Diet, Drug therapies and Emergencies In Inborn Errors of Metabolism (IEM)

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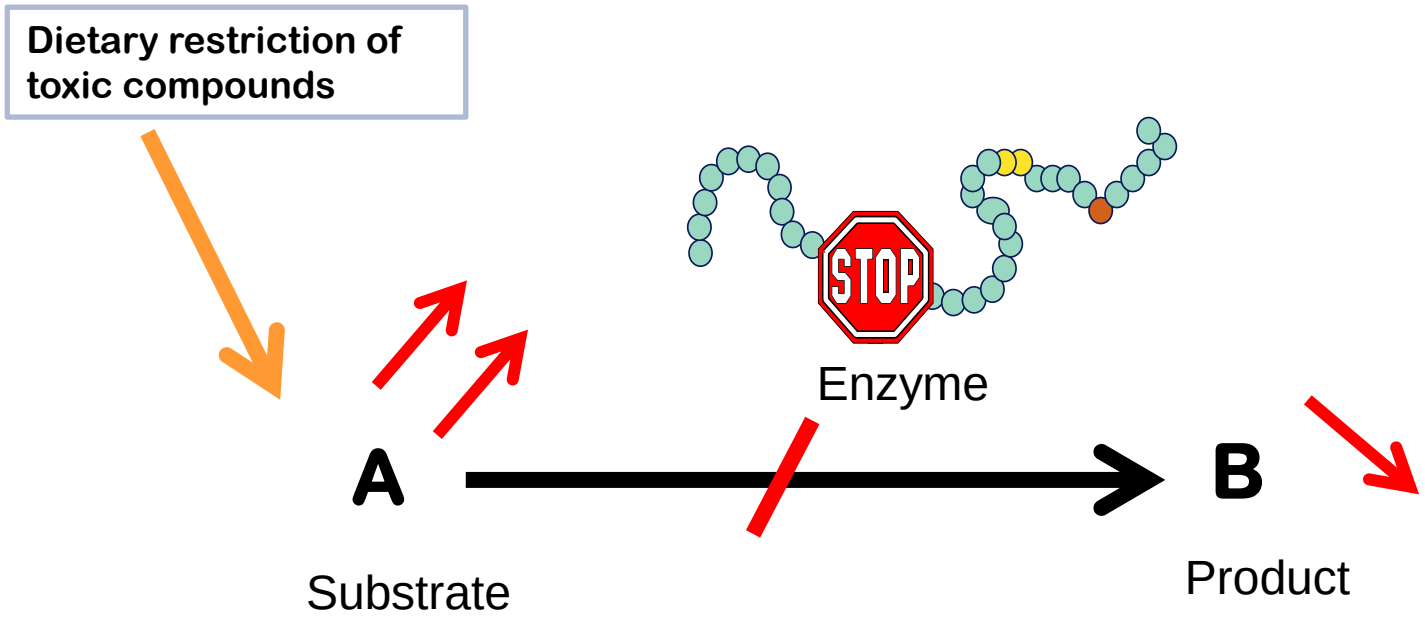
MANAMA, UZ Brussel, 6/12/22

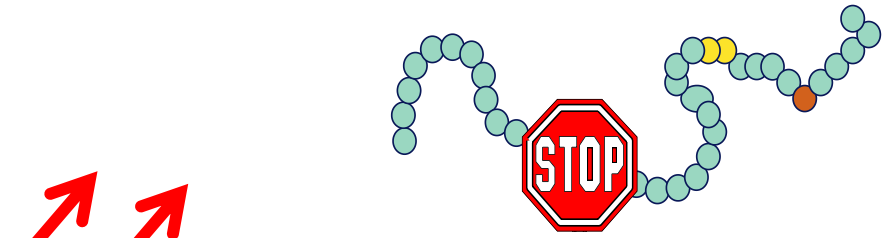
Therapeutic strategies in IEM

In Chronic Intoxication diseases



Phenylketonuria is the First Described First treated Metabolic Disease

Phenylalanine Hydroxylase (PAH)



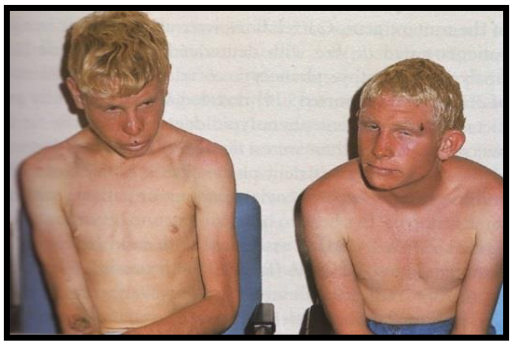
Phenylalanine
=
Toxic compound

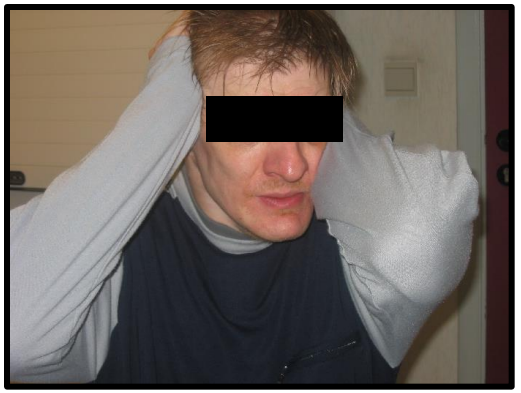
Tyrosine

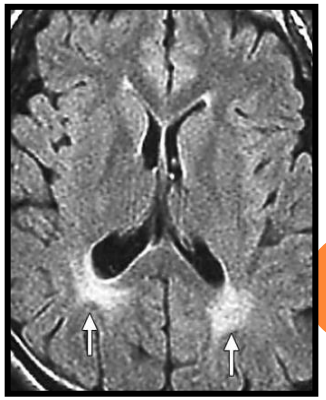
Severity of the disease depends on
the severity of the enz deficiency (genotype/phenotype related)

Untreated classical PKU

- Mild to severe mental retardation
- Neurologic symptoms
  - Microcephaly
  - Gait instability, tremor
  - Epilepsy
  - Autistic behavior
  - Auto and hetero aggressivity
- Structural brain changes on MRI
  (white matter abnormalities)
- Decreased skin and hair pigmentation
  (Blond hair, blue eyes < tyrosine deficiency)
- Eczema/prurigo
- Musty body odor (typical)







Phenylketonuria is the First Treated Metabolic Disease

Phenylketonuria can be treated
with a phenylalanine (PHE) restricted diet

Horst Bickel (1953)

<u>Principle of a phenylalanine restricted diet</u>
(should be initiate before the age of <u>10 days of life</u>)

- Avoidance of high protein food
  (milk, dairy products, meat, fish, chicken, eggs, beans,...)
- Control of natural protein intake
  according to patient's <u>tolerance</u> in phénylalanine (PHE) intake
- Low protein food (manufactured hypoproteic bread, pasta, biscuits, ...)
- Phenylalanine-free formula (amino acids mixture + vitamins and oligoelements)

But ….. no control of '<u>protein-free</u>' food

Lancet, 1953; 2, 812-813

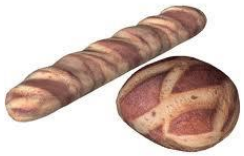
PHE-free
Amino acid supplements
(+Vitamines + Oligoelements)

Allowed
(sugar, lipids)

