JPPT | Review

An Introduction to Pharmacotherapy for Inborn Errors of Metabolism

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Inborn errors of metabolism comprise a wide array of diseases and complications in the pediatric patient. The rarity of these disorders limits the ability to conduct and review robust literature regarding the disease states, mechanisms of dysfunction, treatments, and outcomes. Often, treatment plans will be based on the pathophysiology associated with the disorder and theoretical agents that may be involved in the metabolic process. Medication therapies usually consist of natural or herbal products. Established efficacious pediatric doses for these products are difficult to find in tertiary resources, and adverse effects are routinely limited to single case reports. This review article attempts to summarize some of the more common inborn errors of metabolism in a manner that is applicable to pharmacists who will provide care for these patients.

ABBREVIATIONS ATP, adenosine triphosphate; CoA, coenzyme A; IEM, inborn error of metabolism; MCAD, medium chain acyl CoA dehydrogenase deficiency; NADH, reduced nicotinamide adenine dinucleotide

KEYWORDS dietary supplements; drug therapy; inborn errors; metabolism; review

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Introduction

Inborn errors of metabolism (IEMs) were first described in 1908 and have subsequently grown to more than 1400 different diagnoses described in the literature.[1,2] As the means to identify these disorders has improved, the number of patients receiving a diagnosis of IEM has increased. Each individual disease state is rare, but the combined risk for any form of IEM may be as common as 1 in 800 to 2500 patients.[3,4] Inborn errors of metabolism can occur in almost any metabolic pathway, including carbohydrate, phospholipid, or amino acid production or metabolism. Other energy production pathways may be affected as well, including the citric acid cycle, the electron transport chain, or the production or use of various coenzymes and vitamins. These errors result in substrate accumulation, metabolite accumulation, enzyme deficiency, energy steal, or molecular accumulation, which in turn results in the symptoms associated with IEM.[1,3]

Metabolic errors may present with an array of symptoms. Signs and symptoms of IEM are often non-specific and include a sepsis-like presentation, lethargy, vomiting, acidosis, and developmental delay.[4] Acute and chronic presentations may differ. Initial acute episodes may be life-threatening if not adequately treated and present with acute neurologic changes, metabolic crisis, and death, whereas chronic symptoms, such as poor growth and development, may be more manageable. The non-specific nature of these sequelae results in the treatment of several diagnoses at the same time. Thus, multiple medications may be started around the same time and the elucidation of which agent resulted in benefit is difficult to determine. This may exacerbate the condition of the patient. For example, the patient who has been unable to receive adequate enteral nutrition may be initiated on parenteral nutrition. Situations in which the metabolic disorder lies within lipid or amino acid metabolism can result in sequelae and contribute to the complications the patient is experiencing. The ability of the pharmacist to curtail the medication cocktail is limited until a diagnosis is established. An understanding of each disease state may help the pharmacist to make appropriate recommendations and minimize polypharmacy once a diagnosis has been established.

Diagnosis may be prolonged because a multitude of laboratory assessments will need to be evaluated. Most institutions are unable to perform the specific laboratory analysis for IEM. This results in a delay in disease identification as samples are sent for testing. Large blood volumes are required to provide a complete definitive diagnosis. The amount of blood necessary will be dependent on the patient's presentation and differential diagnosis. However, in an effort to avoid diagnostic phlebotomy, only a few lab tests may be drawn each day. Depending on patient status, only the most likely tests or those with lower blood volumes may be sent. Some institutions may not have a genetic specialist within the organization. Thus, additional time may be needed to transmit the information to a genetic specialist and receive a response. Genetic variation can lead to a wide range of symptoms within a single IEM, further complicating the ability to accurately diagnose and to promptly treat.

Institutional policies may also result in a delay in therapy. Medication therapy used in IEM often consists

of nutritional or herbal supplements or medications that an institution may not routinely carry. Such therapies may be considered non-formulary, requiring further efforts or time to obtain. Institutional policies may label nutritional and herbal supplements as banned substances because of the lack of primary evidence or concern that the US Food and Drug Administration oversight regarding these agents is not as robust as that for prescription medications. Therefore, the likelihood that a pharmacist will assist in caring for these patients is expanding.

Understanding IEM can provide the pharmacist with ample opportunities to impact the care of the patient with a metabolic disorder. The pharmacist can play a critical role in providing care for these patients. This may range from counseling patients and families, providing dosing information to prescribers, assisting the prescriber and family in brand or medication selection, providing inpatient rounding services, and acquiring the needed medications if not available because of formulary restrictions or lack of availability via the wholesaler. The purpose of this review is to provide the pharmacist with an overview of several IEMs, the rationale for using a particular medication, and important pharmacotherapeutic information regarding each agent. This review will not be all-encompassing but should provide the reader with a better understanding of IEM and its medication management. Figures of the metabolic pathways are not provided, but a review of them will greatly help the reader understand the metabolic abnormality, potential symptoms of each disorder, and the rationale for the use of herbal and nutritional supplements.

Errors in Carbohydrate Metabolism

Carbohydrate Metabolism. Carbohydrate metabolism via monosaccharides provides cells with a source of energy as well as a methodology for energy storage. Most organisms use glycolysis in some fashion as a means of energy production.[5] The metabolism of glucose, dextrose, fructose, or mannose initially requires phosphorylation via a molecule of adenosine triphosphate (ATP) and a hexokinase.[6] Phosphofructokinase-1 then phosphorylates glucose once again in preparation for cleavage by aldolase. Once cleaved, the 2 new molecules of glyceraldehyde-3-phosphate can progress through carbohydrate metabolic processes. The metabolic process results in a net gain of 2 molecules of ATP and 4 molecules of reduced nicotinamide adenine dinucleotide (NADH). This process also generates acetyl–coenzyme A (acetyl-CoA) from pyruvate via pyruvate dehydrogenase, which is a vital source for energy production. The enzymatic reactions involved in phosphorylation are irreversible; however, alternative enzymatic processes can recreate the metabolic precursor and allow for gluconeogenesis.

Galactose metabolism begins with a phosphorylation step as well; however, the process results in the formation of uridine diphosphate glucose. Uridine diphosphate glucose can then be transformed in 2 ways. The first is conversion to glucose-1-phosphate, which will then enter carbohydrate metabolism and follow a pathway similar to that described above. The second is via glycogen synthase, which results in the creation of glycogen. Glycogen provides a means to store glucose for future energy need during periods of fasting. The overall process is regulated via substrates, metabolites, and enzymes, along with hormones such as insulin, to ensure that glycolysis, glycogenesis, and glycogenolysis are being adequately maintained.

