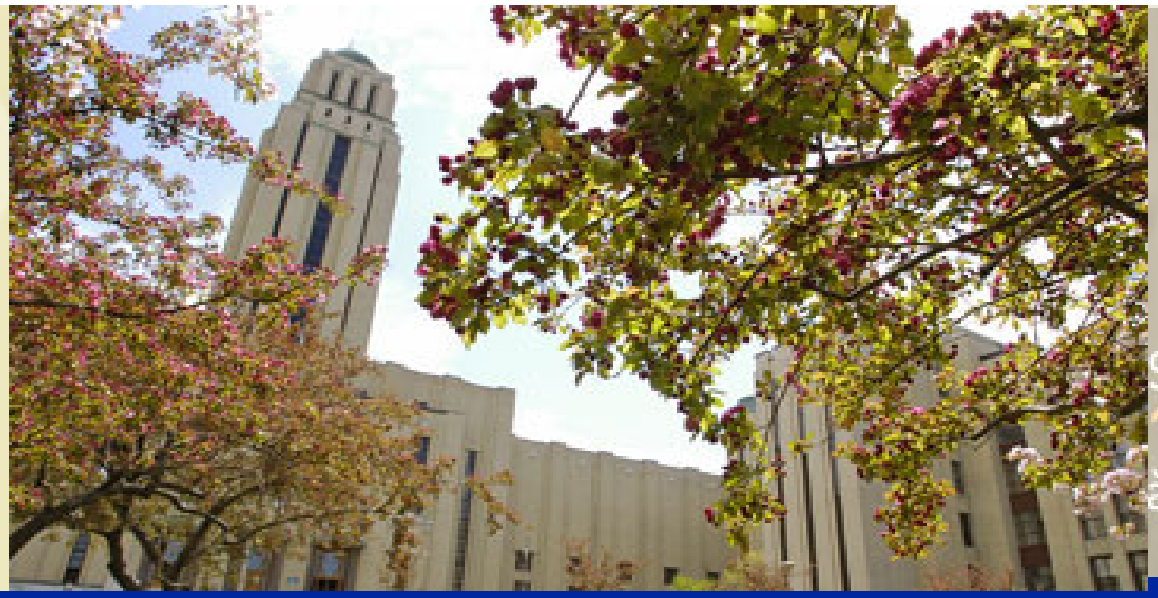
CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

Université de Montréal



Management of life threatening hyperammonemia in Children

P Jouvet MD PhD
Montreal

Conflicts of Interest

- Link with companies:
  - Consultant: Sage Therapeutics Inc
  - Research funds: Air Liquide HC
  - Invited speaker: Air Liquide HC
    Covidien France
    Medunik Canada
  - Equipment:

  Philips Medical, Hamilton Medical, Maquet Inc, Air Liquide HC
- Research salary and funds without company:
  - FRQS
  - MSSS
  - Sainte-Justine Hospital
  - NSERC
  - CIHR

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

NSERC CRSNG

Fonds de la recherche en santé Québec

Santé et Services sociaux Québec

Plan

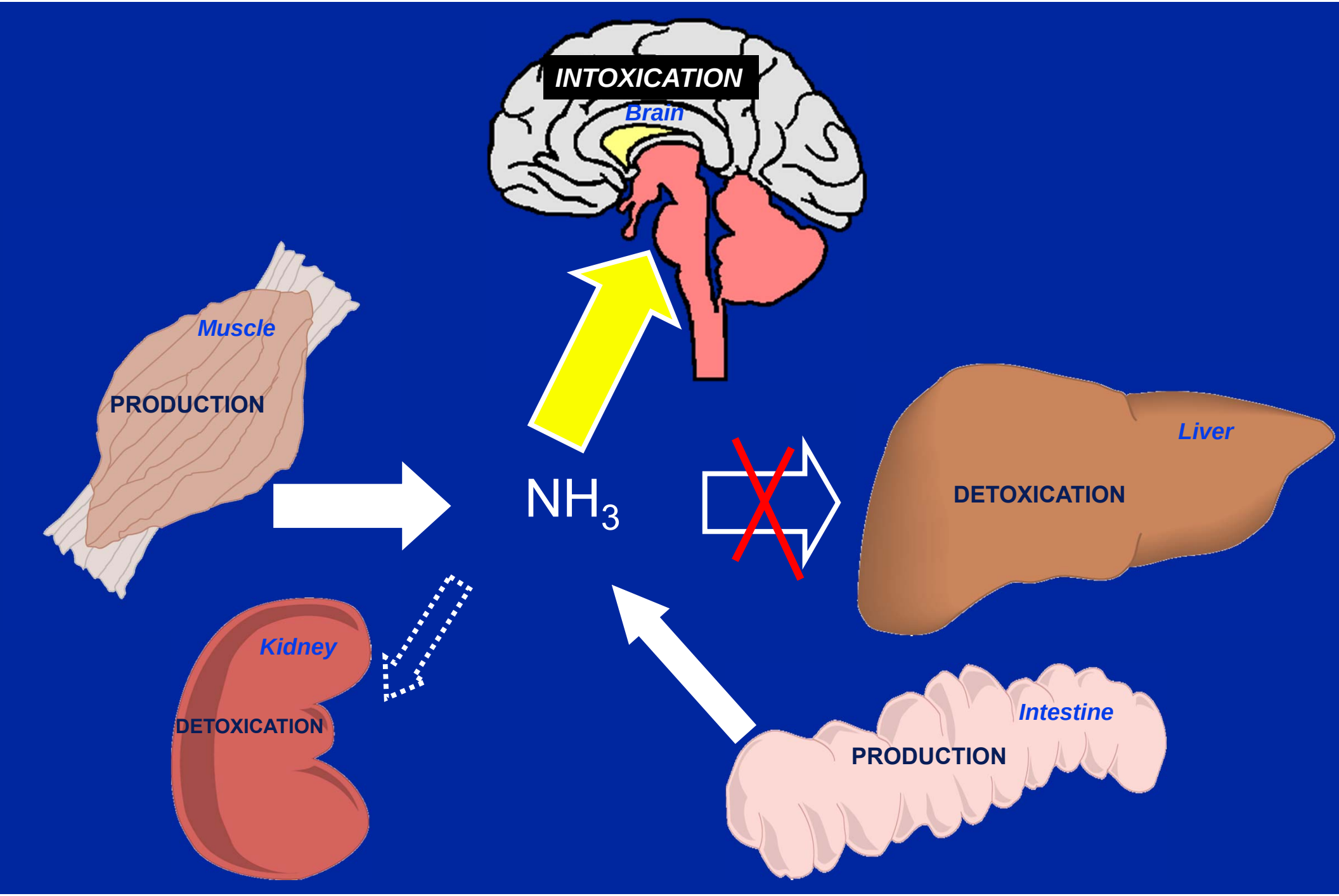
- Definition
- Etiologies
- Therapeutic strategy
- Extra corporeal replacement therapy indications
- Conclusions
- Future

