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TYPE I CITRULLINEMIA: A REVIEW OF A RARE UREA CYCLE DISORDER AND APPROACH TO MANAGEMENT

Denise M. Kolanczyk,PharmD[1,2], Jenna Applegate, RD[3], Evelina Lin, PharmD[2], Allyson Wexler, PharmD[4], and Megan A. Rech, PharmD[2]

[1]Midwestern University, Department of Pharmacy Practice, Downers Grove, IL, USA, [2]Loyola University Medical Center, Department of Pharmacy, Maywood, IL, USA, [3]Loyola University Medical Center, Department of Clinical Nutrition, Maywood, IL, USA, [4] University of North Carolina Medical Center, Department of Pharmacy, Chapel Hill, NC, USA.

ABSTRACT

A 26-year-old female presented with acute signs and symptoms of hyperammonemia related to type I citrullinemia, a rare autosomal recessive urea cycle disorder that is diagnosed on a prenatal screen. It is caused by a mutation in the *ASS1* gene which impacts the urea cycle. Patients often present with altered mental status and other neurologic findings during periods of elevated ammonia levels. Treatment requires a multidisciplinary approach to create a specialized patient-specific plan. Diets are closely monitored with protein-intake restrictions to avoid hyperammonemia. Traditional medications used for hyperammonemia that reduce nitrogen generation and uptake, such as lactulose, have a limited role in this patient population. Arginine, sodium benzoate, and sodium phenylacetate/phenylbutyrate are used for nitrogen excretion. In patients who progress to liver failure or have symptoms that cannot be controlled through diet and medication, an orthotopic liver transplant is an option. It is imperative for health care professionals to understand the key concepts to therapy. The patient presented highlights the importance of communication between general health care disciplines and understanding core treatment

BACKGROUND

Citrullinemia is an autosomal recessive urea cycle disorder.[1] There are two types of citrullinemia that are caused by different mutations, but both result in accumulation of ammonia and glutamine.[2] Type I citrullinemia, also referred to as classic citrullinemia, is caused by a mutation in the *ASS1* gene.[3,4] Out of the two types, it is the most common and affects about 1 in 57,000 births and it can occur in all ethnic groups.[5] Type I citrullinemia usually presents within the first week of life. At birth, infants will appear normal, but as ammonia levels increase, infants will become lethargic and develop poor feeding habits. Vomiting, seizures, and a loss of consciousness are common. Increased intracranial pressure can also develop secondary to the hyperammonenmia and cause increased neuromuscular tone, spasticity, and ankle clonus. A milder form of type I citrullinemia may develop later in childhood or adulthood. Intense headaches, partial loss of vision, ataxia, and lethargy are commonly associated with later onset type I citrullinemia.[5] Type II citrullinemia, caused by a mutation in the *SLC25A13* gene, is predominantly found in the Japanese population, but has also been reported outside of East Asia.[2,6] Type II citrullinemia can be further classified into neonatal intrahepatic cholestasis caused by citrin deficiency, failure to thrive and dyslipidemia caused by citrin deficiency, and adult-onset type II citrullinemia (CTLN2).[1] The remainder of this article will focus on type I citrullinemia.

Since citrullinemia is rare, many health care providers may not be adequately trained or aware of acute management and nutrition. Symptoms may be mistaken for hepatic encephalopathy, and traditional management of hyperammonemia could potentially worsen a patient's clinical state. There are multiple case reports that describe presentations and management for both types of citrulliemia, but there is a lack of all-inclusive reviews that a health care provider may find useful when faced with managing such a rare disorder. This article introduces a patient case followed by a review of the pathophysiology, presentation, and nutrition and medication management of type I citrullinemia.

DATA SOURCES AND SELECTION

A literature search of PubMed (January 1, 1975 through January 31, 2018) was performed with the following terms: citrullinemia, type I citrullinemia, hyperammonemia, or urea cycle disorders. Additional references were identified from a review of literature citations. All English language case reports, reviews, and book chapters were included and reviewed for relevance.

