Häberle et al. Orphanet Journal of Rare Diseases 2012, 7:32
http://www.ojrd.com/content/7/1/32

ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

# Suggested guidelines for the diagnosis and management of urea cycle disorders

Johannes Häberle[1*], Nathalie Boddaert[2], Alberto Burlina[3], Anupam Chakrapani[4], Marjorie Dixon[5], Martina Huemer[6], Daniela Karall[7], Diego Martinelli[8], Pablo Sanjurjo Crespo[9], René Santer[10], Aude Servais[11], Vassili Valayannopoulos[12], Martin Lindner[13*†], Vicente Rubio[14*†] and Carlo Dionisi-Vici[8*†]

## Abstract

Urea cycle disorders (UCDs) are inborn errors of ammonia detoxification/arginine synthesis due to defects affecting the catalysts of the Krebs-Henseleit cycle (five core enzymes, one activating enzyme and one mitochondrial ornithine/citrulline antiporter) with an estimated incidence of 1:8.000. Patients present with hyperammonemia either shortly after birth (~50%) or, later at any age, leading to death or to severe neurological handicap in many survivors. Despite the existence of effective therapy with alternative pathway therapy and liver transplantation, outcomes remain poor. This may be related to underrecognition and delayed diagnosis due to the nonspecific clinical presentation and insufficient awareness of health care professionals because of disease rarity. These guidelines aim at providing a trans-European consensus to: guide practitioners, set standards of care and help awareness campaigns. To achieve these goals, the guidelines were developed using a Delphi methodology, by having professionals on UCDs across seven European countries to gather all the existing evidence, score it according to the SIGN evidence level system and draw a series of statements supported by an associated level of evidence. The guidelines were revised by external specialist consultants, unrelated authorities in the field of UCDs and practicing pediatricians in training. Although the evidence degree did hardly ever exceed level C (evidence from non-analytical studies like case reports and series), it was sufficient to guide practice on both acute and chronic presentations, address diagnosis, management, monitoring, outcomes, and psychosocial and ethical issues. Also, it identified knowledge voids that must be filled by future research. We believe these guidelines will help to: harmonise practice, set common standards and spread good practices with a positive impact on the outcomes of UCD patients.

**Keywords:** Urea cycle disorders, UCD, Hyperammonemia, N-acetylglutamate synthase, Carbamoylphosphate synthetase 1, Ornithine transcarbamylase, Ornithine carbamoyl transferase, Argininosuccinate synthetase, Argininosuccinate lyase, Arginase 1, Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome

## Introduction

Urea cycle disorders (UCDs) are inborn errors of nitrogen detoxification/arginine synthesis due to defects in the urea cycle enzymes (Figure 1), carbamoylphosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) and arginase 1 (ARG1), leading to respective deficiencies (abbreviated CPS1D, OTCD, ASSD, ASLD and ARG1D; corresponding MIM numbers, #237300, #311250; #215700; #207900; #207800 respectively). They also encompass deficiencies of N-acetylglutamate synthase (NAGS) (MIM #237310), associated with lack of the N-acetylglutamate (NAG) essential activator of CPS1 and of the mitochondrial ornithine/citrulline antiporter (ORNT1), causing the hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome (MIM #238970). The prevalence of these disorders may exceed the current estimates (1:8,000-1:44,000 births [1-3],

* Correspondence: Johannes.Haeberle@kispi.uzh.ch; martin.lindner@med.uni-heidelberg.de; rubio@ibv.csic.es; carlo.dionisivici@opbg.net
† Equal contributors
[1]University Children's Hospital Zurich and Children's Research Centre, Zurich 8032, Switzerland
[13]University Children's Hospital, Im Neuenheimer Feld 430, Heidelberg 69120, Germany
[14]Instituto de Biomedicina de Valencia del Consejo Superior de Investigaciones Científicas (IBV-CSIC) and Centro de Investigación Biomédica en Red para Enfermedades Raras (CIBERER), C/ Jaume Roig 11, Valencia 46010, Spain
[8]Division of Metabolism, Bambino Gesù Children's Hospital, IRCCS, Piazza S. Onofrio 4, Rome I-00165, Italy
Full list of author information is available at the end of the article