Carbohydrate Metabolism Dysfunction and Treatment. Given the sheer number of reactions in the metabolic pathways described above, the potential for error is significant. Several IEMs have been identified in carbohydrate metabolism and may affect the ability to break down monosaccharides, such as fructose and galactose, into pyruvate precursors. For example, a patient with aldose B deficiency or hereditary fructose intolerance accumulates fructose-1-phosphate, resulting in corresponding symptoms.[7] The patient may present with vomiting, hypoglycemia, abdominal pain, lethargy, convulsions, jaundice, and hepatomegaly.[8] If the disease is not identified in a timely manner, the patient will continue to experience hypoglycemic events and eventually progress to hepatic failure, renal failure, and death. Symptoms and complications of hereditary fructose intolerance can be avoided by restricting dietary intake of fructose.[7,9] Galactose-1-phosphate uridyl transferase deficiency, or galactosemia, will cause accumulation of galactose-1-phosphate, which may result in symptoms similar to those of hereditary fructose deficiency. In addition, patients with galactosemia may develop cataracts, intellectual disability, verbal dyspraxia, hypergonadic hypogonadism, increased risk for *Escherichia coli* sepsis, and coagulopathies.[10,11] Avoidance of lactose and galactose is the mainstay of treatment. Rapid identification and dietary restrictions for galactosemia can reverse some of the complications and prevent intellectual disability.

A defect in the pyruvate dehydrogenase complex can result in a wide spectrum of dysfunctions ranging from ataxia to death.[12] Neonates may present more severely, with a profound lactic acidosis and eventual progression to encephalopathy and/or death. Those who present within the first few months of life may have psychomotor retardation and significant lactic acidosis. Patients who present at an older age may retain some enzymatic activity and have less severe complications. In rare cases, pyruvate dehydrogenase complex deficiency may be caused by a mutation that alters the affinity for thiamine phyrophosphate, a coenzyme in the metabolic process that may help facilitate normal function and minimize toxic metabolites.[13] Because of this, thiamine is routinely supplemented when pyruvate

dehydrogenase complex deficiency is part of the differential diagnosis. Thiamine may be initiated at a dose of 5 to 50 mg/kg/day based on response, physician preference, and adverse effects (Table 1).[14–16]

Alternatively, dysfunction in the pyruvate carboxylase enzyme may be due to defects in the metabolic processes that create biotin, a necessary coenzyme for the reaction. A dysfunction in biotin production results in multiple carboxylase deficiency and poor function in all carboxylation reactions. Pyruvate carboxylase deficiency and multiple carboxylase deficiency can range from mild to severe and can include lactic acidosis, ketoacidosis, hyperammonemia, organic acidurias, ataxia, motor deficits, neurologic deficits, and death.[68] Biotin stores can be depleted over time by inadequate consumption and absorption. Subsequent supplementation with biotin can be initiated and is generally well tolerated. More information regarding biotin pharmacotherapy can be found in Table 1.

Metabolic errors can impair pathways for energy storage or glucose regeneration. Twelve different glycogen storage diseases have been identified that prevent glycogenolysis and affect glycogen quality, quantity, or both.[69] One of these storage diseases, type II glycogen storage disease, or Pompe disease, is caused by a defect in the lysosomal α-1,4-glucosidase, thus preventing the release of glucose-1-phosphate from glycogen macromolecules in the lysosomes. This disease state results in glycogen accumulation in muscle tissues, and subsequently hypotonia similar to that of muscular dystrophies.[70] Additional complications include feeding difficulties, hypertrophic cardiomyopathy, hepatomegaly, and cardiorespiratory failure. Interestingly, Pompe disease does not present with hypoglycemia, because cytoplasmic glycogen metabolism remains unaffected.[71]

Recently, increased research and drug development for novel therapies has resulted in the creation of several recombinant enzymes for patients with an IEM. A recombinant enzyme has been engineered for Pompe disease. Recombinant therapy may help stabilize the deterioration associated with Pompe disease by improving motor function and preventing pulmonary dysfunction.[72] Other recombinant enzymes have been developed for Fabry disease, Gaucher disease, and various mucopolysaccharidoses. Most of the recombinant enzymes are derived from a Chinese hamster ovary cell line. Thus, the most common adverse medication events are infusion related, such as tachypnea, rash, flushing, urticaria, agitation, rigors, and tachycardia. Antibody development is quite common, and many patients will develop immunoglobin G to these enzymes. This may result in anaphylaxis or a decreased therapeutic response to these agents.[70] Table 2 lists several recombinant enzymes that are used to treat various IEMs, along with each enzyme's indication, dose, and common adverse events. These products are all given via intravenous infusion every 1 to 2 weeks. Given the concern for anaphylactic reactions, the patient must make routine trips to an acute care center or outpatient infusion center to receive their therapy. The method of obtaining the enzymes will depend on the insurer and may require that the product be obtained from the manufacturer. Initiation of enzyme replacement therapy may be delayed while issues around documentation, medication transport, and insurance coverage are addressed.

Errors in Lipid Metabolism

Fatty Acid Metabolism. Fatty acids provide a vital and efficient source of energy for cells. Most fatty acids are obtained through the diet and used for energy or phospholipid production, stored for later use, or converted into bile acids. As with carbohydrate metabolism, hormones and catecholamines play integral roles in determining the ultimate fate of the fatty acid.

A wide variety of fatty acids exist, and fatty acid composition is dependent on carbon chain length, the number of double bonds, and the position of the double bonds in the chain. Despite this, the metabolic processes that fatty acids undergo follow a similar pathway. All fatty acid metabolism begins by activation via acyl CoA synthetase in the outer mitochondrial membrane. The fatty acid molecule binds with CoA to form an acyl CoA molecule. The acyl CoA then combines with carnitine to enter into the inner mitochondrial membrane for metabolism. Carnitine acyltransferase-I facilitates the binding of acyl CoA in the outer mitochondrial membrane, whereas carnitine acyltransferase-II frees the carnitine molecule in the inner mitochondrial membrane for further acyl CoA metabolism. Various subtypes of carnitine acyltransferase exist, and the type used is dependent on the type of the fatty acid.

