医学信息速递

Medical Information Express

医学及信息部　　陈骁康

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尿素循环障碍的诊治

病因与发病机制

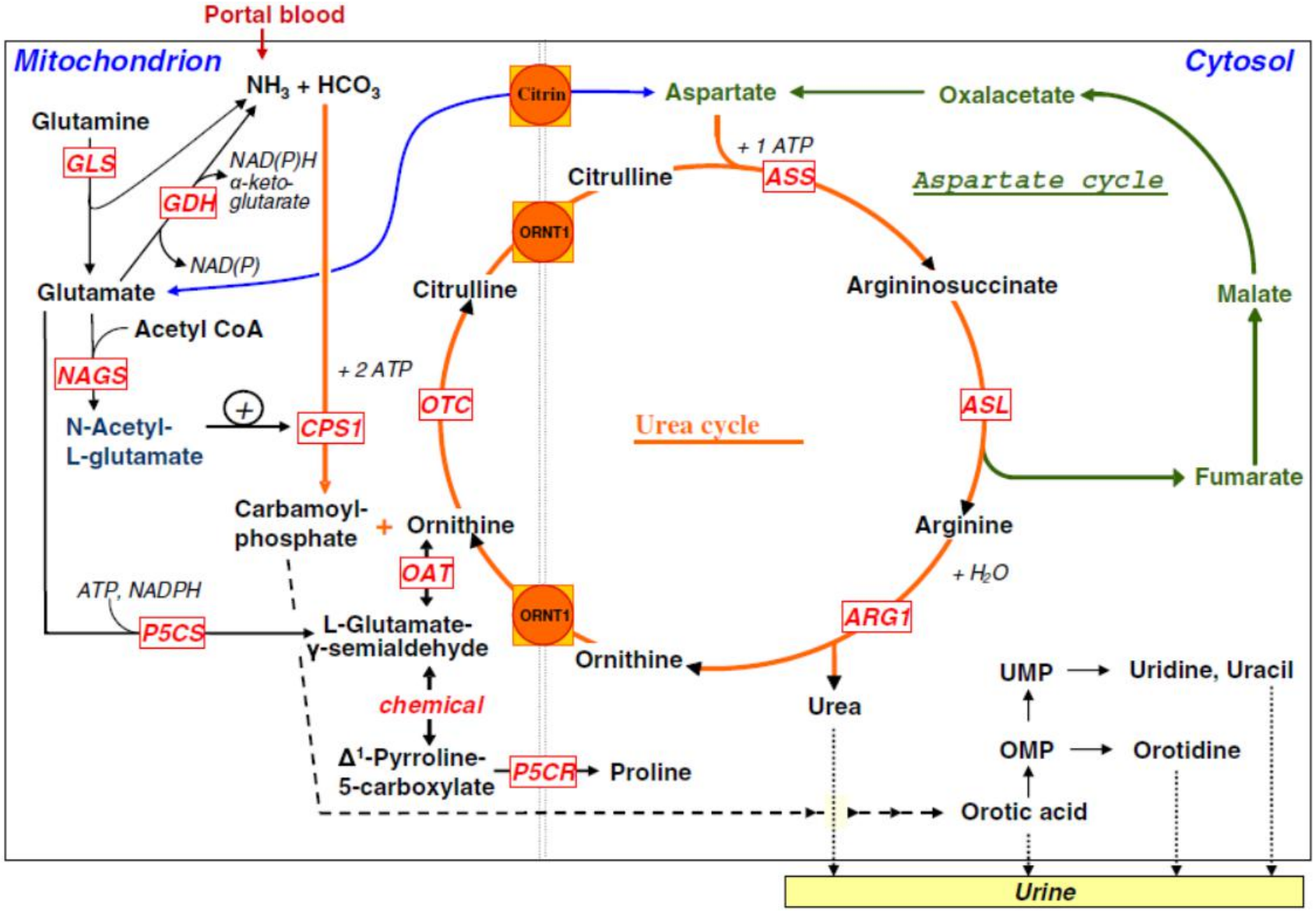
- 尿素循环的功能是将有毒的氨合成无毒的尿素，从而避免高氨血症的发生。

- 该循环是包括6个步骤的系列生化反应，有6种酶参与，依次为N-乙酰谷氨酸合成酶（NAGS）、氨基甲酰磷酸合成酶I（CPSI）、鸟氨酸氨基甲酰转移酶（OTC）、精氨酸代琥珀酸合成酶（AS）、精氨酸代琥珀酸裂解酶（AL）和精氨酸酶（ARG），其中前3者位于线粒体内部，而后3者则位于胞浆。为维持尿素循环的正常进行，AS的反应底物天冬氨酸须通过线粒体内膜的载体citrin从线粒体内部转运到胞浆，而OTC的反应底物鸟氨酸则须通过线粒体内膜的另一转运体ORNT1由胞浆转运到线粒体内部。

- 以上6种酶和2种载体或转运体中任何一种出现结构或功能缺陷，都会影响尿素合成而形成高氨血症，严重者出现发作性脑病的临床表现，这就是尿素循环障碍（urea cycle disorders，UCD）。

宋元宗. 中国实用儿科杂志, 2009, 24(03): 168-171.

病因与发病机制



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

- 在这6种酶的缺乏中，以鸟氨酸氨基甲酰转移酶（OTC）与氨基甲酰磷酸合成酶I（CPSI）的缺乏较常见，且临床症状也最重。
- 越接近循环起始端的酶缺乏，以及酶缺乏的程度越重，临床症状出现的就越早、越重、预后越差。
- 导致UCD的基因突变以点突变和小缺失突变为主，除OTC为X连锁显性遗传外，其他的均属常染色体隐性遗传。

郝虎等. 中国小儿急救医学, 2014(21): 357.

马兰等. 中国临床医生杂志, 2016, 44(12): 108-110.

症状与体征

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Acute presentation

- **Altered level of consciousness (from lethargy and somnolence to coma) mimicking encephalitis or drug intoxication**
- **Acute encephalopathy (see below)**
- **Seizures (mostly under situation of altered level of consciousness)**
- Ataxia: mostly under situation of altered level of consciousness
- Stroke-like episodes
- Transient visual loss

- **Vomiting and progressive poor appetite**