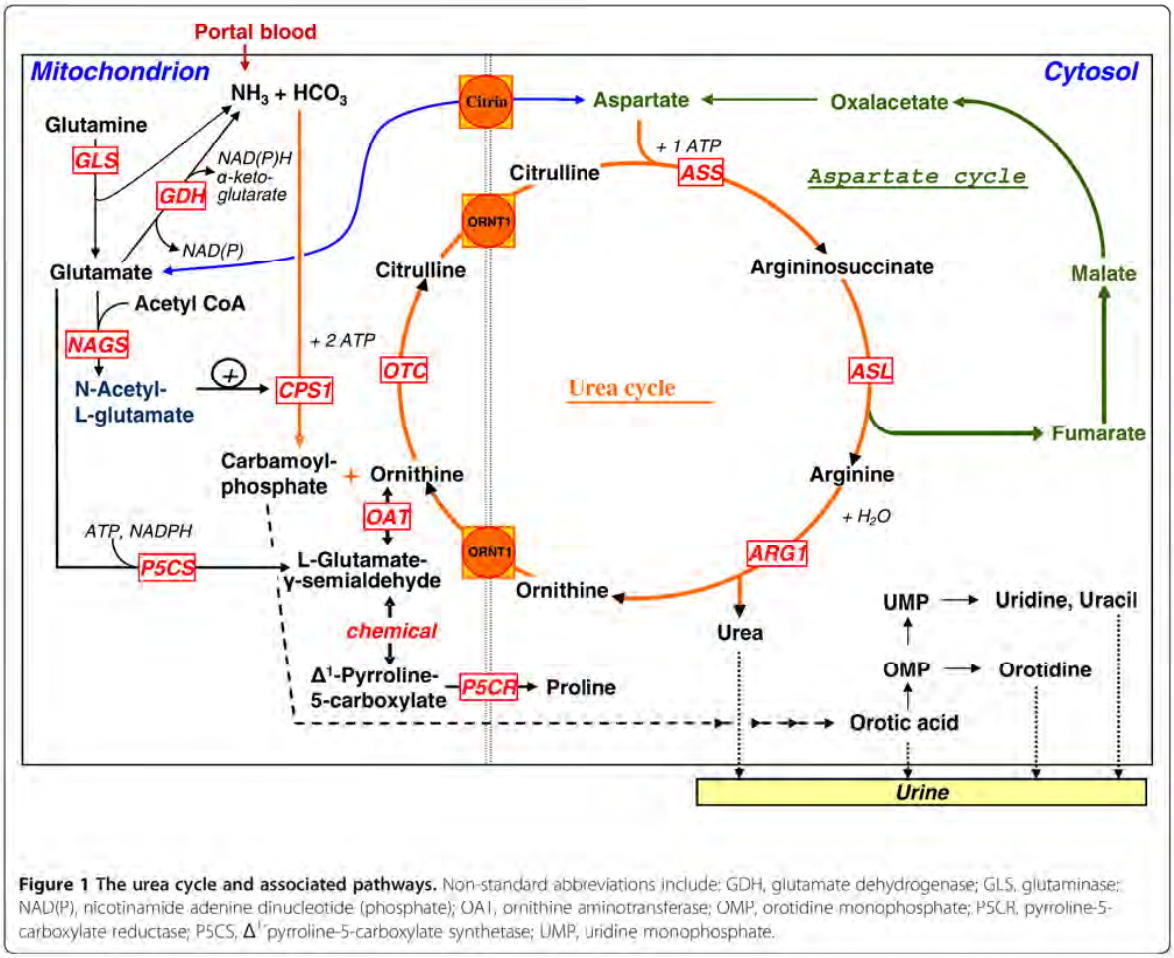


**Figure 1 The urea cycle and associated pathways.** Non-standard abbreviations include: GDH, glutamate dehydrogenase; GLS, glutaminase; NAD(P), nicotinamide adenine dinucleotide (phosphate); OAT, ornithine aminotransferase; OMP, orotidine monophosphate; P5CR, pyrroline-5-carboxylate reductase; P5CS, Δ¹-pyrroline-5-carboxylate synthetase; UMP, uridine monophosphate.

