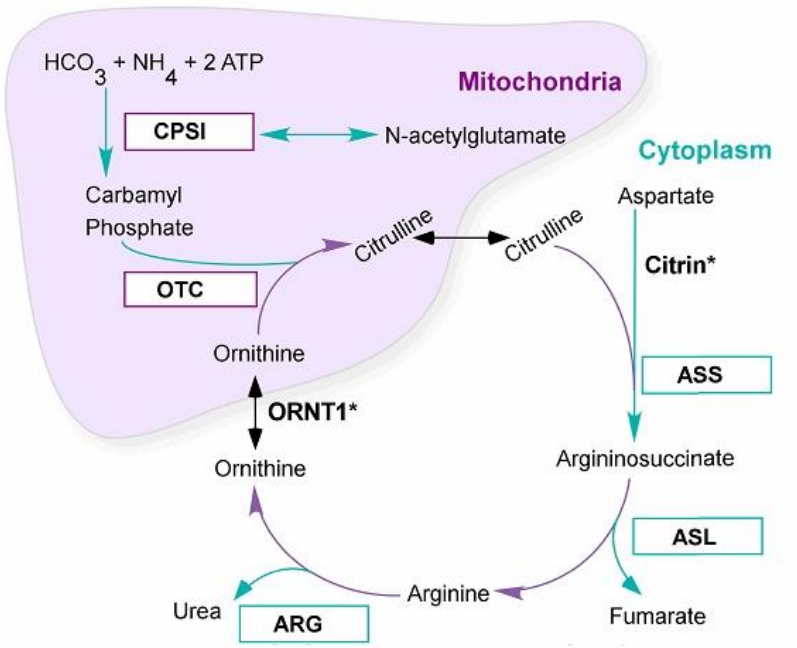
LONG TERM MANAGEMENT ARGININOSUCCINATE LYASE DEFICIENCY

OMIM# 207900

Definition:

- Autosomal recessive disorder, one of the most common urea cycle disorders.
- Caused by deficiency of argininosuccinate lyase (ASL), the enzyme that cleaves argininosuccinic acid to produce arginine and fumarate in the fourth step of the urea cycle.(1)
- It is the second most common urea cycle disorder after Ornithine transcarbamylase (OTC) deficiency.(2)
- In Saudi Arabia, it is the most common urea cycle disorder.(3)

Pathway:



Clinical Presentation:

- Neonatal onset ASL: the most common and most severe form characterized by hyperammonemia within the first few days after birth. Newborns typically appear healthy for the first 24 hours but within the next few days develop vomiting, lethargy, and hypothermia and refuse to accept feeds. Tachypnea and respiratory alkalosis are early findings. If untreated, leads to worsening lethargy, seizures, coma, and death. Other clinical findings includes: hepatomegaly and trichorrhexis nodosa (coarse and friable hair).(1, 4-6)
- Late onset form: range from episodic hyperammonemia (triggered by acute infection or stress or by non-compliance with dietary restrictions and/or medication) to cognitive impairment, behavioral abnormalities, and/or learning disabilities in the absence of any documented episodes of hyperammonemia.(1, 2, 4-6)

Diagnosis:

- Elevated plasma ammonia concentration (>150 µmol/L, sometimes up to ≥2000-3000 µmol/L), elevated plasma citrulline concentration (usually 200-300 µmol/L), and elevated argininosuccinic acid in the plasma or urine establish the diagnosis of ASL deficiency.(1, 2, 4-6)
- Plasma aminoacids showed: in addition to above finding, increase glutamine, alanine and glycine.(5)
- Urine organic acids showed orotic aciduria due to impaired recycling of ornithine which lead to increase in carbamoyl phosphate leading to overproduction of orotic acid.(7)
- ASL is the one of disorders included in Saudi Arabia Newborn Screening Program (NBS) and could be diagnosed through NBS by finding of elevated Citrulline and argininosuccinic acid.

