateral segment
15 (2011)	OTC deficiency	M	0 (8 months)	Father	Lateral segment
16 (2011)	Methylmalonic acidemia	F	1 (23 months)	Mother	Lateral segment
17 (2012)	OTC deficiency	F	1 (22 months)	Mother	Lateral segment
18 (2012)	Methylmalonic acidemia	M	2 (24 months)	Father	Lateral segment

Living-donor liver transplantation at our center

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Disease	ABO compatibility	Rejection	Complications	Outcome
1 Primary hyperoxaluria	Compatible	No	No	Died#1
2 Wilson disease	Identical	No	No	Alive
3 Wilson disease	Compatible	No	No	Alive
4 Wilson disease	Compatible	No	No	Alive
5 Wilson disease	Identical	Yes	No	Alive
(Chronic rejection)				
6 Mitochondrial DNA depletion syndrome	Incompatible	Yes	Yes	Died#2
(Wound infection, bile leak, pleural effusion)				
7 Methylmalonic acidemia	Identical	No	No	Alive
8 Methylmalonic acidemia	Incompatible	No	No	Alive
9 Glycogen storage disease type IV	Compatible	No	No	Died
10 Methylmalonic acidemia	Identical	No	No	Alive
11 Propionic acidemia	Compatible	No	Yes (Bile leak)	Alive
12 Neonatal hemochromatosis	Identical	No	No	Alive
13 Glycogen storage disease type I	Incompatible	No	No	Died#3
14 CPS1 deficiency	Compatible	No	No	Alive
15 OTC deficiency	Compatible	No	No	Alive
16 Methylmalonic acidemia	Identical	No	No	Alive
17 OTC deficiency	Identical	No	No	Alive
18 Methylmalonic acidemia	Incompatible	No	Yes (Hepatic artery occlusion)	Alive

#1 Perforation peritonitis #2 Pulmonary hypertension #3 Heart failure

Biochemical data before, during, and after liver transplantation

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	Pre-LT	Intraoperative	Immediately post-LT	4 months post-LT
C3 (nmol/mL)	13.14	14.27	15.15	10.17
C3/C2	1.06	0.96	0.89	0.39
Methylmalonic acid (mmol/mol Cr)	18,000	14,000	12,000	6,700
Methylcitrate	197	173	250	87
3-Hydroxypropionate	6.0	5.7	5.3	1.5
3-Hydroxybutyrate	0.3	0.2	3.1	0.2
Acetoacetate	0.2	0.2	0.2	0.2
Propionylcarnitine	600	980	450	120
Acetylcarnitine	93	101	142	45
Methylmalonylcarnitine	UD	UD	UD	UD

Living-donor liver transplantation for methylmalonic acidemia

1. metabolic crises → better quality of life and survival
2. Improvement in neurodevelopmental and renal outcomes?
 - One patient developed CKD in their 20s and required dialysis
 - One patient developed rapidly progressive renal dysfunction at age 15 with recurrent crises.
 - One patient experienced metabolic decompensation after rotavirus infection at age 12 and became wheelchair-dependent.
3. Transplantation is not curative → continued medical management is required

At our center, >10-year follow-up has raised questions about the long-term benefit of liver transplantation for severe organic acidemias.



REVIEW

Post-transplantation Outcomes in Patients with PA or MMA: A Review of the Literature

Sufin Yap · Roshni Vara · Ana Morais

Table 1 Overall characteristics of reviewed patients

Characteristic	PA	MMA
Liver transplantation	193	114
Kidney transplantation	2 ^a	21
Combined transplantation	0	32
Retransplantation	9	2
Total transplantation	204	169
Median age at transplant, range, years ^b	0.25–42.0	0.4–28.0
Mortality	27/195 (14%)	18/167 (11%)
Complications ^c	62/115 (54%)	52/106 (49%)

MMA methylmalonic acidemia, *PA* propionic acidemia

^a One patient had a liver transplantation followed approximately 3 years later by a kidney transplant [7]

^b Based on available data

^c Publications not reporting complications and their associated patient numbers were excluded

Today's highlight

Carglumic acid influence (enhance) mitochondria activity

Biogerontology (2018) 19:145–157
<https://doi.org/10.1007/s10522-018-9745-9>



RESEARCH ARTICLE

Repurposed FDA-approved drugs targeting genes influencing aging can extend lifespan and healthspan in rotifers

Terry W. Snell · Rachel K. Johnston · Amelia B. Matthews · Hongyi Zhou · Mu Gao · Jeffrey Skolnick

Biogerontology (2018) 19:145–157

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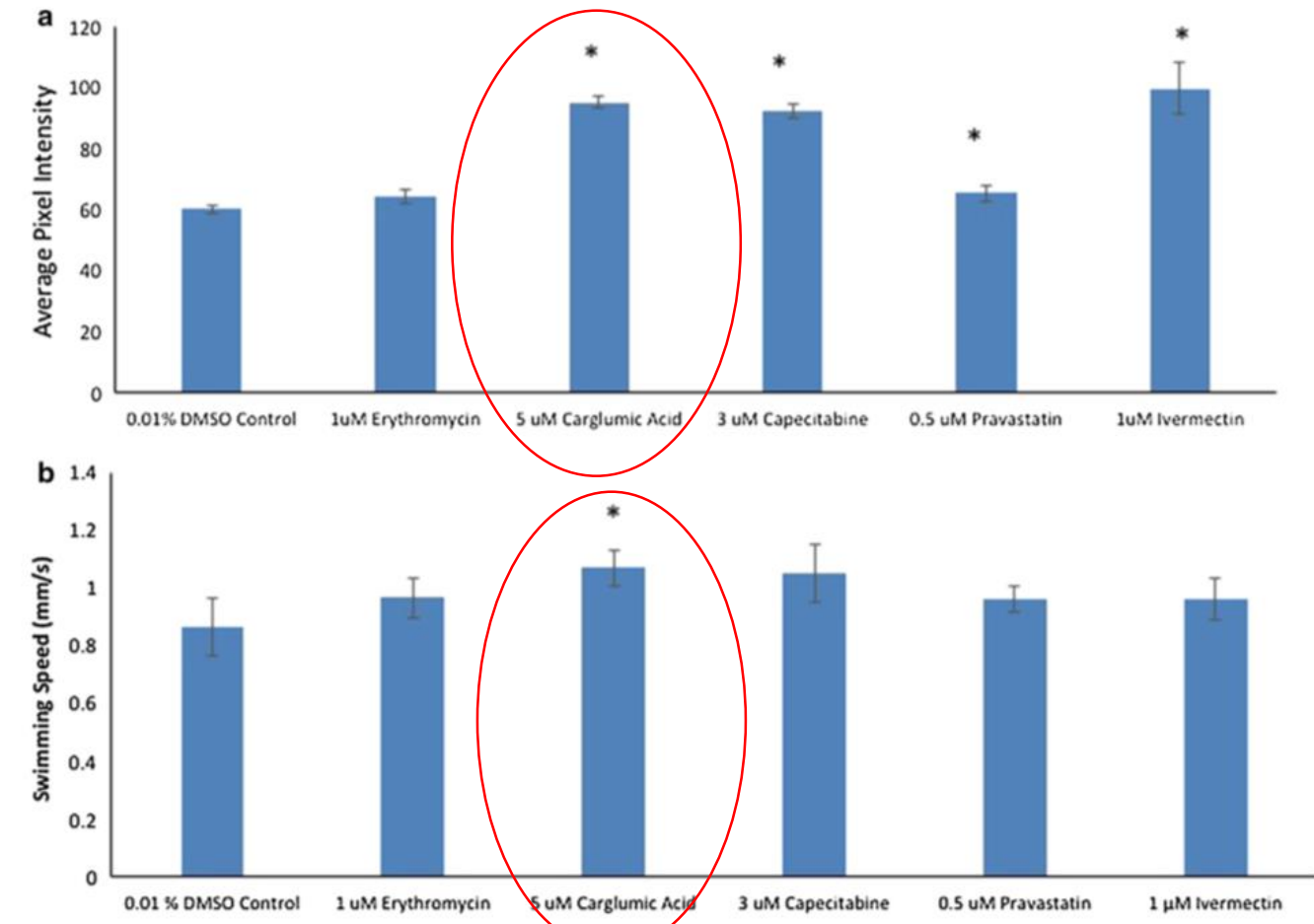