- Liver failure, coagulopathy (esp. in OTCD and HHH)

- **Multiorgan failure**
- **Peripheral circulatory failure**

- **Psychiatric symptoms (hallucinations, paranoia, mania, emotional or personality changes)**
- "Post-partum psychosis"

- **<u>In neonates:</u>**
  sepsis-like picture, temperature instability, respiratory distress, hyperventilation

- 粗体：典型的体征和症状
- 标准：不常见的体征和症状
- 斜体：仅在单例患者中报告过的体征和症状

Chronic presentation

- **Confusion, lethargy, dizziness**
- **Headaches, migraine-like, tremor, ataxia, dysarthria**
  Flapping tremor (in adults)
- **Learning disabilities, cognitive impairment**
- Epilepsy
- Chorea, cerebral palsy
- Protracted cortical visual loss
- Progressive spastic diplegia or quadriplegia starting in childhood (described in ARG1D and HHH syndrome)

- **Protein aversion, self-selected low-protein diet**
- **(Recurrent) abdominal pain, vomiting**
- **Failure to thrive**
- **Hepatomegaly, elevated liver enzymes**

- **Psychiatric symptoms: hyperactivity, mood alteration, behavioural changes, aggressiveness**
- Self-injurious behaviour
- *Autism-like symptoms*

- **Fragile hair (mainly in ASLD)**
- *Dermatitis*

- **Episodic character of signs and symptoms**

- Specific neuropsychological phenotype in heterozygous OTC females

Häberle, J et al. J Inherit Metab Dis. 2019 Apr 14.