Genetics:

- Autosomal recessive disorder.
- Parents of affected child are obligate carriers. At conception, each sib of an affected individual has a 25% chance of being affected, 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- In Saudi Arabia, the most common mutation (Q354X). Q = Glutamine.(8)

Treatment:

1. <u>Acute episode treatment guidelines (Emergency):</u>

- ABC (or now CAB).
- Stop all source of protein central and parenteral nutrition.
- Call the pharmacy to prepare the medications and lipid (see dosages below)
- Check GlucoChecks.
- Insert an IV line (central and peripheral) and take blood for blood gases, chem 1, Ammonia (NH3), & CBC, blood C/S (peripheral and central if patient has central line). Liver transaminase, Ca, alkaline phosphatase as **STAT** order.
- Ammonia should be taken with precaution (without tourniquet, transported on ice to the laboratory, separated within 20 minutes of collection and analyzed immediately.
- Start 1 1/2 to double maintenance I.V.F as D10 1/2NS + kcl 30meq/l until K result available then adjust accordingly (see below).
- Re-adjust according to lab results (Keep GlucoChecks 5-8mmol/L). Consider start insulin if hyperglycemia develop at dose of 0.01-0.05 unit/kg/hour and titrate up until blood glucose controlled. Total glucose requirements: 6-8mg/kg/minutes.
- If ammonia >100umol/l. Give a loading dose of arginine hydrochloride 400mg/kg/day as intravenous infusion over 90 minutes followed by the same maintenance dose divided over 24 hours q6 and start lipid 20 % 2-3gram/kg/day to give additional calories.
    - The amount of potassium supplement through IV line according to the potassium level result :
    - >5.5 = No kcl will be added
    - 3.5-5.5= kcl 20 meq/l .
    - If she is on Ammonul or arginine please give KCl kcl 40 meq/l because it cause hyperchloremic hypokalemic metabolic acidosis.
    - <3.5= 40 meq/l
    - <2.8 = 0.5 meq/kg kcl as a bolus in prediluted solution D5 w over one hour (should be given centrally and patient should be attached to cardiopulmonary monitor during the infusion) or you can give the required dose of kcl through PO/GT if he can tolerate it. KCL can be given through peripheral line up to 60 meq/l, rate must not exceed 0.125meq/kg/hour.
- Repeat ammonia, blood gases, chem 1 after the loading dose completed.
- If ammonia still high give AMMONUL® (sodium phenylacetate and sodium benzoate) 250mg /kg over 90 minutes.This is followed by a sustained intravenous infusion 250 mg/kg/day AMMONUL over 24 hours.
- Reloading has to be done carefully, in particular during the first 24 h, as cumulative doses of >750 mg/kg/24 h of AMMONUL® have been shown to be associated with development of toxicity (vomiting, lethargy). Reloading only in neonates with severe disorders or those who are undergoing dialysis, and should be spaced at least 6 hours.
- Ensure enough caloric intake covering 110% of the recommended daily allowance (RDA) in order to shut down endogenous protein breakage (RDA: for newborn and infant: 110-120 kcal/kg/day, for 1-3 yrs:100, for 4-6yrs: 90, for 7-10yrs: 70, for 11-14yrs: 50-55).
- Do not decrease dextrose rate or amount and DO NOT STOP calorie delivery in the acute stage for any reason (e.g. medications, addition required fluid bolus, or hyperglycemia) as this can precipitate hypoglycemia and catabolism which will further worsen the patient's condition.
- Give prophree or polycose through PO/NG as tolerated
- Call metabolic dietitian on call
- If ammonia <100 start Cyclinex formula with 50% natural protein.
- Continue on Sodium phenylbutyrate and sodium benzoate same dosages at home.
- DO NOT STOP other oral chronic medications.

- According to clinical evaluation, empirical antibiotics may be started.
- Ammonia, electrolyte and blood gases need to be followed at regular intervals during this acceleration of management stage. The frequency is dictated by the patient's condition and the speed at which results can be obtained.
- Proteins should be re-introducing within 24 hours-36 hours of initiation of therapy even if the patients on dialysis.
- Start dialysis if above measures failed to reduce ammonia within4 hours or if initial ammonia is >500 μmol/L(3, 6, 9-11)(See appendix1).