The acyl CoA molecule is then oxidized to generate acetyl-CoA for energy production. A major enzyme responsible for this reaction is acyl-CoA dehydrogenase. Much like acyltransferase, there are several subtypes, and the structure of the fatty acid determines which enzyme will continue the metabolic process. After this step, further metabolism results in the release of 1 molecule of acetyl-CoA and an acyl CoA shortened by 2 carbon groups. Eventually, only a 4- or 5-carbon chain will remain. An additional cycle will produce either 2 molecules of acetyl-CoA or a molecule of acetyl-CoA and propionyl-CoA, depending on the remaining length of the carbon chain.[5]

This process results in the creation of an acetyl-CoA which is a 2-carbon chain. This is known as β-oxidation because the last 2 carbon atoms are cleaved from the fatty acid chain. Fatty acid metabolism can be accomplished via several different mechanisms, such as α-, β-, or ω- oxidation. α-Oxidation results in the shortening of the fatty acid chain via 1 carbon group. β-Oxidation as described is the primary mechanism of fatty acid metabolism in humans. ω-Oxidation results in the ter-

Table 1. Medications Used in Select Inborn Errors of Metabolism (IEMs)

Medication	IEM	Formulations	Initial Dose	Dose Range	FDA Status	Adverse Effects	Additional Pearls
Arginine	Urea cycle disorders (not arginase deficiency)	IV Oral powder	200–600 mg/kg load	200–600 mg/kg/day infusion[17,18] 170–700 mg/kg/day	Drug Supp	Hyperkalemia, hyperchloremia, extravasation, flushing, hypotension, HA, nausea, vomiting, cerebral edema, metabolic acidosis[19,20]	Contraindicated in arginase deficiency;[21] not effective when hyperammonia is 2° to organic acidemias
Ascorbic acid (vitamin C)	Glutathione synthetase deficiency Hawkinsuria Tyrosinemia type III[22]	Capsules, tablets, powders, oral liquid, IV	100 mg	15–25 mg/kg/day (2 g/day max)[23]	Drug	HA, insomnia, GI upset, hyperglycemia, nephrolithiasis, iron overload, zinc deficiency, copper deficiency[24,25]	Pediatric adverse effects may be limited to patients with renal dysfunction or those receiving very high doses[25,26]
Betaine	Homocystinuria	Powder for reconstitution	50 mg/kg/day[27]	50–250 mg/kg/day (20 g/day max)[27,28]	Drug	GI upset, nausea, diarrhea, irritability, agitation, depression, anorexia, body odor, cerebral edema[29]	Monitor methionine levels to minimize risk of cerebral edema
Biotin	Pyruvate or multiple carboxylase deficiency	Tablets, capsules, liquid	10–20 mg/day	5–20 mg/day[13,30,31]	Supp	GI upset[32]	Large doses may interact with thyroid assays[33,34]
Coenzyme Q_{10}	Electron transport chain disorders Primary coenzyme Q_{10} deficiency	Tablets, capsules, wafers, powder, syrup	50 mg/kg/day[35]	1.5–50 mg/kg/day (3 g/day max)[35,36]	Supp	GI upset, thrombocytopenia, purpura, sinusitis, depression, anxiety[37]	Lipophilic, administer with a high-fat meal to facilitate absorption[38]
Carglumic acid	*N*-acetyl glutamine synthetase deficiency	Tablet for suspension (dissolve 200-mg tablet in 2.5 mL of water)[39]	100 mg/kg/day[40]	100–300 mg/kg/day[18,30,40]	Drug	Bitter taste, hyperhidrosis, diarrhea, vomiting, abdominal pain, decreased appetite, anemia, fever, HA, somnolence, tachycardia[40]	
Folic acid	Homocystinuria	Tablet, capsule, IV, compounded solution[41]	5 mg	1–20 mg[27,29,42]	Drug	Loss of appetite, nausea, insomnia, confusion, irritability, depression, eczema, thromboemboli	May interact with hepatically metabolized antiepileptics[43,44]
Hydroxycobalamin	Homocystinuria Disorders of cobalamin metabolism	IV, IM Tablets	1 mg	1-20 mg/day[45,46] or 1 mg/wk[47]	Drug Supp	Red discoloration of urine, hypertension, erythema, rash, GI upset, HA, anaphylaxis[48]	

GI, gastrointestinal; HA, headache; IM, intramuscular; IV, intravenous; Supp, supplement

Table 1. Medications Used in Select Inborn Errors of Metabolism (IEMs) (*cont.*)

Medication	IEM	Formulations	Initial Dose	Dose Range	FDA Status	Adverse Effects	Additional Pearls
Levocarnitine	Carnitine deficiency, Maple syrup urine disease	IV Oral solution, tablets	400 mg/kg/day[49] 50–100 mg/kg/day	100–400 mg/kg/day 100–200 mg/kg/day	Drug	GI upset, muscle weakness, hypertension, hypotension, tachyarrhythmia, anemia, HA[50]	Renally eliminated but toxicity may be related to metabolites[51]
Nitisinone	Tyrosinemia type I	Tablet, capsule, oral suspension	1 mg/kg/day[52]	0.6–2 mg/kg/day[52]	Drug	Eye pain, eye itching, corneal crystals, intellectual decline, developmental delay, seizures[53–55]	Metabolized via CYP2C9 and CYP3A4, may interact with other medications[56]
Phenylbutyrate	Urea cycle disorders	Tablet, powder, oral liquid, compounded suspension[57]	5 g/m^2/day[58]	450–600 mg/kg/day (patients <20 kg) 5–13 g/m^2/day (patients >20 kg)	Drug	Respiratory infections, cough, vomiting, diarrhea, gastroenteritis, decreased appetite, pharyngitis[59]	GI intolerances may decline over time[59]
Pyridoxine	Homocystinuria Pyridoxine-dependent epilepsy, ornithine deficiency, primary hyperoxaluria type 1[22]	Capsules, tablets, IV, compounded suspension [41,60]	100 mg	5–30 mg/kg/day (max 1 g/day)[42,61]	Drug	Peripheral neuropathy, respiratory depression, HA, somnolence, dermatitis, seizures, decreased folic acid levels[30,31]	If pyridoxine is ineffective, trial combined pyridoxine and folic acid therapy[27,29,42]
Riboflavin (vitamin B_2)	Electron transfer flavoprotein defects, Glutaric aciduria, multiple acyl-CoA dehydrogenase deficiency[22]	Tablet, capsule, compounded suspension[62]	100 mg/day[30]	3–20 mg/kg/day (max of 150 mg/day)[22,30]	Supp	Yellow-orange urine discoloration, urticaria, anaphylaxis[63]	
Sapropterin	Phenylketonuria	Tablet, powder for oral solution	20 mg/kg/day (10 mg/kg/day for children younger than 7 yr)	5–20 mg/kg/day[64–66]	Drug	HA, amnesia, dizziness, memory impairment, dysphonia, rhinorrhea, diarrhea, vomiting, bone pain[65,66]	Although sapropterin is a synthetic of BH_4, therapy is used for all forms of phenylketonuria[64,66]
Sodium phenylacetate/ sodium benzoate	Urea cycle disorders	IV	250–500 mg/kg during 1–2 hr	200–500 mg/kg/day as a continuous infusion[17,18]	Drug	Non-pleasant odor, hypernatremia, hypokalemia, hypocalcemia, metabolic acidosis, extravasation, hyperglycemia, anemia	Must be infused via a central line
Thiamine (vitamin B_1)	Pyruvate dehydrogenase complex deficiency, Maple syrup urine disease	Tablets, IV, compounded suspension[67]	100 mg IV daily	5–50 mg/kg/day (max 1 g/day)[14–16,22]	Drug	Diaphoresis, pruritus, edema, injections site pain (with IV), anaphylaxis (rarely)[16]	Contains aluminum (caution in patients with renal dysfunction)

