Seit > 5 Jahren nicht aktualisiert, Leitlinie wird zur Zeit überarbeitet

Reference	Intervention/control	No. of patients	Consensus evaluation	Type of study	Results reported / Conclusion	Comment
biochemical analyses - diagnosis - NBS	**acute management**	**longterm management**	**new therapies**			
AhMew N et al, 2011	review NAGS deficiency	na	+++	review	comprehensive review of genetics, epidemiology, pathophysiology, and treatment	
AhMew N et al, 2014	describe stable isotopes for ureagenesis measurement		+++	review	stable isotopes provide a more accurate measure of phenotypic severity and are suited to evaluate the efficacy of novel therapies	
Amstutz U et al, 2011	to apply Microarray-based target to apply microarray-based target enrichment and next-generation sequencing for UCDs	na	+++	methods paper	use of DNA bar codes and the use of sectored oligonucleotide arrays for target enrichment enable parallel, large-scale analysis of complete genomic regions for multiple genes of a disease pathway use of DNA bar codes and use of sectored oligonucleotide arrays for target enrichment enabled parallel, large-scale analysis of complete genomic regions for multiple UCD genes and for multiple samples simultaneously	
Ayyub OB et al, 2015	to demonstrate a simple methods for quantifying NH3 in 100µL of whole blood	na	++	methods paper	sensor comprises a modified form of the indophenol reaction, accurate reliable quantification of NH3 in whole human blood samples at a minimum range of 25 to 500µM	
Bachmann C, 2014	review of preanalytical aspects of ammonia and amino acid determinations	na	++	review	paper gives practical guidance for preanalytical aspects of ammonia and amino acid measurement	single author, personal opinion, but from person with great experience
Barends M et al, 2014	to identify possible markers that may assist in predicting the need for treatment of infants with UCDs diagnosed through NBS	8 ASSD, 8 ASLD	++	retrospective study	Neonatal presentation did not always predict the need for on-going strict treatment; concentrations of amino acids correlated with severity in ASSD but not in ASLD; prevalence of apparently asymptomatic patients diagnosed through NBS is substantial	
Bolton SM et al, 2015	to determine the role of pre-transplantation neuroimaging and to predict outcome after LTx in children with UCDs	8	na	retrospective case series	patients with severe changes on brain MRI prior to LTx had poor outcome, thus, neuroimaging may be a helpful tool in determining developmental prognosis and outcomes post-liver transplantation for UCDs	not included as only low numbers and conclusion not really surprising
Brassier A et al, 2015	to repot 90 OTCD patients treated between 1971 and 2011	90	+++	retrospective case series	27/90 patients had neonatal onset, mortality was 90% in neonatal onset and 13% in late onset, peak ammonia was 960 umol/L in NO and 500 umol/L in LO, recurrent mutaton R40H in LO patients	
Caldovic L et al, 2015	review on OTC mutations	na	+++	review	novel mutation update for OTCD	
Cartagena A et al, 2013	to describe adult presentation of NAGSD	1	++	case report and review	determining developmental prognosis and outcomes post-livertransplantation	
Cohen YH et al, 2012	to describe the genetic work-up in an ARG1D patient	1	+	case report	for UCDs	
D'Apolito O et al, 2012	to establish age related reference intervals of OA in urine, plasma, and dried blood spot (DBS)		+++	methods paper	orotic acid can be measured in DBS; comparisons with plasma and urine levels are provided	
Diez C et al, 2016	to express CAVA and report 10 novel patients	10	+++	original article	CAVAD is a new differential diagnosis of neonatal onset HA, treatment with carglumic acid was useful in some patients, there is a characteristic biochemical situation, outcome in reported patients was positive	
Doimo M et al, 2012	to perform yeast complementation for assessing ASL residual function	na	++	methods paper (letter)	yeast complementation is sufficiently sensitive to detect the residual activity of ASL alleles associated with mild forms of ASA	
Engel K et al, 2012	to express mutant ASL proteins in vitro	na	++	original article	disease-causing role of several mutant ASL proteins was confirmed, while some ASL proteins show relevant levels of residual ASL function correlating with a mild phenotype	
Grioni D et al, 2011	to review the occurrence of epilepsy in ASLD in own patient cohort	11	+++	case series	in 55% of ASLD patients (6/11), epilepsy was present; seizures responded to treatment in all cases; HA was not a predictor of epilepsy; there was no excess of arginine therapy in this cohort rendering arginine toxicity unlikely as cause of epilepsy in these patients	
Grioni D et al, 2014	to describe two cases of ARGD with epilepsia partialis continua or nonconvulsive status epilepticus	2	+	case reports	first report of EPC in a UCD; correct diagnosis is required in patients with NCSE	
Häberle J, 2013	to review primary and secondary hyperammonemia	na	++	review	comprehensive review of conditions leading to primary and secondary hyperammonemia, eg through inhibition of the urea cycle or substrates deficiency	
Häberle & Huemer, 2015	to evaluate the efficacy of implementation, adaptation, and use of UCD guidelines	na	+++	original article	high interest in UCD guidelines, 18% of hospitals have ammonia testing not available 24/7, more precise targeting of the guidelines necessary	
Heibel SK et al, 2011	investigation of the known NAGS gene enhancer sequence	1	++	original article	in an adult patient, NAGSD was shown to be caused by a mutation in the NAGS gene enhancer sequence	
Held PK et al, 2014	new assay for orotic acid determination in DBS	na	+++	methods paper	orotic acid can be quantified in DBS applying FIA–MS/MS	
Hsu KH et al, 2015	to report case with distal renal tubular acidosis and HA	1	+	case report	ammonia should be measured in distal renal tubular acidosis	
Hu L et al, 2015	to express mutant ASL proteins in vitro	na	+++	original article	variant forms of ASLD have relevant enzyme activity left, some mutant ASL proteins are unstable, chaperone therapy should be considered	
Janzen N et al, 2014	to develop a tool for OTCD NBS	na	+++	methods paper	residual levels of ASL activity	

Jain-Ghai S et al, 2011	to report an infant with severe encephalopathy due to HA in ARG1D	1	+	case report	hyperammonemic encephalopathy may be more common than reported so far; this does advocate for the addition of arginine as a target in NBS	
KenzakaT et al, 2015	to measure ammonia in patients with urinary tract infections	60 (non UCDs)	++	observational study	5/60 patients with UTIs had HA (max ~160 µmol/L), none of the patients had urease-producing bacteria	only few patients, only hospitalised patients