CASE REPORT

A 26-year-old Caucasian female arrived at the emergency department due to increasing confusion, slurred speech, and difficulty walking. Her relevant past medical history included type I citrullinemia diagnosed on a prenatal screen (unknown reason for screening), C*lostridium difficile* infection, fungemia and pneumonia. Her family reported her current symptoms of altered mental status and gait changes were consistent with past episodes of high ammonia levels which they reported as being >100 mcg/dL. The patient acknowledged menstruation and infection as triggers for acute exacerbations of citrullinemia. She reported that her menses started 5 days prior to admission, and watery, green bowel movements had been occurring for more than 15 times a day for one week prior to admission. She also reported a mild headache and intermittent nausea. The patient denied cough, shortness of breath, neck stiffness, dysuria, and hematuria. Her routine medications included arginine, buphenyl, isoleucine, leucine, L-valine, sodium benzoate and valerian. The patient acknowledged compliance and adherence with her home medication regimen, which was frequently adjusted by her geneticist. Her weight on presentation was 102.8 kg and height was 5 feet and 2.75 inches (1.59 meters). Initial vital signs included the following: blood pressure 127/71 mmHg, heart rate 86 beats per minute, respiratory rate 18 breaths per minute and body temperature 36.7° C. Significant laboratory findings on arrival included an ammonia level of 104 µg/dL (reference range 19-60 µg/dL). A glutamine level was not obtained on presentation or throughout the course of the hospitalization. Additional laboratory values included a slightly elevated aspartate transaminase (AST) of 64 IU/L and alanine transaminase (ALT) of 79 IU/L. Other liver function tests were within normal limits. Blood and stool cultures were obtained based on the patient's medical history and acute presentation. The physical exam was positive for altered mental status. Her neurologic exam revealed cranial nerves II-XII were grossly intact, no focal deficits, no asterixis or tremor, and strength 5/5 for both upper and lower extremities. Her retinal exam was within normal limits. Due to improvements after optimizing her nutrition and medications, a CT or MRI of the brain was never obtained during the hospitalization.

In regards to the patient's history of type I citrullinemia, records from infancy were limited. She was delivered at term weighing 7 pounds, 5 ounces, but was hospitalized for four weeks due to complications resulting from type I citrullinemia. She first presented to our institution during her teenage years with a complaint of foot pain and gait issues. Since that initial presentation, there are other documented periods of hyperammonemia. Management of her type I citrullinemia was primarily done at another medical center. As a result, further details such as knowing the mutation of her *ASS* gene were not available to review.

The patient was admitted to the general medicine service. Initial management involved optimization of the patient's home medication regimen in consultation with the patient's geneticist. The patient was given arginine 12.6 g every 30 minutes for four doses, buphenyl 2.37 g every 30 minutes for three doses, and sodium benzoate 5 g every 30 minutes for two doses to complete a total daily dose of 20 g. All medications were administered through a gastrostomy tube (GT). A repeat ammonia level, drawn approximately six hours following medication administration, was 164 µg/dL. Further management of the patient's hyperammonemia required increasing the intensity of the regimen. Intravenous arginine was initiated with a loading dose of 25 g/L of dextrose 10% over 3 hours, followed by arginine IV 50 g/L of dextrose 10% over 24 hours (83 mL/hr). Buphenyl 4.74 g was given every 30 minutes for two doses, followed by 3.16 g every 3 hours. Sodium benzoate 5 g every 30 minutes for two doses was given, followed by 2.5 g every 3 hours. A basic metabolic panel along with an ammonia level was checked every six hours during treatment to monitor for hypochloremia and hypokalemia.

The patient was dependent on receiving most of her nutrition via GT. Her home feedings provided 15.5 gm of protein and approximately 1650 kilocalories. Throughout this acute episode, the patient was kept on a protein-restricted diet with up to 2 grams of protein per meal. Home GT feeds were continued throughout the hospitalization. Tube feed regimen and protein requirements were adjusted based on laboratory findings by the patient's primary dietitian. Prior to admission the patient was also receiving valine, isoleucine and leucine in tube feeds, but these amino acids were held while inpatient. The patient's obesity and chronic nutritional management was not addressed during the admission. **Table 1** provides details on nutrition and medication management throughout her hospitalization.

