Established and Emerging Treatments for Patients with Inborn Errors of Metabolism

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ABBREVIATIONS

BH4	tetrahydrobiopterin
CoA	coenzyme A
CPS	carbamoyl phosphate synthetase
ERT	enzyme replacement therapy
FAH	fumarylacetoacetate hydrolase
FDA	Food and Drug Administration
HPD	4-hydroxyphenylpyruvate dioxygenase
HSCT	hematopoietic stem cell transplantation
HT-1	hereditary tyrosinemia type 1
IEM	inborn error of metabolism
LCT	liver cell transplantation
MCT	medium-chain triglycerides
MMA	methylmalonic acidemia
MPS	mucopolysaccharidoses
NAG	N-acetylglutamate
NTBC	2-[2-nitro-4-(trifluoromethyl) benzoyl]cyclohexane-1,3-dione
OLT	orthotopic liver transplantation
PA	propionic acidemia
PAH	phenylalanine hydroxylase
PKU	phenylketonuria
TPN	total parenteral nutrition
UCD	urea cycle disorder
VLCAD	very-long-chain acyl-coenzyme A dehydrogenase

Education Gaps

Early recognition and treatment of inborn errors of metabolism is essential. Treatment regimens are often complex and may involve a combination of several therapies. Novel therapies are rapidly emerging and can be life-saving. This review serves to assist the neonatologist in keeping abreast of these developments.

Abstract

Inborn errors of metabolism (IEMs) are inherited defects in a metabolic pathway resulting in clinical disease. The overall goal of therapy is to restore metabolic homeostasis while minimizing the deleterious effects of the interruption. Conventional treatments focus on decreasing substrate, providing product, and replacing deficient enzyme or cofactor. We discuss examples of established, novel, and emerging therapies to provide a framework for understanding the principles of management for patients with IEMs.

Objectives

After completing this article, readers should be able to:

1. Describe the principles of treatment for patients with inborn errors of metabolism
2. Apply these principles to selected conditions that are relevant to a neonatal population
3. Recognize the indication for use of emerging therapies, including organ transplantation, enzyme replacement therapy, and gene therapy

INTRODUCTION

Inborn errors of metabolism (IEMs) are a heterogenous group of disorders characterized by an interruption in the complex biochemical network of human metabolism. This network is composed of connected pathways that are responsible for vital processes, including the conversion of nutrients into usable energy,

recycling of waste products, and organelle functioning. IEMs are caused by an interruption or block in a key metabolic pathway because of insufficient or defective enzyme, cofactor, or transporter. Clinical manifestations often arise from the direct and downstream effects of substrate accumulation and/or product deficiency (Fig 1).

The management of IEMs aims to restore the balance between substrate and product on either side of the blockage. This traditionally involves a combination of 1) decreasing substrate and removing toxic metabolites, 2) providing deficient product, and 3) enhancing conversion of substrate to product via enzyme or cofactor replacement. In this review, we will systematically discuss each of these approaches to treatment, with examples of how they have been applied in human disease.

DECREASING SUBSTRATE

Enzymatic deficiency or dysfunction results in accumulation of substrate, which may then be converted into secondary, sometimes toxic, byproducts. Substrate accumulation and/or secondary byproducts are often directly responsible for disease manifestations. Limiting substrate accumulation is therefore an essential component of treating many metabolic conditions. This is achieved by regulating the intake of substrate in the diet, secondary reduction of substrate, and removal of secondary byproducts (Fig 2). (1) We will discuss each of these individually.

Dietary Substrate Restriction

Dietary management is the foundation of treatment for many IEMs and involves limiting disease-specific substrate in the diet. In disorders of protein metabolism, for example, natural protein is restricted, and residual protein needs are met with medical protein that lacks substrate amino acids. This is well exemplified in the management of classic phenylketonuria (PKU) resulting from phenylalanine hydroxylase (PAH) deficiency. PAH is responsible for the conversion of phenylalanine to tyrosine. In the untreated state, phenylalanine accumulates and is neurotoxic, resulting in severe cognitive impairment and psychiatric disability. (2) Dietary management of PKU involves a phenylalanine-restricted diet, attained by restricting natural forms of dietary protein with supplementation of phenylalanine-free and tyrosine-rich amino acid equivalent formula. With lifelong dietary therapy starting at birth, most patients with PKU are able to lead independent lives with normal or near-normal neurocognition. (3)

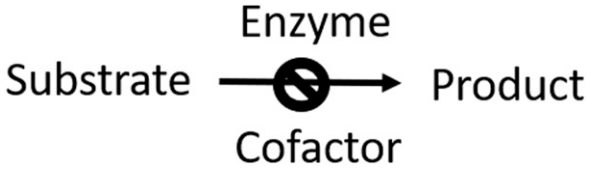

Figure 1. Interruption in an enzymatic pathway (denoted with a circle backslash) may result in decreased product distal to the block and increase in enzymatic substrate proximal to the block.

