Urea cycle disorders: Quick reference guide

Introduction

Urea cycle disorders (UCDs) are a group of inborn errors of metabolism affecting the detoxification of nitrogen and the endogenous synthesis of arginine. The incidence of UCDs is about 1 in 35.000. Patients with a complete enzyme deficiency often present during the first days of life with hyperammonemic coma with about 50% mortality despite early and aggressive treatment. The majority of survivors of a neonatal presentation suffer from severe developmental delay and a high risk of recurrent crises. Late-onset patients may present at any age after the neonatal period and their risk of death is also high (up to about 45%). Brain damage correlates with duration and severity of acute hyperammonemia, especially in neonatal patients. Therefore, at all ages patients must be identified as soon as possible and should be transferred to a metabolic centre very early during the course. These guidelines are a consensus from several European countries on how to diagnose and treat patients with a suspicion of UCD or confirmed UCD.

Clinical presentation*

Table 1 *(below) provides clinical signs and symptoms of acute and chronic manifestations of UCDs irrespective of patient age*

D	**Clinical signs and symptoms of UCDs are non-specific and a high degree of awareness is required. Key questions have to be asked and a detailed family history (pedigree) is mandatory.**
D	**UCDs may cause acute or chronic symptoms at any age. Most common signs are neurological and psychiatric, others are uncommon and few are only described in single patients.**
D	**UCDs must be included in the differential diagnosis of any acute unexplained encephalopathy or acute psychiatric illness in patients of any age. This should always prompt immediate determination of plasma ammonia.**
D	**Any cause of protein catabolism, protein load and some drugs may trigger hyperammonemia in UCD patients.**

Diagnosis*

Figure 1 *(below) provides a diagnostic algorithm for neonatal hyperammonemia*
Table 2 *(below) summarizes the bedside differential diagnosis of IEMs presenting with hyperammonemia*

D	**Ammonia determination is an emergency procedure and the result must be available within 30 minutes. If ammonia is increased, further metabolic investigations should be performed immediately but specific treatment must not be delayed. Ammonia measurement is recommended in patients of any age presenting with unusual or unexplained neurological illness or unexplained liver failure. Moreover, as soon as the clinician suspects any intoxication, an inborn error of metabolism should be considered.**
C	**Mutation analysis is the method of choice to establish the diagnosis of a UCD and to offer genetic counseling.**
D	**Enzyme analysis of UCDs is feasible but not the method of first choice if genetic testing is available. Liver tissue and some other tissues can be used for enzyme analysis of UCDs. In deceased patients with a suspicion of UCD, fibroblasts and/or liver tissue should be preserved.**
D	**Prenatal testing requires careful counselling by human geneticists and metabolic specialists jointly. Various methods for prenatal testing are available comprising investigations of metabolites as well as enzyme and mutation analyses. The preferred method for all disorders is molecular genetic analysis.**
C	**Newborn screening (NBS) for deficiencies of ASS, ASL, and arginase should be seriously considered. Currently NBS cannot be recommended for deficiencies of NAGS, CPS1 and OTC.**

Acute management*

Table 3 *(below) lists levels of hyperammonemia and suggested actions in case of symptomatic patients*
Table 4 *(below) gives dosages of drugs to be used in acute hyperammonemia and acute decompensations of UCDs*
Table 5 *(below) provides an emergency regime for protein-free feeding in infants and children*

D	**The early clinical suspicion and diagnosis of hyperammonemia is crucial for a favourable outcome. The start of ammonia detoxification and measures to reverse catabolism must not be delayed unless a decision for only palliative care is made.**