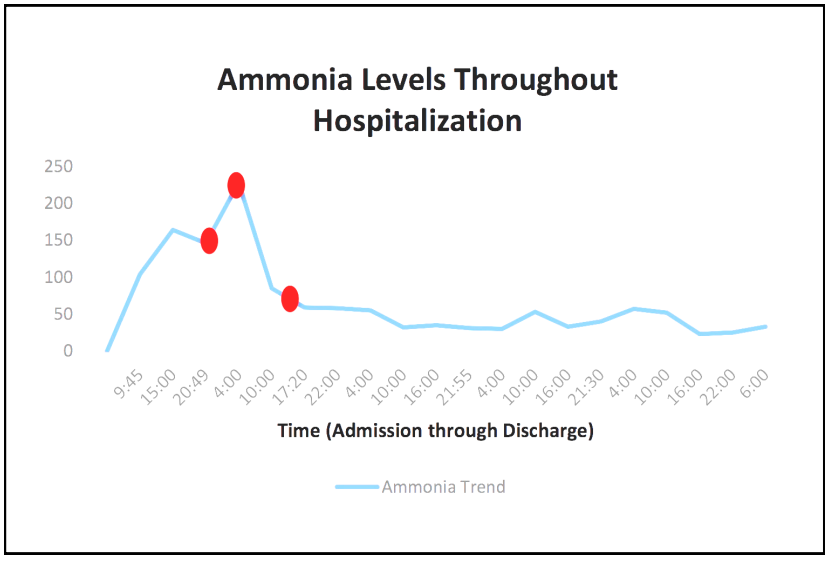
Table 1. Nutrition and Medication Therapies

Tube Feed Regimen	Initial Medication Regimen	Adjusted Medication Regimen
Anamex 0.5 cups **Prophree** 1.5 cups **Solcarb** 1.25 cups **Water** 41 ounces Total tube feed regimen= 50 ounces Run at 62 mL/hour **Calories:** 1653 **Protein**: 15.5 grams	**Arginine (GT)** 12.6 grams every 30 minutes for four doses **Buphenyl (GT)** 2.37 grams every 30 minutes for three doses **Sodium benzoate (GT)** 5 grams for four doses	**Arginine (IV)** *Loading dose:* 25 grams/Liter of Dextrose 10% over 3 hours *Maintenance:* 50 grams in Dextrose 10% over 24 hours. **Buphenyl (GT)** 4.74 grams every 30 min for two doses, then 3.16 grams every 3 hours **Sodium benzoate (GT)** 5 grams every 30 min for two doses, then 2.5 grams every 3 hours

GT= gastrostomy tube; IV= intravenous

Ammonia levels continued to rise and peaked overnight at 228 µg/dL. **Figure 1** demonstrates the change in ammonia levels coupled with changes to medication management. The patient's mental status remained altered, which primarily consisted of slow mentation and speech. The arginine rate was then increased to 100 mL/hr to provide 60 g daily. An improvement in mental status was observed. The following day, the dose was decreased to 1.625 g/hr. Arginine powder 3.15 g was added every three hours and titrated up as the rate of the intravenous arginine was decreased. The buphenyl dose was increased to 4.74 g every three hours and the dose of sodium benzoate remained at 2.5 g every 3 hours. Within 48 hours, the ammonia level normalized to 32 µg/dL. The patient was discharged due to improvements in her mental status and bowel movements, and ammonia levels were within normal limits.

Figure 1. Ammonia Levels Throughout Hospitalization



Legend: Points on the graph indicate changes to drug therapy. The last data point demonstrates the time at which doses of intravenous arginine began to decrease and was tapered off.