GI, gastrointestinal; HA, headache; IM, intramuscular; IV, intravenous; Supp, supplement

Table 2. Select Recombinant Enzymes Available for Inborn Errors of Metabolism

Medication	Disease	Mechanism of Action	Dose	Adverse drug events
Agalsidase beta	Fabry disease	Recombinant α-galactosidase from CHO	1 mg/kg every 14 days	Infusion-related reactions, nausea, chest pain, muscle pain, antibody development
Alglucosidase alfa	GSD type II	Recombinant form of acid-α-glucosidase	20 mg/kg every 14 days	Infusion-related reactions, anaphylaxis, IgG antibody development, nephrotic syndrome, infections
Elosulfase alfa	MPS IVA	Recombinant *N*-acetylgalactosamine-6-sulfatase from CHO	2 mg/kg every 7 days	Infusion-related reactions, nausea, vomiting, headache, abdominal pain, antibody development, fatigue
Galsulfase	MPS VI	Recombinant *N*-acetylgalactosamine from CHO	1 mg/kg every 7 days	Infusion-related reactions, chest pain, muscle pain, abdominal pain, antibody development
Idursulfase	MPS II	Recombinant iduronate-2-sulfatase from human cell line	0.5 mg/kg every 7 days	Infusion-related reactions, fatigue, musculoskeletal pain, antibody development, ear infections
Imiglucerase	Gaucher disease	Recombinant β-glucocerebrosidase from CHO	30–60 units/kg every 2 weeks	Infusion-related reactions, nausea, antibody development, dizziness, headache
Laronidase	MPS I	Recombinant analog of α-L-iduronidase from CHO	100 units/kg every 7 days	Infusion-related reactions, chest pain, facial edema, antibody development, headache, hyperreflexia
Taliglucerase alfa	Gaucher disease	Recombinant analog of glucocerebrosidase from carrot cell culture	60 units/kg every 14 days	Infusion-related reactions, headache, arthralgia, antibody development, dizziness, fatigue
Velaglucerase alfa	Gaucher disease	Recombinant form of glucocerbrosidase from human cell line	60 units/kg every 14 days	Hypersensitivity reaction, headache, dizziness, pyrexia, abdominal pain, back pain, joint pain, asthenia, fatigue

CHO, Chinese hamster ovary; GSD, glycogen storage disease; IgG, immunoglobulin G; MPS, mucopolysaccharidosis

minal carbon group's conversion to succinate or adipic acid. Although they are an infrequent method of fatty acid metabolism, ω-oxidation pathways may become more prevalent in patients with disorders in β-oxidation.

Lipid Metabolism Dysfunction and Treatment. As with carbohydrate metabolism, errors in lipid metabolism have been identified in several steps in the process. Common modalities of dysfunction include dysfunction or deficiency of the carnitine transferase and acyl CoA dehydrogenase enzymes. Because enzymatic function is dependent on the fatty acid structure, dysfunction could occur in any of the various carnitine transferase or acyl CoA dehydrogenase enzymes. In these cases, the most common presentation will be life-threatening coma during periods of fasting and hypoglycemia without ketosis, which is also known as hypoketotic hypoglycemia.[13,73] Additional clinical manifestations will primarily affect cells in the liver, skeletal, and cardiac muscle, where β-oxidation is greatly used.

Two types of levocarnitine deficiencies exist. Primary carnitine deficiency is due to an inability of acyl CoA to effectively bind to levocarnitine and enter the inner mitochondrial membrane. This disorder results in lower carnitine levels. A secondary carnitine deficiency occurs when an acyl CoA dehydrogenase enzyme is dysfunctional, resulting in levocarnitine rebinding with acyl CoA and lower levels of free levocarnitine for transport of fatty acids into the inner mitochondrial membrane. In either disorder, patients may present with cardiomyopathy, skeletal muscle weakness, lower carnitine levels, renal tubular acidosis, hyperammonia, myoglobinuria, rhabdomyolysis, or hypoketotic hypoglycemia. Without levocarnitine supplementation, this disease can progress to rhabdomyolysis or death.[30,74] Levocarnitine supplementation is common in patients with fatty acid metabolism disorders, although use is controversial outside of primary carnitine deficiency.[75] Depending on the severity of presentation, therapy may be initiated with intravenous levocarnitine. Once the patient has stabilized therapy can be transitioned to enteral formulations. More information regarding levocarnitine can be found in Table 1.