Avoidance
High Protein food

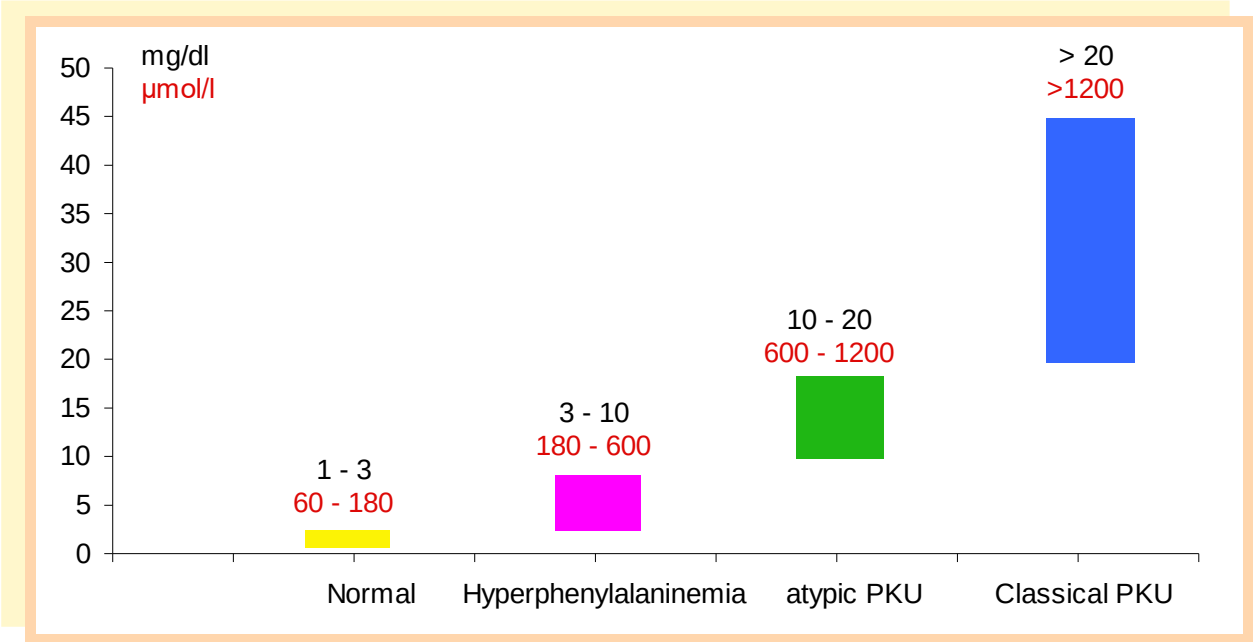
PHE-restricted diet

Control of
Natural Protein intake



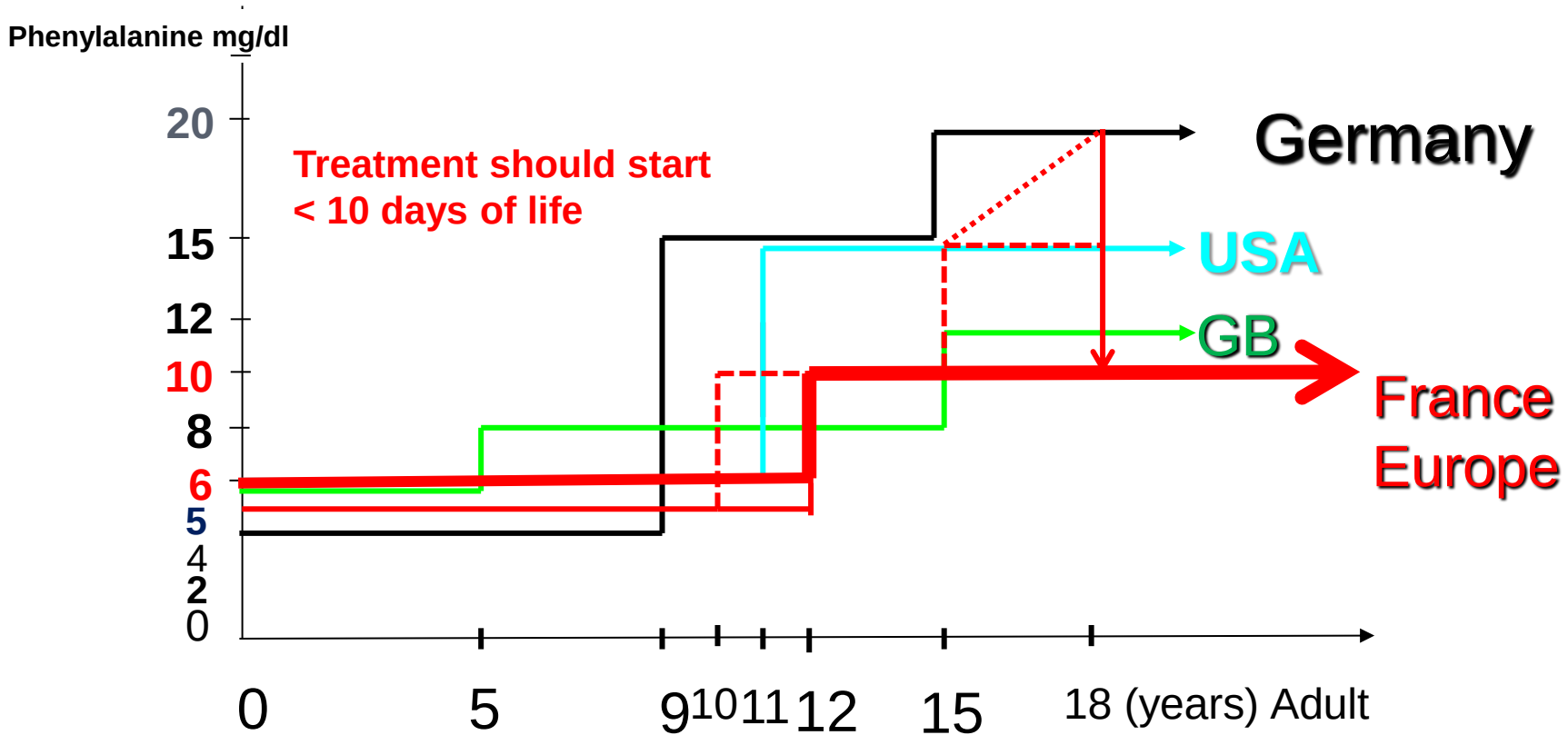
Phe-tolerance depends on enzyme residual activity

Phenylalanine (PHE)



	PAH activity	PHE level without treatment	Daily PHE tolerance in food
Classical PKU	0-1 %	> 20 mg/dl > 1200 µmol/l	200 – 350 mg
Variant PKU or Atypical PKU	1-3 %	10 - 20 mg/dl 600-1200 µmol/l	350 - 850 mg
Hyperphenylalaninemia	3 - 5 %	6 – 10 mg/dl 360-600 µmol/l	> 850 mg

International recommendations for PHE control
according to age / country – no universal consensus for years



Target PHE level

< 12 years : 120 – 360 µmol/l (2 – 6 mg/dl)
> 12 years : 120 – 600 µmol/l (2 – 10 mg/dl)

Orphanet J Rare Dis. 2017 Oct 12;12(1)

Correlation between Phe metabolic control and IQ

Meta-analyses of within-study correlations: intelligence quotient (IQ) and concurrent[a] blood phenylalanine (Phe) level

PKU population	*t*	*n*	*r* (95% CI)[b]
Early treated	29	666	**−0.31 (−0.41, −0.20)***
Classic			
Total	23	499	**−0.23 (−0.32, −0.14)**
Early treated	21	473	**−0.25 (−0.34, −0.15)**
Mixed treatment history	3	32	0.04 (−0.35, 0.42)
Mixed/unspecified			
Total	14	310	**−0.29 (−0.48, −0.07)***
Early treated	9	219	**−0.42 (−0.60, −0.19)***
Mixed treatment history	5	91	0.02 (−0.27, 0.31)
Mild	1	8	−0.28 (−0.82, 0.53)
Hyperphenylalaninemia	1	16	−0.08 (−0.55, 0.43)

0-12 years : Each **100 µmol/l** Phe increase predicted a **1.3 to 3.1 IQ** point reduction

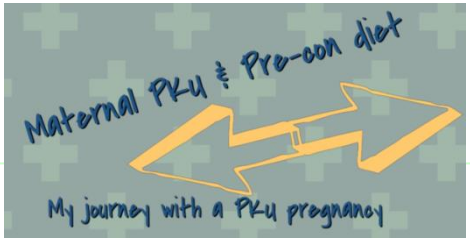
→PHE level is a predictive IQ indicator
A stronger association was observed between Phe levels during early childhood and later IQ.

Mol Genet Metab (2007),92:63-70

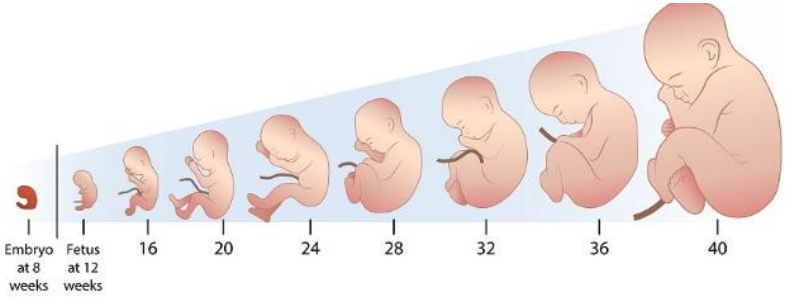
- **Lifelong low phenylalanine diet** (in males and females) to prevent : decreased IQ scores, eczema, behavioral problems, seizures, decreased executive functioning, depression, irritability, headaches, impairment of short term memory, … .

- Important **in Females** who are willing to be pregnant, keep them on a **controlled diet**

- Recommandation to start a strict low PHE diet
  at least **3 months before planned conception**
  and
  throughout pregnancy because of
  teratogenic effects of Phenylalanine on fetus



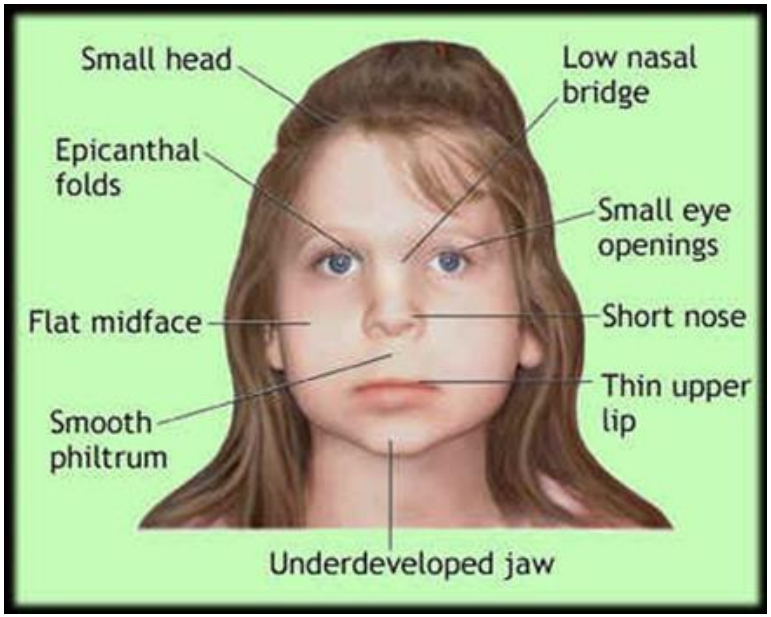
Maternal Phenylketonuria
The toxic effects of Phenylalanine on fetus