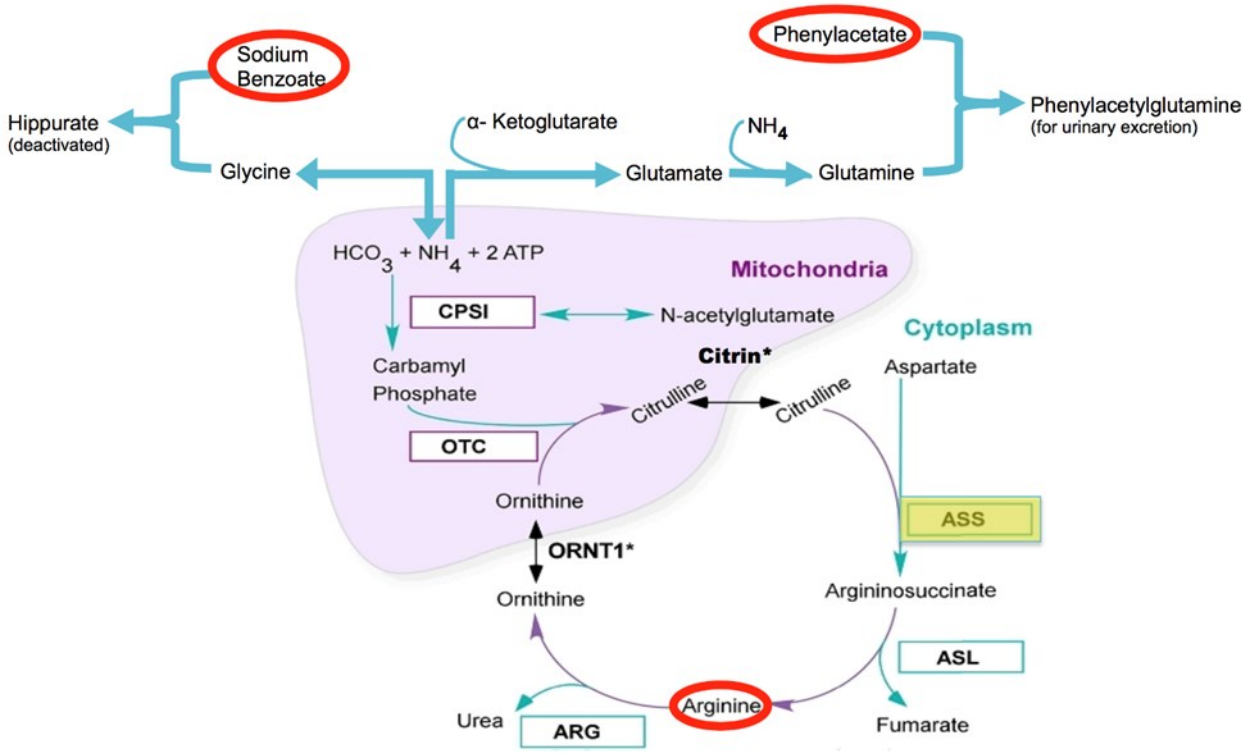
PATHOPHYSIOLOGY

The urea cycle primarily functions to remove nitrogen waste by hepatic conversion of nitrogen to urea.[7] Nitrogen results from the hydrolysis of dietary protein sources and catabolic processes in body tissues (skeletal muscle, liver and brain). Only a small portion of nitrogen is re-incorporated by the body for further use. The remainder is considered waste and is excreted into the urine as water-soluble urea and ammonia. For each cycle turn, two moles of nitrogen are converted into urea: one mole from ammonia and one mole from aspartate.[7]

The entirety of the urea cycle is located on the surface of periportal hepatocytes and requires the major roles of six enzymes and two transporters, as shown in **Figure 2**.[7-9] The six enzymes include one co-factor producing enzyme: N-acetylglutamate synthetase, and five catalytic enzymes: carbamoylphosphate synthetase 1, ornithine transcarbamylase, argininosuccinic acid synthetase, argininosuccinic acid lyase and arginase 1.[7,8] The two transporters are ornithine translocase and aspartate-glutamate solute carrier protein (citrin). The transporters provide shuttling of substrates to the urea cycle.[7]