C	**Total coma duration and peak ammonia levels are the most relevant factors for the prognosis of hyperammonemic decompensations. To better understand all contributing factors, more studies on the outcome of hyperammonemia are needed.**
C	**In neonates and children with symptomatic hyperammonemia, dialysis should be started if there is no response within four hours after start of medical treatment. The method of choice for ammonia detoxification is hemodiafiltration. Peritoneal dialysis is the least effective method and should only be used as a last resort. Exchange transfusion should not be used. Extracorporeal detoxification is the first line treatment in acute hyperammonemic decompensations in adults.**
D	**For treatment of acute hyperammonemia, it is crucial to promote and maintain anabolism. This is best achieved by high dose glucose plus, if a fatty acid oxidation disorder has been excluded, lipids. Protein should be (re)started after an acute hyperammonemic decompensation when ammonia levels fall to < 100 µmol/L. The period of protein free nutrition should aim not to exceed 24-48 hours.**

Long-term management*

Table 6 *(below) gives dosages of drugs to be used perorally for long-term treatment of UCDs*

D	**UCD patients usually need restriction of protein intake. This needs to be individually determined, based on tolerance. The FAO/WHO recommendations can be used as a guide for protein prescription.**
C	**Essential amino acids or branches chain amino acids supplements may form part of the dietary treatment.**
D	**Dietary treatment of UCD patients is one of the cornerstones of therapy and needs to be largely individualised. The fine balance between provision of nutritional requirements and metabolic stability warrants a particular expertise and a specialist metabolic dietician should always be involved.**
C	**Use of nitrogen scavengers seems to be safe at recommended doses but there is a need for more controlled studies on the adverse effects of sodium benzoate and sodium phenylbutyrate.**
C	**All UCD patients should be monitored for plasma arginine levels. Most UCD patients (apart from hyperargininemia) will need a supplementation of L-arginine.**
D	**N-carbamylglutamate is the first line medication for treatment of N-acetylglutamate synthase deficiency and might also be used as an emergency drug during acute neonatal hyperammonemia of unknown etiology.**
C	**Liver transplantation is the only cure of a UCD, it allows a normal diet and avoids the need for alternative pathway therapy. Liver transplantation is recommended for patients with severe neonatal onset UCDs and may be considered as first-line treatment. Liver transplantation is indicated also for patients with progressive liver disease, e.g. in argininosuccinate lyase deficiency and for UCD patients suffering from recurrent metabolic decompensations and hospitalizations despite medical therapy. Liver transplantation should ideally be sought for before the onset of irreversible neurological damage and/or repeated crises. Generally, it should be performed between 3 and 12 months of age.**