MATERNAL PKU : RISKS TO FETUS

Poor metabolic control in mothers → **May cause in fetus**

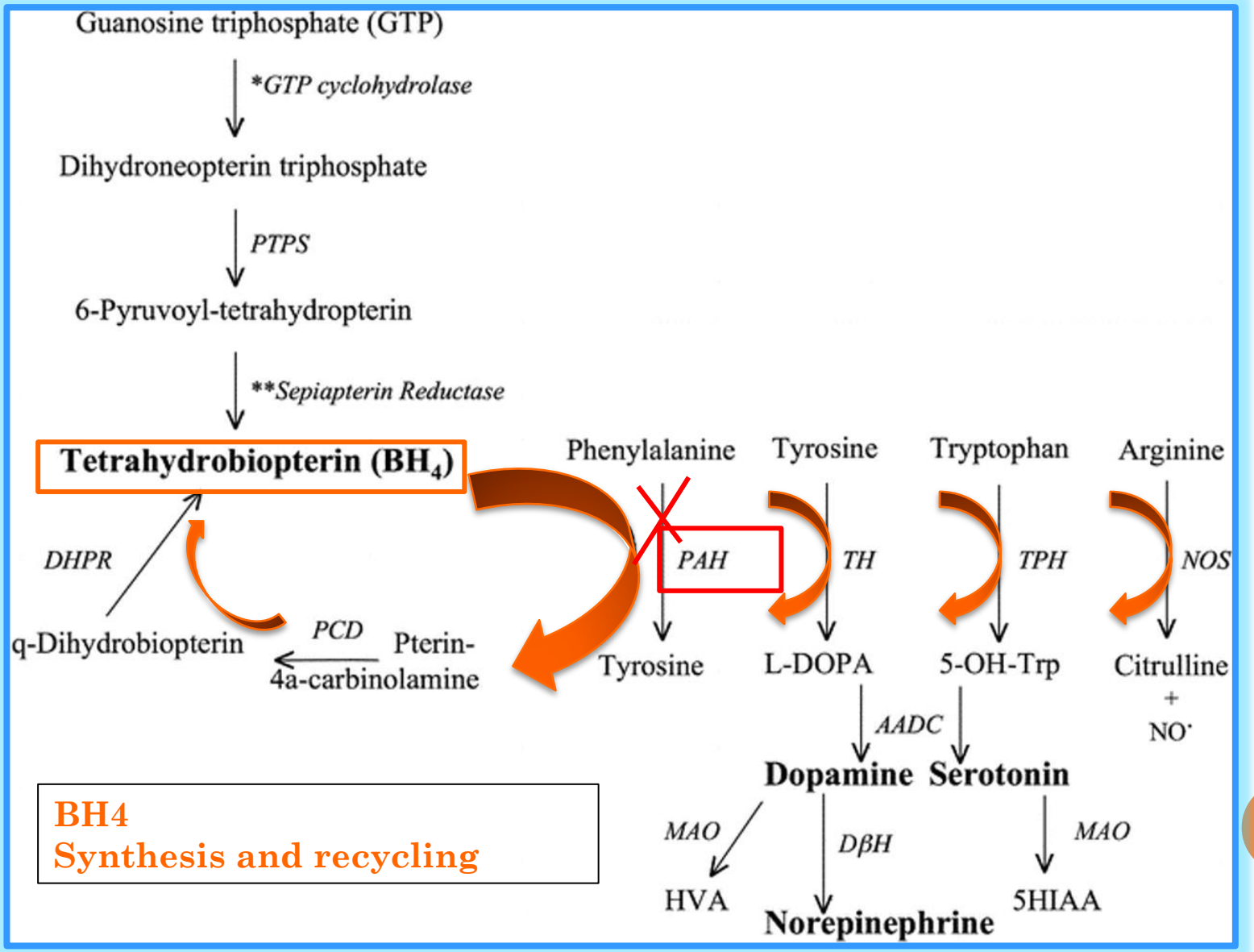
- Congenital heart disease
- Microcephaly
- Low birthweight
- Mental retardation
- Developmental delay



Maternal PKU Syndrome

- Dysmorphism
- Mental retardation 92 %
- Microcephaly 73 %
- Low birth weight 40%
- Congenital cardiac defect 12 %

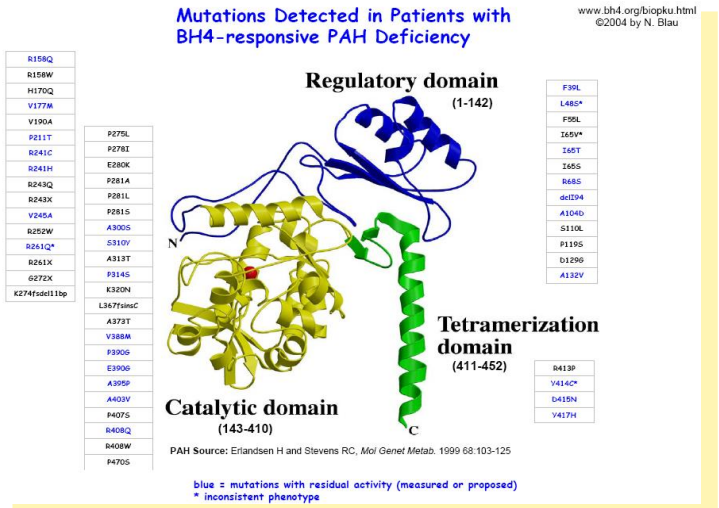
BH4: a natural cofactor of Phenylalanine Hydroxylase (PAH) system



Better Response to cofactor BH4 in missense mutations

~ >1000 PAH mutations worldwide, most are missense mutations

Mutation Type	N°	Graph	
Missense	308		61,85 %
Deletion	66		13,25 %
Splice	52		10,44 %
Silent	30		6,02 %
Nonsense	26		5,22 %
Insertion	8		1,61 %
Sil./Splice	3		0,60 %
Splicing	2		0,40 %
Silent ?	1		0,20 %
Unknown	1		0,20 %
Total	**498**		

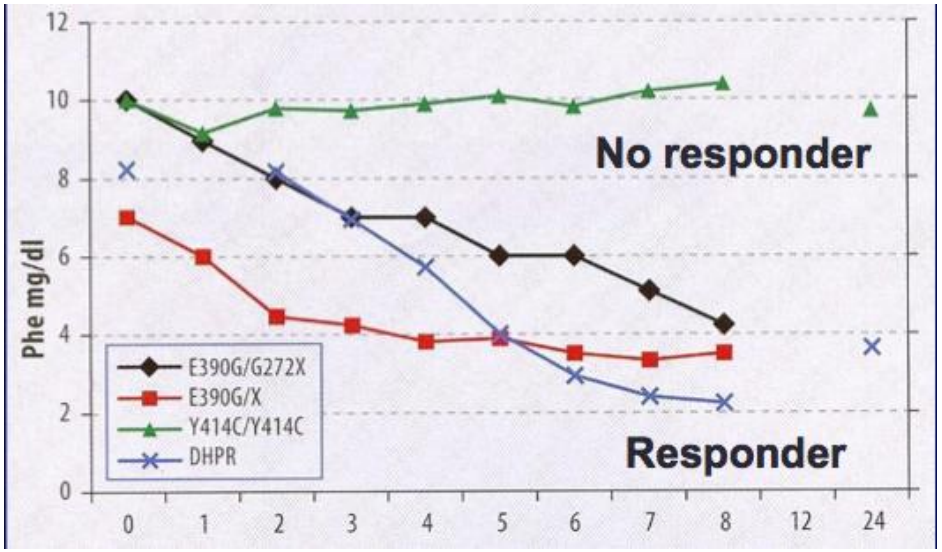


http://www.biopku.org

- Missense mutations : Enzyme is synthesized but activity is null or decreased
- PKU as a model of « misfolding » enzyme ++

- **<u>BH4 = Natural cofactor of aromatic amino acid hydroxylases</u>**
- **Sapropterin (6R-BH4) synthetic form of tetrahydrobiopterin**
- Orphan drug (FDA and EMEA)
- Stabilization of the active tetramer forms of the mutant protein
- Protection from inactivation
- Acts as a « chemical chaperone », preventing misfolding and increase enzyme activity

Different responses to oral BH4 loading test (20mg/kg) according to genotype in PKU patients

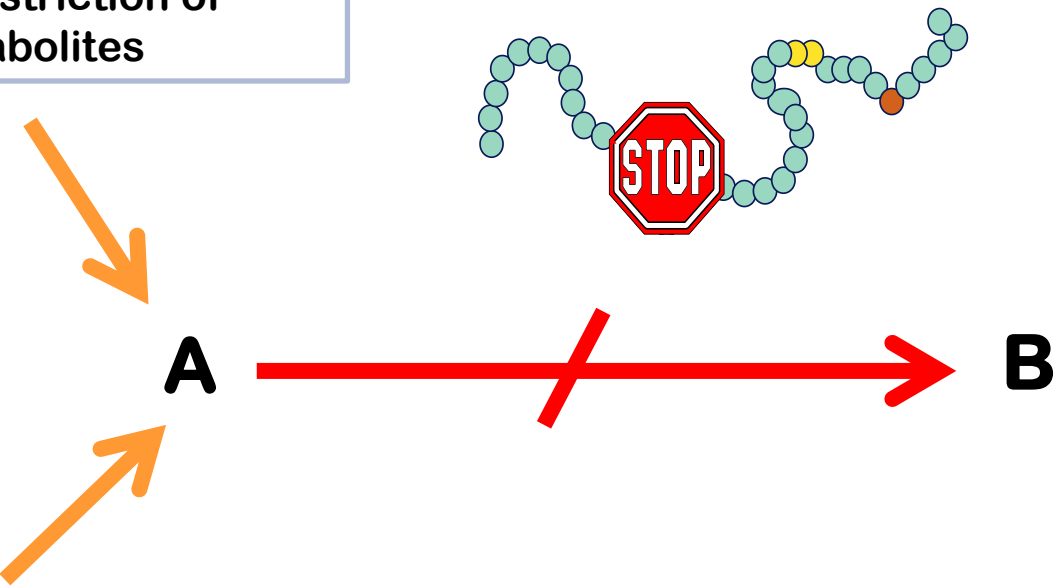


- About **70 %** of mild HPA and mild PKU patients proved to respond to BH4 therapy (reduced Phe level after loading test > 30 %).
- About **10 %** of classical PKU patient respond to BH4 (more severe mutations, null mutations)
- In PKU patients responsive to BH4, oral treatment could be used **in addition** to a restrictive low-phenylalanine diet to reduce blood phenylalanine and increase PHE tolerance, and might even replace the diet in some instances.