Activation of the urea cycle occurs when there is an increased nitrogen load. Ammonia and bicarbonate are irreversibly converted into carbamoylphosphate by carbamoylphosphate synthetase 1 in the mitochondria. Carbamoylphosphate synthetase 1 activity is dependent on co-factor N-acetylglutamate formation, which is generated by N-acetylglutamate synthetase catalyzing glutamate and acetyl coenzyme A. Ornithine transcarbamylase proceeds to work on carbamoylphosphate and ornithine to form citrulline in the mitochondria. In order for ornithine to travel from the cytosol into the mitochondria, the transporter

Figure 2. Alternative Treatment Pathways to Eliminate Nitrogen in Type I Citrullinemia.[8]



Legend: Use of arginine, sodium benzoate and/or sodium phenylacetate serve as nitrogen scavenger therapies in order for the urea cycle to resume normal regulation. ARG, arginase 1; ASL, argininosuccinate lyase; ASS, argininosuccinic acid synthetase; Citrin, aspartate-glutamate solute carrier protein transporter; CPS1, carbamoylphosphate synthetase 1; ORNT1, ornithine translocase transporter; OTC, ornithine transcarbamylase. Adapted with permission from GeneReviews® and modified by authors.

ornithine translocase exchanges ornithine with citrulline. Therefore, citrulline is able to leave the mitochondria to the cytosol and participate in the distal portion of the urea cycle.[7,9]

The remaining three major enzymatic reactions involving argininosuccinic acid synthetase, argininosuccinic acid lyase and arginase 1 occur in the cytosol to assist with regulating amino acid exchange.[9] In the cytosol, intramitochondrial aspartate, a substrate for argininosuccinic acid synthetase, is transported via the citrin transporter in exchange for glutamate. Argininosuccinic acid synthetase combines aspartate with citrulline to form argininosuccinate. Argininosuccinic acid lyase hydrolyzes argininosuccinic acid synthetase to arginine and fumarate.[10] Arginase 1 acts on arginine to release urea and regenerate ornithine. Ultimately, urea is dissolved into the blood and excreted by the kidney as urine.

Type I citrullinemia (also known as argininosuccinate synthetase deficiency or argininosuccinic acid synthetase deficiency) occurs from a chromosomal defect on 9q34.11, originating from the gene encoding argininosuccinic acid synthetase.[5,10] The defect affects the distal portion of the urea cycle due to the absence of argininosuccinic acid, ensuing in a decline of arginine production and thereby impairing ornithine and citrulline substrate exchange. Resultant accumulation of citrulline is a notable laboratory finding, while arginine and ornithine may be within low to normal range. Accumulation of ammonia and glutamine may manifest as altered mental status. Other findings may include low serum urea nitrogen.[9]

PRESENTATION

Enzymatic defects in the urea cycle result in arginine becoming an essential amino acid (except in arginase deficiency where arginine is not essential).[10] Patients will have an elevated baseline citrulline level along with frequent episodes of hyperammonemia.[11]

It is critical to diagnose the root cause of hyperammonemia as it may be due to a urea cycle disorder, organic academia, or drug-induced. Miscellaneous causes of hyperammonemia include hypoglycin intoxication, pregnancy, distal renal tubule acidosis, carnitine transport defects, urinary tract dilatation, and Reye's syndrome.[10] In order to differentiate between the various urea cycle disorders, plasma levels of amino acids can be used to assist in diagnosis.[10] Common findings of citrullinemia include hyperammonemia and low serum urea nitrogen and arginine levels. Ammonia levels in these patients can be significantly elevated. One retrospective study noted that patients with ammonia levels greater than 300 mmol/L at the time of presentation or with a peak ammonia level above 480 mmol/L were unlikely to have complete cognitive recovery.[12] Elevated plasma citrulline in the absence of argininosuccinic acid synthetase confirms this diagnosis.[10]

Symptoms tend to vary with patient age, ammonia level and may include a variety of findings.[10] Most patients with urea cycle disorders present during the neonatal period with nonspecific symptoms such as poor feeding, vomiting, somnolence, irritability, tachypnea, and progressive lethargy secondary to hyperammonemia.[10,12] Newborns may also present with increased intracranial pressure as a result of hyperammonemia and have an increase in neuromuscular tone, spasticity, and ankle clonus.[5]