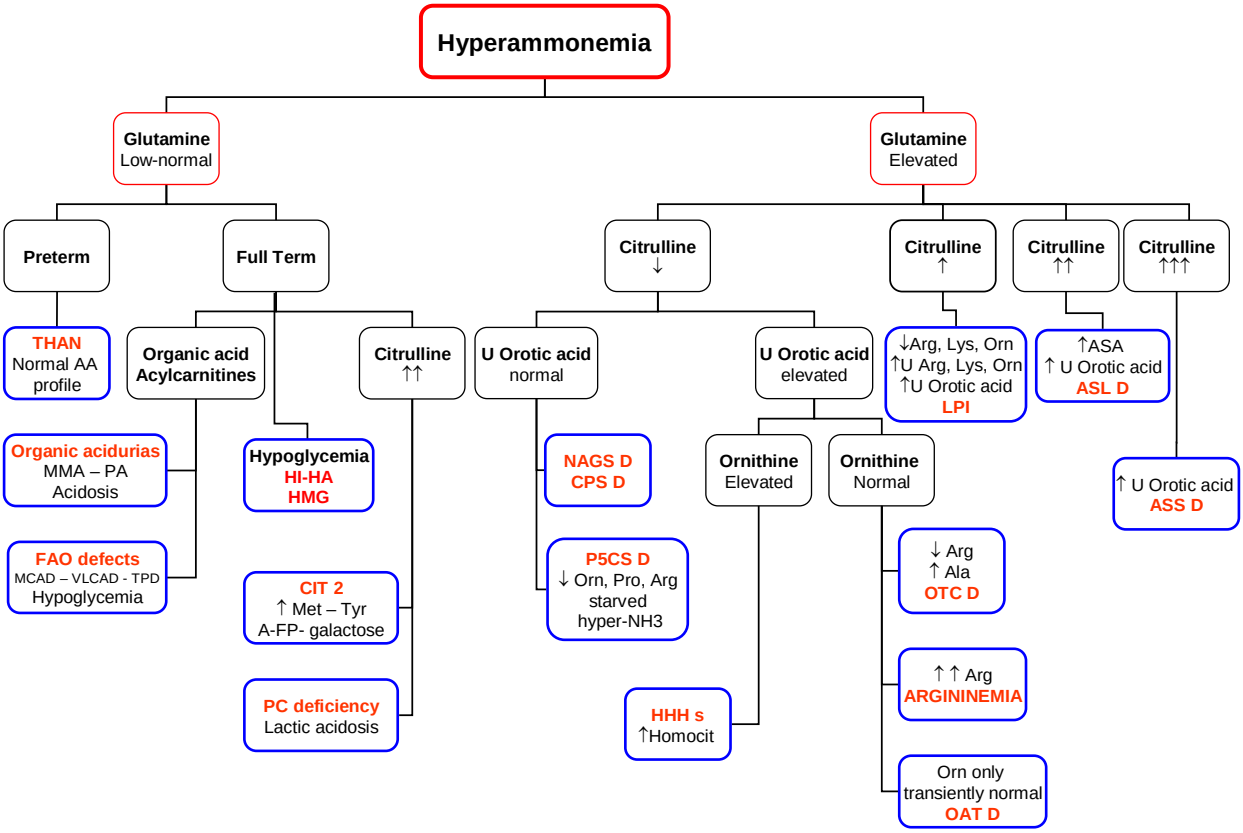
Follow up*

D	**Clinical, biochemical and nutritional monitoring are essential and should follow an individualised plan.**
D	**Regular testing for IQ, development and specific abilities/weaknesses is recommended. Health related quality of life, anxiety, stress and psychosocial factors are meaningful outcome parameters. Psychological management is an important additional task in caring for patients with UCDs and their families.**

***Legend: Grades of recommendations**

A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; **or** A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; **or** Extrapolated evidence from studies rated as 1^{++} or 1^{+}.
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; **or** Extrapolated evidence from studies rated as 2^{++}.
D	Evidence level 3 and 4; **or** Extrapolated evidence from studies rated as 2^{+}.

Figure 1: Diagnostic algorithm for neonatal hyperammonemia



Investigations in plasma if not stated otherwise: U = urine

Table 1: Clinical signs and symptoms of acute and chronic manifestations of UCDs irrespective of patient age

Acute presentation	Chronic presentation
• **Altered level of consciousness (from lethargy and somnolence to coma) mimicking encephalitis or drug intoxication** • **Acute encephalopathy (see below)** • **Seizures (in general seizures do not present isolated but within the context of altered level of consciousness)** • Ataxia: in general associated with altered level of consciousness • Stroke-like episodes • Transient visual loss • **Vomiting and progressive poor appetite** • Liver failure • **Multiorgan failure** • **Peripheral circulatory failure** • "Post-partum psychosis" • **Psychiatric symptoms (hallucinations, paranoia, mania, emotional or personality changes)** • **<u>In neonates:</u>** **sepsis-like picture, temperature instability, respiratory distress, hyperventilation**	• **Confusion, lethargy, dizziness** • **Headaches, migraine-like, tremor, ataxia, dysarthria** • Asterixis (in adults) • **Learning disabilities, neurodevelopmental delay, mental retardation** • Chorea, cerebral palsy • Protracted cortical visual loss • Progressive spastic diplegia or quadriplegia (described in ARG1D and HHH syndrome) • **Protein aversion, self-selected low-protein diet** • **Abdominal pain, vomiting** • **Failure to thrive** • **Hepatomegaly, elevated liver enzymes** • **Psychiatric symptoms: hyperactivity, mood alteration, behavioural changes, aggressiveness** • Self-injurious behaviour • *Autism-like symptoms* • *Dermatitis* • **Fragile hair (typical for ASLD)** • Specific neuropsychological phenotype in heterozygous OTC females • **Episodic character of signs and symptoms**

bold: typical signs and symptoms; standard: uncommon signs and symptoms; *italics*: signs and symptoms only reported in single patients