Therapeutic strategies in IEM

In Intoxication diseases

Dietary restriction of toxic metabolites

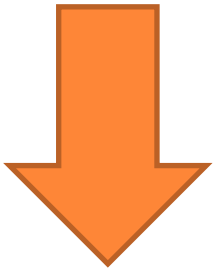


Decreasing metabolite toxicity

- Removing toxic metabolites
- Blocking the effect of toxic metabolites

Principle of treatment in Intoxication type diseases

- Control intake of precursors of toxic compounds (proteins, amino acids)
- Treat catabolic state with energy supply (glucose and lipids)
- Hydratation
- Epuration of accumulated toxic compounds with scavengers/extra renal epuration
- Stimulation of residual enzyme activity (with cofactors)



- **Emergency treatment**
- **Chronic treatment**

Acute management in Intoxication diseases

Metabolic decompensation Triggers

- Prolonged fever
- Vomiting or diarrhoea
- Refusal to eat
- Prolonged fasting / protein overload
- Surgery

Early clinical signs may be subtle

- Lethargy,
- Loss of appetite,
- Change of behaviour or exacerbation of pre-existing neurological problems
- « Unwell »

Management decisions should be based on
clinical status and listening to parents

Acute management in Intoxication diseases

Decompensation	Mildly severe	Severe
Dehydratation	< 10%	≥ 10%
Acidosis: pH HCO_3	> 7.20 > 15 mEq/l	< 7.20 < 15 mEq/l
NH3	< 400 µM	> 400 µM
Glucose	N	N / ↑ / ↓
Lactate	N	> 5 mM
Calcium	N	↓
NFS	N	Neutropenia Thrombocytopenia

Acute management in Intoxication diseases

Nutritional support

1. Stop protein intake …. **FIRST STEP !**

2. Provide adequate calories intake **≥** 100 Kcal/kg/d
   to boost anabolism#reduce catabolism

- **Glucose** 10 mg/kg/min in neonate (oral/NGT/IV)

-- Isocaloric (1 ml = 1 kcal) orale route prefered if digestive tolerance

-- IV route Glucose 15 % (20 % with central catheter)

-- +/- Insuline 0,05 – 0,10 U/kg/H (if hyperglycemia)

- **Lipids** 0,5 g/kg/d up to 3g/kg/d (only contraindication FAO)

Protein should be reintroduce **within 48-72 H** to avoid catabolism

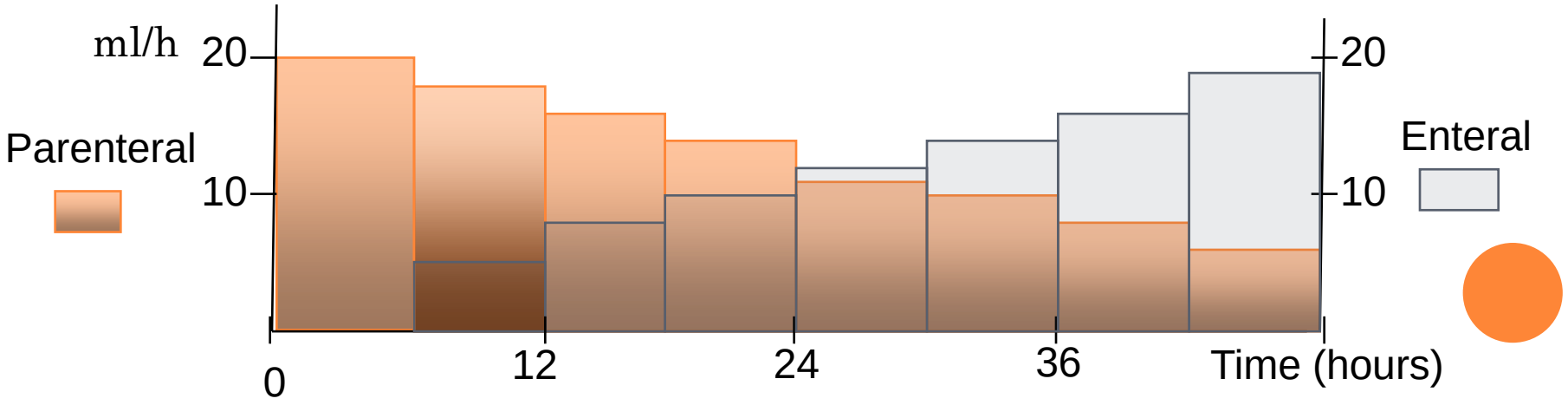
Progressive proteine reintroduction
From intraveinous to oral route

Without protein

- 120 – 130 ml/kg/d
- 90 – 100 Kcal/kg/d
  70-75% Glucose
  + 25-30% lipids
- ions, Ca, Ph,
- vitamins, oligoelements

Protein Controlled diet

- IV **Amino Acids** / milk
- 120 – 130 ml/kg/d
- 90 – 100 Kcal/kg/d
  70-75% Glucose
  + 25-30% lipids
- ions, Ca, Ph,
- vitamins, oligoelements



Example of Emergency diet in MMA (home/hospital treatment – good digestive tolerance)

6 years old boy Calories need : 1700 kcal

Breakfast

2 hypoproteic biscuits

Lunch

1 plate with feculents (pasta, rice or semolina) + fat (oil/butter)
1 hypoproteic toast with butter
A small glass of fruit juice

Afternoon snack

1 bar of hypoproteic chocolate
1 compote

Diner

1 plate with feculents (pasta, rice or semolina) + fat (oil/butter)
1 hypoproteic toast with butter

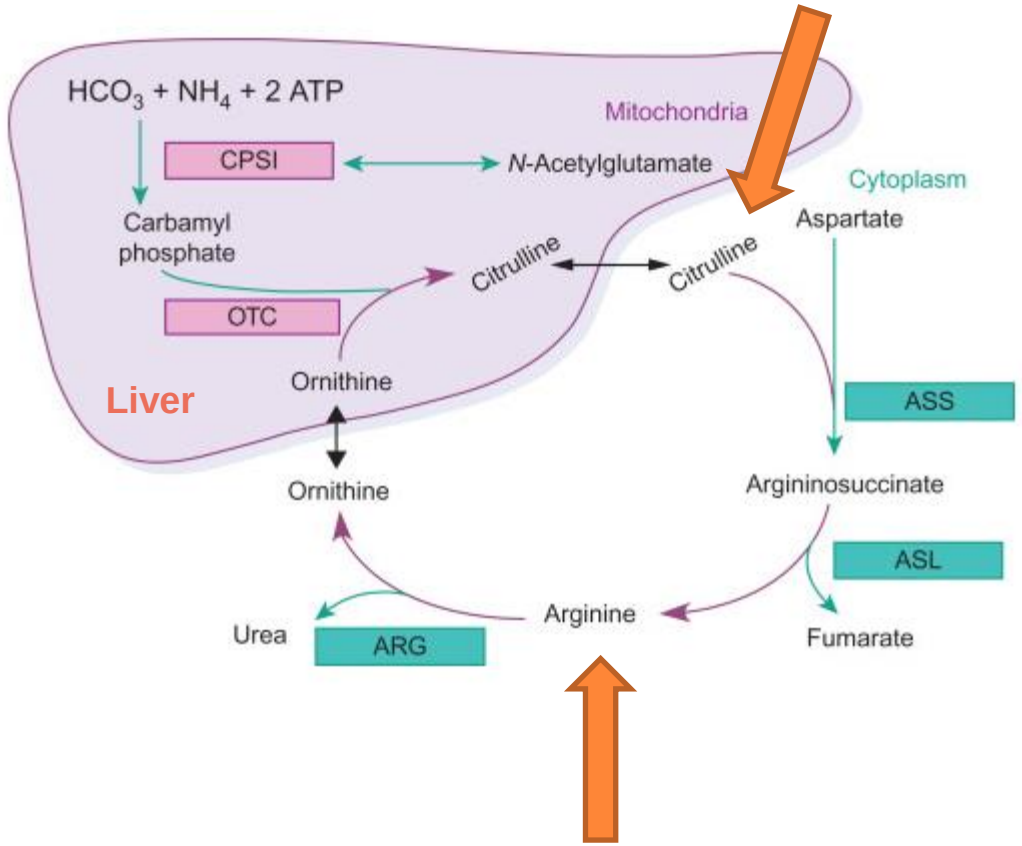
Enteral feeding (NGT) 21H – 6 H (65 mg/ H) :

95 g Basic-P (high carbohydrates and lipids)
20 g maltose dextrin
520 ml water

Management in Intoxication diseases

Amino Acids

Urea cycle defects (UCD)



Management in Intoxication diseases

Amino Acids supplements

- **In Urea Cycle defects = supplier**

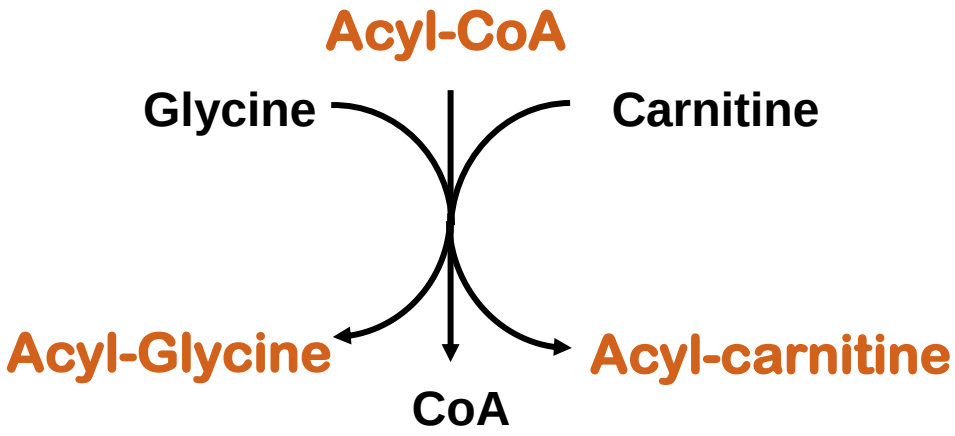
	Dosage	Route	IEM
L-Arginine HCL	200-600 mg/kg	IV/Oral	CPS, OTC ASS1, ASL
L-Citrulline	100-200 mg/kg	Oral	CPS, OTC