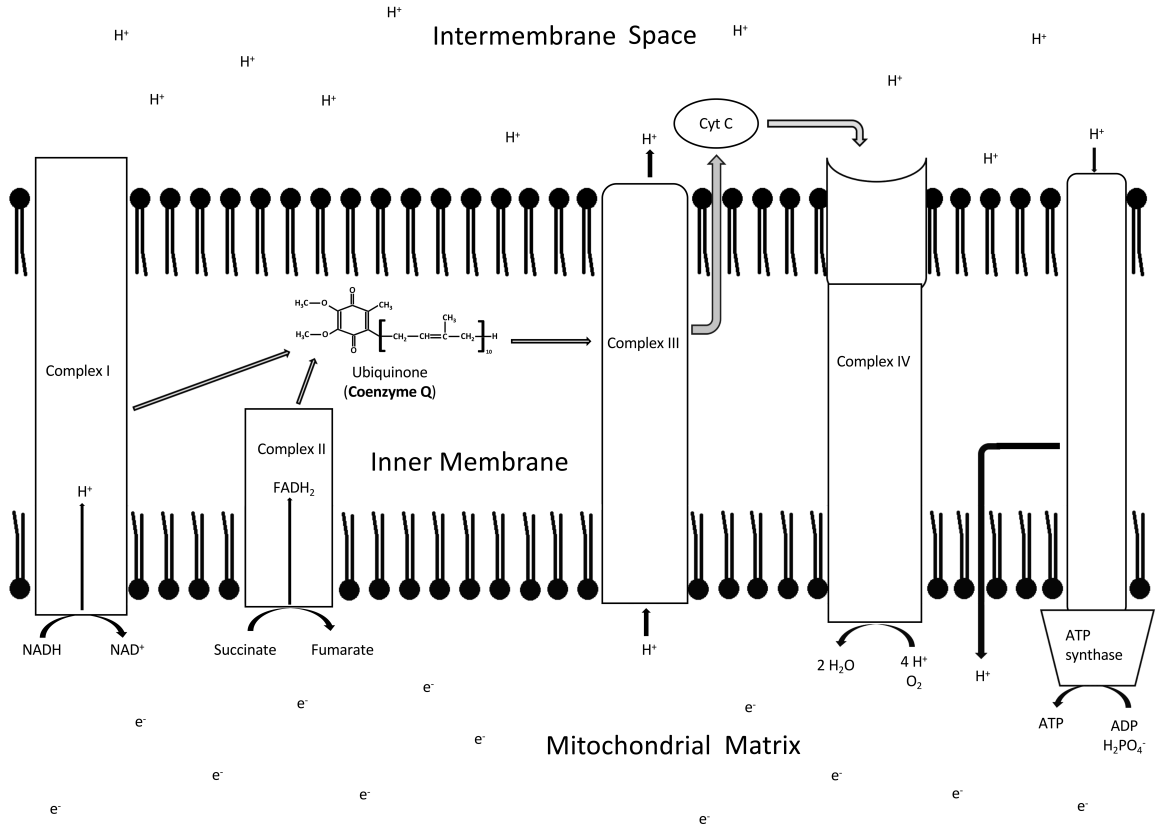
Acyl CoA enzymes comprise the small-, medium-, long-, and very long–chain acyl CoA dehydrogenases, and the acyl CoA enzyme used is dependent on the size of the acyl CoA molecule. The most common fatty acid β-oxidation deficit is in the medium-chain acyl CoA dehydrogenase enzyme.[76] Medium-chain acyl CoA dehydrogenase (MCAD) facilitates the degradation of fatty acids between 4 and 12 carbon units in length.[73] Patients with MCAD deficiency may present with vomiting, hypoketotic hypoglycemia, and lethargy, which can progress to seizures or coma.[76] Secondary carnitine deficiency will develop over time as further acyl CoA metabolism is halted. Patients with very long–chain acyl CoA dehydrogenase deficiency, which metabolizes fatty acids with 14 to 20 carbons, will have symptoms similar to those with MCAD deficiency. However, they will have a greater severity of disease and may also have cardiomyopathy, a Reye-like disease, or rhabdomyolysis.[77] Short-chain acyl CoA dehydrogenase is often identified in patients with elevated blood concentrations of ethylmalonic acid.[78] As with other metabolic disorders, there is a wide range of disease severity, and this may be similar to the other fatty acid oxidation disorders. Patients with any form of acyl CoA dehydrogenase deficiency will most likely be initiated on a 10% dextrose infusion to curtail the acute event. Those with long- or very long–chain acyl CoA dehydrogenase deficiency may eventually be started on medium-chain triglyceride oil. This will provide the patients with calories while avoiding the toxic metabolic pathways.[74,77]

Finally, defects have been identified in the processes needed to convert propionyl CoA to substrates used in aerobic metabolism. Dysfunction of propionyl CoA carboxylase can be due to deficiency of the enzyme itself or due to multiple carboxylase deficiency, as previously described. This will result in propionic acidemia. Furthermore, methionine, threonine, isoleucine, and valine produce propionyl CoA through the course of their metabolism. Hypotonia, lethargy, dehydration, and metabolic acidosis may be present. Over time this disorder may lead to mental retardation and additional neurologic complications.[79–81] Guidelines exist for the treatment of propionic acidemia.[80,82] As with other forms of fatty acid dysfunction, initial support consists of hydration, preferably with a dextrose infusion to halt the use of lipids and amino acids for energy production. Special formulas or parental nutrition may be required to limit the amount of valine, isoleucine, threonine, and methionine given during the crisis. Levocarnitine supplementation may be necessary to help normalize β-oxidation and improve acidosis.[81] In the setting of multiple carboxylase deficiency, biotin may be supplemented. Additionally, metronidazole may be used for 10 days to eradicate gastrointestinal flora that produce branched chain amino acids and contribute to the propionic acidemia.[80]

Errors in the Electron Transport Chain

The Citric Acid Cycle and Electron Transport Chain. The citric acid cycle is a vital component to aerobic metabolism and energy production through the electron transport chain. Acetyl-CoA, generated from either carbohydrate, fatty acid, or amino acid metabolism, is essential to this process. The process begins when acetyl-CoA combines with oxaloacetate to form citrate. During the course of the citric acid cycle approximately 1 molecule of ATP, 1 molecule of reduced flavin adenine dinucleotide, and 3 molecules of NADH are generated and the oxaloacetate is regenerated for further use in the cycle. The molecules of NADH and reduced flavin adenine dinucleotide can then be used for additional energy production in the electron transport chain.

Figure. The electron transport chain.



ADP, adenosine diphosphate; ATP, adenosine triphosphate; Cyt C, cytochrome C; $FADH_2$, reduced flavin adenine dinucleotide; NAD^+, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide

The electron transport chain comprises 4 complexes and ATP synthase. These complexes facilitate the transfer of hydrogen atoms out of the mitochondrial matrix for the creation of an electron gradient. This promotes the flow of hydrogen protons through ATP synthase to generate a vast number of ATPs. Complex I is the NADH dehydrogenase complex. This protein facilitates the transfer of hydrogen atoms from NADH to ubiquinone, or coenzyme Q_{10} (Figure). Ubiquinone acts as a transport molecule, providing a mechanism for the hydrogen ions to pass across the membrane into the intermembrane space. This also restores the oxidized NAD molecules for further use in carbohydrate metabolism and in the citric acid cycle. Complex II, or the succinate dehydrogenase complex, transfers hydrogen atoms from succinate to reduced flavin adenine dinucleotide, and finally to ubiquinone for transport into the intermembrane space. The hydrogen-laden ubiquinone molecules from complexes I and II then interact with complex III, or the cytochrome bc_1 complex. This protein uses the hydrogen molecules to expel hydrogen from the mitochondrial matrix into the intermembrane space and generate an electron gradient. Complex IV, or cytochrome oxidase, then maintains the hydrogen gradient and facilitates the creation of water molecules from O_2 and hydrogen. Finally, ATP synthase uses the protons to spin a central shaft in the molecule and generate molecules of ATP.

The recycling of hydrogen protons in the process results in the generation of around 2.5 and 1.5 molecules of ATP for each molecule of NADH and reduced flavin adenine dinucleotide, respectively.[5] Overall, around 90% of cellular ATP is produced via the electron transport chain and regenerates oxidized NAD without producing lactic acid.[83]

Electron Transport Dysfunction and Treatment. Defects have been discovered in the electron transport chain and in flavoprotein processes necessary for the transfer of electrons into the mitochondrial matrix. A defect in complexes I through IV or in ATP synthase can result in mitochondrial oxidation dysfunction.[84] Because this methodology of energy production is widespread in tissues, the disorder will present with a broad array of complications, including lactic acidosis.