Table 2: Bedside differential diagnosis of IEMs presenting with hyperammonemia

Parameter	Condition				
	UCDs	Organic acidurias	β-Oxidation defects	Hyperinsulinism/ hyperammonemia syndrome	Pyruvate carboxylase deficiency[g]
Acidosis	+/–	+[e]	+/–	–	+
Ketonuria[a]	–	+	–	–	++
Hypoglycemia[b]	–	+/–	+	+	+
↑ Lactic acid[c]	–	+	+/–	–	+
↑ AST/ALT	(+)[d]	–	+	–	+/–
↑ CPK	–	–	+	–	–
↑ Uric acid	–	+	+	–	–
↓ WBC/RBC/Plt	–	+	–	–	–
Weight loss	–	+[f]	–	–	+

[a] In neonates ketonuria (++ - +++) suggests organic aciduria.
[b] Hypoglycemia and hyperammonemia ("pseudo-Reye") can be predominant manifestations of the organic aciduria 3-HMG-CoA-lyase deficiency.
[c] Blood lactate >6 mmol/L, since lower high lactate levels (2-6 mM) may be due to violent crying or to extensive muscle activity.
[d] AST/ALT elevations can be found but are not constant in UCDs.
[e] Can be absent in neonates.
[f] Occurrence only in neonates.
[g] Only type B associated with hyperammonemia but not types A and C.

Table 3 Levels of hyperammonemia and suggested actions in case of symptomatic patients

Ammonia level (µmol/L)	Action in undiagnosed patient	Action in known UCD patient	Comments
Increased > upper limit of normal	▪ Stop protein intake ▪ Give IV glucose at an appropriate dosage to prevent catabolism (10 mg/kg/min in a neonate) ± insulin[$] ▪ Monitor ammonia blood levels every 3 hours	▪ Stop protein intake ▪ Give IV glucose at an appropriate dosage to prevent catabolism (10 mg/kg/min in a neonate) ± insulin[$] ▪ Monitor ammonia blood levels every 3 hours	▪ Stop protein for max 24 – 48 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 ▪ Take into account 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 if >100 and <250 [#]	▪ Start drug treatment with IV L-arginine and sodium benzoate (see Table 4) ▪ Start carbamylglutamate, carnitine, vitamin B12, biotin (see Table 4 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 4), increase dose or give IV ▪ Consider NG carbohydrate and lipid emulsions unless the child is vomiting (enables higher energy intake)	
In addition if 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 if 500 to 1000	▪ As above ▪ Start hemo(dia)filtration immediately	▪ As above ▪ Start hemo(dia)filtration as fast as possible	
In addition if >1000	▪ Evaluate whether to continue specific treatment or to start palliative care	▪ Evaluate whether to aim at curative treatment or palliative care	

*If available, an IV equimolar solution of sodium benzoate and sodium phenylacetate can be used: 250 mg/kg as bolus IV/90-120 min, then 250 mg/kg as continuous IV infusion over 24h. The combination of sodium-benzoate and sodium phenylacetate is available as a drug, registered by the FDA (available in the EU on Named Patient Basis) and indicated as adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.
[#] This limit of action applies for patients outside the neonatal period; for neonates use >150 and <250.
[$] Monitor blood glucose after 30 min and subsequently every hour, because some neonates are very sensitive to insulin.
[§] 1g sodium benzoate and sodium PBA contain 7 mmol Na and 5.4 mmol Na, respectively.