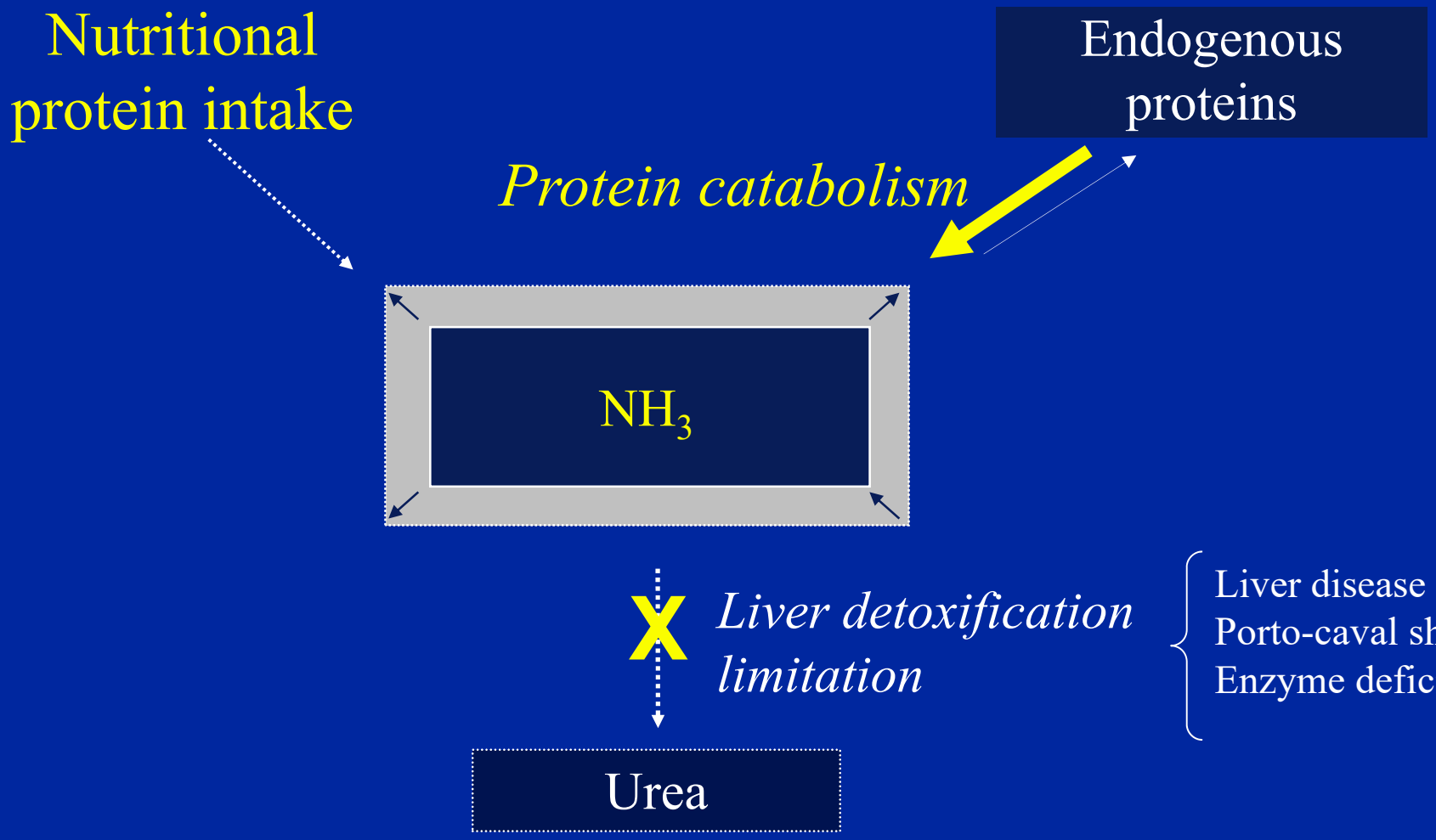
Objectives

- To known the etiologies of hypermmonemia
- To identify the medications to decrease ammonemia in acute onset
- To know the management of severe hyperammonemia

Hyperammonemia definition

- Reference values: < 80 µmol/l (135 µg/dl) ; < 1 month
  < 55 µmol/l (95 µg/dl) ; > 1 month
- Linearity: 9 à 1000 µmol/l


INTOXICATION
Brain
Muscle
PRODUCTION
NH3
Liver
DETOXICATION
Kidney
DETOXICATION
Intestine
PRODUCTION


Nutritional protein intake
Endogenous proteins
Protein catabolism
NH_3
X
Liver detoxification limitation
Liver disease
Porto-caval shunt
Enzyme deficiency
Urea