One such disorder, Leigh disease, encompasses a variety of metabolic dysfunctions that result in similar characteristics and progressive encephalomyopathies.[85,86] Leigh disease is most commonly associated with defects in complex I, complex IV, or in the pyruvate dehydrogenase complex.[10] Patients with Leigh disease will present with hypotonia, developmental regression or arrest, demyelination, marked gliosis, and necrotizing encephalomyopathy.[83] Other dysfunctions in the electron transport chain include mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes otherwise known as MELAS; myoclonus epilepsy with ragged red fibers, or MERFF; and external ophthalmoplegia, myopathies, retinal degeneration, and heart block or Kearns-Sayre syndrome. Coenzyme Q_{10} may be started in any of these disorders. Coenzyme Q_{10} plays an instrumental role in the transfer of hydrogen across the mitochondrial membrane as previously described. When coenzyme Q_{10} is deficient, protons will remain in the mitochondrial matrix, diminish the electron gradient, and result in an overall decline in ATP production.[36] When a defect is suspected in the electron transport chain, coenzyme Q_{10} will often be administered. Additional information about coenzyme Q_{10} can be found in Table 1. Levocarnitine supplementation may be initiated as well if there is concern that stores have been depleted.

Complex II contains electron transfer flavoproteins, such as flavin mononucleotide and flavin adenine dinucleotide. Dysfunction in electron transfer flavoprotein dehydrogenase or in the flavoprotein itself can result in inability to transfer hydrogen atoms across the membrane layer. This results in multiple acyl-CoA dehydrogenase deficiency or glutamic aciduria type 2.[87,88] Patients with this disorder may present with acidosis, urinary organic acidemia, hypoglycemia, coma, hypotonia, and cardiomyopathy.[87] Partial deficiencies may present in a similar manner to MCAD deficiency and subsequent levocarnitine depletion.[88,89] Riboflavin, or vitamin B2, is the key component of flavin mononucleotide and flavin adenine dinucleotide.[87] Humans are unable to make riboflavin and must rely on dietary intake to maintain levels.[87] Supplementation may be used in patients with electron transfer flavoprotein defects or in combination with coenzyme Q_{10} in Leigh disease.[38,88] Providing 100 mg of riboflavin per day in 2 to 3 divided doses to all patients with electron transport flavoprotein defects may limit clinical manifestations of the disease.[30] Refer to Table 1 for more information regarding riboflavin.

Errors in Amino Acid Metabolism

Amino acid synthesis and metabolism is an extremely complex topic and much too broad to completely cover in this overview. With 20 different amino acids, the sheer potential for an IEM can be overwhelming. This section will cover 4 of the more common IEMs that occur in amino acid metabolism, such as phenylketonuria, tyrosinemia, homocystinuria, and maple syrup urine disease.

Phenylalanine and Tyrosine. Phenylalanine is an essential amino acid and is a precursor for tyrosine, dopamine, norepinephrine, and epinephrine in the body. Once ingested, phenylalanine is converted to tyrosine by phenylalanine hydroxylase. Tetrahydrobiopterin is a vital cofactor that facilitates the conversion of phenylalanine to tyrosine via phenylalanine hydroxylase. Tyrosine can then progress along 2 different enzymatic pathways. One pathway results in generation of the neurotransmitters L-DOPA, dopamine, norepinephrine, and epinephrine. When there are excessive levels of tyrosine, or the patient is in a catabolic state, tyrosine will undergo enzymatic degradation via a second pathway. This will result in the creation of fumarate and acetoacetate, which can then be used for energy production.

The most common IEM in amino acid metabolism stems from dysfunction of the phenylalanine hydroxylase enzyme or an inadequate supply of tetrahydrobiopterin.[90,91] This disorder, known as phenylketonuria, results in excessive amounts of phenylalanine and subsequent shunting of the amino acid to secondary metabolic pathways. This secondary pathway produces phenylpyruvate, a ketone that provides the disease with its name. Phenylpyruvate is then metabolized via unknown enzymes to phenyllactate and phenylacetate, which has a distinctive, musty odor.[92,93] The metabolites are excreted in the urine; therefore, patients with an acute bout of phenylketonuria commonly present with malodorous urine. The excessive phenylalanine will negatively impact the ability of other aromatic amino acids to cross the blood-brain barrier, limiting the production of several neurotransmitters and resulting in profound intellectual disability and neurologic abnormalities.[90,94] Fortunately, a screening test for phenylketonuria was one of the first neonatal screenings developed for mass testing, and its relatively inexpensive cost has allowed for early identification in several countries.[95]

Primary treatment for all of these disorders will include dietary restriction of the problematic amino acid and metabolic precursors. By limiting dietary intake of these amino acids and monitoring the amino acid in the blood, disease progression may often be limited or reversed. Warning labels have been added to some food products, such as those with phenylalanine, to alert patients and avoid potential inadvertent ingestion. However, complete avoidance of the problematic amino acid, especially essential amino acids that are not produced within the body, may result in complications as well. Therefore, amino acid level monitoring and maintenance with a goal range is imperative. This goal range for phenylketonuria is between 2 mg/dL and 6 mg/dL. There is a potential for expanding the range when patients enter adolescence; however, dietary restriction should continue because there is

concern for deterioration of intelligence and cognitive performance even into adulthood. Supplementation of cofactors in the errant enzyme may also help to provide complete or partial function to the enzyme. Those with a deficiency in tetrahydrobiopterin may not respond to dietary phenylalanine restriction. These patients will benefit from the initiation of sapropterin, a synthetic form of tetrahydrobiopterin. Sapropterin may be initiated at 20 mg/kg/day, although children younger than 7 years may be at a greater risk for hypophenylalaninemia with this dose.[64–66] Also, tetrahydrobiopterin is regenerated via dihydrofolate reductase and dihydropteridine reductase. Therefore, patients with defects in tetrahydrobiopterin production should avoid agents such as trimethoprim/sulfamethoxazole, methotrexate, and other antileukemic agents that affect the enzymes that regenerate tetrahydrobiopterin.[91] Patients with phenylketonuria not related to a deficit in tetrahydrobiopterin may also benefit from sapropterin supplementation. In these patients, sapropterin may help reduce phenylalanine levels, allowing the patient with phenylketonuria to ingest more phenylalanine while maintaining goal levels.[64,66]