鉴别诊断与产前检查

Parameter	Condition				
	UCDs	Organic acidurias	β-oxidation defects	Carbonic anhydrase Va def.	HMG-CoA lyase def.
Acidosis	+/–	+[e]	+/–	+	+
Ketonuria[a]	–	+	absent	+	absent
Hypoglycemia[b]	–	+/–	+	+/–	+
↑ Lactic acid[c]	–	+	+/–	+	+/–
↑ AST & ALT	(+)[d]	–	+	–	+/–
↑ CPK	–	–	+	–	+/–
↑ Uric acid	–	+	+/–	–	+
↓ WBC/RBC/Plt	–	+	–	–	+/–
Weight loss	–	+[f]	–	–	+/–

Parameter	Condition			
	HI HA syndrome	Pyruvate carboxylase def.[g]	PEPCK def.	TMEM70, SERAC1 def.
Acidosis	–	+	+	+
Ketonuria[a]	–	++	+	+
Hypoglycemia[b]	+	+	+/–	+/–
↑ Lactic acid[c]	–	+	+/–	++
↑ AST & ALT	–	+/–	++	–
↑ CPK	–	–	–	–
↑ Uric acid	–	–		++
↓ WBC/RBC/Plt	–	–	–	–
Weight loss	–	+		–

In addition to the conditions indicated in the table, mitochondrial oxidative phosphorylation defects, citrin deficiency, lysinuric protein intolerance or ornithine aminotransferase deficiency can also cause hyperammonemia.

Disorder	Recommended tests
NAGSD	Mutation analysis using DNA from CVS or AFC[a]
CPS1D	**Mutation analysis using DNA from CVS or AFC**
	Enzyme assay in late fetal liver biopsy[b]
OTCD	**Mutation analysis using DNA from CVS or AFC[c]**
	Enzyme assay in late fetal liver biopsy[b,d]
ASSD	**Mutation analysis using DNA from CVS or AFC**
	Citrulline in amniotic fluid
	Enzyme assay in intact or cultured CVS or in cultured AFC
ASLD	**Mutation analysis using DNA from CVS or AFC**
	Argininosuccinate and its anhydrides in amniotic fluid
	Enzyme assay in intact or cultured CVS or cultured AFC
ARG1D	**Mutation analysis using DNA from CVS**
	Enzyme assay in fetal blood erythrocytes (mid-gestation sampling)
HHH syndrome	**Mutation analysis using DNA from CVS or AFC**
	Enzyme assay in CVS or cultured AFC

First choices are given in bold-type.

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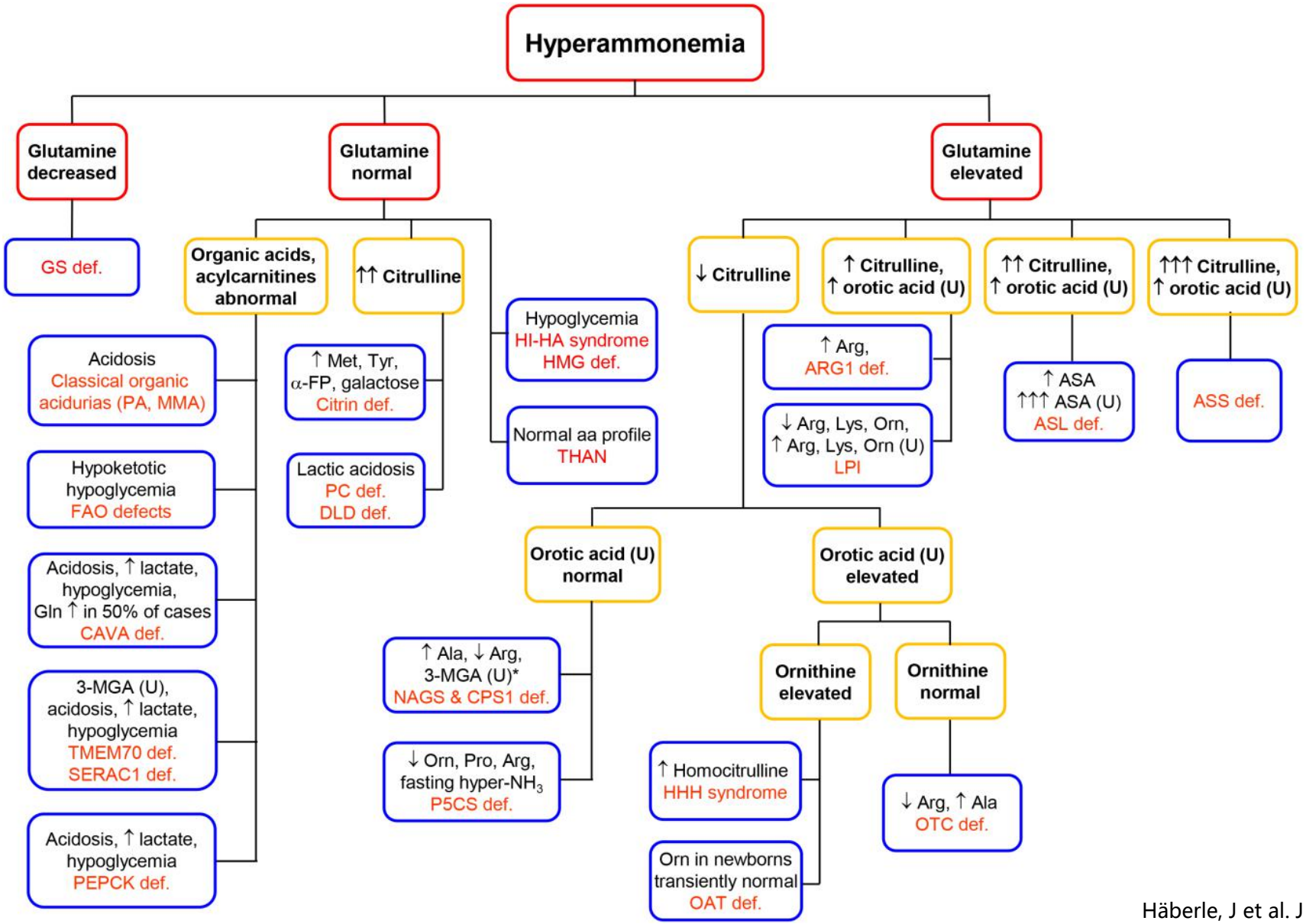
高氨血症的诊断