Kölker S et al, 2015	to report from EIMD patient registry (2 papers)	343	na	original article	wide clinical/phenotypic variability in this cohort, neurological involvement commonly found in this cohort	not included since no additional/new information/aspects
Laemmle A et al, 2016	to evaluate the prevalence of ALF in OTCD	37	+++	original article	ALF was present in 50% of OTCD patients at some stage, ammonia is correlated with INR increase but not always with elevations of transaminases, experimental evidence supports role of ammonia in development of ALF	
Kretz R et al, 2012	to develop RNA based mutation analysis for CPS1D	na	+++	original article	RNA from peripheral lymphocytes stimulated for 3 days with phytohaemagglutinin can be used for CPS1 mutation analysis	
Lee B et al, 2015	to examine predictors of NH3 exposure and hyperammonemic crises in patients with UCDs	>100	++++		fasting NH3 correlated strongly with daily NH3 exposure; fasting glutamine correlated weakly with daily NH3 exposure assessed as 24-hour AUC and was not a significant predictor of hyperammonemic crisis; patients with UCDs may benefit from tight NH3 control	
Martinelli D et al, 2015	to review HHH syndrome from literature and own experience	111	+++	review	comprehensive review of clinical, metabolic and genetic profiles of 111 HHH syndrome patients, clinical phenotype is extremely variable, severity does not correlate with genotype or ammonium/ornithin plasma levels	
Miller M et al, 2014	we review our experience with prenatal diagnosis of to review experience with prenatal testing in citrullinemia type I over the span of 11 years in 41 at-risk pregnancies	15	+++	retrospective case series	amniotic fluid citrulline/ornithine ratio may be superior over citrulline/(arginine + ornithine), significant elevations in amniotic fluid citrulline levels in at-risk pregnancies even with unaffected fetus, thus importance of using amniotic fluid from carrier mothers when setting up reference ranges	
Pillai U et al, 2013	report on a patient with HA after PEN	1	na	case report	PEN induced HA in an 28 y o male; no UCD could be confirmed but data are supportiv of either CPS1D or NAGSD	not included as no UCD was confirmed
Posset R et al, 2016	to determine the effect of diagnostic and therapeutic interventions on neurological outcome	456	++++	evaluation of prospective register study	NBS lowered the age at diagnosis for late-onset patients, trend towards improved outcome in ASSD, ASLD, and ARG1D detected in NBS, neuroloical outcome was mainly influenced by non-interventional variables such as age at onset and peak ammonia	
Prada CE et al, 2012	recurrent pancreatitis in OTCD	3	+	case reports	3 OTCD patients had recurrent pancreatitis, the relation the OTCD remained unclear	
Sancho-Vaello E et al, 2016	to review mutation spectrum in NAGSD and study mutated enzyme function	na	+++	original article	disease-causing role of NAGS mutations confirmed, mutation update, structural inferences	
Serrano M et al, 2011	to analyze the association between ammonia and glutamine	26	++++	original article	total 921 paired plasma amino acid-ammonia data were analysed showing increased plasma glutamine values in UCD patients, despite normal plasma ammonia concentrations	
Sokoro et al, 2010	To determine the incidence of HHH syndrome in northern Saskatchewan		++		heterozygote frequency for the mutant allele for HHH syndrome to be about 1 in 19 individuals; ornithine levels, by tandem MS, were not abnormal in newborns with F188Δ mutation but ornithine rises to abnormally high levels past the time that the NBS blood spot is collected	
Summar M et al, 2013	to determine the incidence of UCDs	na	++++	epidemiological	using newborn screening data on over 6million births and data from the large US and European longitudinal registries, incidence of UCDs were calculated	
van Karnebeek CD et al, 2014	first description of CAVA deficiency as differential diagnosis for neonatal HA	4	+++	original article	CA-VA deficiency should be added as a treatable differential diagnosis of HA in the neonate and young child	
Vergano SA et al, 2013	to retrospectively evaluate the hospitalizations of prior hyperammonemic infants to identify codable elements	na	+++	retrospective study	implementation of an EMR-based warning system can improve surveillance for HA	
Wang J et al, 2011	to study array CGH for improvement of CPS1 mutation detection	4	+++	original article	array CGH allowed identification of large CPS1 gene deletions	
Arafa MH and Atteia HH, 2013	to test the hypothesis that sildenafil has a protective effect on the brains of HA rats	na	++	experimental study	sildenafil exerts a protective effect on the brain by reversing oxidative stress during HA; exact protective mechanism of sildenafil has to be still investigated; therapeutic modulation of the NO/cGMP pathway might have important clinical applications to improve brain functions in patients with HA	
Bireley WR et al, 2012	to correlate brain MRI findings in UCDs during HA	6	+	retrospective case series	brain MRI abnormalities may assist in determining prognosis and may help with clinical decisions	
Cartagena A et al, 2013	describes 38 yo male with NAGS deficiency	1	+	case report	almost 20 y history of fluctuating behavioural changes with nausea and vomiting	daily cost $1961.00 Canadian dollars for NCG vs. $8.46 for sodium PBA
Daniotti et al, 2011	to review potential uses of CG	na	++	review	reviews tests of CG not only in NAGSD but also in CPS1D, organic acidemias, MSUD, HIHA syndrome, and proposes use in valproic acid induced HA	
Fassier T et al, 2011	to report a case of post-partum psychosis in late-onset CPS1D	1	+	case report	routine monitoring of plasma ammonia levels in women with postpartum psychosis is recommended	
Gunz AC et al, 2013	MRI findings of 2 patients with neonatal-onset UCDs (ASLD, ASSD) at presentation and at 2-year follow-up, and review of literature	2	++	case reports	2 distinct patterns: (1) a central and focal pattern of involvement limited to the basal ganglia, perirolandic regions, and internal capsule (better outcome); (2) diffuse involvement of the cerebral cortex, internal capsule, basal ganglia, and variably thalami and brain stem (worse outcome)	brain MRI may have prognostic value in neonatal UCDs

Häberle J, 2011	to review role of NCGA in treatment of NAGSD	na	++	review	review focussing on the role of NCGA in the treatment of acute hyperammonemia in primary and in secondary NAGSD	
Ihara K et al, 2013	to study coagulopathy in OTC deficiency	5 late-onset OTCD, 3 additional	++	original article	prothrombin times were far below the normal level and remained low in remission; newly described complication in OTCD	also relevant for other UCDs?