Tyrosinemia may result from a defect in 1 of 3 different enzymes. Each form of tyrosinemia presents with different manifestations and complications. Tyrosinemia type I is caused by a defect in fumarylacetoacetate hydrolase. This results in degradation to secondary metabolites, including succinylacetone, which is believed to be the primary toxic metabolite.[96,97] Patients with tyrosinemia type I, or hepatorenal tyrosinemia, will present with an acute hepatic crisis, fever, irritability, vomiting, hepatomegaly, jaundice, and elevated transaminases. Patients may also experience peripheral neuropathy, renal dysfunction, a Fanconi-like syndrome, and hepatocellular carcinoma.[52,96–98] Tyrosinemia type II results from dysfunction at the tyrosine aminotransferase enzyme. This disorder is referred to as oculocutaneous tyrosinemia and produces sequelae such as excessive ocular redness, tearing, and pain; photophobia; herpetiform corneal ulcers; and, eventually, palmar and plantar hyperkeratosis.[97,99] Tyrosinemia type III is the least common tyrosinemia and is due to a deficiency in 4-hydroxyphenylpyruvate dioxygenase.[47] Patients with tyrosinemia type III may be asymptomatic or present with neurologic manifestations, such as self-destructive behavior, intermittent ataxia, seizures, and developmental delay.[47,97] Although 4-hydroxyphenylpyruvate is found in liver and kidney tissue, a deficit in the enzymatic function does not result in injury to these organs.[47]

Treatment of all three types of tyrosinemia begins with dietary restriction of tyrosine in addition to its precursor, phenylalanine. For type II tyrosinemia, dietary restriction may be the only therapy needed to avoid disease-related complications.[99] In other tyrosinemias, additional therapies may be warranted. Nitisinone is the drug of choice for tyrosinemia type I. Nitisinone inhibits 4-hydroxyphenylpyruvate, essentially changing those with type I tyrosinemia to type III. This decreases liver involvement and may negate the need for future liver transplantation, but it does not eliminate the risk for hepatocellular carcinoma.[96] Given the conversion from type I to type III, side effects will be similar to the symptoms of type III tyrosinemia. Ascorbic acid supplementation may be attempted for patients with tyrosinemia type III. Ascorbic acid acts as a coenzyme and electron donor in 4-hydroxyphenylpyruvate conversion of 4-hydroxyphenylpyruvate to homogentisate.[24] Additional information about these therapies can be found in Table 1.

Methionine. Methionine catabolism begins with the generation of *S*-adenosylmethionine. *S*-adenosylmethionine plays an essential role in methylating more than 115 different reactions, including those required for phospholipid, neurotransmitter, and glutathione production.[5] Once *S*-adenosylmethionine has performed its function as a methyl donor, it is converted to homocysteine, where methionine can be regenerated via N^5-methyl tetrahydrofolate.[29] Alternatively, homocysteine can be degraded in a catabolic state to create the amino acid cysteine. Further metabolism of cysteine results in propionyl-CoA production and eventually molecules that will result in the generation of ATP.

Homocysteine is created in all cells but detoxified in the kidney and liver.[29] Dysfunction of homocysteine metabolism results in homocystinuria as the excessive quantities of homocysteine are eliminated in the urine. There are 3 different dysfunctions that can lead to homocystinuria. Deficiency of cystathionine β-synthase is the most common cause. Subluxation of the ocular lens is a common presenting symptom and results in a host of ocular dysfunctions.[27] Additional effects include neurodegenerative disorders, seizures, osteoporosis, scoliosis, pectus excavatum, and thromboembolic episodes.[27,29] A second form of homocystinuria can occur due to a defect in methylcobalamin formation and subsequent inability to regenerate methionine from homocysteine. This may present with vomiting, poor feeding, lethargy, hypotonia, seizures, poor growth, ocular disorders, and peripheral neuropathy. Patients can develop a pigmentary retinopathy despite appropriate treatment.[100] The third deficit occurs due to dysfunction in the $N^{5,10}$-methylenetetrahydrofolate reductase preventing production of N^5-methyltetrahydrofolate and regeneration of methionine from homocysteine. This is the most common metabolic defect of folate metabolism.[101] Resultant sequelae include thromboembolic defects, apnea, ataxia, seizure, developmental delay, coma, and death.[42,101]

Methionine restriction may be warranted in homocystinuria only after supplementation with pyridoxine and folic acid has failed. An initial trial of pyridoxine in this disease will result in dramatic improvement in the

responsive patient. An initial dose of 100 mg may be administered regardless of age or size.[42,61] Pyridoxine may decrease folic acid levels, and if pyridoxine seems ineffective, concomitant folic acid may be initiated at 5 mg for all patients.[27,29,42] Folic acid supplementation is also warranted in homocystinuria secondary to $N^{5,10}$-methylenetetrahydrofolate reductase deficiency. Both folic acid and pyridoxine are hepatically metabolized to active metabolites. Although the metabolic processes involved in metabolism are unknown, literature suggests that these agents may affect antiepileptic medication concentrations.[43,44] Additional monitoring may need to be performed with medications that are significantly cleared by the liver. If both pyridoxine and folic acid are ineffective, dietary restriction may still be avoided if a trial of betaine is successful. Betaine acts as a methyl donor and can subsequently regenerate methionine from homocysteine through an alternative metabolic pathway. Methionine levels should be monitored closely with betaine therapy to avoid the risk for cerebral edema with elevated levels. Hydroxycobalamin may also be used in homocystinuria if there is concern for abnormalities with methylcobalamin formation. See Table 1 for further details regarding dosing, availability, and adverse effects of these agents.

If homocystinuria is suspected, all 4 agents may be initiated at the same time in an effort to resolve the metabolic crisis. An exact knowledge of the metabolic pathways of these medications is unknown, and subsequent information regarding drug interactions is limited. This is not limited to just patients with homocystinuria. Literature regarding many of the herbal and nutritional supplements is sparse. Addition of these agents to a medication regimen may result in drug interactions that go unnoticed until complications arise and warrant further investigation. The pharmacist should be vigilant for drug interactions and monitor therapy appropriately.

Maple Syrup Urine Disease. Branched-chain amino acids comprise valine, isoleucine, and leucine. These amino acids are essential amino acids and play an important role in energy production, non-essential amino acid production, and protein structure.[102] The catabolism of these 3 molecules begins very similarly with the creation of a ketone via branched-chain amino acid aminotransferase. The subsequent reaction results in the production of NADH and is enabled by branched-chain α-ketoacid dehydrogenase. Cofactors play an important role in these enzymatic processes; pyridoxine is integral in the first enzymatic step and thiamine in the second. The enzymatic degradation of valine and isoleucine begins to differ from leucine at this point. After several metabolic steps, valine and isoleucine are eventually metabolized to propionyl-CoA. Leucine will eventually be metabolized to acetyl-CoA and acetoacetate.