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急性高氨血症的管理

- 停止蛋白质摄入。
- 开始静脉注射葡萄糖（含适当电解质Na^+，K^+）。
- 启用一线药物。
- 治疗同时收集血浆和尿液用于诊断目的。
- 迅速将高氨血症危象患者转移到专科中心。
- 体外解毒（CRRT、血液透析）。

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各级治疗措施及药物用法用量

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Ammonia level (μmol/L)	Action in undiagnosed patient	Action in known UCD patient	Comments
Increased above upper limit of normal	▪ Stop protein intake ▪ Give IV glucose at an appropriate dosage to prevent catabolism (10 mg/kg/min in a neonate, 8 mg/kg/min in infants, and 6 mg/kg/min in all others) ± insulin[$] ▪ Monitor ammonia blood levels every 3 hours	▪ Stop protein intake ▪ Give IV glucose at an appropriate dosage to prevent catabolism (10 mg/kg/min in a neonate, 8 mg/kg/min in infants, and 6 mg/kg/min in all others) ± insulin[$] ▪ Monitor ammonia blood levels every 3 hours	▪ Stop protein for maximum 24 h ▪ Avoid exchange transfusions as cause of catabolism ▪ Hyperglycemia can be extremely dangerous (hyperosmolarity) ▪ If major hyperglycemia occurs with high lactate (>3 mmol/L) reduce glucose infusion rate rather than increase insulin ▪ Avoid hypotonic solutions ▪ Add sodium and potassium according to the electrolyte results ▪ Consider the sodium intake if sodium benzoate or sodium PBA are used[§] ▪ L-arginine not to be given in ARG1D ▪ Some concerns of sodium benzoate use in OAs ▪ Avoid repetitive drug boluses ▪ Monitor phosphate levels and supplement early especially during hemodialysis
In addition when >100 and <250 [#]	▪ Start drug treatment with IV L-arginine and sodium benzoate (see Table 5) ▪ Start carbamylglutamate, carnitine, vitamin B_{12}, biotin (see Table 5 and its legend)	▪ Continue drug treatment with L-arginine (plus continue or add L-citrulline for mitochondrial UCDs) and sodium benzoate ± sodium PBA/phenylacetate* (see Table 5), increase dose or give IV ▪ Consider protein free energy (glucose polymer and lipid emulsions) by NG tube unless the child is vomiting (10 g CHO from glucose polymer and 4 g lipids = ~76 kcal/100 ml)	
In addition when 250 to 500	▪ As above ▪ Prepare hemo(dia)filtration if significant encephalopathy and/or early high blood ammonia level or very early onset of disease (day 1 or 2) ▪ Begin hemo(dia)filtration if no rapid drop of ammonia within 3-6 hours	▪ As above, but all drugs per IV ▪ Prepare hemo(dia)filtration if significant encephalopathy and/or early high blood ammonia level or very early onset of disease (day 1 or 2) ▪ Begin hemo(dia)filtration if no rapid drop of ammonia within 3-6 hours	
In addition when 500 to 1000	▪ As above ▪ Start hemo(dia)filtration immediately	▪ As above ▪ Start hemo(dia)filtration as fast as possible	
In addition when >1000	▪ Evaluate whether to continue specific treatment or to start palliative care	▪ Evaluate whether to aim at curative treatment or palliative care	