Ituk U et al, 2012	report management of labor and delivery in 2 parturients with OTCD	2	+	case reports	arginine, citrulline and sodium PA with restricted protein intake during pregnancy; successful management of pregnancy in both OTCD patients	
Iyer H et al, 2012	describes the clinical characteristics of a young man with first presentation of HA (due to OTCD) in adult life	1	+	case report	high energy drink consumption after wisdom tooth extraction followed by crisis; before: self-selection against meat	one of the fewer case reports on adult presentation but no new information
Lamb S et al, 2013	report a successful pregnancy in a 29 yo OTCD patient diagnosed in infancy	1	+	case report	Sodium PBA and sodium benzoate were used throughout pregnancy. Essential amino acid, multivitamin and ω3 supplements started in first trimester. Protein allowance increased to 60 g a day in late third trimester.	Only < 15 successful pregnancies in known OTCD patients reported.
Lichter U et al, 2011	phase 2 comparison of NaPBA and GPB	11	++++	phase 2 switch-over study	GPB is at least equivalent to NaPBA in terms of ammonia control; U-PAGN is a clinically useful biomarker for dose selection and monitoring	
Lichter-Konecki U et al, 2013	Gene Reviews Article	na	++	review	very comprehensive paper dealing with all aspects of OTCD	
Marini JC et al, 2011	to study the effect of PBA on whole-body metabolism in OTCD patients and controls	7 (plus 7 controls)	+++	original article	PBA reduced ureagenesis without changing total-body protein breakdown and amino acid catabolism	only small number of patients
McGuire PJ et al, 2013	to prospectively characterize acute hyperammonemic episodes in UCD patients	128	++++	prospective, longitudinal observational study	Infection is the most common precipitant of acute HA; is associated with indicators of increased morbidity; catabolic and immune effects of infection may be a target for clinical intervention	
Nagamani S et al, 2012 (Genet Med)	review of current management for ASLD	na	++	review	Standard treatment is described; OLT is recommended only in patients with recurrent HA or metabolic decompensations resistant to conventional medical therapy or with cirrhosis	report on hypokalemia (authors observation)
Nagamani S et al, 2012 (MGM)	review of current management for ASLD	na	++	review	discuss natural history of ASLD and requirement of ASL for systemic NO production; this may have therapeutic implications and may help optimize therapy in ASLD	
Picca S et al, 2015	to compare extracorporeal dialysis with PD in neonatal HA	45 (26 UCDs)	na	retrospective	23 treated with PD, 22 treated with ECD; delayed ECD treatment was not superior to PD in improving the short-term outcome of neonates with HA	we don't aim for delayed ECD but early start, thus, study is of limited value and is thus not included
Rodney and Boneh, 2013	to analyse NH3 and amino acid profils in UCD patients on admission for acute HA	14 (96 admissions)	+++	retrospective (1982-2010)	plasma concentrations of all measured EAAs were low or low-normal in almost all samples; at admission, protein deficiency is common in patients with a UCD with HA; results challenge the current guideline of stopping protein intake during acute decompensation in UCDs; supplementation with EAAs (particularly BCAAs) at these times should be considered	
Ruder J et al, 2014	repeated MRI and EEG during acute neonatal HA	1	+	case report	Early and aggressive management of HA can result in improved MRI findings in the acute setting	MRI changes similar to those resulting from hypoxic-ischemic injury
Spinale JM et al, 2013	to present 2 cases with neonatal OTCD treated with CRRT	2	+	case reports	CRRT proved efficacious; modalities are discussed, CRRT is suggested to be superior over HD due to lower rates of complications	
Tsai IJ et al, 2014	to study the role of intermittent hemodialysis in pediatric patients with UCD, MSUD, MMA from 2001-2012	15 (25 intermittent, 15 standard cycles)	+++	retrospective	median duration of dialysis and median 50 % toxin reduction time were shorter in IHD than in non-IHD RRT	
Tummolo A et al, 2013	13 yo girl with OTCD and "metabolic stroke"	1	+	case report	gradual normalization of symptoms within 30 h after prompt start of CVVHD and NCG	term "metabolic stroke" in title may be misleading, rather "normal" coma; editorial funding by Orphan Europe; not included
van Leynseele A et al, 2013	acute management of neonatal HA	1	+	case report	NCG resulted in a rapid normalisation of HA in neonate, NCG should always be started together with the standard management of HA	not included as no additional information is provided
Wakiya T et al, 2011	to assess results after living donor liver transplantation in OTCD	12	++	retrospective case series	outcome of LDLT was satisfactory with 92% post-operative survival, even one heterozygous donor mother, but no change of neurological impairment	
Zhang et al, 2012	investigates the etiology of recurrent episodic HA in a 14 yo male with arginase deficiency	1	+	case report	report on the recurrent hospitalizations due to HA	only few AR1D patients suffer from recurrent HA
Adam S et al, 2012	to describe dietary practice for UCD patients in UK	175	++++	cross-sectional	median protein intake decreased with age; high variation in use of EEAs; only 3% supplement BCAAs	In the UK, protein restriction based on WHO 'safe intakes of protein', is the principle dietary treatment for UCD
Adam S et al, 2013	comparison of dietary management of UCDs in different European countries	464	++++	cross-sectional	Prescribed median protein intake/kg bw decreased with age with little variation between disorders; UK tended to give more total protein than other European countries; supplements of EAAs were prescribed for 38% with high variability between countries; 18% have tube feeds; 21% receive oral energy supplements	