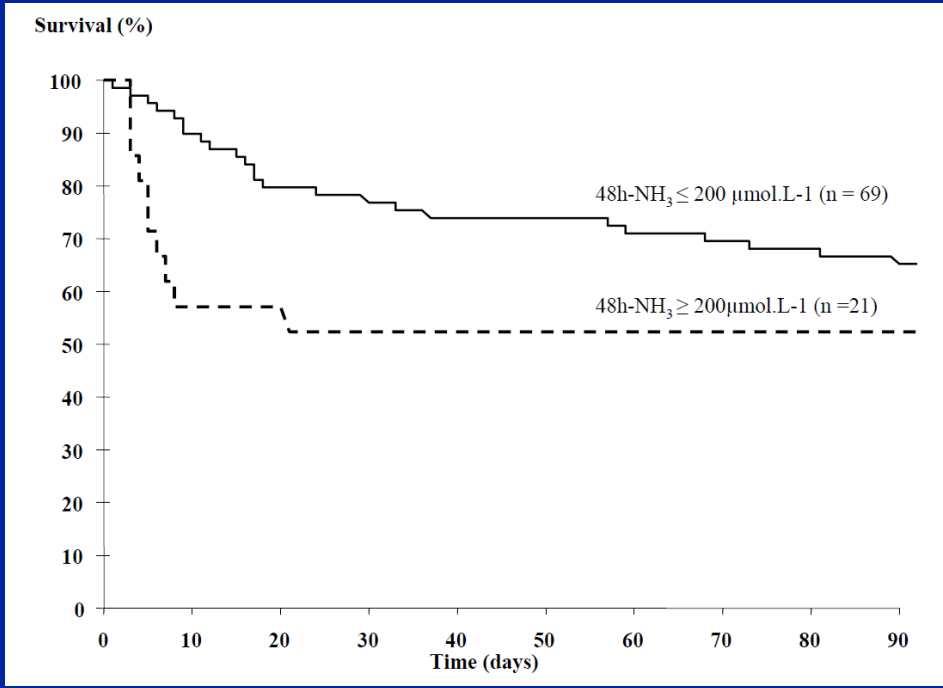
Etiologies of hyperNH$_3$ in children

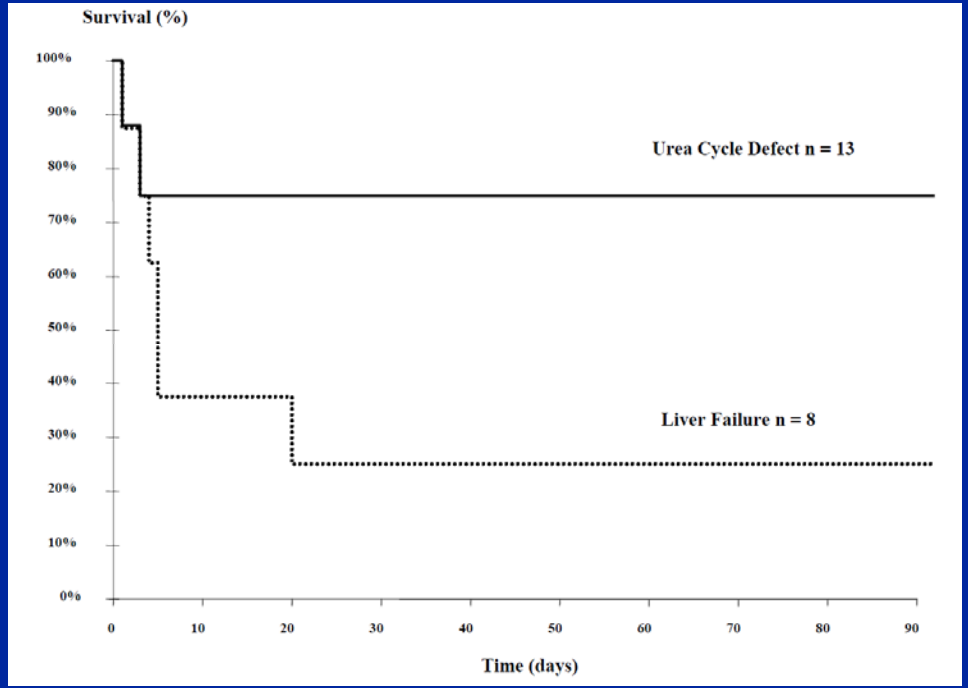
2000 to 2009
1 Pediatric Intensive Care

Etiology n (%)			
Liver failure	57 (63.3)		
Primary hepatic disease		38 (42.2)	
Biliary atresia			12 (13.3)
Congenital			
Hemochromatosis			1 (1.1)
Fructosemia			1 (1.1)
Galactosemia			1(1.1)
Cystic fibrosis			1(1.1)
Post-viral			5 (5.6)
Auto-immune			5 (5.6)
Toxic			
Acetaminophen			2 (2.2)
Chemotherapy			3 (3.3)
Tumoral			
Lymphoma			1 (1.1)
Hepatic tumor			1 (1.1)
Other			
VOD			3 (3.3)
Unknown			2 (2.2)
Secondary to MODS of extra-hepatic origin		19 (21.1)	
Urea cycle defect	21 (23.3)		
Primary urea cycle defect		9 (10)	
CPS defect			2 (2.2)
OTC defect			3 (2.2)
Arginase defect			1 (1.1)
ASL defect			1 (1.1)
ASS defect			1 (1.1)
NAGS defect			1 (1.1)
Other urea cycle inhibition		12 (13.3)	
Organic aciduria			
Methyl-malonic aciduria			2 (2.2)
Propionic aciduria			4 (4.4)
Glutaric aciduria			1 (1.1)
β-oxydation defect			2 (2.2)
Respiratory chain defect			3 (3.3)
Others	12 (13.3)		
Valproïc acid toxicity			4 (4.4)
Unknown			8 (8.9)

B Ozanne et al.J Hepatol 2012;56:123-8.

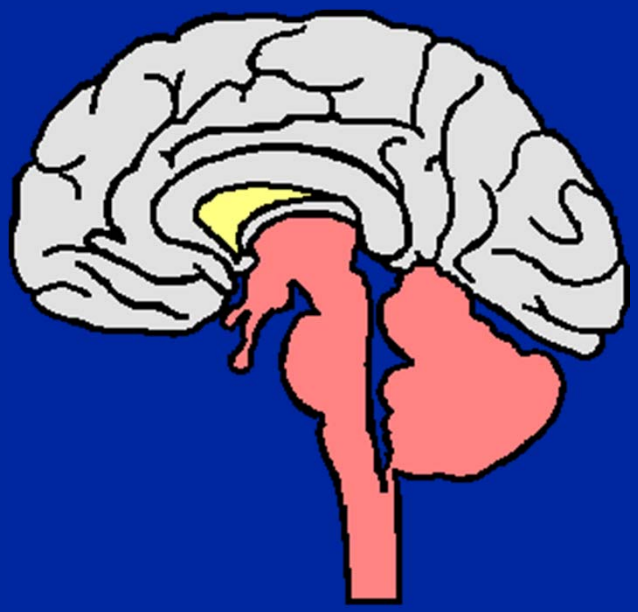
Hyper NH_3 mortality threshold

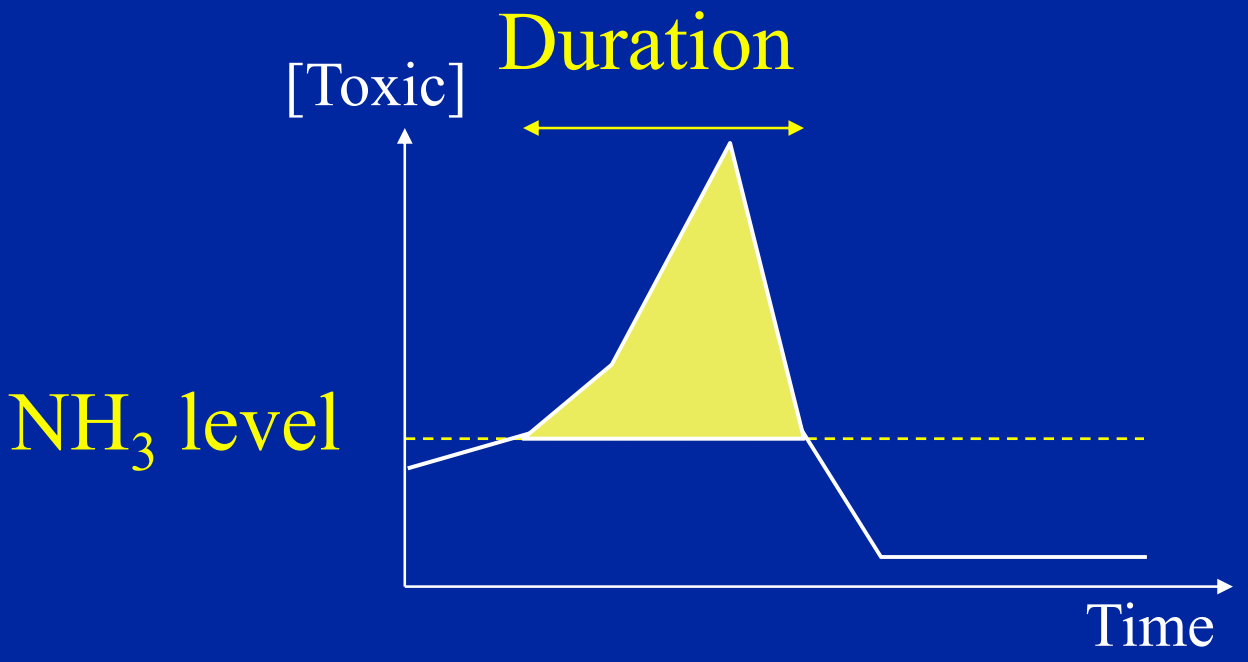




B Ozanne et al.J Hepatol 2012;56:123-8.