Fig. 4 a, b Drug effects on proxies for rotifer healthspan. Mitotracker estimate of mitochondrial activity is for individual rotifers. Asterisks indicate treatments where mitochondrial activity is significantly higher than control ($P < 0.05$). Asterisks for swimming speed indicate that it is significantly higher than control on day 6 for 5 μ M carglumic acid

Carglumic acids

+



Enhanced
Mitochondria activity
Swimming speed



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Background of OAs

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3. Long-term treatment for OA



Clinical experience with N-carbamylglutamate in a single-centre cohort of patients with propionic and methylmalonic aciduria

Alberto Burlina *, Chiara Cazzorla, Elisa Zanonato, Emanuela Viggiano, Ilaria Fasan, Giulia Polo

Division of Inherited Metabolic Diseases, University Hospital of Padova, Padova, Italy

Decreasing metabolic decompensations

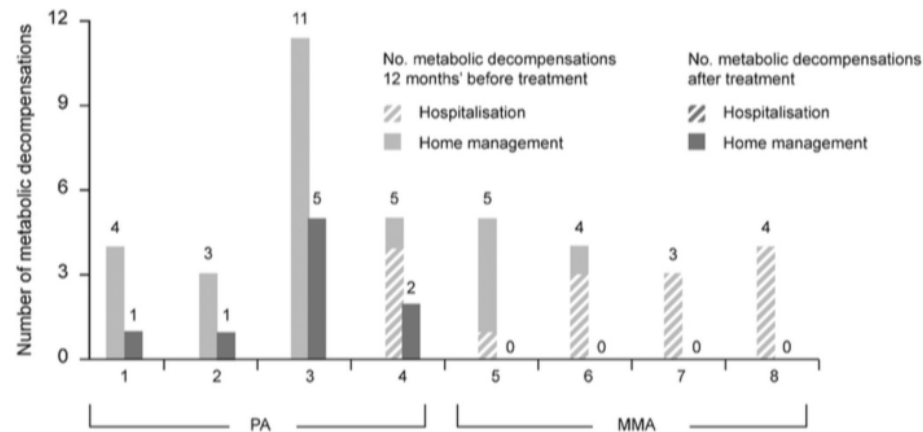
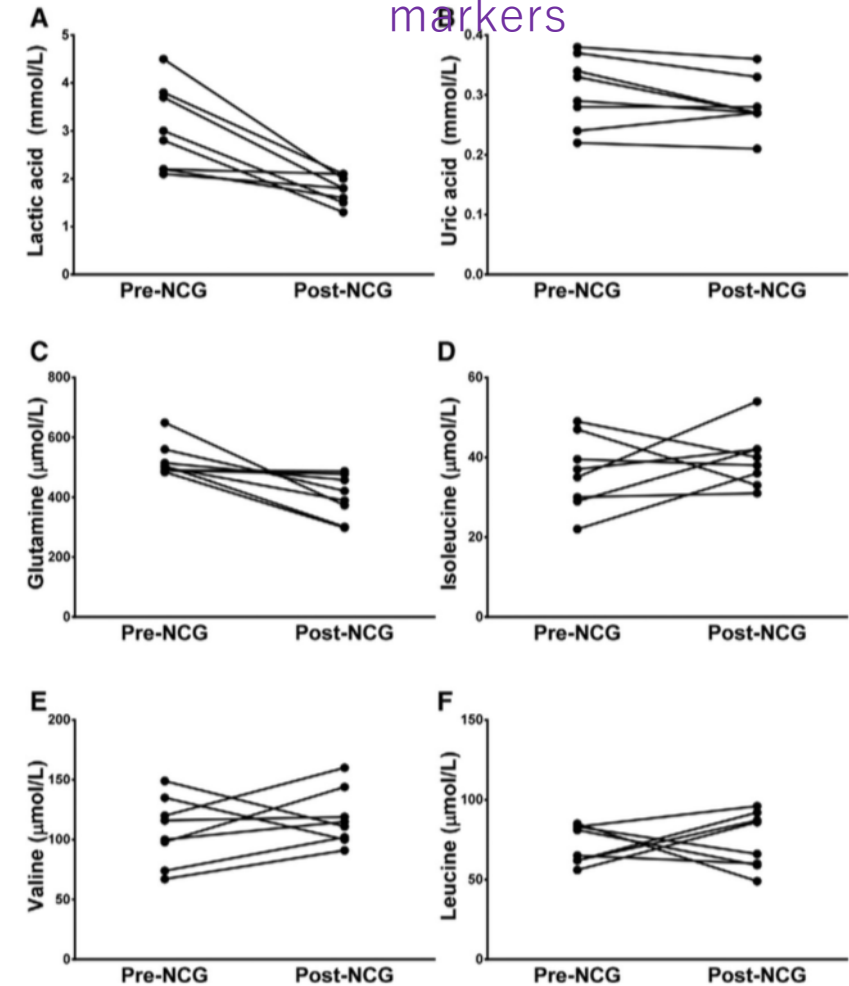


Fig. 1. Metabolic decompensations before and after long-term treatment with NCG (50 mg/kg/day) in patients with PA and MMA. MMA, methylmalonic aciduria; NCG, N-carbamylglutamate; PA, propionic aciduria.

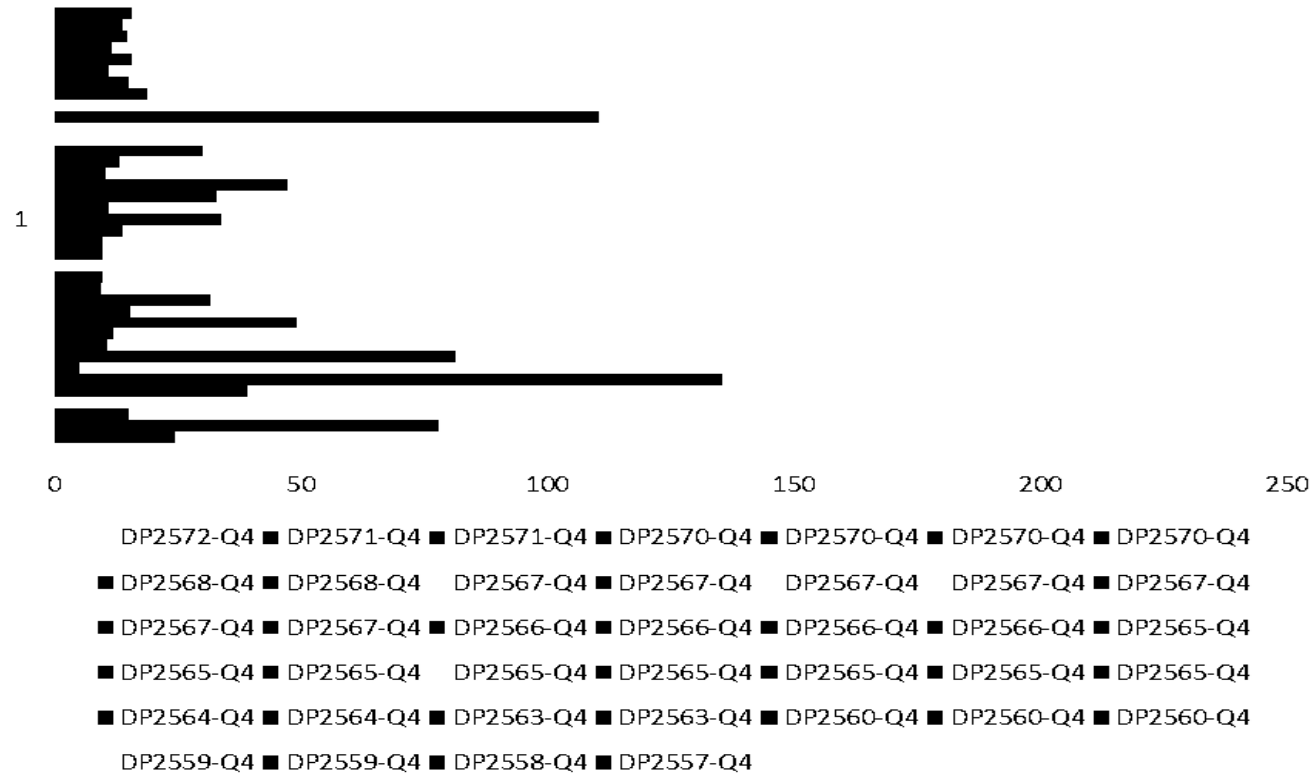
Improved metabolic markers



asma levels of: A) lactic acid, B) uric acid, C) glutamine, D) isoleucine, E) valine, and F) leucine levels after long-term treatment with NCG fMA, methylmalonic aciduria; NCG, N-carbamylglutamate; PA, propionic aciduria.