Patients with type I citrullinemia will present with common symptoms such as encephalopathy, hypotonia, vomiting, lethargy, seizures, coma, ataxia, anorexia, abnormal behavior patterns, dysarthria, weakness, liver enlargement and dementia at the time of diagnosis and during acute exacerbations.[10] Although feeding intolerance is present in these patients, weight gain and obesity are possible due to a high calorie and low protein diet.[10] Ammonia and glutamine have shown to have neurotoxic effects, which can ultimately lead to cerebral edema and cell death.[12]

MANAGEMENT

Patients with type I citrullinemia must vigilantly monitor nutritional intake and pharmacologic therapies in order to avoid hyperammonemic exacerbations and long-term consequences such as mental retardation, delayed growth and seizures.[13] Treatment requires a multidisciplinary approach between geneticists, pediatricians, neurologists, dietitians and metabolism departments to create a specialized patient-specific plan.[5] Treatment includes a protein-restricted diet, and medications that increase nitrogen excretion. These include arginine, sodium benzoate, sodium phenylbutyrate and sodium pyruvate.[14] Early identification and treatment of citrullinemia is essential in order to prevent long-term neurologic sequelae.[15]

General Nutrition Management

A Western diet consists of more protein than what can be used for growth and development. Excess nitrogenous waste is eliminated mostly in the form of urea.[16] In citrullinemia, patients cannot process urea.[17] This results in an accumulation of nitrogenous compounds, namely glutamine and ammonia, leading to exacerbations.[17] A protein-restricted diet, limited to only what is necessary for growth and maintenance of physiologic processes, is necessary to avoid overproduction of waste in patients with citrullinemia. This can be difficult to adhere to as protein requirements change depending on phases of growth, age and state of health.[16] Close clinical and laboratory monitoring is necessary for individual nutrition management.[18]

General recommendations for dietary protein intake vary by age and developmental growth factors, with typically higher weight-based protein needs for earlier stages of life.[16,19] It is important to achieve and maintain positive nitrogen balance through nutrition management, particularly in the growth and development stages of life, to prevent protein catabolism.[19]

Providing adequate calories is also important to prevent catabolism, poor growth and development, and weight loss.[18,20] Calorie needs will vary on an individual basis, but a general recommendation is to aim for a calorie intake of 5-10% above the recommended daily allowance for age and gender.

Essential amino acids should make up 50-60% of daily protein intake and is often achieved through supplementation via medical foods.[19] Essential amino acids will provide some nitrogen, however the overall nitrogen load delivered to the urea cycle is reduced.[21] Adequate hydration is also necessary to excrete metabolic waste.[19] To meet minimum fluid needs, recommendations for adults include 1.5 mL/kcal or 1-1.5 times the amount of maintenance fluids. In some cases, GTs are placed to improve dietary compliance via enteral nutrition.[19]

Acute Nutrition Management

Establishing a sick-day nutrition plan can help prevent catabolism or a hyperammonemic event.[19] Precipitating factors include menarche, menses, pregnancy, childbirth, postpartum and menopause. Additionally, immunizations, infection, trauma, surgery, chemotherapy and glucocorticoids can precipitate hyperammonemic events. Some patients may require up to a 50% increase in calories provided by non-protein sources. A stricter protein restriction compared to baseline may also be necessary for the first 24-48 hours of illness, and some cases may require complete cessation of protein during this time period.[18,19] Inadequate calories and protein intake for greater than 48 hours may result in rebound hyperammonemia due to protein catabolism; therefore, withholding nutrition for longer than 24-48 hours should be avoided.[8,18] Fluid requirements may also be higher and may require a 150% increase during illness.[19] In the event a patient requires prolonged fasting for surgery or illness, intravenous maintenance fluids, glucose and electrolyte supplementation is recommended to prevent catabolism and hyperammonemia.[18]