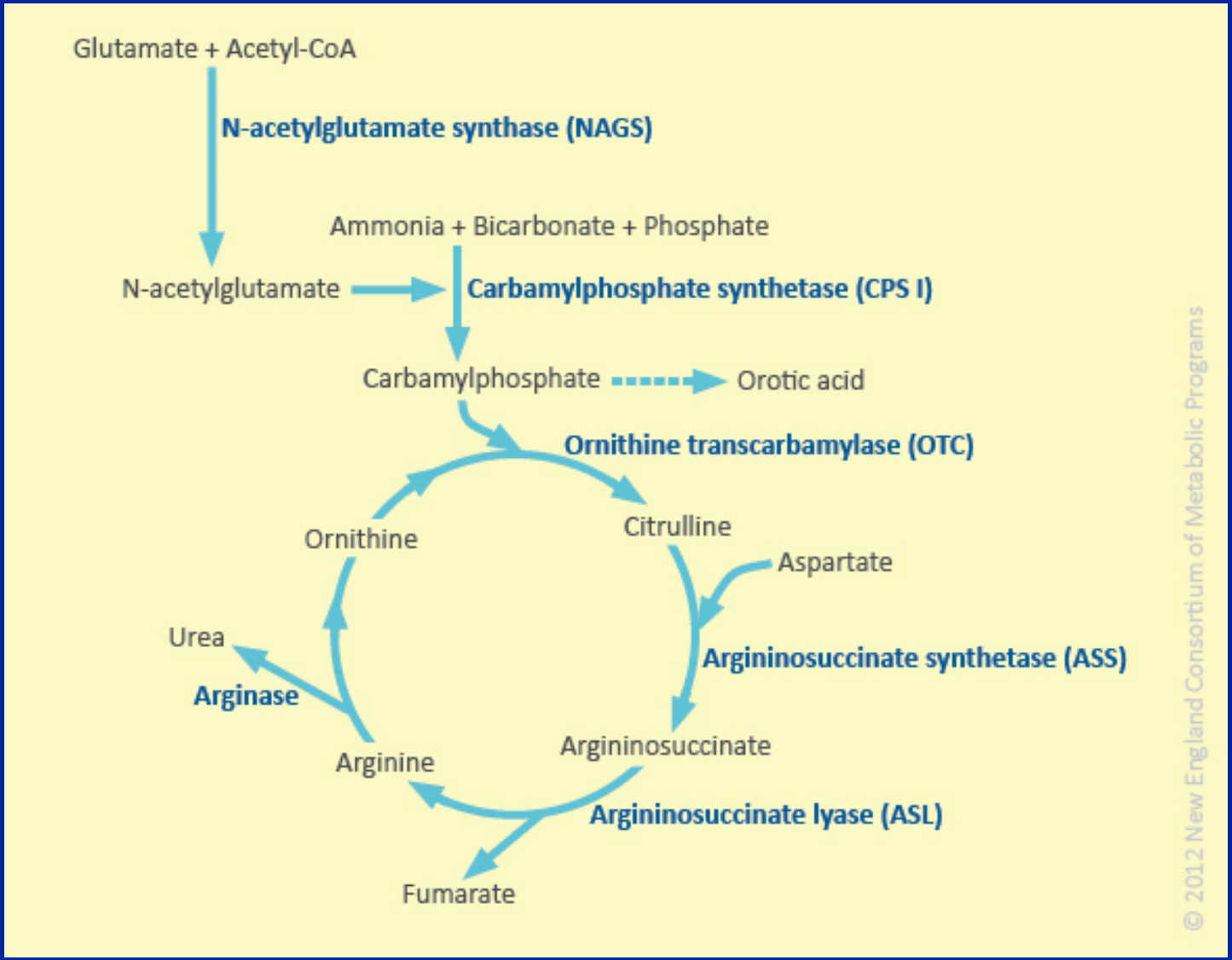
Cerebral edema mainly cytotoxic



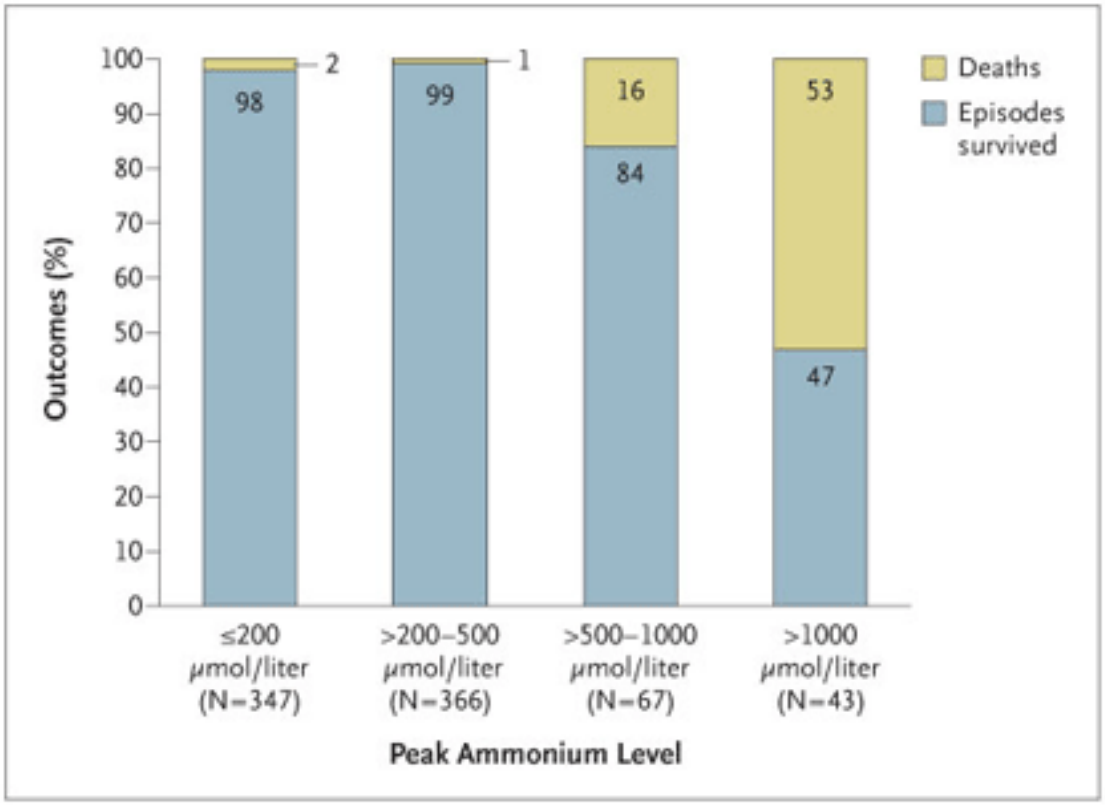


HyperNH_3: V Felipo et al. Prog Neurobiol 2002

Hyperammonemia and Inborn Errors of Metabolism



Urea cycle disorders



G Enns et al. NEJM 2007

Peak NH_3 < 480 μmol/L

C Bachmann. Eur J Pediatr 2003

Coma duration < 33 hours

S Picca et al. Pediatr Nephrol 2001

Reduction with dialysis

F Schaeffer et al. NDT 1999

Clinical case (1)

14-year-old boy
Normal development
Intermittent headaches

Headaches + visual blurred
48h later vomitting and anorexia

<u>96h later general practitioner consultation</u>:
Clinical examination normal
Hemoglobine : 16 g dl–1, leucocytes : $5.2.10^9$ /L, creatininemia : 70 µmol/L,
ASAT/ALAT: 22 UI/L normal

<u>Emergency room at night:</u>
Obnubilated without neurological focal symptom
Blood pressure 180/80, HR 75/min

14-year-old boy

Normal development

Clinical case (2)

- Protidemia: 78 g/L
- ASAT/ALAT normal range
- Cerebral TDM normal
- CSF: 1 cell/mm^3, 250 Red Cell/mm^3
- Toxics negative (amphetamines, cannabis, cocaïne, opioids, barbiturates, benzodiazepines, carboxyhemoglobine, alcohol, paracetamol)
- EEG non specific

14-year-old boy

Normal development

Clinical case (3)

- Ammonemia of 344 mumol/L and it rapidly increased to 755 µmol/L.
- Death of one uncle after a coma in the year 1992 +++
- Diagnosis of hereditary ornithine transcarbamylase deficiency was confirmed later on by liver biopsy