Raw data for drug screening

488 screening test (SGIMA)
1400 screening test (TOKYO UNIV.)



6 candidates



NCG

The latest trial: long-term treatment of OA and PA

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Population:

1. Carbaglu treatment

	Diagnosis	Weight	Purification	Initial attack	Peak NH3	Recovery from Hyperammonaemia by treatment	CDHF
Case 1	MMA	2446g	CHDF(PAN)	Day 2	623 μ mol/L	5 hours	22 hours
Case 2	MMA	2728g	CHDF(PS)	Day 1	381 μ mol/L	21 hours	129 hours
Case 3	MMA	2882g	CHDF(PS)	Day 5	137 μ mol/L	24 hours	53 hours
Case 4	PA	2488g	CHDF(PS)	Day 4	879 μ mol/L	24 hours	74 hours

2. Liver transplant

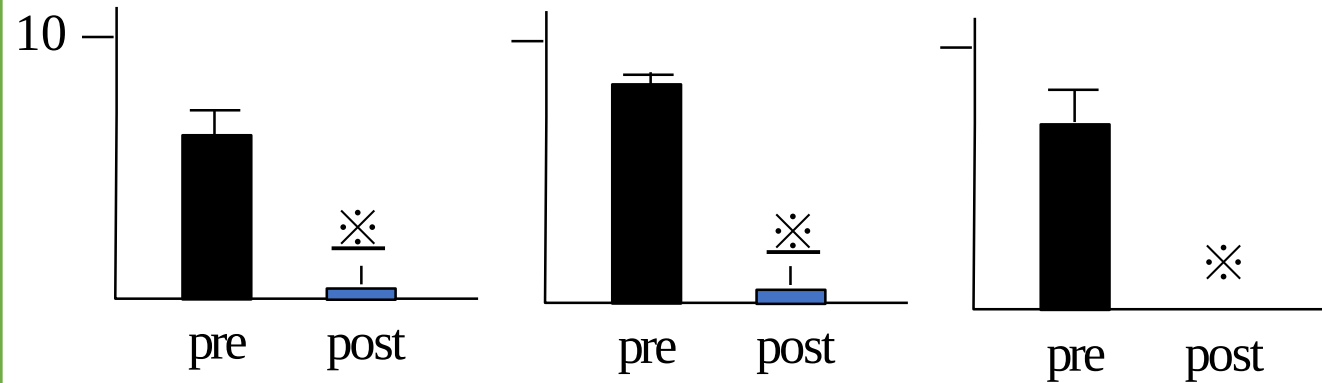
	Diagnosis	Weight	Purification	Initial attack	Peak NH3	Recovery from Hyperammonaemia by treatment	CDHF
Case 1	MMA	2366g	CHDF(PAN)	Day 6	1089 μ mol/L	48 hours	128 hours
Case 2	MMA	28121g	CHDF(PS)	Day 3	520 μ mol/L	52 hours	128 hours
Case 3	MMA	2813g	CHDF(PS)	Day 3	255 μ mol/L	48 hours	98 hours
Case 4	PA	2653g	CHDF(PS)	Day 1	512 μ mol/L	48 hours	74 hours

Method:

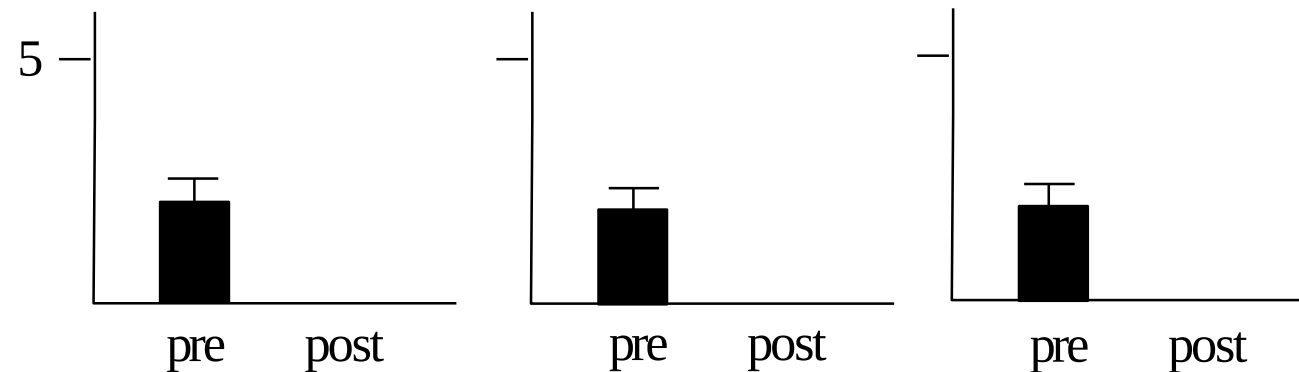
Their plasma concentration of by-products such as methylmalonic acid, propionic acid, ammonia, glucose, lactate, and pyruvate, etc. and their neurological state were evaluated.

Clinical changes in MMA patients treated with carglumic acid

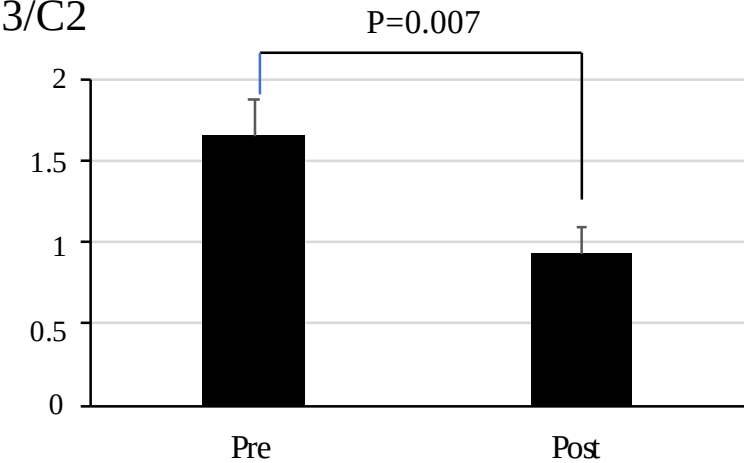
Frequency of hospital admission / month



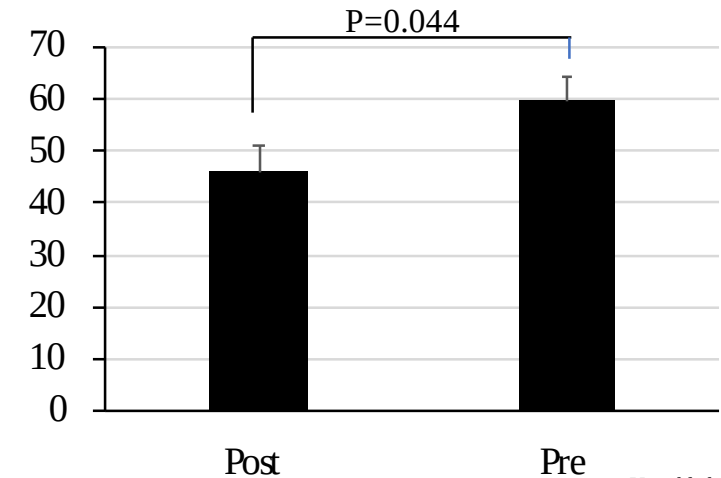
Frequency of vomiting/ day



C3/C2



Developmental index



Challenging for long-term treatment with carglumic acid

Results – Blood analysis before and after carglumic acid and carnitine treatment

Blood acylcarnitine

	At the onset time (before carglumic treatment)	3 months after carglumic treatment	Cut-off values (μ mol/L)
C0	23.96	42.78	<10.00
C2	10.76	24.91	
C3	73.85	9.78	≥ 3.50
C3/C2	6.86	0.39	≥ 0.25
C4	0.32	0.29	≥ 0.60
C5	0.21	0.2	≥ 1.00
C5:1	0.04	0.01	≥ 0.025
C5DC	0.08	0.06	≥ 0.25
OH-C5	0.19	0.24	≥ 0.60
C6	0.08	0.08	
C8	0.09	0.06	≥ 0.30
C8/C10	1	0.79	≥ 1.00
C10	0.09	0.07	≥ 0.40
C12	0.09	0.11	
C14	0.1	0.28	
C14 :1	0.07	0.05	≥ 0.40
C16	0.97	1.73	≥ 3.00
OH-C16	0.01	0.02	≥ 0.05
C0/(C16+C18)	18.75	17.25	≥ 100.00
C18	0.31	0.76	
C18 : 1	0.47	1.02	
C14 : C18 : 1	0.21	0.21	≥ 0.25