Nitrogen-Scavenging Therapy

Pharmacologic treatments are aimed at enhancing nitrogen excretion in type I citrullinemia, and maintaining plasma ammonia concentration <100 µmol/L and plasma glutamine concentration near-normal.[22] Nitrogen-scavenging agents provide an alternative route for nitrogen excretions through conjugation with amino acids, thus decreasing the concentrations and preventing accumulation of nitrogenous waste.[23,24]

Arginine has been shown to be an indispensable amino acid, though its mechanism is not fully elucidated.[17] In other urea cycle disorders, it works by facilitating excretion of nitrogen as L-citrulline and argininosuccinate, which restores the ammonia-lowering activity of the urea cycle.[25] It effectively reduces ammonia and glutamine concentrations in citrullinemia.[5,22]

Sodium benzoate couples with coenzyme A (CoA) to form benzoyl-CoA. The benzoyl moiety is transferred to glycine forming hippurate, which prevents its degradation. Glycine is an ammonia-forming amino acid; thus, sodium benzoate enhances elimination of ammonia.[25,26] In combination with sodium phenylacetate it decreases plasma ammonia levels and contributes to high survival rates in acutely hyperammonemic patients.[27] It has a favorable adverse effects profile, with the most common being nausea and headache.[28]

Similar to sodium benzoate, sodium phenylacetate creates an alternative pathway for nitrogen excretion. It is β-oxidized by phenylacetyl-CoA ligase to phenylacetate CoA, which conjugates glutamine in the liver and kidneys to form phenylacetylglutamine, which is then is excreted in the urine.[25,27,29]

Phenylbutyrate is an odorless pro-drug of phenylacetate that rapidly undergoes β-oxidation in the liver to

phenylacetate.[30] These agents may offer an advantage over sodium benzoate in that they can scavenge twice as much nitrogen, though comparative clinical trials are limited.[24,31] According to consensus guidelines, sodium benzoate should be used preferentially and sodium phenylacetate/phenylbuterate should be given together with sodium benzoate in patients in which benzoate alone is not enough.[24]

One issue with taking the oral formulation sodium phenylacetate or sodium phenylbuterate is palatability.[32] Sodium phenylacetate had an offensive odor that limits use. Though sodium phenylbuterate is odorless, it is reported to have a bitter or salty taste, and therefore a newer formulation was developed to mask the taste through microgranular sucrose spheres (Pheburane®).[24,32] Finally, glycerol phenylbutyrate is an ester pro-drug of phenylbutyrate that is slowly hydrolyzed by pancreatic enzymes and is considered a more palatable and less odorous option.[25] Glycerol phenylbutyrate should also be considered in hypertensive patients as it contains much less sodium than the other agents.[33] Dosing for these agents are displayed in **Table 2**.[5,22,24]

Reducing Nitrogen Generation and Uptake

There is limited data supporting typical interventions for hyperammonemia secondary to hepatic failure, most of which are case reports with variable results. However, others have reported success with lactulose in combination with a protein restricted diet and arginine.[34,35] Whether the lactulose was beneficial in addition to protein restriction has yet to be determined. Lactulose is a non-absorbable disaccharide that acidifies the proximal gastrointestinal tract, which harms urease-producing bacteria and decreases absorption of ammonia.[25] Antimicrobial therapies, such as rifaximin, neomycin or kanamycin, also target urease-producing bacteria and limit intestinal ammonia production.[25] These therapies may be considered as adjunctive agents, but therapy should target the pathology of citrullinemia.

Liver Transplantation

In patients whose symptoms cannot be controlled by diet, those with life-threatening complications, or progressive liver disease, orthotopic liver transplantation (OLT) is a treatment option.[36] The liver is the primary site of urea cycle activity. As such, OLT generally results in metabolic correction of urea cycle pathology, allowing for cessation of diet precautions and supplementation, and is the only curative intervention available.[37-39]
Further neurologic degradation is prevented and improvement in neurologic deficit may be observed, particularly with early transplantation.[36,38] A case series of five children less than one year found modest improvement in neurological development after OLT.[38] A 14-year-old female was found to have increased intellectual capacity after OLT.[37] However, in a case series of 16 patients with urea cycle disorders, of which 3 had citrullinemia, neurological outcome after