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°	250 mg/kg as bolus in 90-120 min, then maintenance 250-500 mg/kg/d[$] > 20 kg bw: 5.5 $g/m^2/d$	250 mg/kg as bolus in 90-120 min, then maintenance: 250-500 mg/kg/d[$]	250(-400) mg/kg (1-2 mmol/kg) as bolus in 90-120 min, then maintenance 250 mg/kg/d (1.2 mmol/kg/d)	100 mg/kg bolus per NG tube then 25-62.5 mg/kg every 6h
NAGSD	same[$]	same[$]	250 mg/kg (1.2 mmol/kg) as bolus in 90-120 min, then maintenance 250 mg/kg/d (1.2 mmol/kg/d)	same
CPS1D & OTCD	same[$]	same[$]	same	-
ASSD	same[$]	same[$]	same	-
ASLD[‡]	same[$]	same[$]	200-400 mg/kg (1-2 mmol/kg) as bolus in 90-120 min, then maintenance 200-400 mg/kg/d (1-2 mmol/kg/d)	-
ARG1D*	same[$]	-	**AVOID**	-
HHH syndrome	same[$]	same[$]	250 mg/kg (1.2 mmol/kg) as bolus in 90-120 min, then maintenance 250 mg/kg/d (1.2 mmol/kg/d)	-

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尿素循环障碍长期管理

- 用药（氮清除剂）增加废氮排泄。
- 低蛋白饮食。
- 补充精氨酸和/或瓜氨酸。
- 补充维生素和矿物质等必需营养素。
- 补充必需氨基酸（部分患者）。
- 治疗并发疾病。
- 必要时行肝移植。

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长期治疗的口服药物剂量

Disorder	Sodium benzoate[$]	Sodium PBA°[$], or GPB	L-arginine[$] (hydrochloride and/or free base)	L-citrulline[$]	Carbamyl-glutamate[$]
NAGSD	-	-	-	-	10-100 mg/kg/d
CPS1D	up to 250 mg/kg/d*[#] max. 12 g/d	<20 kg: up to 250 mg/kg/d*[#] >20 kg: 5 g/m^2/d[#] max. 12 g/d	<20 kg: 100-200* mg/kg/d or: 0.5-1 mmol/kg/d >20 kg: 2.5-6 g/m^2/d max. 6 g/d	100-200 mg/kg/d[§] max. 6 g/d	-
OTCD	same	same	same	100-200 mg/kg/d[§] max. 6 g/d	-
ASSD	same	same	<20 kg: 100-300*[#] mg/kg/d or: 0.5-1.5 mmol/kg/d >20 kg: 2.5-6 g/m^2/d[#] max. 8 g/d	-	-
ASLD	same	same	<20kg: 100-300*[#] mg/kg/d or: 0.5-1.5 mmol/kg/d >20kg: 2.5-6 g/m^2/d[#] max. 8 g/d	-	-
ARG1D	same	same	-	-	-
HHH syndrome	same	same	<20 kg: 100-200* mg/kg/d >20 kg: 2.5-6 g/m^2/d max. 6 g/d	100-250 mg/kg/d[§] max. 6 g/d	-

All medications should be divided into three to four doses daily taken with meals and distributed as far as possible throughout the day.

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谢谢关注！

thanks for your attention.