Blood amino acids

	At the onset time (before carglumic treatment)	3 months after carglumic treatment	Cut-off values (μ mol/L)
Valine	1.62	0.25	≥ 2.93
Methionine	0.21	0.07	≥ 1.20
Isoleucine + leucine	1.14	0.58	≥ 4.59
Tyrosine	0.77	0.26	≥ 8.00
Phenylalanine	0.48	0.33	≥ 3.00
Citrulline	0.13	0.18	≥ 0.88
Arginine	0.24	0.2	≥ 2.61

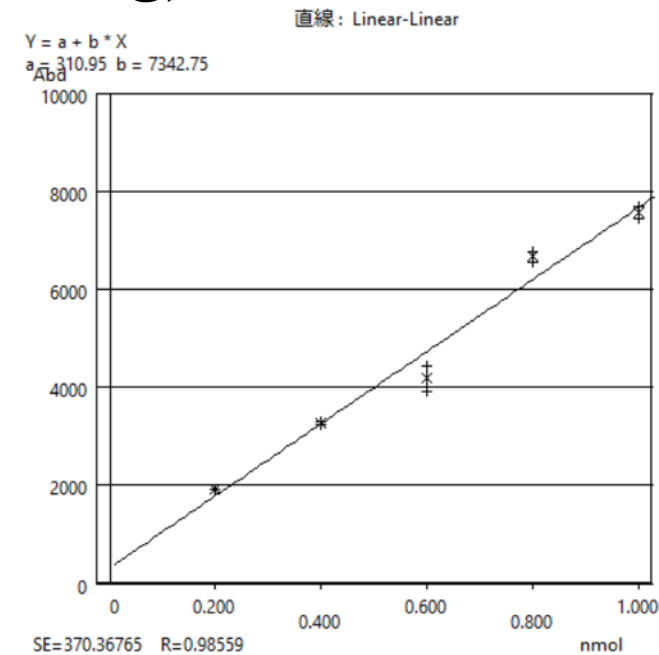
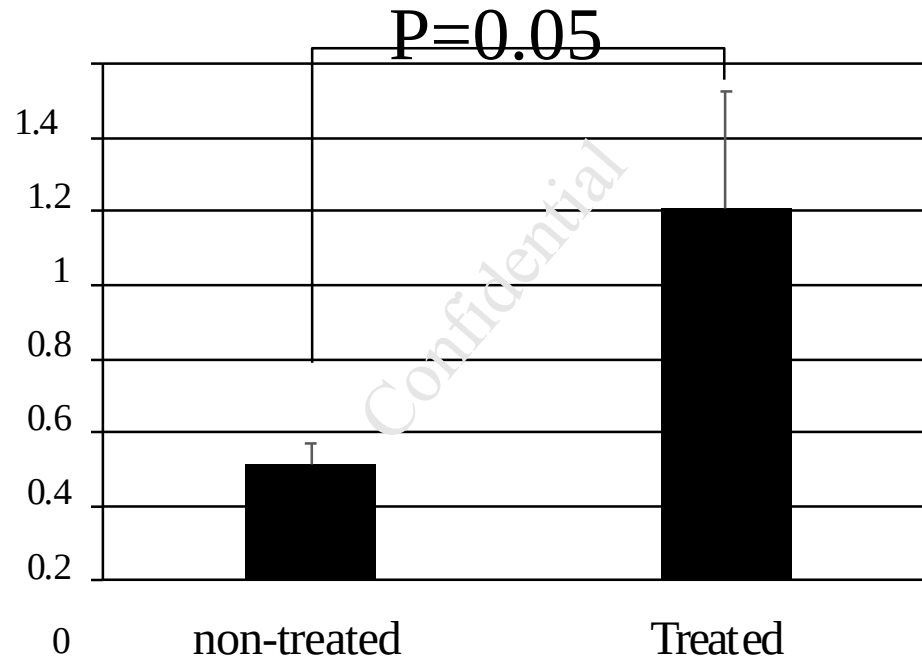
C0: free carnitine; C2: acetylcarnitine; C3: propionylcarnitine; C4: butyrylcarnitine; C5: isovalerylcarnitine; C5:1: tiglylcarnitine; C5-DC: glutaryl carnitine; OH-C5: 3-hydroxy isovalerylcarnitine; C6: hexanoylcarnitine; C8: octanoylcarnitine; C10: decanoylcarnitine; C12: lauroylcarnitine; C14: myristoylcarnitine; C14 : 1: myristoylcarnitine; C16: palmitoylcarnitine; OH-C16: 3-hydroxy palmitoylcarnitine; C18: octadecanoylcarnitine C18 : 1: octadecenoylcarnitine; OH- C18:1: 3-hydroxy octadecenoylcarnitine.



ATP concentration increase in patients' fibroblast after carglumic acid treatment

Patients' fibroblasts were cultured for 14 days & treated with carglumic acid ATP assay undertaken

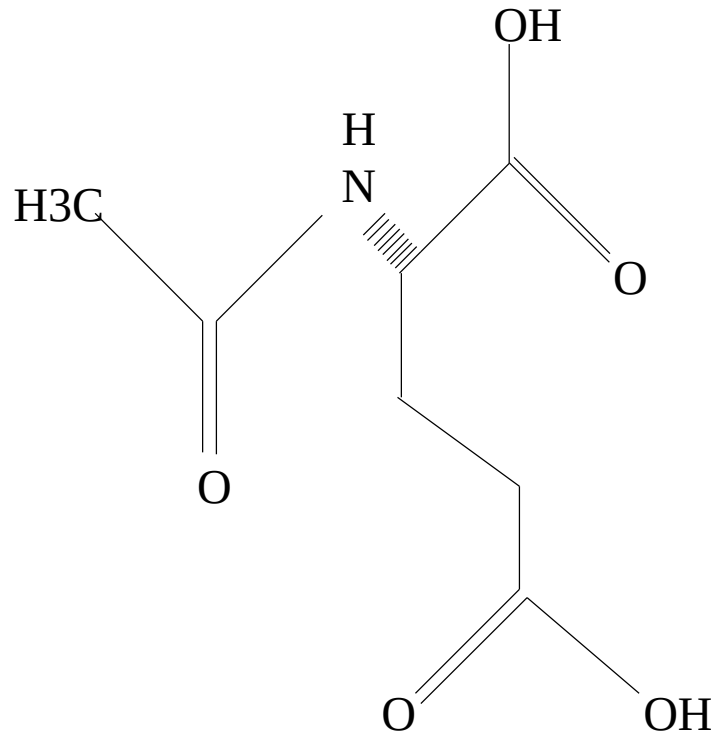
Intracellular ATP concentration (nmol/ml/g)



