A urea cycle disorder is a genetic liver disorder caused by a deficiency of one of the six enzymes in the urea cycle which is responsible for removing ammonia from the blood stream. The urea cycle involves a series of biochemical steps in which nitrogen, a waste product of protein metabolism, is removed from the blood and converted to urea. Normally, the urea is transferred into the urine and removed from the body. In urea cycle disorders, the nitrogen accumulates in the form of ammonia, a highly toxic substance, and is not removed from the body resulting in hyperammonemia (elevated blood ammonia). Ammonia then reaches the brain through the blood, where it causes irreversible brain damage, coma and possibly death.

Urea cycle disorders are included in the category of inborn errors of metabolism. Current medicine has no cure. Inborn errors of metabolism represent a substantial cause of brain damage and death among newborns and infants. In April 2000, research experts at the Urea Cycle Consensus Conference estimated the incidence of the disorders at 1 in 10,000 births. This represents a significant increase in case identification and diagnosis in the last few years.

In lay terms, the symptoms in adulthood that tell if this is needed are:

1. Smell of ammonia when urinating
2. Liver digestion difficulties. This will make other liver diseases and infections worse.
3. Kidney problems as indicated by low back pains. This will make other kidney issues worse.
4. Difficulty thinking after eating.
5. A general sense of toxicity which is often hard to determine. Most general toxicity comes from the intestines. Sluggishness coupled with one of the above often helps to determine the blood state.

### SUMMARY OF REMEDIES
(with range of mega bottles needed)
(The boosting enzyme is listed beneath each UCD)

<table>
<thead>
<tr>
<th>Enzyme Name</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCD ARGINASE</td>
<td>5-6</td>
</tr>
<tr>
<td>ARGINASE</td>
<td>3-5</td>
</tr>
<tr>
<td>UCD ARGININOSUCCINASE</td>
<td>5-6</td>
</tr>
<tr>
<td>ACID LYASE</td>
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</tr>
<tr>
<td>ARGININOSUCCINIC ACID LYASE</td>
<td>3-5</td>
</tr>
<tr>
<td>UCD ARGININOSUCCINIC ACID SYNTHETASE</td>
<td>5-6</td>
</tr>
<tr>
<td>ARGinine</td>
<td>3-5</td>
</tr>
<tr>
<td>CITRULLINE</td>
<td>3-5</td>
</tr>
<tr>
<td>UCD CARBAMOYL PHOSPHATE SYNTHETASE</td>
<td>5-6</td>
</tr>
<tr>
<td>N- CARBAMYL-GLUTAMATE SYNTHETASE</td>
<td>5-6</td>
</tr>
<tr>
<td>N- CARBAMYL-GLUTAMATE</td>
<td></td>
</tr>
<tr>
<td>UREA CYCLE DISORDER</td>
<td></td>
</tr>
<tr>
<td>ORNITHINE</td>
<td>3-5</td>
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<tr>
<td>TRANSCARBAMYLASE</td>
<td>5-6</td>
</tr>
<tr>
<td>ARGinine</td>
<td>3-5</td>
</tr>
<tr>
<td>CITRULLINE</td>
<td>3-5</td>
</tr>
</tbody>
</table>
GENERAL SYMPTOMS

THE NEONATAL PERIOD: Children with severe urea cycle disorders typically show symptoms after the first 24 hours of life. The baby may be irritable at first, or refuse feedings, followed by vomiting and increasing lethargy. Soon after, seizures, hypotonia (poor muscle tone, floppiness) (resembles Polio), respiratory distress (respiratory alkalosis), and coma may occur. These symptoms are caused by rising ammonia levels in the blood. Sepsis and Reye’s syndrome are common misdiagnoses.

CHILDHOOD: Children with mild or moderate urea cycle enzyme deficiencies may not show recognizable symptoms until early childhood. Earliest symptoms may include failure to thrive, inconsolable crying, agitation or hyperactive behavior, sometimes accompanied by screaming, self-injurious behavior, and refusal to eat meat or other high-protein foods. Later symptoms may include frequent episodes of vomiting, especially following high-protein meals, lethargy and delirium, and finally, if the condition is undiagnosed and untreated, hyperammonemic coma or death may occur. Undiagnosed children may be referred to child psychologists because of their behavior, developmental delays and eating problems. Childhood episodes of hyperammonemia (high ammonia levels in the blood) may be brought on by viral illnesses including chickenpox, colds or flu, teething, growth spurts, high-protein meals, or even exhaustion. Common misdiagnoses include Reye’s syndrome.

Early clinical manifestations (symptoms) of arginase deficiency (similar to those of the other disorders), may be seen as early as one year of age, but some children with AG remain asymptomatic at four years of age. AG symptoms are usually progressive and include growth failure, spastic tetraplegia (lower limbs more severely affected than upper limbs), seizures, psychomotor retardation and hyperactivity.