AhMew N et al, 2013	to compare the clinical course and outcome of patients with neonatal proximal vs. distal UCDs	103	++++	observational	88% of the subjects presented clinically by age 7 d; mean peak NH3 level was 963 µM in patients with proximal UCDs and 589 µM and 573 µM in distal UCDs; poor cognitive outcome was not correlated with peak NH3 level or duration of initial admission; neurocognitive outcomes do not differ between patients with proximal UCDs and those with distal UCDs	
Bates TR et al, 2011	49 y o male CPS1D patient receiving liver transplantation	1	+	case report	good outcome with resumption of work	
Batshaw M et al, 2014	update on UCDC study	614	+++	data mining from registry	overall prevalence of UCDs to be 1/35,000, with 2/3rds presenting initial symptoms after the newborn period; mortality rate to be 24% in neonatal onset cases and 11% in late onset cases; NH3 and glutamine appeared to be biomarkers for neurocognitive outcome; low protein diet appeared to result in normal weight but decreased linear growth; high risk for hepatic dysfunction in patients with OTCD	bias in UCDC registry with (too) many female OTCD
Berry SA et al, 2014	to evaluate GPB in the treatment of pediatric patients with UCDs	26	++++	12-month, open label	GPB was associated with 24-h NH3 exposure that was non-inferior to that during dosing with NaPBA; long-term GPB: normal levels of glutamine and EAAs and BCAA, age-appropriate growth and fewer HA crises as compared with the 12month period preceding enrollment	
Boenzi S et al, 2012	to assess creatine metabolism in UCDs	32	+++	original article	patients with OTCD and ASSD and HHH syndrome presented a significant creatine decrease, whereas in ASLD creatine levels were significantly increased; monitoring creatine may help optimizing arginine dose	
Boneh A, 2014		28	++	retrospective dietary review	further restricting protein intake because of persistent HA may aggravate the deficiency and potentially lead to episodes of metabolic decompensation; patients may need on-going supplementation with EAAs to prevent protein malnutrition; supplementation with EAA should be considered at times of metabolic decompensation; enteral supplementation always preferred	
Brunetti-Pierri N et al, 2012	30-year follow-up of a patient with classic citrullinemia	1	+	case report	31 yo woman with classic, neonatal-onset citrullinemia who developed progressive hypertrophic cardiomyopathy and cataracts, neither of which has been recognized previously as a complication of the disease or a consequence of long-term drug treatment	
Burgard P et al, 2015	to review UCDs in order to integrate evidence for benchmarks for new diagnostic and therapeutic strategies	1542	++++	meta-analysis	literature on UCDs was reviewed between 1978 and 2014, applying strict criteria, 24 papers were included in analysis, no improvement of survival over 3 decades was found, relevant but unexplained geographic variation	
Burrage L et al, 2014	to evaluate whether treatment with NaPBA leads to a decrease in plasma BCAA levels in UCD patients	553 UCD patients, with 38% on NaPBA	++++	Longitudinal natural history study	generalized linear model comparison to evaluate covariates showed a significant inverse correlation between NaPBA and BCAA	
Cazzorla C et al, 2012	study to evaluate the QoL of a group of adult IMD patients (n=82)	7	++	mixed-method study	adult patients with IMD can have a normal value of general QoL, importance of applying multidimensional instruments	
Combescot E et al, 2015	to develop solid, multiparticulate formulations of sodium benzoate	na	+++	method report	benzoate formulation was made suitable for pediatric patients with i.e. flavor-masked, easy to swallow drug	
de Bie I et al, 2011	8-year follow-up of a ASSD patient with neonatal HA (peak ammonia level of 1,058 mmol/L)	1	+	case report	Hemodialysis was instigated 2 h after admission; adequate cognitive and neurological development at 8 y; good long-term neurological outcome following rescue from neonatal HA coma is rarely reported but attainable	
Diaz G et al, 2013	to compare NH3 control as 24-hour area under the curve and pharmacokinetics under GPBA versus NaPBA in adult UCD patients and the combined results of 4 studies involving short- and long-term GPBA treatment of UCD patients >6 y	65	++++	Phase 3, randomized, double-blind, crossover	NH3 -AUC0-24hr was lower on GPB in each study, and significantly lower in the pooled analysis, as was plasma glutamine; 24-h NH3 profiles were consistent with the slow-release behavior of GPB and better overnight NH3 control	
Eckert C et al, 2014	to develop a child appropriate, individually dosable, and taste masked dosage form of sodium benzoate utilizing lipids in melt granulation process and tableting	na	++	original article	minitablets of a child-appropriate, taste improved dosage form of sodium benzoate was produced	
Erez A et al, 2011	to review clinical characterization, biochemical, enzymatic, and molecula features of ASLD	na	++	review	comprehensive and up-to-date review on ASLD	
Fabre A et al, 2013	to compare the QoL of the children and parents affected by IEMRD with the QoL of the general population and leukemia; total 21 families	6	+++	cross-sectional	altered 'physical' and 'social' QoL scores compared with the norms and patients with leukemia and their families	
Gallagher R et al, 2014	to determine the frequency of significant liver injury and acute liver failure (ALF) in OTCD patients	71	+++	historical cohort	57% of the 49 patients with symptomatic OTCD had liver involvement; episodes of hepatocellular injury, liver dysfunction, and ALF were identified in a high proportion of children with symptomatic OTCD;	
Go A et al, 2012	describes 2 ASSD patients in 1 family	2	na	case report	prospective treatment in younger sibling avoided severe crisis	not added in guidelines

Gropman A et al, 2013	UCDs and their effects on functional imaging	?	+++	case series	neuroimaging methods become more sophisticated and allow assessment of clinical monitoring in UCDs	