2. <u>Transition to long term management (Wards protocol):</u>

- Continue on above measures including high caloric intake, aminoacids mixture eg. CYCLINEX ®- formula with close monitoring of ammonia level, blood gas and electrolytes until normalization of their levels.
- Ensure appropriate caloric intake and medication dosages by calculating calories and medication dosages/ kg daily and document it in the chart.
- Provide remaining prescribed energy with Polycose® or Pro-Phree ®.
- Discontinue IV lipid when target calories intake can be achieved through other sources because long administration of lipid may cause fatty liver.
- Patient need daily evaluation from metabolic dietitian with gradually introduction of natural protein 50% of normal intake at home then upgrade to 100% if patient improve clinically and normalization of ammonia level, blood gas and electrolytes.
- Titrate IVF according to PO intake until discontinue.
- Discharge the patient if the following parameters achieved:
    1. Normal clinical status as home before crises.
    2. Normal plasma level ammonia achieved (see appendix2).
    3. Normal electrolytes and blood gas
    4. For new diagnosed case: parents educated about the disease natural history, formula, medications and sick day protocol.
    5. For new diagnosed case: Emergency card provided to the parents
    6. Family are comfortable with preparation of formula and sick day protocol
    7. Calculate the dosage of medications and ensure that had appropriate dosages / kg.
- Give appointment with General Metabolic Genetics Clinic 2 week after discharge with plasma aminoacids and electrolytes, prealbumin prior to appointment.

3. <u>Long term management (home and outpatient visits)</u>

a. Nutritional management:

The aim of dietary management includes:

- Normal weight gain, linear growth, and head growth.
- Normal psychomotor development, as assessed by serial examinations and valid developmental screening tools (e.g., Denver Developmental Screening Test II).
- Protein is restricted in the diet to provide limited amounts of isoleucine, methionine, threonine, valine and odd chain fatty acids and the further supplemented with aminoacids mixture to provide additional amino acids without the offending amino acids (see table 1 and 2).
- Avoidance of essential amino acid, fatty acid, and micronutrient deficiencies.

Metabolic dietitian should ensure the following:

- Home formula supplies include aminoacids mixture eg: CYCLINEX®-1 (for infant and toddler), CYCLINEX®-2 (for children; adolescents, and adults) see appendix 1.
- For infant: Breast milk or regular formula as a natural protein source. For older children: the source of natural protein from regular diet.
- Compliance of the mother with weighing skills, appropriate preparation of formula and 3-days diet records prior to clinic visit.

- Monitoring of amino acid concentrations. The frequency of amino acid monitoring varies by age, metabolic stability, compliance, and regional clinical practice. For rapidly growing infants, monitoring weekly is recommended (see monitoring section).

Table 1: Treatment Ranges for Target Amino Acids in ASL deficiency

Amino Acid (µmol/l)	(2-4 hr postprandial)			
	Newborn	1-3 m	3m-6y	6-18y
GLYCINE	106-254	105-222	125-318	158-302
ALANINE	132-455	134-416	148-475	193-545
GLUTAMINE	243-822		475-746	360-740
LYSINE	71-272	37-168	85-218	108-233
ARGININE	17-119	21-74	32-142	44-130
ILEUCINE	27-80	32-87	13-81	38-95
LEUCINE	61-183	43-165	40-158	79-174
VALINE	78-264	96-291	85-334	156-288
CITRULLINE	3-36	6-36	8-47	19-52

Note: These levels based on BC Children Hospital reference ranges. The optimal level depends on the normal range for age established in the local laboratory.

Biochemical target for optimal ASL deficiency control(12):

- Plasma ammonia <40 µmol/L.
- Plasma glutamine <1000 µmol/L.
- Normal plasma levels of alanine, glycine, lysine, and arginine
- No subnormal concentrations of essential amino acids (eg, leucine, isoleucine, valine).
- Normal urinary orotate excretion (<3 µmol/mmol creatinine).
- Normal plasma protein concentrations (eg, albumin).