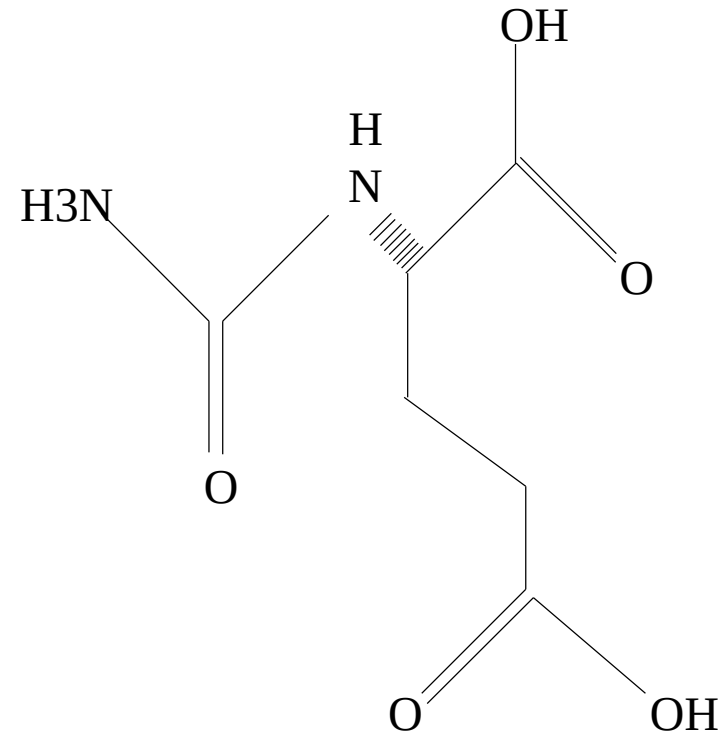
➤ Fundamentals of carglumic acid

Three horizontal lines in blue, yellow, and purple colors spanning the width of the slide.

Figure 1. Chemical structures of carglumic acid and NAG



N-acetylglutamate
(NAG)



N-carbamyl-L-glutamate
(carglumic acid)

Carbaglu[®]

(carglumic acid) tablets for oral suspension
200mg



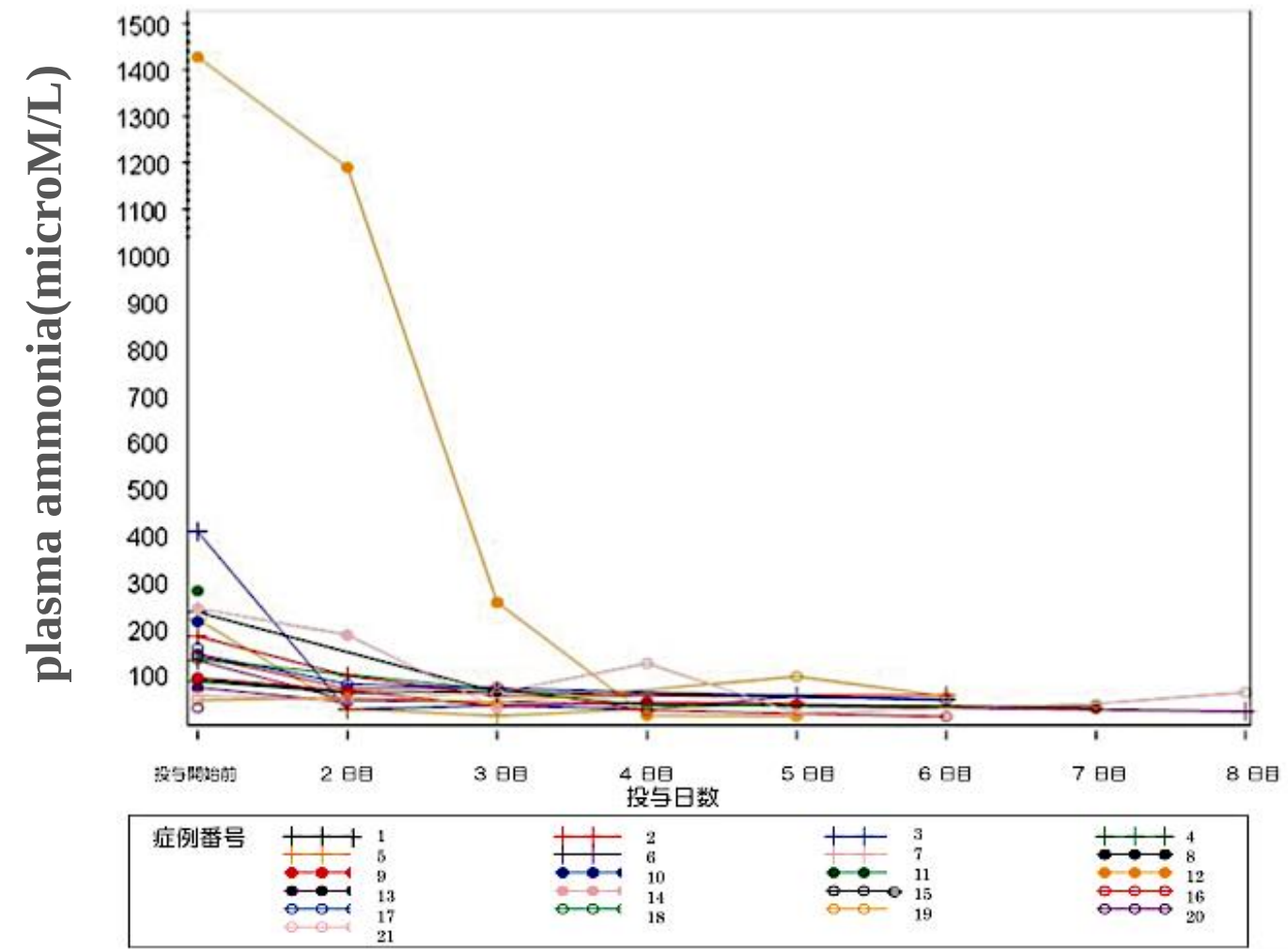
Initial dose

Start at 100–250 mg/kg/day

Administer orally in 2–4 divided doses after dispersion in water.

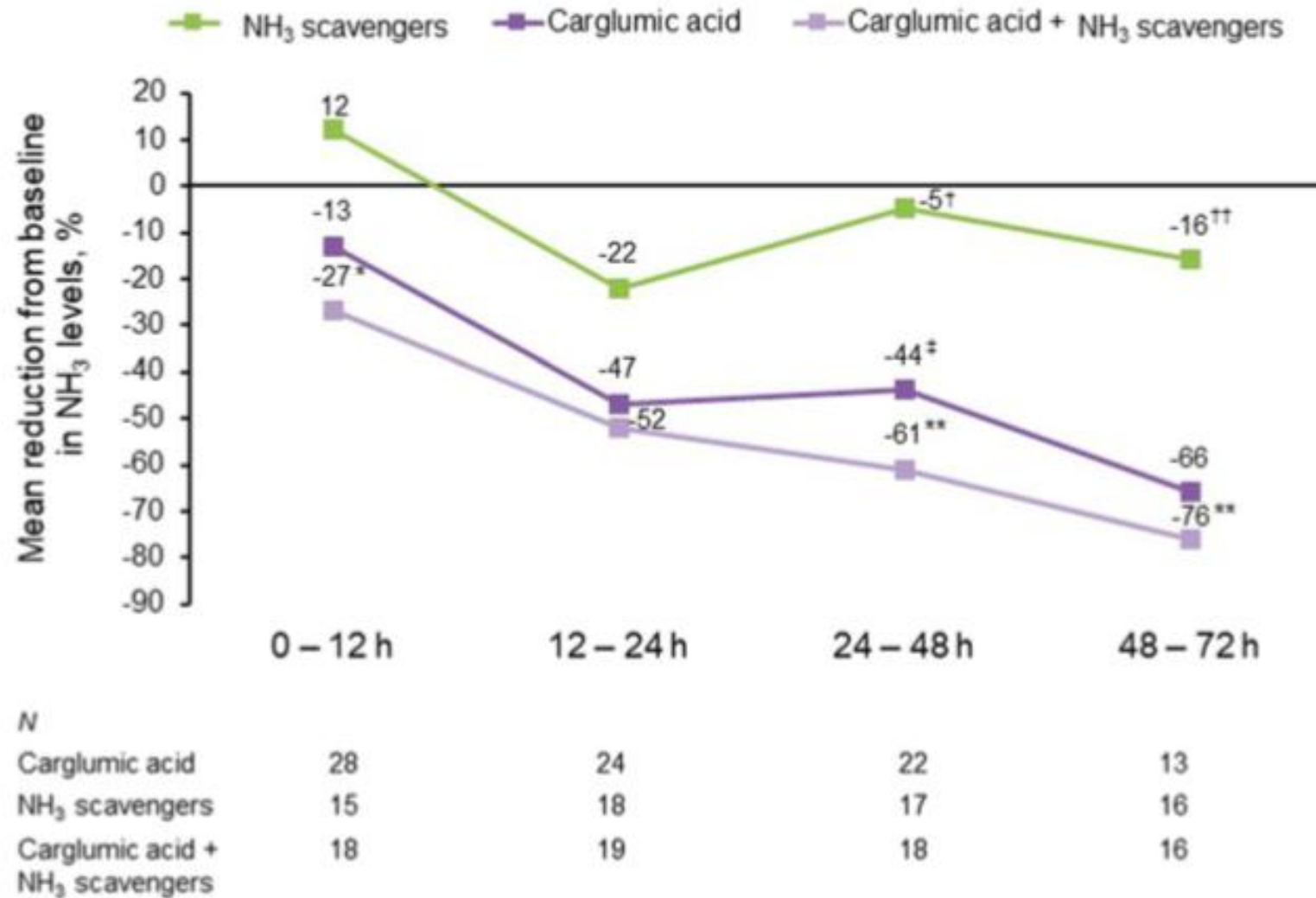
Therapeutic effect in NAG synthase deficiency