Guffon N et al, 2012	to develop more palatable PBA formulation	na	++	original article	a new, taste-masked, coated-granule PBA formulation (Luc 01) was developed; bioequivalence to NaPBA of a single 5 g dose of the two products was shown in 13 healthy adult volunteers; newly developed granules can be swallowed before release of the bitter active substance	new formulation should improve compliance
Huemer M et al, 2016	to explore the clincial phenotype, metabolic profiles, genotypes, and treatment in a cohort of ARG1D patients	19	+++	retrospective study by questionnaire	paraparesis, cognitive impairment, and seizures were common findings, plasma GAA exceeded normal ranges, plasma ADMA and nitrate were significantly elevated, the nitrite:nitrate ratio significantly lower in subjects with ARG1D suggesting an advantage for NO synthesis by inducible NO synthase, arginine and protein restriction had no impact on long-term outcome	
Kasahara M et al, 2014	analysis of data for all pediatric LDLTs performed between Nov 1989 and Dec 2010 (n=2224; n=198 metabolic)	40 OTCD	+++	cohort retrospective	UCDs associated with better patient survival; in X-linked OTCD, symptomatic heterozygote maternal donors should not be considered potential donor candidates	
Kibleur Y et al, 2014	to analyze safety and efficacy of Pheburane in UCD patients	13 healty volunteers, 20 UCD patients	++++	Switchover trial from NaPBA to the new formulation	The experience is positive on efficacy and safety endpoints. 10 of 13 healthy volunteers referred increased palatability. Very much increase in ease of administration, metabolic control (ammonia/glutamine levels) and frequency of hyperammonemic episodes improved significatively with new medication. No taste loss or vomiting, observed with NaPBA.	
Kido J et al, 2012	Japanese UCD cohort from Jan 1999 to Mar 2009	177	+++	observational, cross-sectional, multicenter		see study by Nakamura K et al, 2014
Kim SZ et al, 2012	to present a long-term follow-up for HHH syndrome patients	4	+	case reports	long-term follow-up in all patients showed serious neurological complications despite overall good metabolic control; one patient with 2/3 successful pregnancies is reported; hypothesis, that intracellular ornithine deficiency adversely affects brain function	
Kim IK et al, 2013	to determine the long-term outcomes of LT for UCDs	23	+++	retrospective chart review	mean 5 y patient survival was 100%, and allograft survival was 96%; after transplantation, there were no episodes of HA; developmental delay before transplantation remained stable or improved	
Langendonk JG et al, 2012	report on pregnancies in IEMs, includes 2 pregnancies in 1 OTCD female		++	case series	total 12 pregnancies (different IEMs including OTCD), normal fetal outcome in 1 OTCD pregnancy	
Martin-Hernandez E et al, 2014	describe the characteristics of patients with UCDs treated in Spanish centers from Feb 2012 to Feb 2013	104	++++	observational, cross-sectional, multicenter	67 OTCD, 22 ASSD, 10 ASLD, 2 CPS1D, 2 ARGD, 1 NAGSD; median ammonia level at onset was 298 µmol/L; 52.5% of the cases present neurological sequelae; 5 patients detected by NBS; pH at diagnosis (in n=91) 7.43 (7.36-7.46); majority of patients (n=50) on PBA alone, 10 combination with benzoate; calculated incidence 1:70,922; more than half of the cases (55.8%) were diagnosed after 1 year of age; need to establish adult centers; z-score of the weight and height was in the normal range; 80% of ASLD patients had neurological damage; 75% of the patients without sequelae had ammonia levels at diagnosis ≤270 µmol/L; many patients still receiving carnitine despite proven benefit	great wealth of data
Mokhtarani M et al, 2012	analysis of pharmacokinetic data for GPBA and NaPBA with respect to possible dosing biomarkers in UCD patients	65	+++	cross over	plasma levels of drug metabolites have limited utility for therapeutic monitoring; by contrast, 24-h urinary and morning spot urine phenylacetylglutamine correlate strongly with dose and appear to be clinically useful non-invasive biomarkers for compliance and therapeutic monitoring	GPBA exhibits favorable pharmacokinetics and NH3 control relative to NaPBA ad was associated with improved executive function in pediatric patients; some authors are from company
Mokhtarani M et al, 2013	to investigate the relation between neurological adverse events and phenylacetic acid levels	180	+++	longterm protocols + cross-over study	PAA levels are in 99.8% of samples within the desired range; there is no relation between elevated PAA levels and adverse neurological events; there is a relation between PAA and PAA:PAGN levels indicating patients at risk for elevated PAA levels	some authors are from company
Mokhtarani M et al, 2015	to evaluate urinary phenylacetylglutamine (U-PAGN) concentrations in spot urine samples as a dosing biomarker during glycerol phenylbutyrate treatment	66	na	original article	U-PAGN concentrations may be useful for optimal dosing of GPB, may help monitoring compliance	authors employees and shareholders of company producing GPB, paper not included because similar study already published in 2012 is included
Nagamani S et al, 2012	to compare the effects of low-dose arginine plus NaPBA vs. monotherapy with high-dose arginine on liver function tests in ASLD	12	++++	double-blind, placebo-controlled, cross-over	high-dose arginine led to significantly increased argininosuccinate and AST; synthetic liver functions (PT, INR, and coagulation factor levels) were not different; multi-tracer stable isotope protocol showed no difference in glutamine flux; low-dose arginine plus nitrogen scavengers should be considered as a therapeutic option for treatment of ASLD in patients with elevations of aminotransferases	rather high dose of PBA (500 mg/kg); duration of study only 1 week