Management of hyperNH_3 due to Inborn Errors of Metabolism

Initial management

Toxic production decrease

Toxic removal therapies

Initial management

Rehydration (goal: urine output of 2-4 ml/kg/hr)

Treatment of Intracranial hypertension:

Mechanical ventilation, sedation, …

If deepening encephalopathy: Mannitol or NaCl 3-5%

→ Blood osmolarity ≥ 300 mOsm/L

NB: In hyperammonemia, hyperventilation is not recommended as blood brain barrier seems to have a lower permeability to NH_4^+ than NH_3

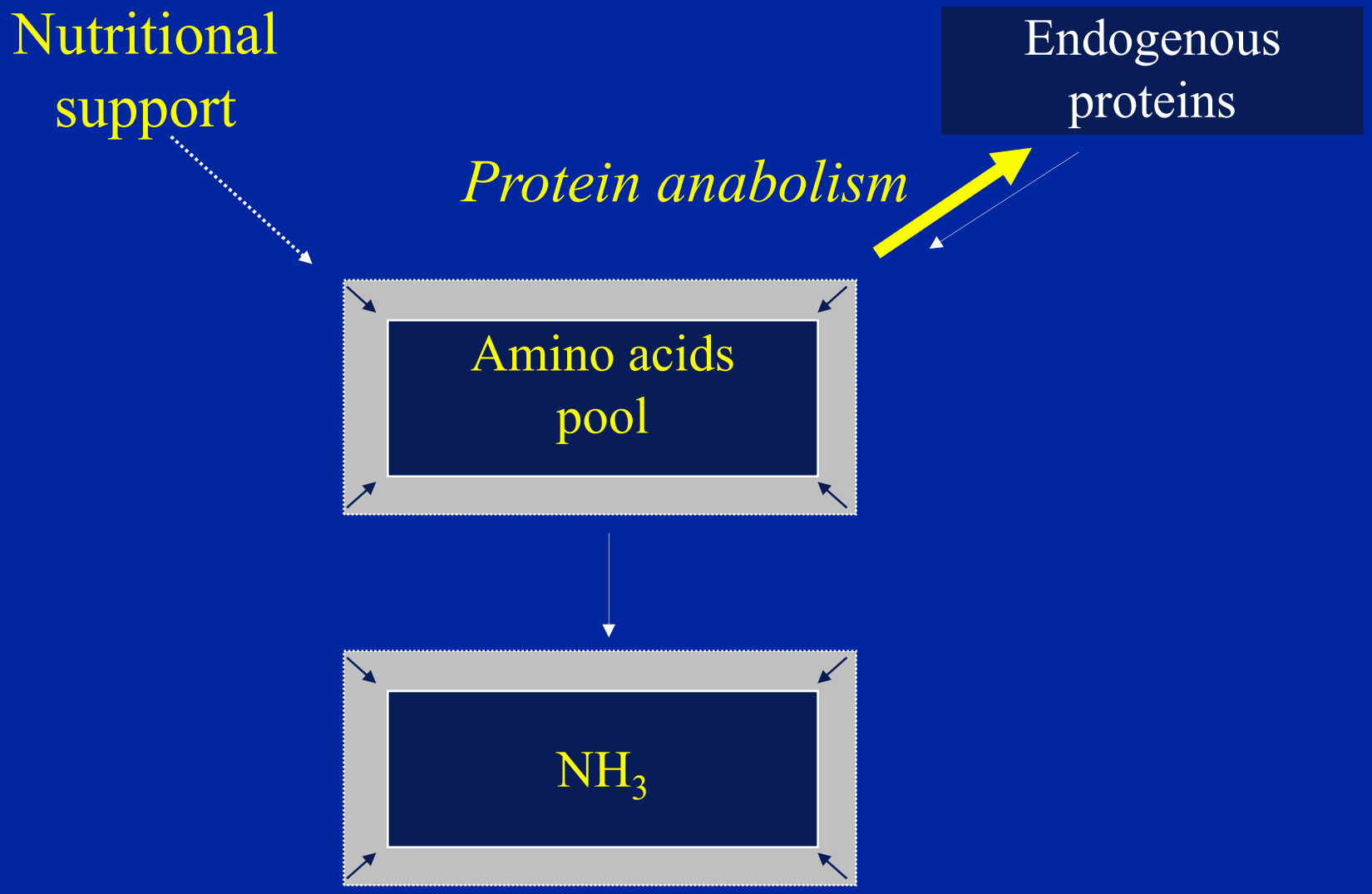
JR Stabenau et al.J Clin Invest 1959.