→ Disease-specific replacement therapy



Refer from clinical trial

Therapeutic effect in organic acidemias



Refer from clinical trial in Japan

Pathophysiology in an animal model of methylmalonic acidemia

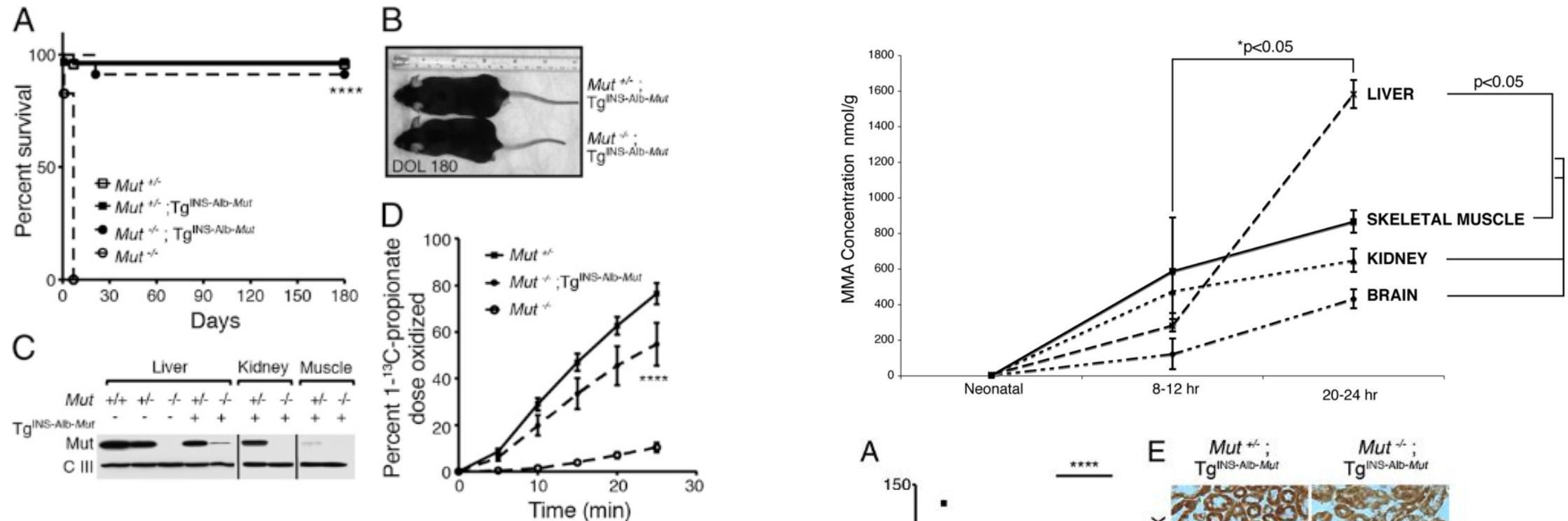
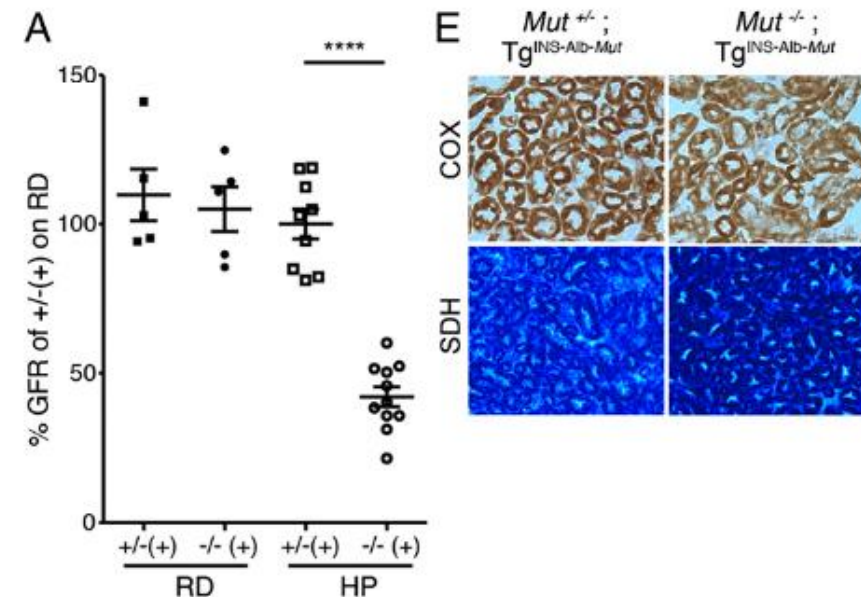


Fig. 1. Phenotypic characterization of the *Mut*^{-/-};Tg^{INS-Alb-Mut} mice. (A) *Mut*^{-/-};Tg^{INS-Alb-Mut} mice (*n* = 23) exhibit normal survival compared with the immediate neonatal lethality of the knockout strain (*n* = 29; *P* < 0.0001) and comparable to their heterozygote littermates with or without the transgene (*n* = 32 and 24, respectively; *P* = NS for both). (B) At 6 mo of age, *Mut*^{-/-};Tg^{INS-Alb-Mut} mice appear normal and are 14 ± 0.56% smaller than their littermates (*n* = 4 per group; *P* < 0.001). (C) Mut (78 kDa) was detected in whole-tissue lysates from *Mut*^{-/-};Tg^{INS-Alb-Mut} liver but not in kidney or muscle. (D) [1-¹³C]Propionate oxidation showed a significant improvement of the in vivo oxidative capacity by the hepatic transgene-mediated *Mut* expression. (*n* = 11, 9 and 6 for *Mut*^{+/-}, *Mut*^{-/-};Tg^{INS-Alb-Mut}, and *Mut*^{-/-}, respectively; values are means ± SEM, *****P* < 0.0001 between *Mut*^{-/-};Tg^{INS-Alb-Mut} vs. *Mut*^{-/-} mice.)