Table 4: Dosages of drugs to be used in acute hyperammonemia and acute decompensations of UCDs

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[$] > 20 kg bw: 5.5 g/m^2/d	250 mg/kg as bolus in 90-120 min, then maintenance: 250-500mg/kg/d[$]	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	-	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	250 mg/kg as bolus in 90-120 min, then maintenance: 250(-500) mg/kg/d[$]	same	-
ASSD	same	same	same	-
ASLD[‡]	same	250 mg/kg as bolus in 90-120 min, then maintenance: 250 mg/kg/d[$]	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	-	-	-

°In undiagnosed patients, consider additional use of carnitine 100 mg/kg IV, hydroxycobalamin 1 mg IM/IV, and biotin 10 mg IV/PO
*The risk for acute hyperammonemic decompensation is low in ARG1 deficiency
[$]If citrulline is given, there is usually no need for concomitant use of L-arginine
[$]If on hemodialysis/hemodiafiltration doses should be increased to 350 mg/kg/d (maintenance dose)
[‡]In ASL deficiency, L-arginine therapy for acute decompensations might be sufficient for some patients
Maximal daily drug dosages: sodium benzoate 12 g/d, sodium PBA 12 g/d, L-arginine 12 g/day

Cave: The doses indicated in Table 4 can be used at the start of treatment but must be adapted depending on plasma ammonia and amino acids. Sodium benzoate and sodium PBA/phenylacetate should be given in parallel in severe acute decompensation. In less severe cases, a step-wise approach with initial sodium benzoate and if hyperammonemia persists or worsens, the addition of sodium PBA/phenylacetate can be chosen.

Table 5: Emergency regime for protein-free feeding in infants and children

Age	Glucose polymer concentration % CHO	Energy/100ml Kcal	kJ	Suggested daily fluid volume ml/kg	Feeding frequency
up to 6 m	10	40	167	150 ml/kg	2 to 3 hourly oral/bolus day and night or continuous tube feeds using enteral feeding pump
7-12 m	10-15	48	202	120 ml/kg	
1 y	15	60	250	1200 ml	
2-9 y	20	80	334	*	
>10 y	25	100	418	*	

* For children > 10 kg normal fluid requirements can be calculated as:
11-20 kg: 100 ml/kg for the first 10 kg, plus 50 ml/kg for the next 10 kg
20 kg and above: 100 ml/kg for the first 10 kg, plus 50 ml/kg for the next 10 kg, plus 25 ml/kg thereafter up to a maximum of 2500 ml/day

Table 6: Dosages of drugs to be used perorally for long-term treatment of UCDs

Disorder	Sodium benzoate[$] mg/kg/d	Sodium PBA[°$] mg/kg/d	L-arginine[$] (hydrochloride and/or free base) mg/kg/d	L-citrulline[$] mg/kg/d	Carbamyl-glutamate[$] mg/kg/d
NAGSD	-	-	-	-	10-100
CPS1D	up to 250*[#] max. 12 g/d	<20 kg: up to 250*[#] >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[§] max. 6 g/d	-
OTCD	same	same	same	100-200[§] 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	-	<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[§] 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.
° PBA is the second choice drug for long-term treatment and should be given in patients not responsive to benzoate alone
* serum/plasma levels of benzoate/PBA and plasma levels of arginine should be monitored
[#] in some patients higher doses are needed (the US FDA studies consider doses up to 13 g/m^2/d), according to expert advice
[§] if citrulline is given, there is usually no need for concomitant use of L-arginine
[$] 100 mg equal 0.694 mmol sodium benzoate; 0.537 mmol sodium PBA; 0.475 mmol arginine hydrochloride; 0.574 mmol arginine base; 0.571 mmol citrulline; 0.532 mmol carbamylglutamate, respectively