# Hyperammonemia

Hyperammonemia is a metabolic disturbance characterized by excess ammonia the in the blood. Ammonia is a nitrogen-containing substance, with nitrogen being a product of protein breakdown. Ammonia can be extremely toxic to the body, and is converted to the less-toxic urea via the urea cycle. This urea is then excreted by the kidneys. Hyperammonemia can be primary or secondary in origin. Primary hyperammonemia is caused by hereditary urea cycle enzyme defects, and secondary hyperammonemia can be caused by liver failure. Build up of ammonia causes depletion of alpha-ketoglutarate and inhibition of the TCA cycle. Symptoms of hyperammonemia include tremor, slurring of speech, somnolence, vomiting, cerebral edema and blurry vision. Treatment includes limiting protein in the diet, because protein is a source of ammonia. Benzoate and phenylbutyrate can also be used to help with in hyperammonemia, as they bind amino acids and lead to excretion of ammonia. Lactulose is also commonly used to treat hyperammonemia. Lactulose is metabolized in the colon by bacterial flora into short chain fatty acids, increasing the concentration of hydrogen ions in the gut. This favors the formation of NH4+, which is nonabsorbable and easily excreted, rather than NH3.


PLAY PICMONIC

## Pathophysiology

### Hereditary Urea Cycle Defects

Broken U-rainbow Cycle

Hyperammonemia can be primary or secondary in origin. Primary hyperammonemia is caused by hereditary urea cycle enzyme defects. Normally, the urea cycle converts ammonia to less toxic urea, which can be excreted by the kidneys. However, a defect in the urea cycle will cause a buildup of ammonia, leading to hyperammonemia.

### Acquired Through Liver Disease

Diseased Liver

Hyperammonemia can be of primary or secondary origin. Liver failure is a common cause of secondary hyperammonemia, as patients with liver disease can have cell dysfunction, leading to metabolic errors. These metabolic errors can be seen in the urea cycle, which takes place primarily in the liver, resulting in hyperammonemia. Keep in mind that patients with congenital liver disease, along with acquired liver disease (toxins, hepatitis, alcoholic cirrhosis), are at risk for hyperammonemia.

### Inhibits the Citric Acid Cycle

Inhibited Acidic-lemon Wheel-in-cage

The tricarboxylic acid cycle (TCA cycle) is inhibited in patients with hyperammonemia because of alpha-ketoglutarate depletion, a substrate of the citric acid cycle. In hyperammonemia, alpha-ketoglutarate is depleted when it is deaminated by NH3, forming glutamate. Thus, excess ammonia depletes alpha-ketoglutarate, leading to inhibition of the TCA cycle.

## Signs & Symptoms

### Somnolence

Sleepy-guy

Somnolence is a commonly seen symptom of increased ammonia levels in the blood. Increased blood ammonia levels also lead to disorientation, confusion, combativeness, agitation, stroke-like symptoms, lethargy, and delirium.

### Slurring of Speech

Slurpee

In hyperammonemia, patients may display slurring of speech. Increased blood ammonia levels also lead to disorientation, confusion, combativeness, agitation, stroke-like symptoms, lethargy, and delirium.

### Tremor

Weed-trimmer

In cases of abnormal ammonia metabolism, such as hyperammonemia, patients can display asterixis, which is also called a flapping tremor or liver flap. This tremor is described as a tremor of the hand when the wrist is extended and is sometimes said to resemble a bird flapping its wings.

**Cerebral Edema**
Cerebral Edamame
Cerebral edema is a potentially life-threatening complication of hyperammonemia, as patients can rapidly develop intracranial hypertension and death.

**Vomiting**
Vomit
High levels of ammonia in the blood can lead to nausea and vomiting. Older patients may display cyclic vomiting and episodic headaches, which are related to the cerebral edema that develops in hyperammonemia.

**Blurring of Vision**
Wavy-eyes
Another consequence of hyperammonemia is visual disturbances, as patients may complain of blurred vision or, in some cases, intermittent blindness.

## Treatment

**Limit Protein in Diet**
Protein-truck Can't Enter
Dietary protein is a metabolic source of ammonia, and thus, patients should limit the protein ingested in their diet. In these patients, caloric intake should be mainly through glucose and fats.

**Lactulose**
bLack-tulip
Lactulose is commonly used to treat hyperammonemia. Lactulose is metabolized in the colon by bacterial flora into short-chain fatty acids, working to increase the concentration of hydrogen in the gut. This favors the formation of $NH_4$, which is nonabsorbable, rather than $NH_3$. Through this mechanism, lactulose helps prevent the absorption of nitrogenous substances in the body. Rifaximin is another medication that can be used to treat hepatic encephalopathy.

**Benzoate Binds Amino Acid for Excretion**
Benzo-car with Amigo Acidic-lemon Leaving the Building
Benzoate can be used to help with ammonia excretion, as it binds to amino acids, leading to the excretion of nitrogen groups.

**Phenylbutyrate**
Phoenix-butt
Phenylbutyrate can be used to help with ammonia excretion, as it binds to amino acids and leads to the excretion of nitrogen groups.