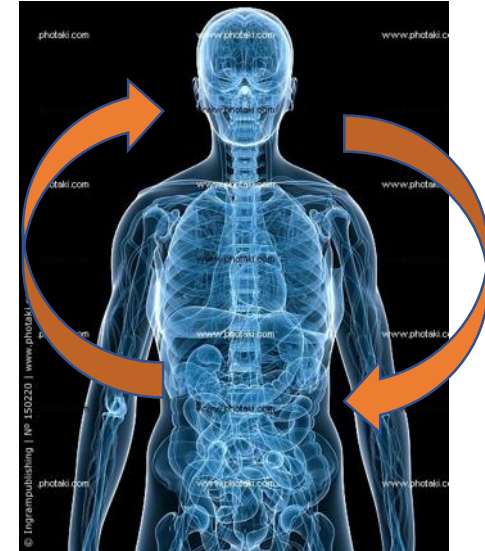
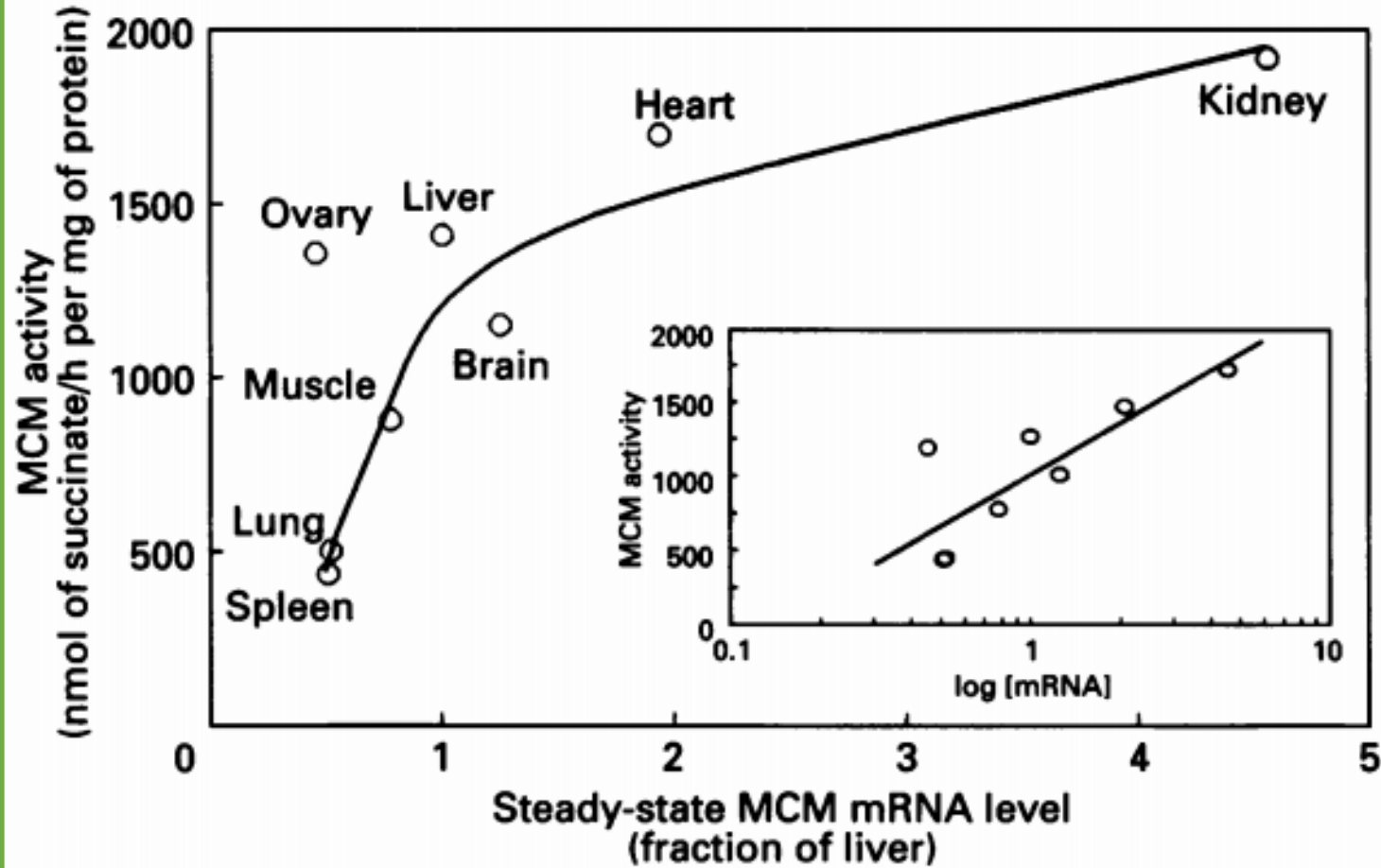


Yamato University

Analysis using the Muto mouse model of MMA

Collaboration with Prof. Charles Venditti, NIH

RRD Webinar
3rd of September 2026



Circulating methylmalonic acid may f

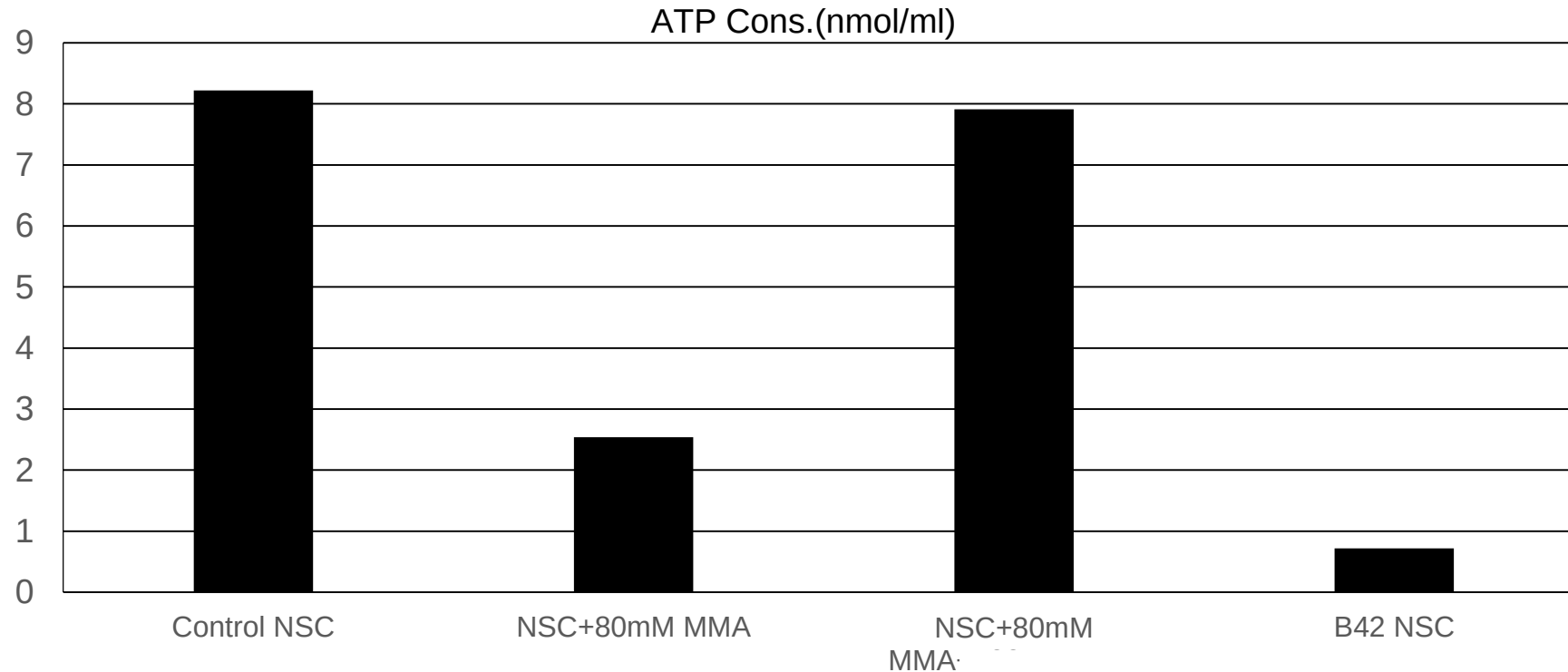


Reduced acute toxicity
Reduced chronic toxicity
Reduced chronic nutritional imp



Methylmalonic acid reduced intracellular ATP content in NSCs.

Neural stem cells (NSCs) were exposed to 80 mM methylmalonic acid and cultured at 37° C under 5% CO₂, with or without 100 μ M db-cAMP. Intracellular ATP was measured after 24 h.