- **In Organic Aciduria = scavenger**

	Dosage	Route	IEM
L-Carnitine	100-400 mg/kg/d	Oral/IV	MMA, PA, IVA 3-MCC
L-Glycine	150-300 mg/kg/d	Oral	IVA, 3-MCG

Management in Intoxication diseases

Amino Acids supplements



	L- Glycine	L – Carnitine
MMA	0	Methylmalonyl-carnitine + Propionyl-carnitine
PA	0	Propionyl-carnitine
IVA	Isovaleryl-glycine	Isovaleryl-carnitine
3- MCG	3-CH3-crotonyl-glycine	3-OH-isovaleryl-carnitine

Acute management in Intoxication diseases

Pharmacologic epuration

- **In UCD and OA**

NH_4

≥ 110 µMol/L in NN 1-7d
≥ 90 µMol/L in NN 8-14d
≥ 50 µMol/L in NN 15d - adult

1. Stop protein intake …. **FIRST STEP !**

2. Provide adequate calories intake **≥** 100 Kcal/kg/d
   - Infuse Glucose 8 -10 mg/kg/min
   - Infuse lipids 0,5 g/kg/d up to 3g/kg/d

❑ Protein should be reintroduce **within 48 H** after return of ammonia levels to 80–100µmol/l to avoid catabolism and nitrogen release

❑ Control blood NH_3/3 H (heparin tube on dry ice **within 15-30 min**)

Nat Rev Nephrol. 2020 Aug;16(8):471-482

Acute management in Intoxication diseases

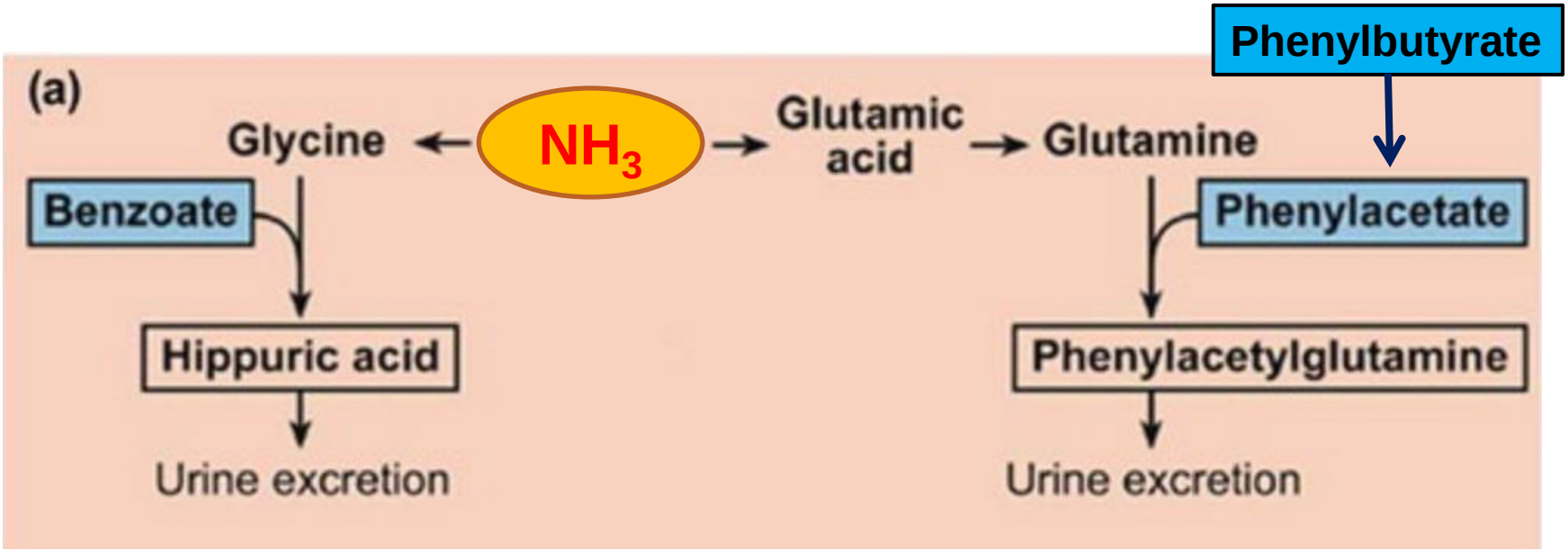
Pharmacologic epuration

- **In UCD and OA**

NH_3 **≥ 150 µMol/l**

Nitrogen Scavenger	Dosage	Route	IEM
Sodium Benzoate	250 mg/kg	IV/oral	UCD, OA
Sodium Phenylacetate	250 mg/kg	IV	UCD, OA
Sodium Phenylbutyrate Ammonaps®	250 mg/kg	oral	UCD, OA
Glycerol Phenylbutyrate (Ravicti®)		oral	UCD
Carbamylglutamate (Carbaglu®)	100 -250 mg/kg/d	oral	NAGS, OA

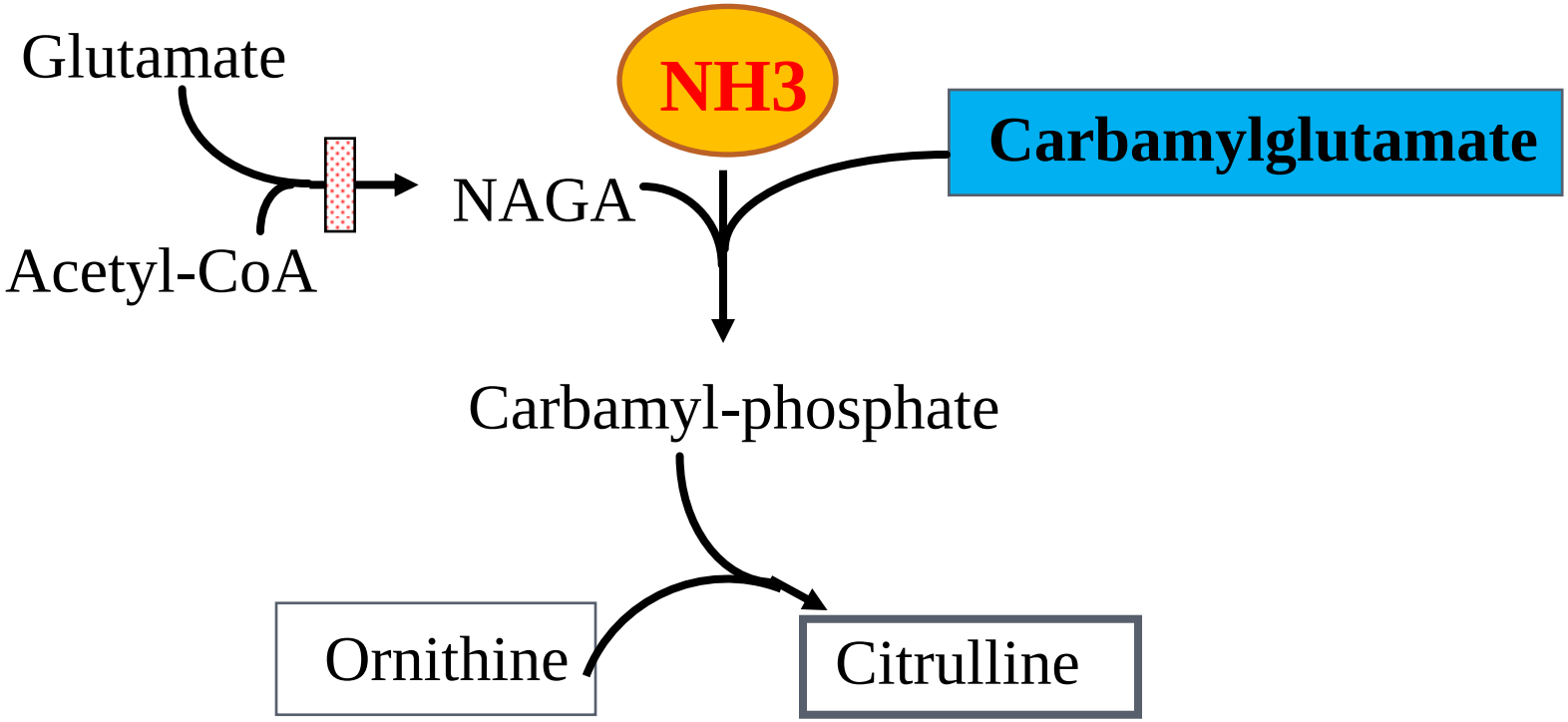
Nitrogen Scavenger
How they trap toxic NH3 to transform into a non toxic compound ?