Table 2: Recommended daily nutrient intake in urea cycle disorders (13):

Fluid (mL/kg)	**Energy (kcal/kg)**	**Total Protein (g/kg)**	**Age**
			Infants
160–130	150–125	2.20–1.25	0 to <3 mo
160–130	140–120	2.00–1.15	3 to <6 mo
130–120	120–110	1.60–0.90	9 to <12 m
(mL/day)	(kcal/day)	(g/day)	Girls and boys
945–1890	945–1890	8–12	1 to <4 yr
1365–2445	1365–2415	12–15	4 to <7 yr
1730–3465	1730–3465	14–17	7 to <11 yr
(mL/day)	(kcal/day)	(g/day)	Women
1575–3150	1575–3150	20–23	11 to <15 yr
1260–3150	1260–3150	20–23	15 to <19 yr
1875–2625	1785–2625	22–25	≥19 yr
(mL/day)	(kcal/day)	(g/day)	Men
2100–3885	2100–3885	20–23	11 to <15 yr
2200–4095	2200–4095	21–24	15 to <19 yr
2625–3465	2625–3465	23–32	≥19 yr

Table 3: safe daily protein intake in urea cycle disorders(14)

11-12	7-10	4-6	3y	2y	18m	12m	6m	3m	2m	1 m	Age
0.90	0.92	0.87	0.90	0.97	1.03	1.14	1.31	1.36	1.50	1.77	Protein intake (gm/kg/day)

- Protein requirements for child with urea cycle disorders varies depend on the age and growth rate and severity of the disease.
- For patient with severe disease some of natural protein (a mixture of essential and non essential aminoacid may be replaced with an essential aminoacid mixture (20-30%).(14)

- Requirement for many trace element and vitamins in children with urea cycle disorders have not been established.

- Several of the supplements appear to be very low in vitamin B12 in the their diet , some centers measure urinary methylmalonic acid to monitor the adequacy of their supplement.

Table 4: Chronic medications for life (1,12):

Comment	Route	Dose	Medication
Other reference <20: 100-300mg/kg/day. >20kg: 2.5-6 g/m^2/day(14)	PO	<20kg: 400-700 *mg/kg/day. >20kg: 8.8-15.4 g/m^2/day*	L-Arginine
In case of frequent metabolic decompensations or episodes of elevated ammonia Other reference: <20 kg: ≤250mg/kg/day >20 kg: 5g/m2/day maximum:12g/day(14)	PO	<20: 450-600mg/kg/day. >20kg: 9-13 g/m^2/day	Sodium phenyl butyrate
In case of frequent metabolic decompensations or episodes of elevated ammonia maximum: 12g/day(14)	PO	250-500mg/kg/day	Sodium benzoate

* Despite good ammonia control, many ASL deficiency patients experience unremitting intellectual decline, suggesting brain toxicity by ASA, decreased amounts of guanidinoacetate], arginine therapy or alterations in NO production. Thus, dosages of L-arginine exceeding those in other UCDs are not recommended, with a target plasma arginine level < 200 µmol/L (generally considered a safe level).(14)

Look for complications of ASL deficiency which includes (1,14)

- **Iatrogenic essential amino acid deficiency**: inadequate protein intake will result in failure to thrive in infants; weight loss, low plasma prealbumin concentration, osteopenia, and hair loss in children and adults; and may result in hyperammonemia.
- **Neurocognitive deficiencies:** includes intellectual disabilities, developmental delay, seizure disorders, abnormal EEG, attention deficit hyperactivity disorder.

- **Liver disease:** ranges from hepatomegaly to elevations of liver enzymes to severe liver fibrosis.
- **Trichorrhexis nodosa:** nodular swellings of the hair shaft accompanied by frayed fibers and loss of cuticle.
- **Hypertension**
- **Electrolytes imbalance:** eg, hypokalemia.