Nakamura K et al, 2014	clinical manifestations, treatment, and prognosis of 177 patients with UCD from Jan 1999 to Mar 2009; to evaluate prognosis and its relationship with peak blood ammonia and hemodialysis	177	+++	observational, cross-sectional, multicenter	larger number of patients survived without MR than in previous studies; peak blood NH3 >360 µmol/L is an indicator of poor prognosis; sufficient infusion (60–100 kcal/kg per day) of glucose electrolyte solution should be carried out to inhibit protein catabolism. Insulin should be used simultaneously in cases of hyperglycemia. Arginine should be used for UCD other than argininemia. Citrulline is effective for OTCD and CPSID and is thought to be more effective than arginine. Sodium benzoate and NaPBA should be used for excretion of excess nitrogen; NH3 may decrease within several hours, but, if 8 h later NH3 is >360 mol/L, hemodialysis or hemofiltration dialysis should be started immediately. After decreasing the blood NH3, oral intake should be considered with increasing EAAs while adjusting the total energy and protein intake with a protein removal formula. The treatment should aim for an intake of total protein 1.0–1.2 g/kg/d with spontaneous protein and required amino acid preparation	see study by Kido J et al, 2012
Perito ER et al, 2014	to analyse LTx from 2002-2012	186	+++	retrospective	graft survival improved as the age at transplant increased; within 5 y after LTx, graft survival rate was 78% for children < 2 yo at transplant and 88% for children ≥ 2 yo at transplantat; 5 y patient survival rate was 88% for children with UCDs/OAs who were <2 yo at transplant and 99% for children who were ≥2 yo at transplant	
Peuscher R et al, 2011	case reports on use of ketogenic diet in ASLD patients with refractory epilepsy	2	+	case reports	KD was well tolerated, did not cause metabolic derangement, and was beneficial for control of epilepsy in one of the ASLD patients	therapy was stopped in the other patient due to lack of efficacy
Pillai U et al, 2013	report a 28 yo man with HA following parenteral nutrition	1	+	case report	fatal outcome despite resolution of HA with cessation of PN and the use of CRRT	
Rüegger C et al, 2014	to describe non-classical UCDs	208	+++	cross-sectional observational	mean delay from first symptoms to diagnosis of 1.6 years; cognitive impairment was present in 36% of all patients thus high risk of neurological complications	
Schlune A et al, 2015	to review ARG1D and report the course in the first three patients ever described	3	+	review and case reports	comprehensive and up-to-date review on ARG1D and update on the first patients ever described	
Shchelochkov O et al, 2016	to assess patients and families perspective on UCD diet and drugs	52	+++	online survey	diet and drugs pose serious barriers to adherence although patients regard them as effective	only adult patients
Smith W et al, 2013	to examine NH3 levels, pharmacokinetics, and safety of GPB and NaPBA in young children with UCDs (ages 29 d to < 6 y)	15	+++	open label switch-over	daily NH3 exposure (24-h AUC) was lower on GPB; no serious adverse events; urine PAGN was greater on morning voids and varied less over 24 h on GPB vs. NaPBA	GPB results in more evenly distributed urinary output of PAGN over 24 h; some authors from company
Unsinn C et al, 2016	to study the course in neonatal UCDs	63	+++	retrospective study	68% had ammonia > 500 umol/L at initial presentation, 60% of patients were encephalopathic at pesentation, 25% of patients died during first crisis	
Vargha R et al, 2012	report a 50-hour-old newborn with inborn UCD and HA of 2320 µmol/L	1	+	case report	venovenous hemodiafiltration and therapeutic hypothermia	no new information
Wakiya T et al, 2011	retrospective analysis of LTx results for OTCD in 1 center	12 (6 males)	++	case series	survival rate was 91.7%; 9/12 achieved satisfactory quality-of-life improvement; neurological impairment associated with HA is unlikely to subside after LTx; more objective and concrete guidelines for OTCD management to be established to facilitate LDLT with optimal timing	single center
Wakiya T et al, 2012	to describe the practice of living donor evaluation for LTx in OTCD	3	+	case reports	3 heterozygous donor candidates, all underwent OTC activity analysis, 1 was chosen based on high OTC activity, candidates with activity <40% were not employed	
Wakiya T et al, 2012	to clarify the OTC activity in cases that were indicated for LTx	13 OTCD (8 males)	++	original article	OTC activity in neonatal onset was 0% to 7.2%, in late onset 4.4% to 18.7%; OTC activity might be an indicator for and the timing of LT in late onset type, but further investigations are necessary	general problem of OTC activity in female patients not solved
AhMew N et al, 2014	to study ureagenesis by using stable isotopes in late onset CPS1D	5	++	3-day trial	NCG augmented ureagenesis and decreased plasma NH3 in 4 of 5 subjects	results need critical review
Alexander IE et al, 2012	review on gene therapy for metabolic disorders / OTCD	na	++	review	successful phenotype correction in mouse models is now commonplace; research effort now directed towards addressing translational challenges in human clinical trials	
Ballantyne LL et al, 2015	Strategies to rescue the consequences of inducible ARGD in mice	na	+++	Exptl rodent and gene therapy	About 30% of inducible arginase KO mice recovered by AAV10 gene therapy	
Bosoi CR et al, 2011	to evaluate the capacity of AST-120 to adsorb ammonia in vitro and to lower blood ammonia, oxidative stress and brain edema in cirrhotic rats	na	+++	Experimental original paper in rats	AST-120 treatment decreased arterial ammonia levels, normalized brain water content and locomotor activity but did not demonstrate an effect on systemic oxidative stress. Also, AST-120 acts as an ammonia sink, efficiently removing blood-derived ammonia.	