1 mole Benzoate
=
1 mole NH3 detoxification

1mole Phenylbutyrate
=
2 moles NH3 detoxification

Nitrogen Scavenger Carbamylglutamate



The only form currently available is an oral preparation

Acute management in Intoxication diseases

Vitamins Cocktail

	Dosage	Route	IEM
Thiamine (B1)	100 (- 400) mg/d	Oral/IM/IV	Beri-Beri, PDH, MSUD
Riboflavine (B2)	50 mg/d	Oral	GA1, IVA, MADD, resp chain (CI and CII)
Biotin (B8)	10-20 mg/d	Oral/IM	PA, PC, MCD, BGBRD, MCG, resp chain
Hydroxocobalamine B_{12}	1–2 mg/d	IM/IV	MMA, HCYST, CblC
Pyridoxine (B6)	0.5–1 g/d 100 mg/d (NN)	Oral/IV	HCYST (CBS) B_6-responsive seizures
Pyridoxal-P	30 mg/kg/d	Oral	PNPO
Folic acid	10–40 mg/d	IV	HCYST (MTHFR)
Folinic acid	5–15 mg/d	IV	HCYST (Remethylation), Cerebral folate transporter

Extrarenal epuration is the best way for a rapid ammonia decline

NH_3

NN and children **≥ 200-300 µMol/l** if no response within hours
≥ 400-500 µMol/l definitely

Adolescents and adults **≥ 200 µMol/l**

Table 3 | **Dialysis ammonia clearance and filtration fractions**

Number of patients	Dialysis modality	Qb (ml/min)	Qd (ml/min)	Ammonia clearance (ml/min/kg body weight)	Ammonia filtration fraction (%)
3	CAVHD	10–20	8.3 (0.5 l/h)	0.87–0.97	12.5–14.3
3	CVVHD	20–40	33.3–83.3 (2–5 l/h)	2.65–6.80	53.0–58.0
2	HD	10–15	500	3.95–5.37	95.0–96.0

CAVHD, continuous arteriovenous haemodialysis; CVVHD, continuous venovenous haemodialysis; HD, haemodialysis; Qb, blood flow rate; Qd, dialysis fluid flow rate. Based on data from REF.[34].

Nat Rev Nephrol. 2020 Aug;16(8):471-482.

Diet controlled in natural proteins
Amino acids mixtures supplements

1. Protein restriction Low protein diet,
minimal protein requirement/safe levels (FAO/WHO/UNU)

2. Specific AA mixtures supplements
(not in all diseases, not in emergency situation to not overload metabolism)

- For each disease, depending on affected metabolic pathway
- Different forms (powder, gel, liquid)
- Different compositions (according to age : baby, infant or adult)
- Supplemented with trace elements, minerals and vitamins

Enteral Night nutrition
- Malnutrition prevention
- Prolonged fasting prevention
- Emergency diet

Safe Protein levels and Energy needs in general population - FAO/WHO/UNU recommendations

PROTEIN INTAKE		
Age	**Intake**	
months	*g/kg bw/day*	
1	1.77	
2	1.50	
3	1.36	
6	1.31	
12	1.14	
years		
1.5	1.03	
2	0.97	
3	0.90	
4-6	0.87	
7-10	0.92	
	Females	**Males**
years		
11	0.90	0.91
12	0.89	0.90
13	0.88	0.90
14	0.87	0.89
15	0.85	0.88
16	0.84	0.87
17	0.83	0.86
18	0.82	0.85
> 18	0.83	0.83

ENERGY REQUIREMENTS				
Age	**Females**	**Males**	**Females**	**Males**
years	*kJ/kg bw/day*		*kcal/kg bw/day*	
0.5	340	335	81.3	80.0
2.5	334	348	79.8	83.2
5.0	305	315	72.9	75.3
10	248	275	59.3	65.7
15	193	230	46.1	55.0
Adults, moderate activity level, 70kg body weight				
18-29	159	183	38.0	43.7
30-59	148	175	35.4	41.8
Adults, moderate activity level, 50kg body weight				
18-29	180	212	43.0	50.7
30-59	183	212	43.7	50.7

Häberle J, Orphanet J Rare Dis. 2012 May 29;7:32.

Treat intercurrent illness as soon as possible at home first, according to emergency plan

To prevent metabolic decompensation during poor feeding, vomiting, fever, etc

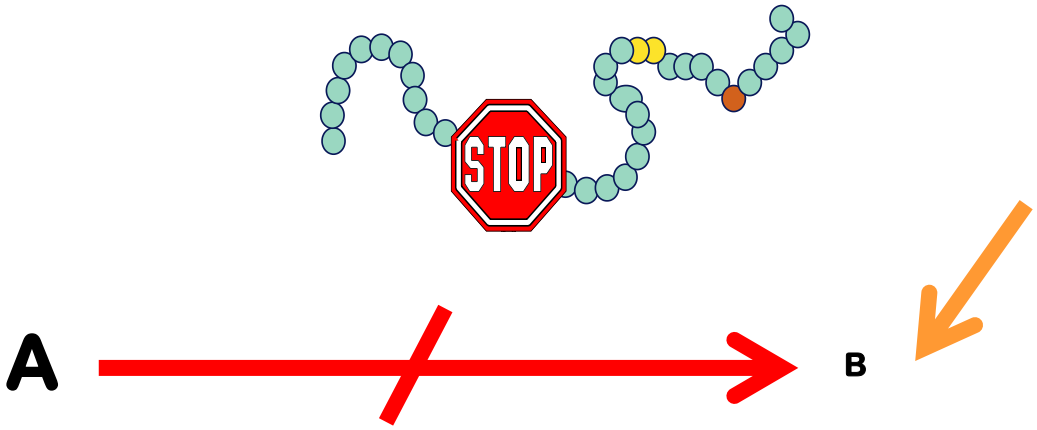
- Stop protein intake
- Give sufficient fluids (water, tea, ..) and calories (carbohydrates as glycose polymers/maltodextrin) with some salt every 2 H

Age	Glycose polymers/ Maltodextrin %	Kcal/ 100 ml	Daily volume
0-1 y	10	40	150-200 mg/kg
1-2 y	15	60	95 ml/kg
2-10 y	20	80	1200-2000 ml/day
> 10 y	25	100	2000 ml/day

Product	Sachet size	Make up to final volume	Carbohydrate concentration provided	Recommended age group*
S·O·S10™	21g	200ml	10%	Birth - 1 year
S·O·S15™	31g	200ml	15%	1 - 2 years
S·O·S20™	42g	200ml	20%	2 - 10 years
S·O·S25™	52g	200ml	25%	10 years +

Therapeutic strategies in IEM

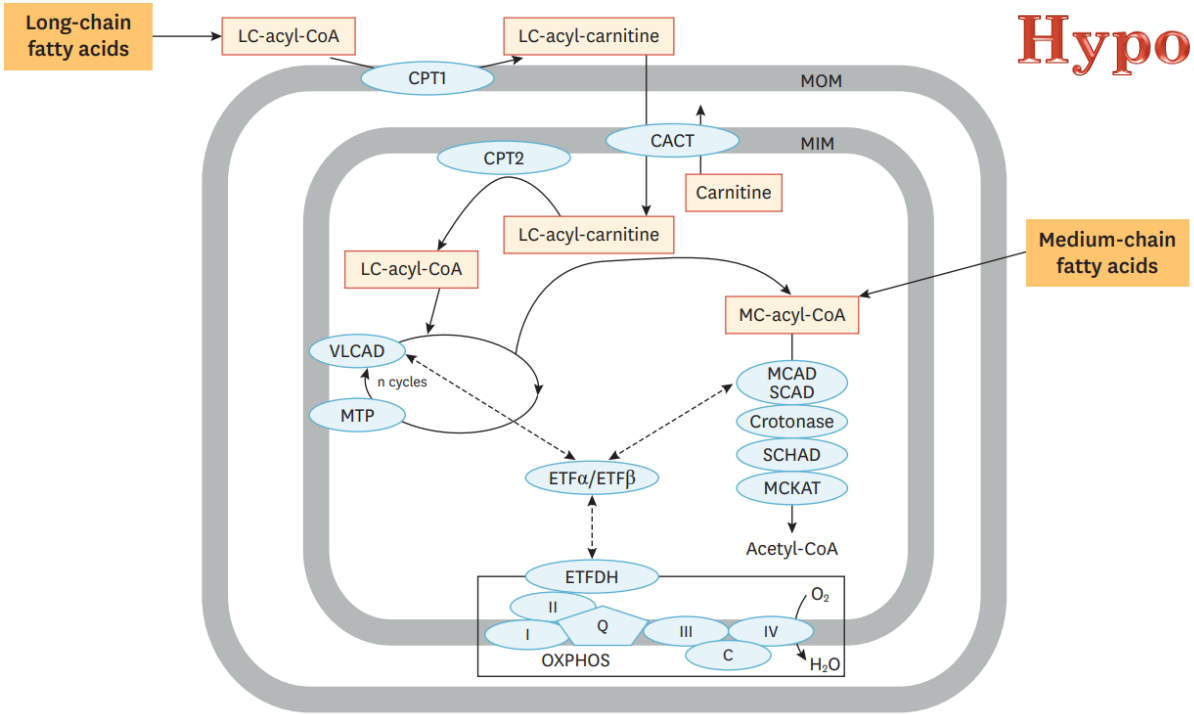
In Carbohydrate metabolism defects



Management in Carbohydrate metabolism is Based on diet and prevention of hypoglycemia

- In FAO defects

Hypoketotic Hypoglycemia



Avoid prolonged fasting; variable according to age

Provide high glucose amounts

Control lipids supply

Management in Carbohydrate metabolism is Based on diet and prevention of hypoglycemia

- **In FAO defects**

Hypoketotic Hypoglycemia

Avoid prolonged fasting time; according to age

Age	Recommended fasting time	Maximal fasting time
Newborn	3 H	4 H
1 – 6 months	4 H	6 - 8 H
6 – 12 months	4 H (day)/ 6 – 8 H (night)	10 – 12 H (night)
1 – 6 years	4 H (day)/ 10 H (night)	12 H (night)
> 6 years	4 H (day)/ 12 H (night)	14 H (night)

FAO deficiency PNDS, HAS website

Management in Carbohydrate metabolism is Based on diet and prevention of hypoglycemia

- **In FAO defects** **in Emergency**

If unwell, fever, vomiting, hospitalisation

Hypoketotic Hypoglycemia

Provide 120 – 200 % of daily glucose
Keep Glucose > 100 mg/dl

Age	Recommended glucose IV/oral
Newborn	10 – 12 mg/kg/min
1 month – 6 y	8 – 12 mg/kg/min
6 y – 14 y	6 – 8 mg/kg/min
Adult	3 – 4 mg/kg/min

- **Give enough glucose to block lipolysis**
- **Stop lipids**

Routes : - Oral (mouth / nasogastric tube / gastrostomy)
- Depending on digestive tolerance (continous or intermittent enteral feeding)
- IV if digestive intolerance

Management in Carbohydrate metabolism is Based on diet and prevention of hypoglycemia

- **In FAO defects**

Control Lipids in diet

IEM	LCFA in diet	MCT in diet	% Total Energy
VLCAD, LCHAD/MTP CPT-I, CPT-II CACT	Max 10 %	20 – 25 % 	25 – 30 %
MCAD		**Contraindicated** (e.g. coco milk/oil,..)	