Monitoring(13, 14):

A. Clinical monitoring:

- ✓ Weight, height, and head circumference
- ✓ Developmental assessment
- ✓ Neurologic assessment
- ✓ Liver examination

B. Biochemical lab monitoring :

- ➢ Plasma amino acid and ammonia weekly since diagnosis till 6months of age then every other week till 1year then monthly .
- ➢ Ammonia target less than 40micromol/l (in other reference: <80micromol/l)(14).
- ➢ Plasma glutamine target less than 1000 micromol/ l, however, high glutamine concentration do not invariably indicate encephalopathy.
- ➢ Normal concentration of essential amino acid (eg : leucine ,isolucine,valine)
- ➢ Normal urinary orotate excretion less than 3 micromol/l creatinine.
- ➢ CBC ,Retic, Ca ,Phosphorus , AST,ALT ,GGT, alkaline phosphatase, vitamine B12, zinc, selenium, urine for orotic acid, lipid profile, blood sodium benzoate and/or sodium PBA/phenylacetate assays to be done every 3 month until 1year age then every 6 months.
- ➢ Albumin and prealbumin monthly until 1 year then every 3 months.
- ➢ Plasma ferritin concentration evaluate at 6,9, 12 months then every 6 months.
- ➢ Magnetic resonance imaging (MRI) early on in each coma or stroke-like episode, and at 2-year intervals.

C. Other monitoring parameters :

15	12	9	6	5	4	3	2	1	0.5	Age(years)
				*		*		*	*	**EEG**
*	*	*	*		*		*		*	**Bone Age**
		*		*		*		*		**Bone densitometry**

D. Clinic follow up :

- ➢ **Metabolic and Dietitian clinic :** every 2 months till 1 year of age then every 3 months till 6 years of age then every 6 months till 17 years of age then every year **.**
- ➢ **Neurology clinic:** at Dx then every 6 months till 1 year then every 2 years till 9 years of age then at 15 years of age .
- ➢ **Psychology clinic:** at 3 years of age then every 2 years till 9 years then at 13 and 15 years**.**
- ➢ **Physiotherapy :** at Dx then at 4 months ,8months, 18 months ,3 years,5 years
- ➢ **Occupational therapy :** at 18 months , 3 years.
- ➢ **Social service:** at Dx then at 1 year and 3 years.

Note: this is general guidelines for monitoring that could be adjusted on individual basis.

Sick day management: (12)

- In females with deterioration during or prior menstruation, instituting a "sick day" dietary regimen for the premenstrual or menstrual period would seem reasonable**.**
- Home Sick-day regimen is also indicated in case of URTI, trauma, surgery etc**.**
- Reduce protein intake to 50% for 24 to 48 h
- Increase total calories by 10 to 25%
- 1 -1.5 imes increased fluid intake
- Maximize Na phenylbutyrate if possible**.**
- Maximize arginine hydrochloride if possible**.**
- Aggressively treat the underlying illness**.**
- If the patient does not improve within 24-48 h – bring the patient to ER

Management with immunizations:**(12)**

- Give sick day formula 50% for 24 hours
- Manage fever >38 C with ibuprofen. Acetaminophen should be avoided because this drug could be hepatoxic, especially in large doses.
- If not improved within 24 hours bring to ER

Management with surgical procedure:**(12)**

- Ensure that the patient on his usual state of health prior to procedure
- Ensure stability of metabolic parameters including leucine, isoleucine and valine prior to procedure**.**
- Plasma aminoacids, chem1, blood gas, prior to procedure.
- High caloric intake with IVF D10 and lipid which provide 110 to 120% of normal energy needs starting 12-24 hours prior to procedure.
- After surgery follow the guidelines mentioned in Transition to long term management (Wards protocol).

Liver transplantation:

- Liver transplantation should ideally be carried out before irreversible neurological damage and/or repeated crises, generally between 3 and 12 months of age and/or 5 kg body weight.(14)
- For those suffering recurrent metabolic decompensation and hospitalizations despite medical therapy, as well as those with poor quality of life.(9)
- Standard orthotopic liver transplantation (OLT) is preferred to auxiliary liver transplantation because it has fewer complications.(15)
- Transplantation of liver lobes from living relatives can reduce waiting times and gives results comparable to those obtained with cadaveric organs, albeit that it entails a small risk for donors. Heterozygosity for the disease in the living related donor is not a problem, except in OTCD females, although asymptomatic OTC heterozygotes have been successful donors.(16).