Management of hyperNH_3 due to Inborn Errors of Metabolism

Initial management

Toxic production decrease

Toxic removal therapies


Nutritional support
Endogenous proteins
Protein anabolism
Amino acids pool
NH_3

Toxic production decrease
=
Nutritional support

- Promote protein anabolism

  IV Rehydration

  Caloric intake > 1500 $Cal.m^{-2}.d^{-1}$

  IV switched to PO

  Carbohydrates (+/- Insuline) + lipids

  Infection treatment, no steroid

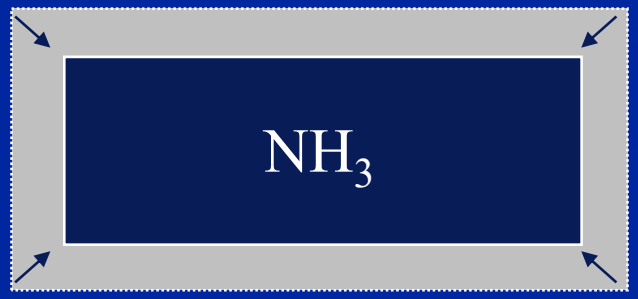
- Protein free nutrition

Management of hyperNH_3 due to inherited enzyme deiciciency

Initial management

Toxic production decrease

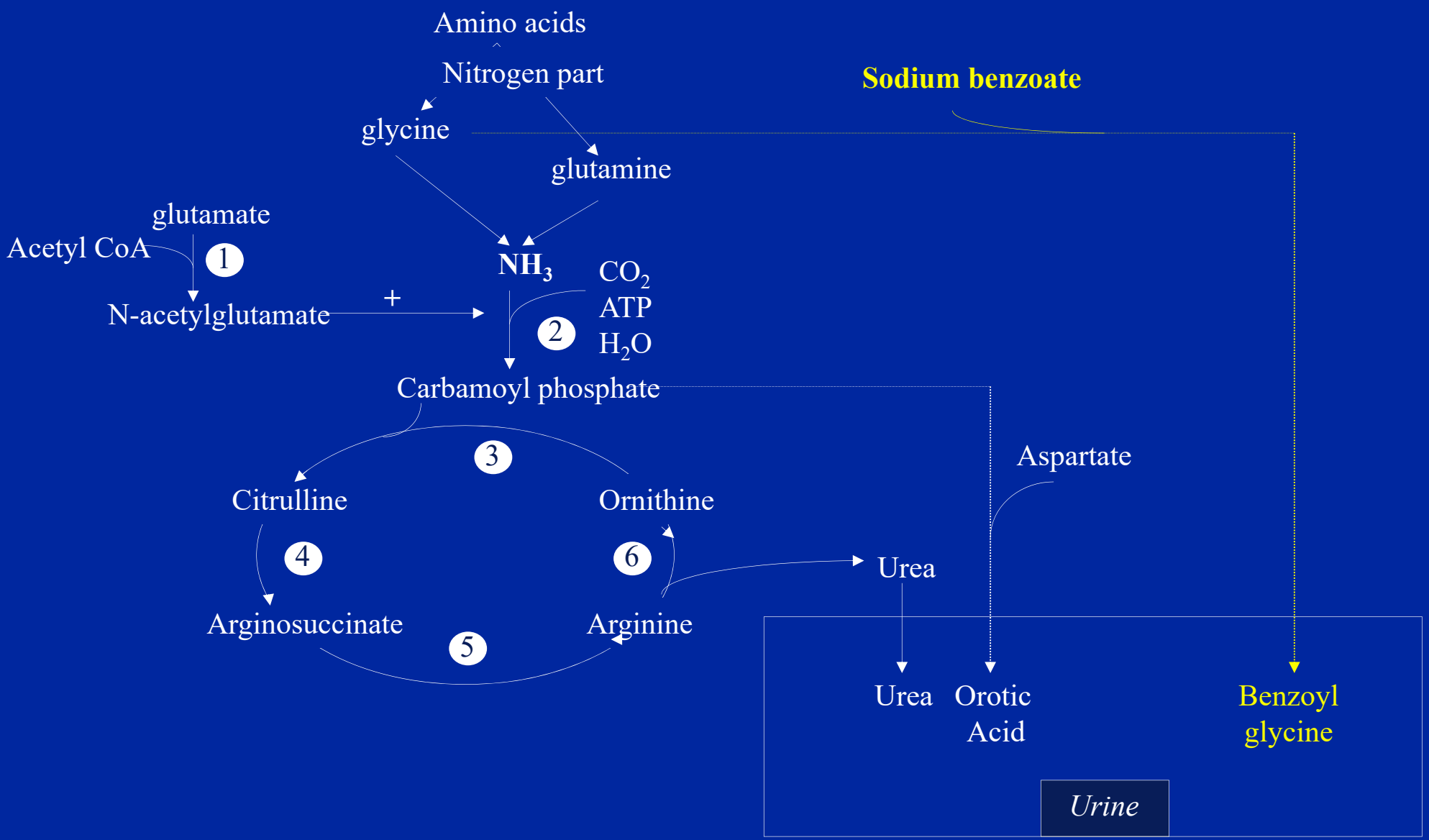
Toxic removal therapies



Medications for alternative pathway

Extra-corporeal removal therapies

Nitrogen scavenging medications



HyperNH_3 episodes and IV Sodium Benzoate

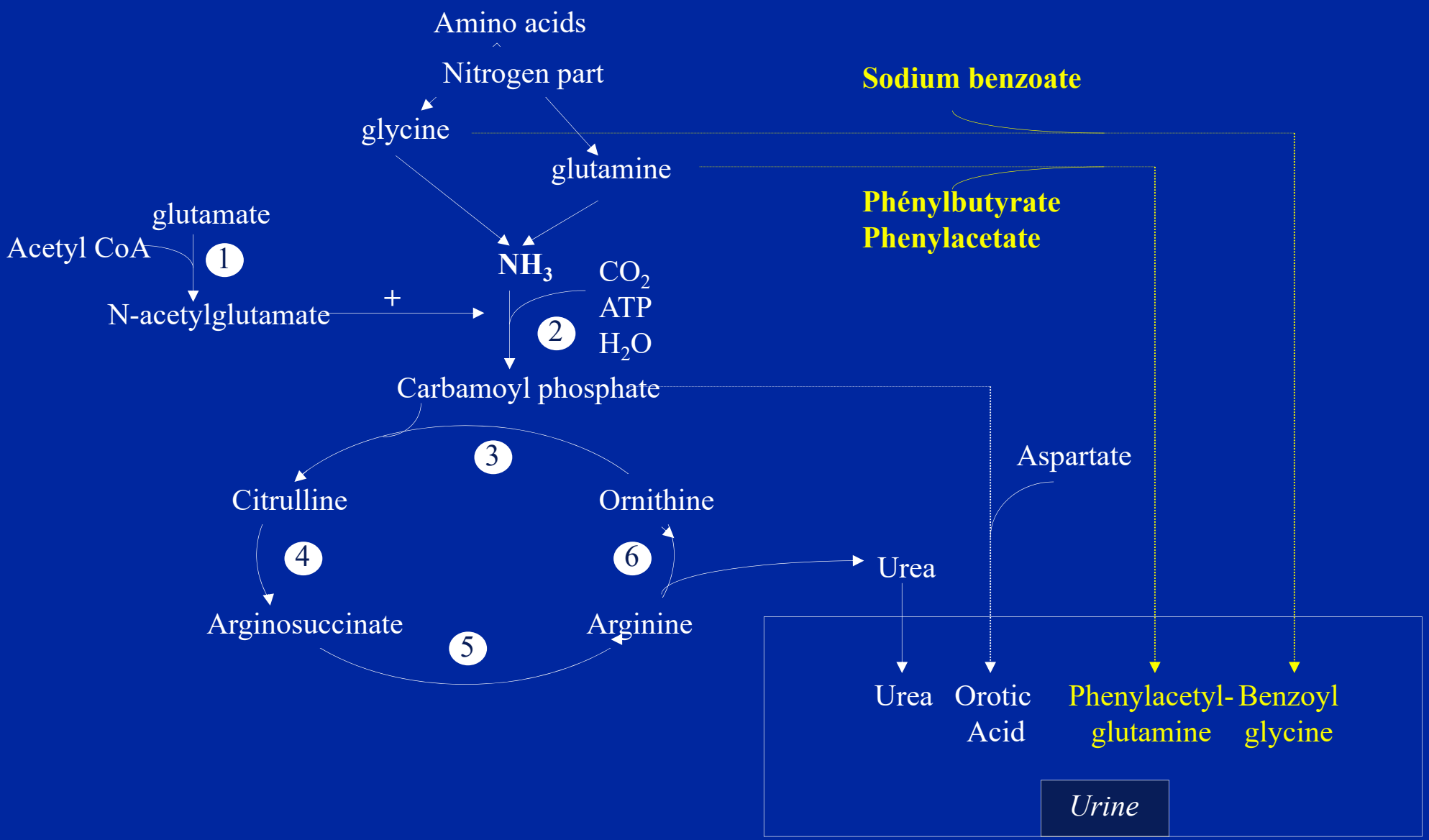
Episodes with NH_3 > 100 µmol/l (n=69)

Before i.v. sodium benzoate treatment	At the end of i.v. sodium benzoate treatment
291 µmol/L [101 –2274]	41 µmol/L [13 –181]