Table 2. Treatment of Type I Citrullinemia[5,20,23,25]

Nutrition Management	Recommendations
Calories	RDA for age/gender + 5-10%
Protein	Limited to what is physiologically necessary; changes with age and development; majority should come from essential amino acids
Fluids	1.5 mL fluid/kg
Agent	**Regimen**
Nitrogen Scavengers	
Arginine	9-12 grams per day or 400-700 mg/kg divided into three doses with meals (Maximum: 6 grams/day)
Sodium benzoate	≤ 250mg/kg/day divided into three doses with meals (Maximum: 12g/day)
Sodium phenylacetate or sodium phenylbutyrate	450-600 mg/kg/day or 5g/m2/day divided into three doses with meals (Maximum: 12g/day)
Glycerol phenylbutyrate	Phenylbutyrate-naïve: 4.5-11.2 mL/m2/day (5-12.4 g/m2/day) divided into three doses with meals Conversion from sodium phenylbutyrate: daily dose of glycerol phenylbutyrate (mL) = daily dose of sodium phenylbutyrate (g) x 0.86

RDA= recommended daily allowance

transplantation correlated closely with baseline status prior to transplantation.[40] Overall, outcomes in OLT patients with inherited metabolic disease are consistently more favorable than in patients with primary liver disease.[36] However, given the lifelong commitment to immunosuppressive therapies and complications associated with OLT, this pathway should be avoided unless the patient has failed medical management.

Acute Decompensation

All patients with citrullinemia are at risk of acute decompensation from metabolic stress. Exacerbating factors include fasting, acute illness, particularly gastroenteritis, anesthesia and protein load such as gastrointestinal hemorrhage.[36] Patients should have an emergency regimen including a high-energy, low protein diet and increased doses of arginine and sodium benzoate. Ammonul® is a combination product of 10% sodium benzoate and 10% sodium phenylacetate that is FDA-approved as an adjuvant in treatment of hyperammonemic episodes.[25] Consultation with the patient's geneticist should be considered in the event of acute decompensation. Measures should be taken to decrease ammonia serum concentrations, prevent reversal of catabolism, and avoid increased intracranial pressure. The doses recommended for acute decompensation are displayed in **Table 3.**[5,41]

Hemodialysis (HD) is the most effective measure for rapid removal of ammonia and should not be delayed when scavenger therapies fail to control ammonia levels.[5] Detoxification of ammonia occurs through synthesis of urea and glutamine, of which ~20% is excreted renally.[42] Currently the preferred renal replacement modality for ammonia removal and clinically significant time at which dialysis should be initiated is unknown.[43] Both intermittent HD and continuous venovenous hemofiltration (CVVH) effectively reduce ammonia, but differ in the rate of removal.[42-44] Intermittent HD removes 50% of ammonia within 2 hours, while CVVH takes up to 15 hours.[45] The goal of therapy should be to achieve resolution of symptoms associated with hyperammonemia.

CONCLUSION

Though citrullinemia is a rare urea cycle disorder, it is essential to understand the pathophysiology for proper management. Providing protein restricted diets and selecting medications that enhance nitrogen excretion are key therapy concepts. Consultation with providers who specialize in urea cycle disorders should be considered to assist in both acute and chronic management.

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Table 3. Treatment of Acute Decompensation.[5,42]

Agent	Regimen
10% arginine hydrochloride	600 mg/kg or 12.0 g/m^2 over 90 minutes, then 600 mg/kg or 12.0 g/m^2 over 24 hours
Sodium benzoate	250 mg/kg or 5.5 g/m^2 over 90 minutes, then 250 mg/kg or 5.5 g/m^2 over 24 hours
Sodium phenylacetate (in combination with sodium benzoate)	250 mg/kg or 5.5 g/m^2 over 90 minutes, then 250 mg/kg or 5.5 g/m^2 over 24 hours

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Corresponding Author

Denise M. Kolanczyk
555 31st Street
Downers Grove, IL 60515
Phone: 630-515-6204
Fax: 630-515-6958