for all UCDs jointly) because of unreliable newborn screening and underdiagnosis of fatal cases. Clinical features are typical in complete deficiencies, which present with hyperammonemic coma a few days after birth with ~50% mortality [4-7], whereas the survivors experience severe developmental delay and recurrent hyperammonemic crises [4-7]. Even in partial deficiencies, which have more variable clinical presentations and later onset (any age), there is increased risk of premature death [5,8]. The duration and severity of hyperammonemia strongly correlates with brain damage [6,9,10]; prompt diagnosis and treatment of UCD is essential in order to optimise the outcome. [11]. However, the rarity of UCDs prevents single centres or even countries to have all the expertise for evidence-based management. Therefore, we have developed consensus guidelines based on the highest available level of evidence, by pooling all the published evidence and experience of leading centres from several European countries, to help standardise, systematise and harmonise across Europe the diagnosis, therapy, procedures and management of UCDs. These guidelines, developed with the Delphi methodology are intended to be used by metabolic specialists, pediatricians, dietitians, neonatologists, intensive care specialists, adult physicians, neurologists, nurses, psychologists and pharmacists involved in the care of UCD patients. Excluded from these guidelines because of insufficient European experience, or of tangential relationship with UCDs are: citrin deficiency (citrullinemia type 2, MIM #605814 and #603471), lysinuric protein intolerance (LPI, MIM #222700), deficiencies of pyrroline 5-carboxylate synthetase (MIM #610652) and ornithine aminotransferase deficiency (OAT, MIM #258870), despite the fact that they may cause hyperammonemia.

## Methodology and objectives

### Guidelines development

Development of these guidelines spanned the time period, October 2008 until August 2011 and involved one preliminary meeting and four working meetings of the guideline development group (GDG), formed by

pediatric metabolic specialists (S. Baumgartner [Innsbruck, retired after the first meeting], AB, AC, CDV, S. Grünewald, [London, retired after the first meeting], JH [chairman], DK, ML [secretary], DM, PS, VV), a medical biochemist (VR), a psychologist (MH), a specialist metabolic dietitian (MD), a metabolic specialist caring for adult patients (AS) and a neuroradiologist (NB). Each meeting was supervised by a moderator (P. Burgard, Heidelberg [first meeting] and RS) who oversaw the discussion but did not contribute to the content. In the initial working meeting the GDG was trained on standardising literature evaluation and working groups focusing on specific topics were formed. Thereafter GDG members discussed and performed systematic literature review and drafted the guidelines. These drafts were further reviewed by external specialists on intensive care (L. Dupic, Paris), genetics (A. Gal, Hamburg), child neurology (A. Garcia-Cazorla, Barcelona), nephrology (S. Picca, Rome), liver transplantation (J. de Ville de Goyet, Rome), epidemiology (A. Tozzi, Rome) and ethics (C. Rehmann-Sutter, Basel) and a patient group representative (S. Hannigan, London). After further recommendations/comments by three highly renowned external reviewers (C. Bachmann, Bottmingen; J.V. Leonard, Oxford and H. Ogier, Paris), the final version of the guidelines was written and its applicability pilot-tested by non-specialist pediatricians in training, with subsequent review and revision by the GDG. The guidelines will be sent for endorsement to all European societies for inherited metabolic diseases.

### Systematic literature review and evidence grading

The guidelines evidence base was collected according to the Scottish Intercollegiate Guideline Network (SIGN, http://www.sign.ac.uk). Systematic literature review encompassing from each disease description until early 2011 was carried out using mainly Medline, Embase, the Cochrane Library, MedLink, and Orphanet. Searches also included websites of societies and parents groups for inborn errors. Relevant papers were evaluated by at least two GDG members before considering conclusions as evidence.