In case of suspicion of FAO,
do not give IV lipids in emergency situations

Management in FAO
Based on diet - lipid restriction risks

- **Supply enough Polyinsaturated Fatty Acids (FA) :**

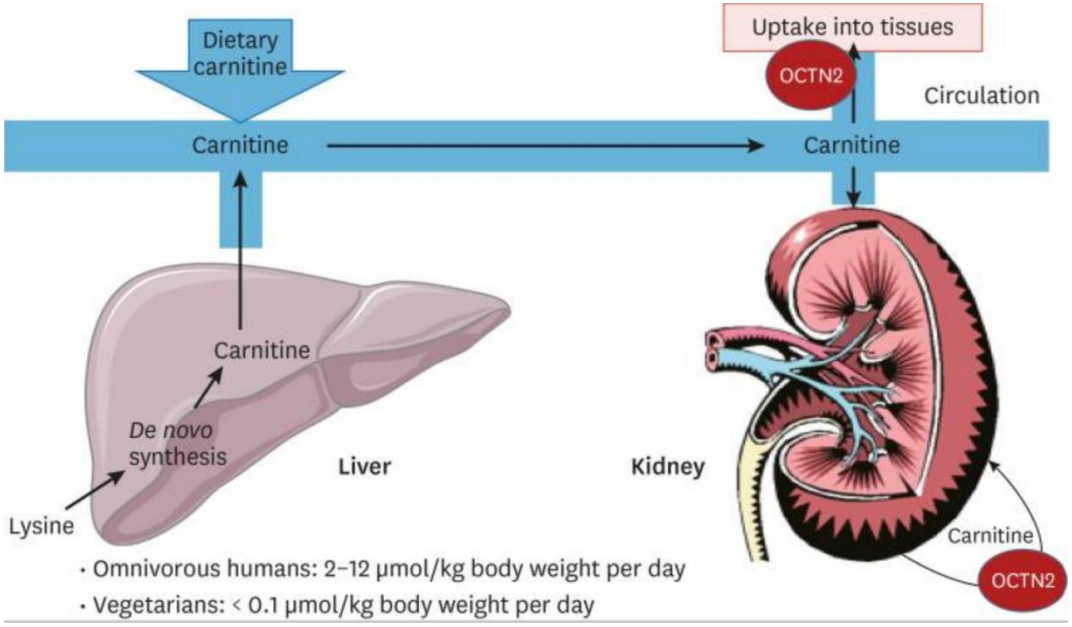
  risk of omega-3 (EPA & DHA), omega-6 FA deficiency

  in lipid- restricted diet

- **Control Fat-soluble vitamins** (A, D, E, K)

Other therapeutic options in FAO defects

- **L-Carnitine**

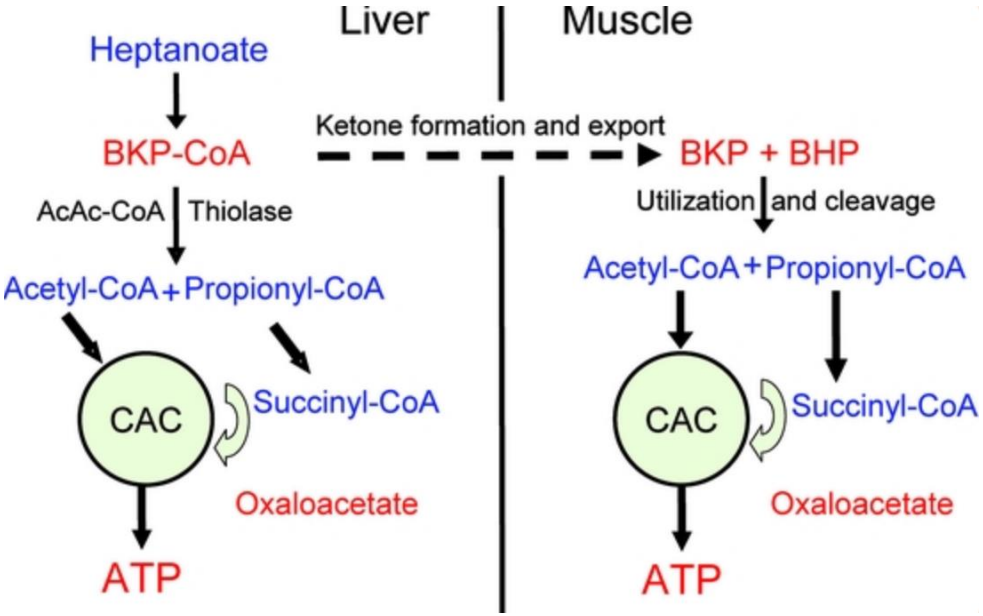


	Dosage	Route	IEM
L-Carnitine	50 – 100 mg/ kg	IV / oral	Systemic primary carnitine deficiency (OCTN2)
	20 – 50 mg/kg	IV / oral	MCAD
	10 – 50 mg/kg	IV / oral	CACT, CPT2, VLCAD, LCHAD & MTP, MAD

Controversial use in long chain FAO/carnitine cycle defects (cardiotoxicity)

Other therapeutic options in FAO defects

- **Triheptanoin (C7)** **an anaplerotic therapy for Lc FAO**



Triheptanoin (C7) produces 2 Acetyl-CoA and 1 propionyl-CoA units used by the Citric Acid Cycle (CAC)

- In studies, some improvements in cardiac parameters (decrease in LVM, small increase in ejection fraction)
- No effect on rhabomyolysis crises in LcFAO (Vockley et al; 2020)

Management in Carbohydrate metabolism defects Based on diet and prevention of hypoglycemia

- **In Glycogenosis**

Ketotic Hypoglycemia

- Prevent hypoglycemia to avoid neurologic and long term complications (hepatic, renal, ..)
- Monitor daily caloric intake
- Assure normal growth

Avoid fasting; variable according to tolerance, to age

Provide frequent Carbohydrate (CH) rich feeding (day time)

Continuous nocturnal enteral supply of slow release (complex) CH

Nutritional Management in Glycogen Storage diseases

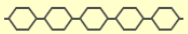
GSD 0a	**Protein enriched diet (20%)**
GSD Ia GSD Ib	High complex CH intake (55 – 70 %) Moderate fat restriction (20 – 30 %) Moderate protein restriction Galactose / Lactose restriction
GSD III	High complex CH intake (55 – 70 %) Moderate fat restriction (20 – 30 %) **Protein enriched diet (20 %)**

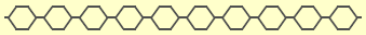
Management in Carbohydrate metabolism defects
Based on diet and prevention of hypoglycemia

Provide frequent CH rich feeding

Glucose 

Only in an emergency!

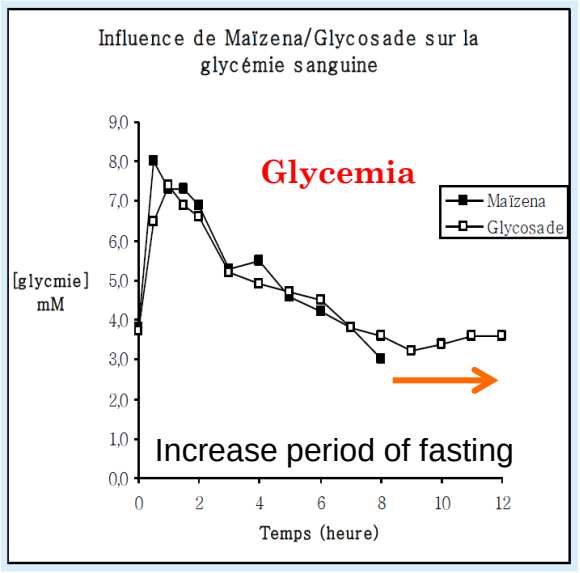
Maltodextrin (industrially produced sugar)
Short chains of glucose 

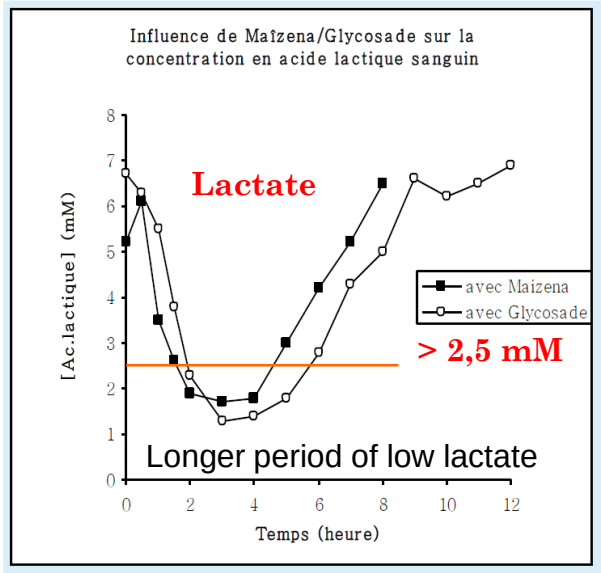
Starch (also uncooked – depot effect)
Long chains of glucose 