Chandler RJ et al, 2013	to determine the efficacy of AAV gene transfer as a potential therapy for ASSD	na	+++	original article	AAV8 vector was engineered to express the human ASS1 cDNA under the control of a liver-specific promoter; delivered to 7-10 days old mice via intraperitoneal injection; >95% of the mice were rescued from lethality and survival was extended beyond 100 d after receiving a single dose; experiments highlight a gene transfer approach using AAV8 vector for liver-targeted gene therapy that could serve as a treatment for ASSD	
Cunningham SC et al, 2011	induction and prevention of severe HA in the spf ash mouse using shRNA and rAAV-mediated gene delivery	na	+++	Exptl spfash OTCd mouse gene ther	the dose of an AAV rescue construct encoding the mOTC cDNA required to prevent HA is fivefold lower than that required to control orotic aciduria	

Cunningham SC et al, 2013	to test the efficacy of AAV gene therapy in adult mice after neonatal vector injection	na	+++	Exptl spfash OTCd mouse gene ther	AAV-encoded OTC activity persisting to adulthood following delivery to newborn spf ash mice is insufficient to prevent shRNA-induced HA	
Cunningham SC et al, 2015	to improve efficacy of OTC gene therapy	na	+++	methods paper in mice	stable therapeutic protection inASSD and OTCD mouse models by use of hybrid rAAV/piggyBac transposon vector system	
Diez C et al, 2013	to characterize 8 human CPS1D mutations and test the role of CG	na	+++	original article with pure enzyme	Human CPS1 expressed in vitro is protected from protease degradation and thermal inactivation by NCG in the presence of ATP	
Diez C et al, 2014	to study hCPS1 integrating domain mutations: misfolding and decreased stability	na	+++	original article with pure enzyme	mutations in small central domain of CPS1 cause misfolding and low stability that could be improved by chaperone therapy	
Enosawa S et al (letter)	hepatocyte transplantation (HT) in an 11-day-old male OTCD with HA (1940 ug/dL at max)	1	+	case report	cryopreserved hepatocytes (7.4 x 10^7 and 6.6 x 10^7 cells/body) prepared from the remnant tissue from unrelated living donors; transplanted twice at 11 and 14 days of age with a double-lumen catheter inserted into the left portal vein via the umbilical vein; immunosuppressive treatment with same protocol used for LDLT with tacrolimus and low-dose steroids; 3 months of follow-up: no HA, normal neurology	unfavorable issues related to the use of marginal donors, including low viability and vulnerability to cryopreservation
Forster V et al, 2014	to develop liposome-supported peritoneal dialysis for detoxification of drugs and endogenous metabolites	na	+++	Experimental original paper in rats	Acidic liposomes injected into the peritoneum of rats concentrated endogenous ammonia at 20-fold concentrations relative to plasma. This effect was fast (30 min).	
Hansel et al, 2014	Review on first 100 patients receiving hepatocyte therapy	10	++	review	Evidence of efficacy based on retrospective review of reported cases	
Hu C et al, 2014	to test a codon-optimized arginase cDNA and compare the chicken β-actin promoter to liver and muscle-specific promoters	na	+++	Exptl argininemia mice gene ther	plasma arginine can be controlled in arginase deficiency by muscle-specific expression	
Hu C et al, 2015	to examine the flux through the urea cycle by [1-13C] acetate administration to both littermate controls and AAV-treated arginase 1 knockout mice	na	+++	Exptl argininemia mice gene ther	ureagenesis was present in the treated knockout liver at levels as low at 3.3% of control animals; only minimal levels of hepatic arginase activity are necessary for survival and ureagenesis in arginase-deficient mice and that this level of activity results in control of circulating ammonia	
Jorns et al, 2012	Review on hepatocyte transplantation for inherited metabolic diseases	10	++	review		
Kaminsky and Kosenko, 2012	development of arginase nanoparticles into mouse erythrocytes to reduce blood arginine	na	+++	original article	arginase-loaded erythrocytes (argocytes) infusion to hyperargininemic mice led to a rapid decrease in blood arginine concentration within 1 h, effect persisted for at least 4 h	
Kasten J et al, 2013	to create an adult conditional knockout mouse to determine whether later onset of arginase deficiency also resulted in lethality	na	+++	experimental mouse paper	the absence of arginase in adult animals results in a disease profile (leading to death) similar to that of the targeted knockout; the phenotypic abnormalities seen in the juvenile-onset model are not exclusive to the age of the animal but instead to the biochemistry of the disorder	
Kok CY et al, 2013	AAV-mediated rescue of neonatal lethality in ASS-deficient mice	na	+++	Exptl citrullinemia mice gene ther	Lethal neonatal HA was prevented by prenatal and early postnatal vector delivery; however, HA subsequently recurred limiting survival to no more than 33 d despite vector readministration	
Lee EK et al, 2012	to address the development of a gene therapy approach for arginase deficiency	na	+++	original article	100% of untreated ARGD mice died by DOL 24, whereas 89% of AAV-treated ARGD mice survived for >8 months; AAV-based therapy for ARGD is effective	
Lee EK et al, 2013	to report longterm follow-up of AAV treated ARGD mice	na	+++	original article	no signs of brain dysfunction; near complete resolution of metabolic abnormalities early in life; development of some derangement later with decline in transgene expression	nitrogen challenging reveals that these mice remain impaired in the handling of waste nitrogen