Evidence levels were classified in accordance with the SIGN methodology:

**"Evidence level & criteria"**

$1^{++}$ High quality meta-analyses, systematic reviews of randomized control trials (RCTs), or RCTs with a very low risk of bias.
$1^{+}$ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
$1^{-}$ Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias.
$2^{++}$ High quality systematic reviews of case–control or cohort studies or high quality case–control or cohort studies with a very low risk of confounding bias, or chance and a high probability that the relationship is causal.
$2^{+}$ Well conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
$2^{-}$ Case–control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
3 Non-analytic studies, e.g. case reports, case series.
4 Expert opinion.

Recommendations given in the guidelines are graded depending on their level of evidence:

**"Grade of recommendation & criteria"**

A If level 1 evidence was found (not the case).
B If level 2 evidence was found.
C If level 3 evidence was found (mainly non-analytical studies such as case reports and case series).
D If level 4 evidence was found (mainly expert opinion).

### Disclaimer

These guidelines aim at helping decision making in UCD patient care. Although based on the best available evidence, the recommendations given often reflect only expert opinion and are thus not meant to be rigidly implemented. Furthermore, although as exhaustive as possible, these guidelines cannot include all possible methods of diagnostic work-up and care and may therefore fail to mention some acceptable and established procedures. Guidelines cannot guarantee satisfactory diagnosis and outcome in every patient. Although helping optimise the care of individual patients and assist decision-making by basing clinical practice on the existing scientific and medical knowledge, they should not substitute well-informed, prudent clinical practice.

## Diagnosis

### The clinical picture

The clinical manifestations of UCDs (Table 1) can occur at any age [12-16], with hyperammonemic crises being frequently triggered by catabolic events, protein overload or certain drugs. Most symptoms are neurological but nonspecific. A UCD should be immediately suspected in neonates if there are any neurological symptoms or at any age if there is an acute encephalopathy. Hepatic-gastrointestinal and psychiatric nonspecific manifestations (Table 1) are second in frequency. Only the hair shaft abnormalities with hair fragility (trichorrhexis nodosa) found mainly in ASLD [12,17-19] and the progressive spastic diplegia beginning in childhood (or later) in ARG1D and the HHH syndrome,

**Table 1 Clinical signs and symptoms of acute and chronic presentations of UCDs, and triggering factors for hyperammonemia in UCD patients**

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

**Potential triggers of hyperammonemic crises in UCD patients**

- Infections
- Fever
- Vomiting
- Gastrointestinal or internal bleeding
- Decreased energy or protein intake (e.g. fasting pre surgery, major weight loss in neonates)
- Catabolism and involution of the uterus during the postpartum period (mostly OTC females)
- Chemotherapy, high-dose glucocorticoids
- Prolonged or intense physical exercise
- Surgery under general anesthesia
- Unusual protein load (e.g. a barbecue, parenteral nutrition)
- Drugs: Mainly **valproate and L-asparaginase/pegaspargase.** Topiramate, carbamazepine, phenobarbitone, phenytoine, primidone, furosemide, hydrochlorothiazide and salicylates have also been associated with hyperammonemic decompensation.

Typical and uncommon signs and symptoms are highlighted in bold- and normal-type, respectively, whereas italic type marks signs and symptoms reported in single patients. *Grade of recommendation, D.*

frequently without hyperammonemic episodes [20-22], are specific manifestations of this group of diseases. Symptoms can be subtle, particularly after the neonatal period, and in some patients symptomatic episodes can resolve with non-specific interventions. Women can first manifest a UCD as acute unexplained neurological symptoms in the postpartum period (reported for CPS1D, OTCD, and ASSD [23-25]). Variability in disease severity is characteristic for OTCD heterozygous females (due to lyonization) [11,26], but is also found in all UCDs, being mainly attributable to differences in the severity of the genetic change [27-30]. However, the same genetic defect can yield both mild and severe presentations even in different members of the same family (reported for OTCD and for one CPS1D family)

[31-33]. Acute liver failure has been reported as the presenting sign in patients with OTCD, ASSD and HHH syndrome [34-39]. Although rare, a number of other presentations have been reported in UCDs, including stroke-like episodes (metabolic strokes) [10,40-44] that may resolve with treatment, chorea [45], cerebral palsy without hyperammonemia or cerebral edema [46,47], episodic transient or protracted cortical visual losses [48,49], dermatitis (most probably because of treatment-related malnutrition) [50,51], autism-like symptoms [52,53], behavioural problems during childhood [53] and in postpuberal patients and other episodic psychiatric symptoms that may be the only manifestation [54].