Major characteristics of NAGS deficiency, considered the rarest urea cycle disorder, include severe hyperammonemia (elevated blood ammonia), deep encephalopathy despite only mild hyperammonemia, recurrent diarrhea and acidosis, movement disorder, hypoglycemia and hyperornithinemia.

ADULTHOOD: Recently, the number of adults being diagnosed with urea cycle disorders has dramatically increased. These individuals have survived undiagnosed to adulthood, probably due to less severe enzyme deficiencies. Many adults are being identified due to improved diagnostics and increased awareness among medical professionals. These individuals exhibit stroke-like symptoms, episodes of lethargy, and delirium. These adults are likely to be referred to neurologists or psychiatrists because of their psychiatric symptoms. However, without proper diagnosis and treatment, these individuals are at risk for permanent brain damage, coma, and death. Adult-onset symptoms have been observed following viral illnesses, childbirth, dieting, use of valproic acid (an anti-epileptic drug which causes excess ammonia), and chemotherapy.

OTC CARRIERS: Approximately 85% of adult female carriers (heterozygotes) for OTC deficiency are asymptomatic (exhibit no symptoms). The remainder show symptoms including protein intolerance, headache, and episodes of confusion or trouble concentrating, behavioral or neurological abnormalities, cyclical vomiting and episodes of hyperammonemia. Studies have shown carriers to be of normal to above-normal intelligence, but some have been shown to demonstrate subtle deficits in fine motor, visual-spatial and non-verbal functions. Concerns are beginning to emerge about carriers with regard to common health issues (diabetes, hypercholesterolemia, cancer) and negative effects that treatments or drugs used to treat these common conditions may have on urea cycle function.
NEWBORN SYMPTOMS

The most recorded symptomology exists about neonates because this was originally thought to be only a neonatal disorder. Some children show no signs for 24 hours and some show no signs for weeks. The constellation of symptoms includes:

- Cerebral Edema
- Lethargy
- Anorexia
- Hyperventilation or
- Hypoventilation
- Hypothermia
- Seizures
- Neurological Posturing to Quadriplegia
- Coma
- Ammonia accumulation
- Failure to Feed
- Mental slowness

AGE 1 TO 25 SYMPTOMS

Less severe deficiencies have milder demonstrations that may show intermittently. They include:

- Loss of appetite
- Cyclical vomiting or
- Stress vomiting
- Lethargy
- Behavior Abnormalities
- Sleep disorders
- Delusions
- Hallucinations
- Psychosis
- Brain Atrophy
- Aversion to protein (especially for teenage to early 20s females)
- Encephalopathy
- Coma and/or death by brainstem swelling and compression
- Mental Retardation
- Hyperactive (sometimes with screaming and self-injurious behavior)
- Chickenpox and other viral illnesses have been triggers

AGE 26ISH THROUGH ADULTHOOD

This is uncharted territory as science has noted an alarming increase in the 22nd century. So far, identified symptoms include:

- Stroke-like
- Episodes of Lethargy
- Delirium
- Psychiatric aberrant behavior
- Mothers have died in childbirth because their disease was unknown
- Neurological Weaknesses
- Post chemotherapy and other toxic drugs have been noted by science to precipitate Urea Cycle Disorders
- Different cancers have been identified by science as related to the latent disease.
## SPECIFIC SYMPTOMS

Severe neonatal symptoms are more commonly seen in both boys and girls with OTC and CPS deficiency, but can also occur with citrullinemia or argininosuccinate lyase deficiency (ASA lyase). Findings of each individual urea cycle disorder relate to this constellation of symptoms and rough temporal sequence of events. Symptoms include the following:

- Anorexia
- Irritability
- Heavy or rapid breathing
- Lethargy
- Vomiting
- Disorientation
- Somnolence
- Asterixis (rare)
- Combativeness
- Obtundation
- Coma
- Cerebral edema
- Death (if treatment is not forthcoming or effective)

## Neurologic

- Poor coordination
- Dysdiadochokinesia
- Hypotonia or hypertonia
- Ataxia
- Tremor
- Seizures and hypothermia
- Lethargy progressing to combativeness, obtundation, and coma
- Decorticate or decerebrate posturing
SPECIFIC CYCLE DISEASES

<table>
<thead>
<tr>
<th>Location</th>
<th>Abb.</th>
<th>Enzyme</th>
<th>Disorder</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondria</td>
<td>NAGS</td>
<td>N-Acetylglutamate synthetase</td>
<td>N-Acetylglutamate synthase deficiency</td>
<td>+Ammonia</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>CPS1</td>
<td>Carbamoyl phosphate synthetase I</td>
<td>Carbamoyl phosphate synthetase I deficiency</td>
<td>+Ammonia</td>
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<tr>
<td>Mitochondria</td>
<td>OTC</td>
<td>Ornithine transcarbamylase</td>
<td>Ornithine transcarbamylase deficiency</td>
<td>+Ornithine, +Uracil, +Orotic acid</td>
</tr>
<tr>
<td>Cytosol</td>
<td>ASS</td>
<td>Argininosuccinic acid synthetase</td>
<td>&quot;AS deficiency&quot; or citrullinemia</td>
<td>+Citrulline</td>
</tr>
<tr>
<td>Cytosol</td>
<td>ASL</td>
<td>Argininosuccinase acid lyase</td>
<td>&quot;AL deficiency&quot; or argininosuccinic aciduria (ASA)</td>
<td>+Citrulline, +Argininosuccinic acid</td>
</tr>
<tr>
<td>Cytosol</td>
<td>ARG</td>
<td>Arginase</td>
<td>&quot;Arginase deficiency&quot; or argininemia</td>
<td>+Arginine</td>
</tr>
</tbody>
</table>