No severe side effects were attributed to i.v. sodium benzoate

MC Husson et al. Orphanet Journal of Rare Diseases 2016;11:127

Nitrogen scavenging medications



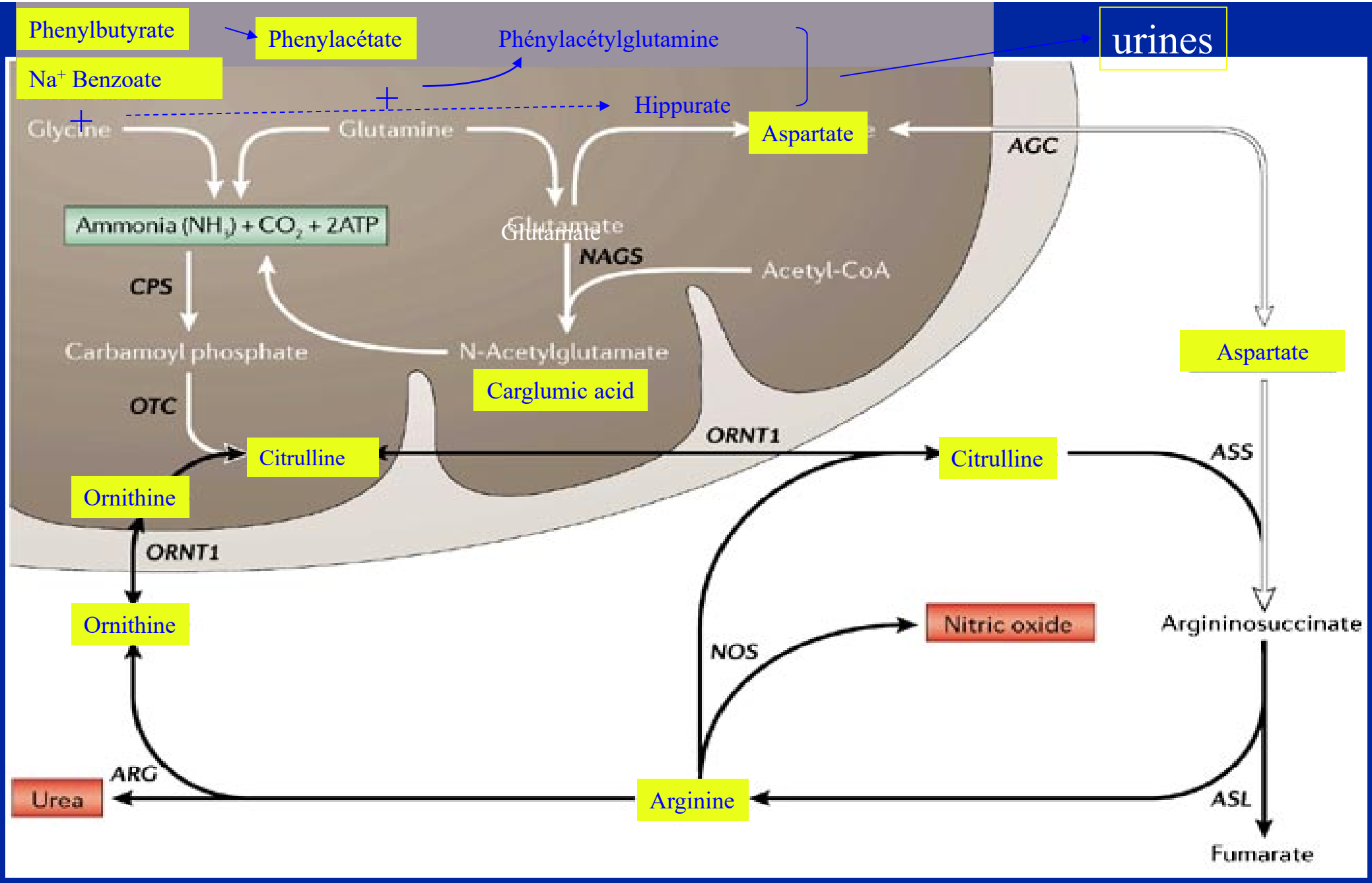
Most of the NH_3 episodes are controlled with IV Sodium Benzoate

Other NH3 treatments provided at the end of treatment with i.v. sodium benzoate (Emergency regimen was performed in all cases)

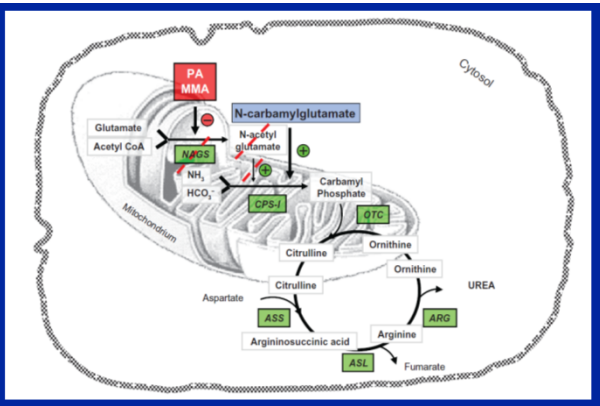
Treatments	Episodes $N = 95$ (%)
Missing	12 (12.6 %)
Sodium benzoate p.o.	65 (78.3 %)[a]
Sodium benzoate p.o. + Phenylbutyrate p.o.	3 (3.6 %)[a]
Combination Sodium phenylacetate + Sodium benzoate (central i.v. infusion)	3 (3.6 %)[a]
Combination Sodium phenylacetate + Sodium benzoate (central i.v. infusion) + Haemofiltration	3 (3.6 %)[a]
Haemofiltration	2 (2.4 %)[a]
Haemofiltration + Phenylbutyrate p.o.	1 (1.2 %)[a]
Phenylbutyrate p.o.	1 (1.2 %)[a]

[a]Calculated as a percentage of the non-missing data

MC Husson et al. Orphanet Journal of Rare Diseases 2016;11:127



Lanpher *et al. Nature Reviews Genetics* **7**, 449–459.



Carglumic acid

Carglumic acid is an analog of N-acetylglutamate

Inborn errors of metabolism that can benefit of this treatment:

- Some urea cycle defects (N-acetylglutamate synthase deficiency, Carbamoyl-phosphate synthase I deficiency)
- Organic aciduria (propionic acidemia and methylmalonic acidemia, isovaleric acidemia),
- Other hyperammonemia with secondary inhibition of NAGS

Can avoid hemodialysis

M Daniotti et al. International Journal of General Medicine 2011;4 :21

Extra-corporeal toxic removal therapy in hyperNH_3

Criteria: Two of the three following criteria :
coma, gastro-intestinal intolérance, NH_3 > 300-400 µmol/L

Modality: Intermittent or continuous

Solute transfer: Diffusion

Dialysis dose: ≥ 35 ml/min/1.73 m^2 in neonates
and 50 ml/min/1.73 m^2 in children
Increase until dialysate flow = twice the blood flow
(Schaefer F Nephrol Dial Transplant 1999)

Duration: until NH_3 in a normal range

Multidisciplinary approach : genetics, intensivist, nephrologist, biochemist

Treatment of HyperNH_3 in Pediatric Intensive Care

Treatments implemented in order to lower plasma ammonia.

	All patients n = 90	Liver Failure n = 57	Primary or secondary Urea Cycle Defect n = 21
Inhibitors of intestinal production n (%)	**31 (34.4)**	**29 (50.9)**	**2 (9.5)**
Antibiotics	20	18	2
Disaccharides	20	20	0
NH_3 scavengers n (%)	**12 (13.3)**	**2 (3.5)**	**10 (47.6)**
Sodium Benzoate	12	2	10
Phenyl acetate	11	2	9
Phenyl butyrate	0	0	0
Arginine	9	1	8
Carglumic acid	2	0	2
Citrullin	1	0	1
Renal replacement therapy n (%)	**22 (24.4)**	**16 (28.1)**	**6 (28.6)**
Continuous VenoVenous therapies	16	14	6
Peritoneal Dialysis	4	4	0
Intermittent Hemodialysis	2	2	0
Liver transplant n (%)	**10 (11.1)**	**10 (17.5)**	**0 (0)**
None n (%)	**35 (38.9)**	**16 (17.8)**	**9 (10)**

B Ozanne et al. J Hepatol 2012;56:123-8.