	ATP Cons.(nmol/ml)	SD
Control NSC	8.22	0.369
NSC+80mM MMA	2.54	0.199
NSC+80mM MMA+100 μ McAMP	7.91	0.252
B42 NSC	0.72	0.144



Figure 1. Plasma and Intracellular ATP contents of Pt003 (50mg/kg/day)

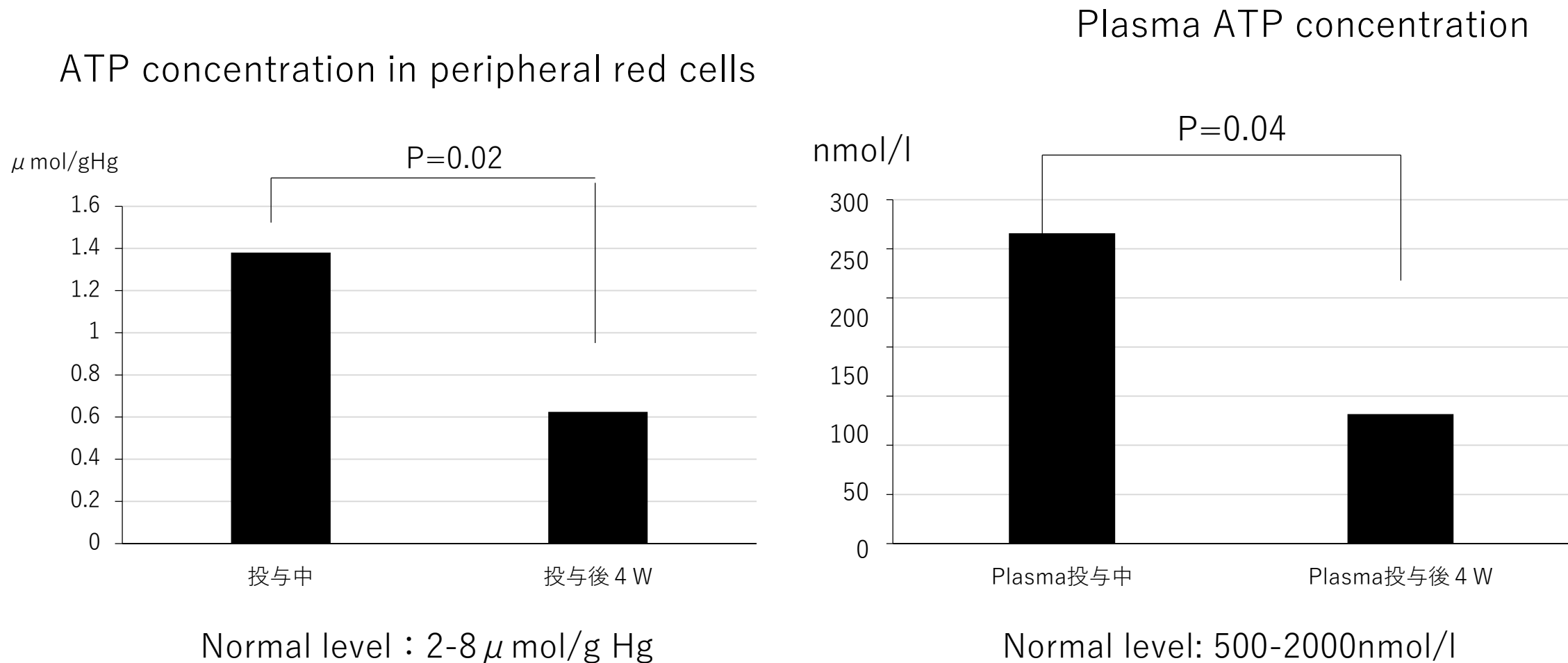
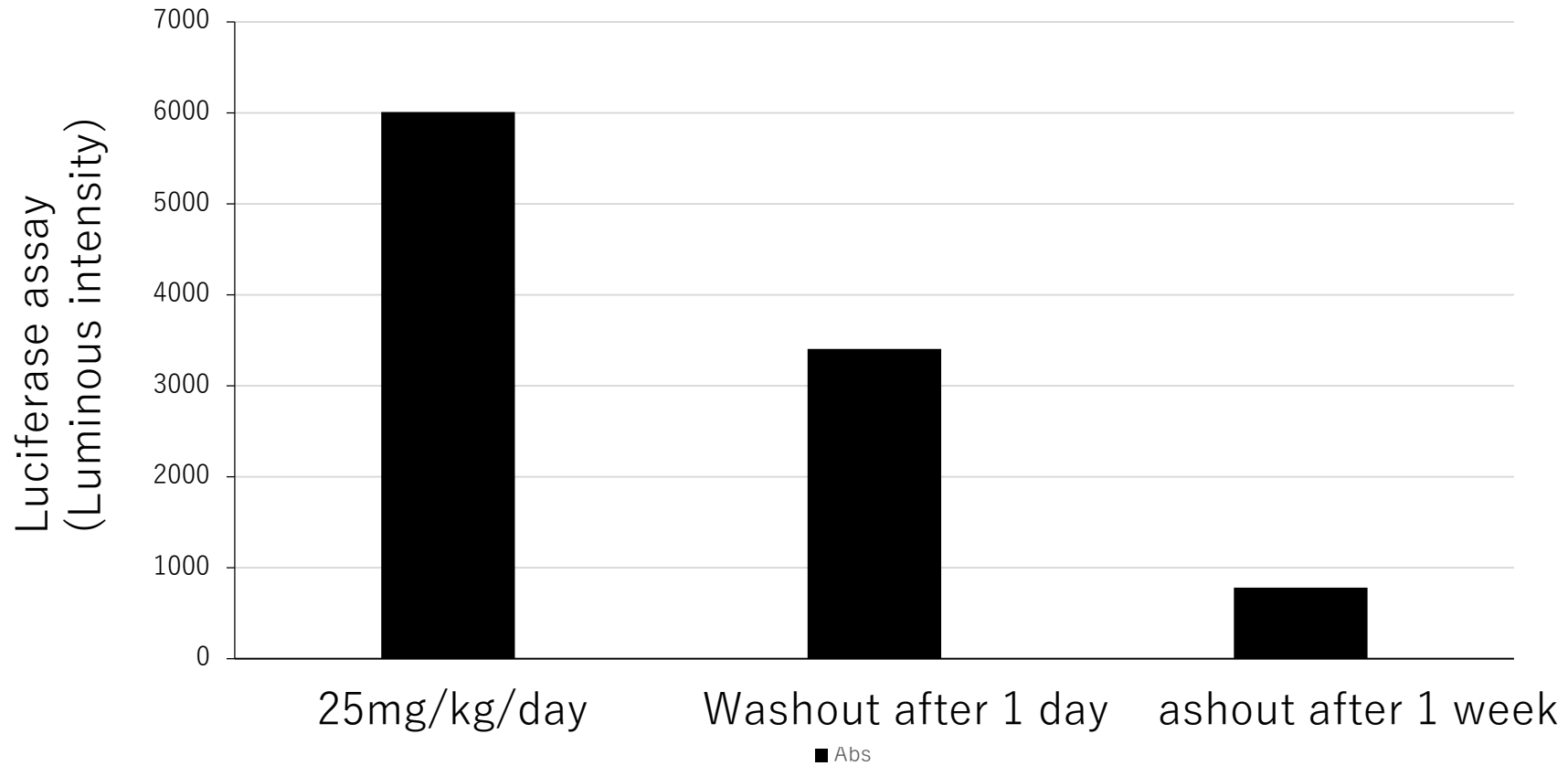




Figure 2. Plasma ATP concentration treated with/without carglumic acid of Pt001



Conclusions

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- Hyperammonemia is a time-critical metabolic emergency; plasma ammonia should be measured promptly in any neonate or patient with unexplained encephalopathy.
- Immediate reversal of catabolism, ammonia-scavenging therapy, and timely extracorporeal detoxification are essential to prevent irreversible neurological injury.
- Carglumic acid is an established replacement therapy for NAGS deficiency and has a strong pathophysiological rationale for secondary hyperammonemia associated with organic acidemias.
- Our clinical experience suggests that carglumic acid may improve both acute ammonia control and long-term metabolic stability in patients with methylmalonic or propionic acidemia; however, further prospective studies are required.
- Liver transplantation can reduce metabolic crises and improve survival, particularly in UCDs, but it is not curative for organic acidemias, and lifelong multidisciplinary follow-up remains essential.

Treat hyperammonemia immediately, identify the underlying cause in parallel, and tailor long-term management to the specific metabolic defect.