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Appendix 1:

- Hemodialysis is the preferred method.
- Continuous arteriovenous hemodialysis (CAVHD) or continuous venovenous hemodialysis (CVVHD) with flow rates greater than 40 to 60 mL/min is optimal. Some centers use extracorporeal membrane oxygenation (ECMO) with hemodialysis.

- Although this combination of techniques provides very high flow rates (170-200 mL/min) and rapidly decreases ammonia levels, morbidity is greater because of the need for surgical vascular access.
- Nitrogen scavenging therapy needs to be continued during hemodialysis.
- Continue nitrogen scavenging therapy for 12-24 hours after the patient has been stabilized and is able to accept enteral feeds and medications.(1)

Appendix 2 (1):

Table 5: normal ammonia level by age

Upper limit (umol/l)	Age
94	**0-7 day**
80	**8-30 days**
48	**1 m-15yr**
26	**>16**

Note: The optimal level depends on the normal range for age established in the local laboratory.

Appendix 3:

Table 6: Differences between cyclinex-1 and cyclinex-2

Nutrient	Cyclinex-1		Cyclinex-2	
	(per 100 g pwd)	(per g protein equiv)	(per 100 g pwd)	(per g protein equiv)
Energy, kcal	510	68	440	32
Protein equiv, g	7.50	1.000	15.00	1.000
Nitrogen, g	1.20	0.160	2.40	0.160
Amino acids, g	9.65	1.287	19.30	1.287
Cystine, g	0.30	0.040	0.60	0.040
Histidine, g	0.36	0.048	0.72	0.048
Isoleucine, g	1.28	0.170	2.56	0.170
Leucine, g	2.17	0.289	4.34	0.289
Lysine, g	1.11	0.148	2.22	0.148
Methionine, g	0.34	0.045	0.68	0.045
Phenylalanine, g	0.75	0.100	1.50	0.100
Threonine, g	0.75	0.100	1.50	0.100
Tryptophan, g	0.28	0.037	0.56	0.037
Tyrosine, g	0.88	0.117	1.76	0.117
Valine, g	1.43	0.190	2.86	0.190
Other Nitrogen-Containing Compounds				
L-Carnitine, mg	190	25.00	370	24.67
Taurine, mg	40	5.3	60	4.00
Carbohydrate, g	57.0	7.60	45.0	3.00
Fat, g	24.6	3.28	17.0	1.13
Linoleic acid, g	2.00	0.266	1.82	0.121
α-Linolenic acid, g	0.41	0.055	0.28	0.019
Minerals				
Calcium, mg	650	86	1,150	77
Chloride, mg/mEq	390/11.00	52.0/1.47	1,325/37.37	88.3/2.49
Chromium, µg	12	1.60	37	2.47
Copper, mg	1.25	0.167	1.30	0.09
Iodine, µg	80	10.67	150	10
Iron, mg	10.0	1.33	17.0	1.13
Magnesium, mg	55	7.3	300	20.0
Manganese, mg	0.50	0.067	1.00	0.07
Molybdenum, µg	13	1.73	40	2.67
Phosphorus, mg	455	60	1,020	68
Potassium, mg/mEq	760/19.44	101/2.59	1,800/46.03	120/3.07
Selenium, µg	25	3.33	37	2.47
Sodium, mg/mEq	215/9.35	28.7/1.25	1,175/51.11	78.3/3.41
Zinc, mg	9.5	1.27	17.0	1.13
Vitamins				
A, µg RE	480	64	908	61
D, µg	7.50	1.00	8.12	0.54
E, mg α-TE	11.40	1.52	16.11	1.10
K, µg	60	8.0	70	4.67
Ascorbic acid, mg	60	8	75	5
Biotin, µg	75	10	150	10
B_6, mg	0.85	0.113	1.75	0.12
B_{12}, µg	5.60	0.750	7.30	0.487
Choline, mg	100	13.3	130	8.7
Folate, µg	250	33.00	530	35.33
Inositol, mg	50	6.7	110	7.3
Niacin equiv, mg	16.70	2.23	30.3	2.02
Pantothenic acid, mg	7.80	1.040	10.90	0.726
Riboflavin, mg	1.0	0.133	2.4	0.160
Thiamin, mg	2.0	0.267	4.0	0.267

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