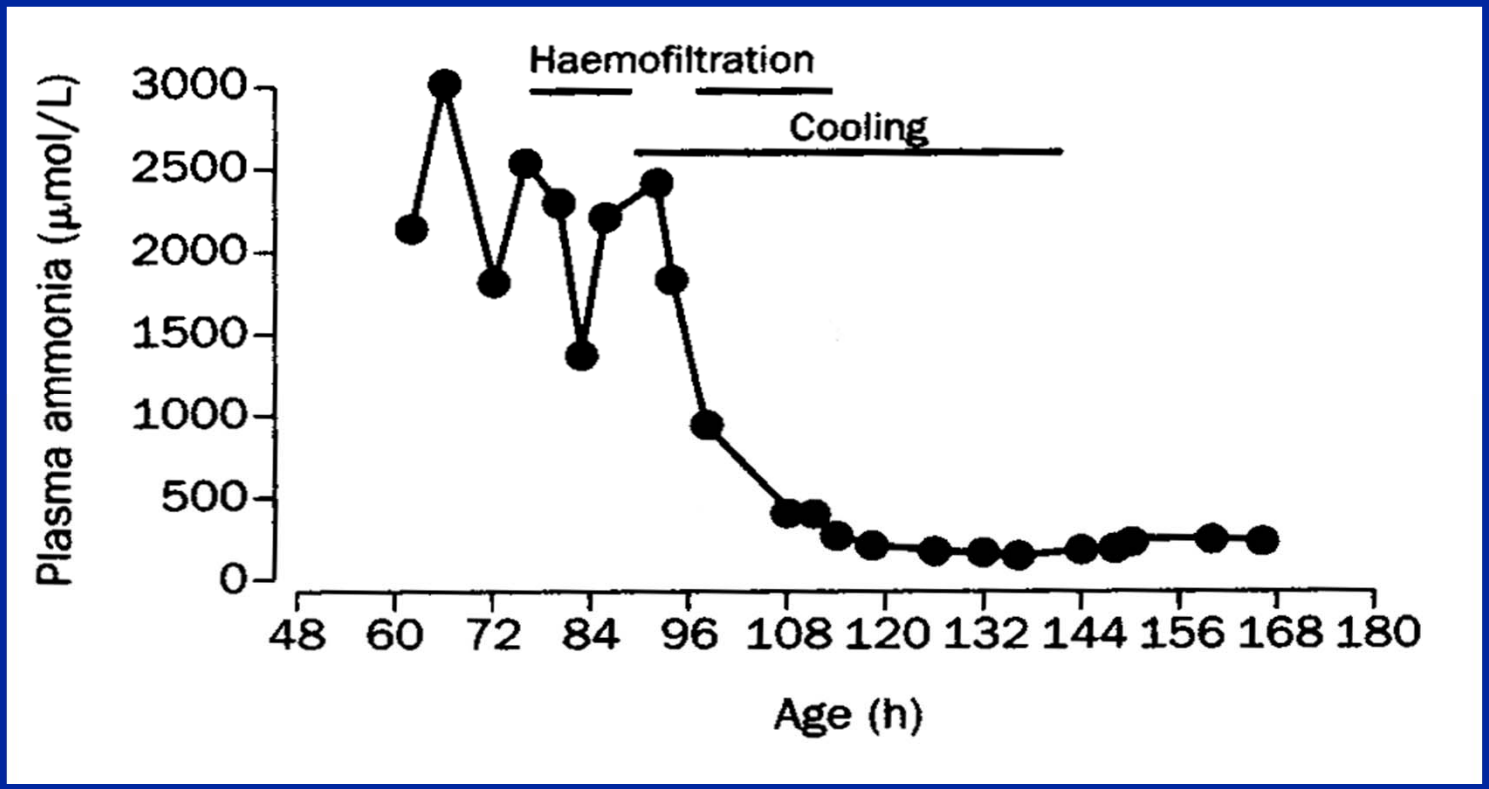
Management consequences

Initial NH_3 Level (x2)* / clinical condition	Intensive care admission	Central line	Hemodialysis catheter
< 150 µmol/l (250 µg/dl) **without** encephalopathy	+/-	consider	-
150-300 (250 - 500 µg/dl) **and/or** encephalopathy	+	+ (jug or fem vein)	-
>300 (500 µg/dl)	+	+	+

Multidisciplinary approach : genetics, intensivist, nephrologist, biochemist

* Due to false positives risk, 2 NH_3 blood levels are required (B Maranda et al. Clin Biochem 2007;40:531)

Hypothermia?



Whitelaw A. Lancet 2001;358:36.

Differences in the management of HyperNH_3 due to liver failure

- Non-Absorbable Disaccharide (lactulose, …)
- Neomycin, Metronidazole and other Antibiotics
- Rifaximin

May be inappropriate in acute liver failure.

W Bernal et al. N Engl J Med 2013;369:2525

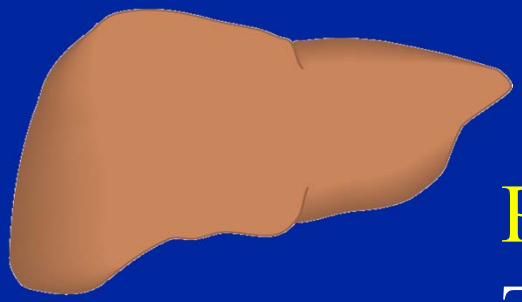
- Probiotics
- Zinc
- L-Ornithine L-Aspartate
- Molecular Adsorbent Recirculating System (MARS)

No proof of efficacy

M Leise et al. Mayo Clin Proc 2014;89: 241
Z Poh et al. Intern J Hepatology 2012;2012,:1
A Merouani et al. PCCM 2014;15:681

- Occlusion of large portosystemic shunts

M Leise et al. Mayo Clin Proc 2014;89: 241



Liver transplantation

Primary goal:

To restaure all liver functions (synthesis, metabolic, …)

Urgent liver transplantation in acute liver failure

Elective liver transplantation in some inborn errors of metabolism

Disease	Author	year	n	Survival (%)
UCD	D Morioka	2005	51	90
MMA	M Kashara	2006	18	83
PA	J Meyburg	2005	21	76
MSD	KA Strauss	2006	10	100

CONCLUSIONS

- Ammonia blood level in case of unexplained encephalopathy
- Hyperammonemia decreases with nitrogen scavenging medications, and carglumic acid can have a dramatic impact on some hyperammonemia
- Intensive care admission and hemodialysis are required in severe hyperammonemia

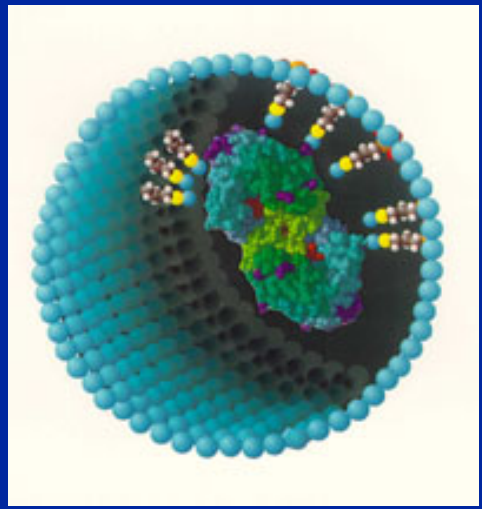
Future

Development of Enzyme therapies:

Enzyme replacement therapy

Hepatocyte transplantation

Gene transfer



J Häberle et al. Orphanet Journal of Rare Diseases 2012;7:32.

↘ PICU admissions