Lichter-Konecki U et al, 2013	Adjunct whole body hypothermia in addition to standard treatment in neonatal HA (6 UCDs and 1 OAs) requiring dialysis. Patients were maintained at 33.5 °C ± 1 °C for 72 h, then rewarmed by 0.5 °C every 3 h over 18 h.	7 (6 UCD, 1 IVA)	++++	case control (historical) study	Adjunct therapeutic hypothermia was feasible and safe. A randomized clinical trial is needed to prove efficacy. TH may be neuroprotective in conditions where HA is the major cause of the encephalopathy. However, adjunct TH adds another challenge to the rescue treatment of critically ill patients with HA and encephalopathy	main complication: hypotension
Matoori & Leroux, 2015	Recent advances in the treatment of HA	na	++	review	review of all the presently existing treatment alternatives and of novel promising alleys	
Nagamani S et al, 2012	to determine role of NO supplementation in ASLD	1	++	original article	systemic hypertension in ASLD mice could be corrected by NO; in 1 ASLD patient with severe refractory hypertension, NO monotherapy resulted in longterm control of hypertension and a decrease in cardiac hypertrophy; ASLD is model of congenital human NO deficiency; ASLD patients could potentially benefit from NO supplementation	NO supplementation should be investigated for the longterm treatment of ASLD

Rangroo Thrane et al, 2013	to determine how astrocytes contribute to the initial deterioration of neurological functions characteristic of HA in vivo	na	+++ original article	Two-photon imaging and electrophysiology in awake head-restrained mice showed that ammonia rapidly compromises astrocyte K+ buffering, increasing extracellular potassium concentration and overactivating the Na+-K+-2Cl−cotransporter isoform 1 (NKCC1) in neurons. Inhibition of NKCC1 with the clinically used diuretic bumetanide potently suppresses ammonia-induced neurological dysfunction. Astrocyte swelling or brain edema in the acute phase was not observed, calling into question current concepts regarding the neurotoxic effects of ammonia. Instead, the findings identify failure of potassium buffering in astrocytes as a crucial mechanism in ammonia neurotoxicity and demonstrate the therapeutic potential of blocking this pathway by inhibiting NKCC1.	
Senkevitch E et al, 2012	new mouse model for NAGS deficiency	na	+++ original article	NCG and L-citrulline used to rescue the NAGS knockout pups; 85% survival rate of Nags(-/-) mice with i.p. injections with NCG and Cit during newborn period and p.o. later; allowed for normal development, apparent health, and reproduction; reliable model of induced HA	
Sin YY et al, 2013	to generate an inducible Arg1 deficient mouse model	na	+++ original article	mice were nearly devoid of of Arg1 mRNA, protein and liver arginase activity and were hyperammonemic; this model will help evaluating potential treatments for ARG1D	
Sokal E, 2011	to describe role of liver derived progenitor cells as source of liver cell therapy		++ review	liver derived progenitor cells may have some advantages over stem cells derived from other tissues	
Sokal E et al, 2013	3 yo female OTCD received human liver stem cells	1	+ case report	previously unsuccessful LCT; received 2 intraportal infusions (percutaneous portal catheter) of Adult Derived Human Liver Stem/Progenitor Cells (ADHLSCs) expanded in vitro; biopsies taken 100 days after transplantation showed 3% and 5% of male donor cells; limited follow-up, thus no conclusions on long-term improvement; child died from LTx	proof of concept; partial left portal vein thrombosis after second infusion
Sokal E, 2014	to review the development from first hepatocyte therapies to stem cell therapy	na	++ review		
Torres-Vega MA et al, 2015	to explore role of glutamine synthetase (GS) gene therapy for treating HA	na	++ original article	A baculovirus containing the GS gene was constructed for the in vitro and in vivo treatment of HA; gene delivery for overexpressing GS in muscle tissue is a promising alternative for the treatment of HA	
Wang AH et al, 2011	to test acetic acid as water phase in a water in oil microemulsion to remove colonic ammonia	na	++ original article	study in healthy rats showed efficacy of w/o microemulsion to remoce colonic ammonia	no follow-up study since 2011
Wang et al, 2012	Preclinical evaluation of a clinical candidate AAV8 vector for OTCD	na	+++ original article	Functional expression of hOTC in 40% of liver areas was found in mice treated with a low vector dose of 1×109 GC	
Zhong L et al, 2013	to study rAAV integration sites in Otc-deficient mice	na	+++ original article	the role of rAAV integration in causing tumors in the OTC model reported here is unclear; potential rAAV genotoxicity associated with integration in this locus warrants monitoring	
Zhong L et al, 2013	to investigate a possible association between the development of a tumor and prior adenoviral gene transfer	2	++ original article	not detect any Ad vector DNA in either tumor or normal tissue from the two patients who had participated in phase I gene therapy trial for OTCD	
Zhu S et al, 2014	to develop mouse liver repopulation with hepatocytes generated from human fibroblasts	na	++ original article	human fibroblasts were converted into mature hepatocytes without passing through pluripotency, and populated a mouse liver which is a model for tyrosinemia type 1	