CPS - Carbamoyl Phosphate Synthetase

In patients with homozygous CPS I deficiency, the ability to fix waste nitrogen is completely absent, resulting in increasing levels of free ammonia with the attendant effects on the CNS.

Signs of CPS1 deficiency usually occur soon after birth, usually right after the first feeding, but sometimes symptoms may not be noticeable until days or weeks later. Here is a list of common signs or symptoms: 1. lethargy that may lead to coma 2. persistent vomiting 3. heavy or rapid breathing 4. poor feeding, lack of appetite 5. enlarged liver 6. seizures 7. decreased muscle tone 8. hypothermia 9. irritability 10. loss of coordination 11. disorientation

Citrulline and arginine supplementation help in the reversal of this disease. Vibrational N-Carbamyl Glutamate is available to help the reversal.

NAGS- N-Acetylglutamate Synthetase

**N-acetylglutamate synthetase** is an enzyme that catalyses the production of N-acetylglutamate from acetyl-CoA and glutamate. N-acetylglutamate, activates carbamoyl phosphate synthetase I, which catalyses the initial reactions of urea cycle.

N-carbamylglutamate supplementation help in the reversal of this disease.

Over-restriction of protein/amino acids is one of the most common causes for reaccumulation of ammonia and poor growth in children.
### OTC - Ornithine Transcarbamylase Deficiency

Men manifest this form most often; women carry or develop late in life. This enzyme’s role is to combine a molecule named ornithine with a molecule named carbamoyl phosphate to make citrulline. This is the first step of the urea cycle. The reversal is best supplemented by arginine and citrulline.


Some severe forms have been successfully treated by liver transplant.

### Argininosuccinic Acid Synthetase (Citrullinemia)

This later-onset form is associated with intense headaches, partial loss of vision, problems with balance and muscle coordination (ataxia), and lethargy.

Type II citrullinemia chiefly affects the nervous system, causing confusion, restlessness, memory loss, abnormal behaviors (such as aggression, irritability, and hyperactivity), seizures, and coma. Type II citrullinemia is found primarily in the Japanese population.

The features of adult-onset type II citrullinemia may also develop in people who as infants had a liver disorder called neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD). NICCD blocks the flow of bile (a digestive fluid produced by the liver) and prevents the body from processing certain nutrients properly.

### Argininosuccinate Lyase

(Argininosuccinic Aciduria)

Treatment of these patients often only requires supplementation of arginine. Vibrational Argininosuccinic Acid Lyase is available to help the reversal. This disorder is marked by chronic hepatic enlargement and elevation of transaminases.

### Arginase

Patients with Arginase Deficiency may present with hyperammonemia with severe stress, but are more likely to present with progressive neurologic symptoms unrelated to hyperammonemic episodes these patients develop progressive spasticity. They can also develop tremor, ataxia, and choreoathetosis.

Arginine and citrulline amino acids are not useful in the treatment of arginase deficiency because the disorder is characterized by increased arginine levels and arginine supplementation will worsen the disease. The vibration of the enzyme, Arginase was developed to supplement the progress.
HEALERS WHO SHARE IS RESEARCHING THE CONNECTION TO THE FOLLOWING DISEASES:

- Diabetes with Deafness
- Myoclonic Epilepsy with Raged Red Fibers
- Lafora Disease
- Neuronal Ceroid Lipofuscinosis
- Sialidosis
- Unverricht-Lundborg Disease
- Mitochondrial Encephalomyopathy
- Subacute Sclerosing Encephalopathy
- Retinitis Pigmentosa with ataxia, ptosis, dementia and neuropathy
- Kearns-Sayre Syndrome (sight, hearing, cardiac)
- Leber’s (optic)
- Mitochondrial Neurogastrointestinal Encephalomyopathy
- Lactic Acidosis
- Wolff-Parkinson-White Syndrome

SUMMARY OF REMEDIES
(with range of mega bottles needed)
Research remedies made so far

LEBER’S 6
MITOCHONDRIAL ENCEPHALOMYOPATHY 6
MYOCLOUNIC EPILEPSY with RAGGED RED FIBERS 6
NEURONAL CEROID LIPOFUSCINOSIS See GMO Spectrum Disease
SIALIDOSIS See Mucopolisaccharidosis