Maple syrup urine disease is caused by a dysfunction of the branched-chain α-ketoacid dehydrogenase or its coenzyme, thiamine. Five different types of maple syrup urine disease have been discovered, with variations in symptom severity.[103] However, all patients present with the disease's namesake, sweet-smelling urine similar to that of maple syrup. Further complications may include poor feeding, irritability, vomiting, hypertonicity, hypotonicity, convulsions, lethargy, mental retardation, coma, and death.[79,103] The final metabolic products of valine and isoleucine include propionyl-CoA, which may be of concern in patients with propionic acidemia and has already been described.

Dietary restriction of leucine, valine, and isoleucine is imperative in maple syrup urine disease. In an acute crisis, initial therapy should consist of hydration and cessation of the catabolic state. As with disorders of the fatty acid pathway, this can be facilitated via an infusion of 10% dextrose. Because thiamine is a cofactor in this process, it may be initiated in those with a new diagnosis. Some patients may respond to thiamine supplementation and continue on therapy indefinetly.[103] More information regarding thiamine can be found in Table 1.

Errors in the Urea Cycle

The Urea Cycle. Deamination of amino acids results in the production of ammonia which can be extremely toxic to neurologic function. The urea cycle is a 6-step process that converts ammonia molecules to urea for transport in the bloodstream and removal in the kidneys. The first step in the process prepares ammonia for entrance into the urea cycle by combining ammonia and bicarbonate, creating carbamate. Next, carbamoyl phosphate synthetase and ATP convert carbamate to carbamoyl phosphate. This enzymatic reaction is activated by *N*-acetyl glutamine, which is a metabolite of the amino acid glutamine. The molecule of carbamoyl phosphate will combine with ornithine and enter the urea cycle. After a few intermediary steps, urea and ornithine are produced. Urea is then transported in the bloodstream to the kidneys, where it is removed. Ornithine will combine with another molecule of carbamoyl phosphate and continue the process.

Urea Cycle Disorders and Treatment. Urea cycle disorders can occur in any of the enzymatic processes in the urea cycle except for ornithine α-aminotransferase. Most of these disorders will result in hyperammonemia and subsequent neurologic toxicity, including lethargy, irritability, seizures, and coma.[104] Additional generalized sequelae include poor feeding, vomiting, tachypnea, hypothermia, ataxia, intellectual disability, and increased intracranial pressure.[21,104,105] Each particular disease state may present with additional manifestations. For example, carbamyl phosphate synthetase and *N*-acetyl glutamine acid synthetase deficiencies may present with headaches or migraines. Patients with ornithine transcarbamylase deficiency may develop gallstones. A defect in argininosuccinate synthetase or lyase may result in dry, brittle hair in addition to the usual effects of hyperammonemia. These patients are more

likely to have developmental delay and intellectual disability.[106] Arginase deficiency may present with spastic paraplegia, peripheral neuropathy, choreoathetotic movements, and loss of developmental milestones.[17,18,107]

Treatment for errors in the urea cycle primarily revolves around stopping the catabolic state and ammonia removal. Frequently, these patients will present with hyperammonemic crisis secondary to an acute process that limited oral intake and resulted in energy production shifting from carbohydrate metabolism to lipid and amino acid metabolism. Therefore, first-line therapy generally consists of an infusion of dextrose.[18,21] Once intravenous access has been established and adequate calories provided, attention can shift to the removal of excess ammonia.

Several medications are used to remove excess ammonia. In the acute setting, an intravenous mixture of sodium phenylacetate and sodium benzoate are combined with the 10% dextrose infusion. This provides the patient with the calories to stop the metabolic crisis, along with agents to remove the excess ammonia. Phenylacetate binds to glutamine to create phenylacetylglutamine, which contains 2 moles of nitrogen; benzoate binds with glycine to form hippuric acid, which contains 1 mole of nitrogen.[18] The molecular products can then be excreted, eventually resulting in resolution of the hyperammonemia state. When ammonia levels have sufficiently declined, enteral sodium phenylbutyrate, a prodrug for phenylacetate, can be initiated. This may help the patient avoid subsequent acute hyperammonemic crisis. Arginine may also be used to help facilitate ammonia removal and is often combined with sodium phenylacetate and sodium benzoate in the 10% dextrose mixture during the initial crisis. Supplementation with this therapy supplies the urea cycle with ornithine and *N*-acetyl glutamine. Depending on the metabolic disorder, arginine can facilitate the removal of 1 or 2 moles of ammonia.[106] Arginine should not be used in patients with arginase deficiency because the arginine will not be metabolized, resulting in worsening of the metabolic process.[21] In patients with *N*-acetyl glutamine synthetase deficiency, carglumic acid may be supplemented once the acute crisis is controlled. This agent acts as a replacement for *N*-acetyl glutamine and allows the urea cycle to function normally. Additional agents for treatment or control of hyperammonia include dietary modifications, lactulose, and levocarnitine.[108] Levocarnitine can be used in the acute crisis to help mitigate the hyperammonemia and encephalopathy.[93] More information regarding the medication therapies used in urea cycle disorders can be found in Table 1.

Overall, the treatment and mitigation of acute hyperammonemic crisis in patients with urea cycle disorders has led to a robust improvement in treatment outcomes. Improvements in screening, standardization of treatment protocols, and other factors have enhanced patient outcomes. Specifically, mortality in the newborn period has declined from 50% before 2002 to 24%.[109] Pharmacists can help maximize this benefit by familiarizing themselves with the medications used in an acute crisis, providing children and family members with education regarding their medications, and monitoring for potential adverse effects and drug interactions.

Conclusions

Although a number of dietary supplements and pharmacologic options have been discussed, this has not been all-encompassing. Additional medication therapies, active forms of medications, and metabolic disorders have not been discussed. Hopefully, this document has provided the reader with a baseline level of knowledge necessary to understand the metabolic process associated with IEMs and potential treatment options. Review of the metabolic disorder, normal metabolic processes, and any available literature will be vital to the pharmacist providing care to these patients.

As has been shown, IEMs comprise a vast and complex array of disorders. Literature is often limited because of the rare nature of the diseases. Treatment often comprises a working understanding of the metabolic processes involved and speculation as to what therapies may be beneficial. A pharmacologic cocktail may be initiated to cover several potential metabolic disorders. Because many of these agents are dietary or nutritional supplements, literature regarding efficacy, adverse events, and potential drug interventions is lacking. Therefore, it is necessary that the pharmacist understand the disease process when providing care for patients with IEMs to ensure appropriate medication therapy and minimize the potential risk to patients with these rare disorders.

ARTICLE INFORMATION

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