Management in Carbohydrate (CH) metabolism defects
Based on diet and prevention of hypoglycemia

Provide frequent CH rich feeding to increase metabolic control

	Maïzena	Glycosade ®
	Uncooked cornstarch	Modified cornstarch
Amylopectine	73 %	**99,5 %**
Resistant starch	60,5 %	**68 %**
From	6 months - 1 year	2 years





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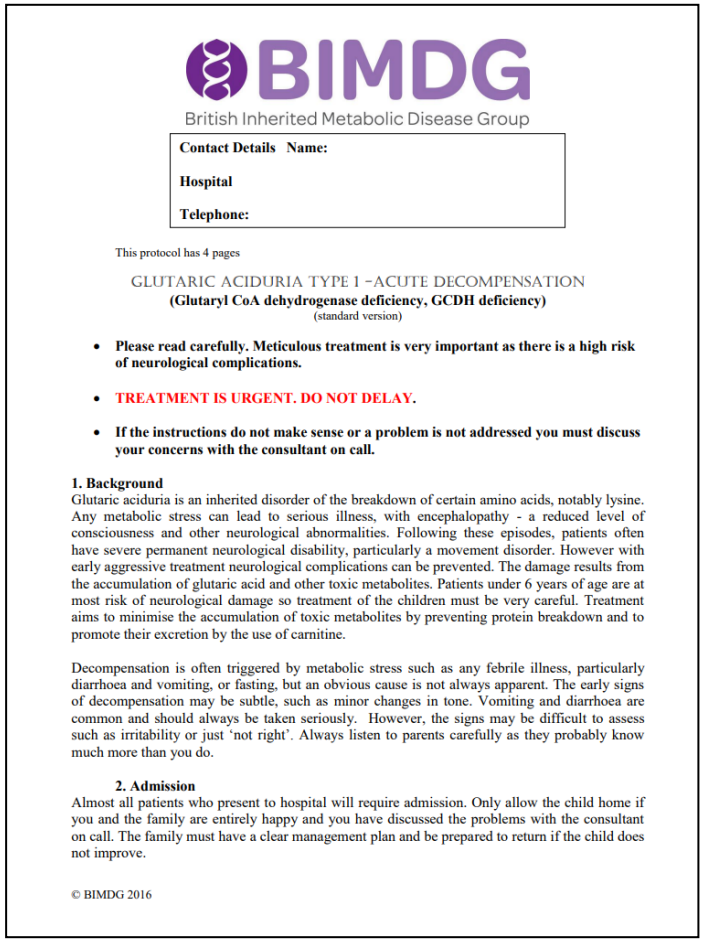
Management in Carbohydrate metabolism deficiency Based on diet and prevention of hypoglycemia

Overnight Continuous enteral feeding of slow release CH

- **Nasogastric or gastrostomy tube** or waking up every four to five hours to take cornstarch
- High-carbohydrate, lactose- and sucrose-free enteral formula (GSD I).
- An optimal infusion provides : 8-10 mg/kg/min glucose in infants,
  6-8 mg/kg/min glucose in older children,
  3-7 mg/kg/min glucose in adults.
- Safety concerns (tube dislodgement, leakage, and pump failure) that can cause serious hypoglycemia
- Safety precautions
  - bed-wetting devices (to detect formula leakage)
  - feeding pump alarms

Personalized Emergency card for every patient with metabolic decompensation risk



BIMDG

British Inherited Metabolic Disease Group

Contact Details Name:

Hospital

Telephone:

This protocol has 4 pages

GLUTARIC ACIDURIA TYPE 1 –ACUTE DECOMPENSATION

(Glutaryl CoA dehydrogenase deficiency, GCDH deficiency)

(standard version)

- **Please read carefully. Meticulous treatment is very important as there is a high risk of neurological complications.**
- **TREATMENT IS URGENT. DO NOT DELAY.**
- **If the instructions do not make sense or a problem is not addressed you must discuss your concerns with the consultant on call.**

1. Background

Glutaric aciduria is an inherited disorder of the breakdown of certain amino acids, notably lysine. Any metabolic stress can lead to serious illness, with encephalopathy - a reduced level of consciousness and other neurological abnormalities. Following these episodes, patients often have severe permanent neurological disability, particularly a movement disorder. However with early aggressive treatment neurological complications can be prevented. The damage results from the accumulation of glutaric acid and other toxic metabolites. Patients under 6 years of age are at most risk of neurological damage so treatment of the children must be very careful. Treatment aims to minimise the accumulation of toxic metabolites by preventing protein breakdown and to promote their excretion by the use of carnitine.

Decompensation is often triggered by metabolic stress such as any febrile illness, particularly diarrhoea and vomiting, or fasting, but an obvious cause is not always apparent. The early signs of decompensation may be subtle, such as minor changes in tone. Vomiting and diarrhoea are common and should always be taken seriously. However, the signs may be difficult to assess such as irritability or just 'not right'. Always listen to parents carefully as they probably know much more than you do.

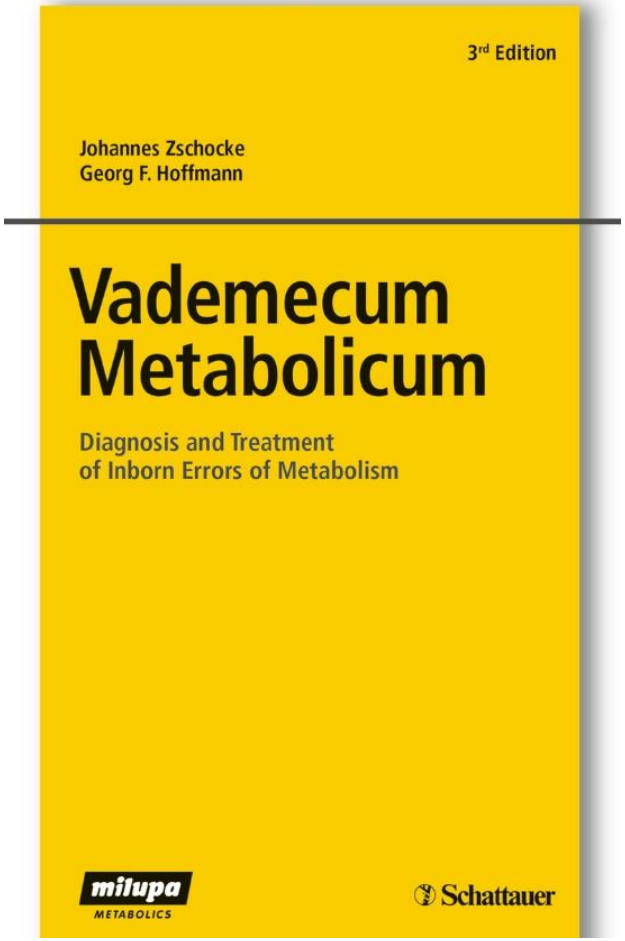
2. Admission

Almost all patients who present to hospital will require admission. Only allow the child home if you and the family are entirely happy and you have discussed the problems with the consultant on call. The family must have a clear management plan and be prepared to return if the child does not improve.

- https://www.bimdg.org.uk/site/guidelines.asp
- https://www.orpha.net/consor/cgi-bin/Disease_Emergency.php?lng=EN
- For intercurrent illness management at home/in hospital
- Should explain the disease, and management of risks

A book to have in your pocket !

http://www.vademetab.org/



ANDROID APP ON Google play

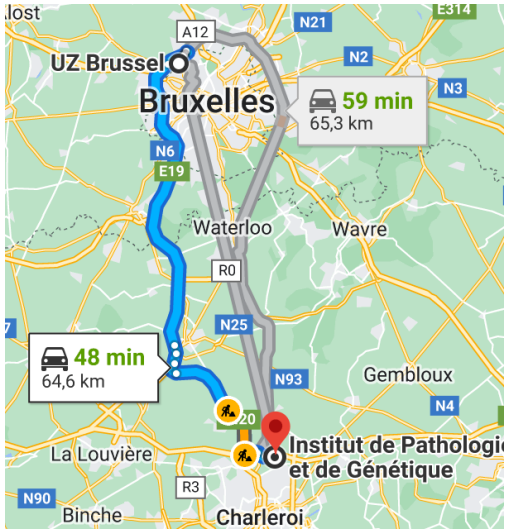
Download on the App Store

CONTACT YOUR LOCAL METABOLIC TEAM

8 belgian centers for IEM – see their contacts on

www.metabolics.be

Institut de Pathologie et de Génétique
25 Avenue Lemaître, 6041 Gosselies (Charleroi)



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Mrs Cécile Minet *(Social Nurse)*
Mrs Camille Rouyer *(Social Nurse)*
Mrs Aude Lombard *(Genetic counsellor)*

Lexical

CblC, cobalamin C deficiency;
FAO, Fatty acid oxydation defects
GA1, glutaric aciduria type 1;
HCYST (CBS), hyperhomocystinuria due to cystathionine beta synthase;
HCYST (MTHFR), hyperhomocysteinemia due to methyltetrahydrofolate deficiency;
IVA, isovaleric acidemia;
MADD, multiple acyl CoA dehydrogenase def;
MMA, methylmalonic aciduria;
Resp chain (CI and CII), mitochondrial respiratory chain complex I and II deficiency;
MCD, multiple carboxylase deficiency;
MCG, methylcrotonyl CoA carboxylase def;
MSUD, Maple Sirup Urine Disease;
NGT, nasogastric tube
PA, propionic aciduria;
PC, pyruvate carboxylase deficiency;
PDH, pyruvate dehydrogenase deficiency;
PNPO, pyridox(am)in 5' phosphate oxidase
UCD, urea cycle disorders