A careful medical and family history is mandatory and should include questions about unexplained neonatal deaths, neurological or psychiatric disorders in the family, consanguinity (frequent in all UCDs except in OTCD, which is X-linked), evidence of protein avoidance in patient and family members and drug intake by the patient.

*Statement #1. Grade of recommendation: C*

UCDs may present with acute or chronic presentations at any age and are often triggered by catabolic events, protein load or some drugs. In many cases a precipitating factor cannot be identified. Clinical signs and symptoms are nonspecific and commonly neurological, gastrointestinal or psychiatric. It is essential that healthcare professionals have an awareness of these diseases. Key questions should be asked and a detailed family history with pedigree is mandatory.

*Statement #2. Grade of recommendation: D*

UCDs must be included in the differential diagnosis of acute unexplained encephalopathy or acute psychiatric illness at any age, which must prompt plasma ammonia determination.

### Laboratory findings

*Hyperammonemia,* a nonspecific marker of inadequate nitrogen detoxification [55], is the hallmark for most UCDs. The absence of hyperammonemia in symptomatic newborn patients (but not in older patients) renders a UCD highly unlikely. Rapid ammonia measurement in an emergency setting is crucial since patient outcome correlates with the duration and peak level of hyperammonemia [4,6,56]. Respiratory alkalosis in a newborn should prompt immediate ammonia measurement because it is present initially in 50% of acute UCDs [5]. Otherwise the acid–base status is of limited use [57].

*Statement #3. Grade of recommendation: C*

Ammonia should be determined in an emergency setting with results available in 30 minutes.

*Statement #4. Grade of recommendation: D*

Ammonia should be measured in patients of any age presenting 1) an unexplained change in consciousness; 2) unusual or unexplained neurological illness; 3) liver failure; 4) suspected intoxication.

If hyperammonemia is confirmed, determination of plasma amino acids, blood or plasma acylcarnitines, urinary organic acids and orotic acid should be urgently requested together with basic laboratory investigations, not waiting for the results (which should be obtained in <24 h) for treating the patient. When taking samples after recovery from an acute episode, plasma amino acid levels and/or urinary orotic acid (measured with a specific method e.g. high performance liquid chromatography) can be particularly helpful for diagnosis. In patients with fatal outcome, procurement of anticoagulated blood for DNA isolation and storage of frozen aliquots of all samples obtained of plasma, serum, urine and cerebrospinal fluid (CSF) is recommended [16,58].

*Statement #5. Grade of recommendation: D*

If ammonia is found elevated, further metabolic investigations should be immediately carried out without delaying specific treatment.

## Differential diagnosis

The most common misdiagnosis of early onset UCD patients is neonatal sepsis. A number of conditions that increase ammonia production and/or secondarily decrease ammonia detoxification can cause hyperammonemia and mimic a UCD [16,59-63]. Thus, *neonatal hyperammonemia* can be due to UCDs, to other inborn errors that cause secondary hyperammonemia, to liver failure or to congenital infection. Premature infants can have transient hyperammonemia, a condition which is characterised by a normal blood glutamine level [64] and which is possibly due to ductus venosus shunting of portal blood [65-67]. *Late-onset hyperammonemia* can be triggered by most conditions that can also cause neonatal hyperammonemia, by chronic liver failure, exogenous intoxications (e.g. amanita phalloides), drugs (e.g. valproic acid), portocaval shunt and Reye syndrome, by conditions that vastly increase either direct ammonia production (e.g. asparaginase treatment, urease-positive bacteria overgrowth or genito-urinary infection) or protein catabolism (e.g. myeloma, chemotherapy, steroid therapy, trauma, gastrointestinal hemorrhage) and when there is excessive nitrogen supply (reported in total parenteral nutrition or after glycine-solution irrigations in transurethral prostate resection) [5,17,68-72]. Table 2

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.