The success of dietary management in PKU has inspired the application of dietary treatment to many other IEMs. In fact, 16 of the core conditions on the Recommended Uniform Screening Panel for newborn screening are treated with nutritional management. (4) This includes other disorders of protein metabolism (amino acidopathies, urea cycle disorders, and organic acidurias) as well as disorders of fatty acid oxidation. For each condition, the paradigm of reducing the offending substrate is tailored to the enzymatic defect. In disorders of long-chain fatty acid oxidation, for example, long-chain fats (containing ≥14 carbons) are restricted in the diet. (5) In galactosemia, a disorder of galactose metabolism, the use of galactose-free formulas can be lifesaving. (6)

Despite the potential for success with strict dietary therapy alone, many factors limit adherence to such regimens. These include issues of palatability, cost, complexity of care, and caregiver burden. (7) In total parenteral nutrition (TPN)–dependent patients, specialty formulations of TPN lacking the offending amino acids may be considered. However, such preparations are not readily available at most institutions.

Substrate Reduction Therapy

Substrate reduction therapy is an alternative approach to decrease substrate intake. Unlike nutritional management, substrate reduction therapy acts upstream of the enzymatic block to decrease production of substrate. Hereditary tyrosinemia type 1 (HT-1) is a condition in which substrate reduction therapy is commonly used.

HT-1, also known as classic or hepatorenal tyrosinemia, is caused by fumarylacetoacetate hydrolase (FAH) deficiency. This enzyme is the fifth and final enzyme in tyrosine metabolism. In the untreated state, patients with HT-1 develop acute liver failure in infancy, followed by renal disease in early childhood. Dietary therapy alone, even when started in the first year of age, falls short of preventing these complications. (8) Substrate reduction therapy with 2-[2-nitro-4-(trifluoromethyl) benzoyl]cyclohexane-1,3-dione (NTBC) has changed the prognosis of this disease. NTBC acts as a potent inhibitor at the site of 4-hydroxyphenylpyruvate dioxygenase (HPD), the second enzyme in tyrosine metabolism (Fig 3). (9)

By blocking HPD activity, the substrate load delivered to the deficient FAH downstream is greatly decreased. This results in a block in production of the hepatotoxic metabolite succinylacetone. With the combination of NTBC and dietary therapy started in the newborn period, the major clinical manifestations of HT-1 can be prevented, and liver transplantation can be prevented. NTBC therapy is recommended to be started at the time of diagnosis of HT-1. (8)

Scavenger Therapy

For many IEMs, substrate accumulation leads to secondary production of a toxic byproduct. Scavenger therapies offer a sink for these toxic byproducts and are particularly relevant to the care of patients with urea cycle defects and organic acidemias.

The urea cycle disorders (UCDs) are a group of disorders characterized by an inherited defect in the urea cycle. This cycle is responsible for the conversion of waste nitrogen in the form of ammonia into urea, which can be excreted in the urine. Disruption of the urea cycle results in accumulation of nitrogen in the form of ammonia. Elevation of ammonia, known as hyperammonemia, results in cerebral edema and risk of irreversible neurologic injury and death. As such, tight ammonia control is an absolute priority in the care of patients with UCDs.

Ammonia accumulation results in secondary accumulation of nitrogen in the form of glutamine and, to a lesser extent, glycine. Ammonia scavengers conjugate to these secondary metabolites, allowing for urinary excretion of nitrogen (Fig 4). Sodium benzoate and sodium phenylbutyrate, 2 widely used ammonia scavengers, conjugate with glycine and glutamine, respectively, and allow for urinary nitrogen excretion. (10) This results in reduction of whole-body nitrogen stores, thereby decreasing ammonia levels while bypassing the urea cycle.

A new medication, glycerol phenylbutyrate, is a pre-prodrug of phenylbutyrate with superior palatability, which has been found to be not inferior to sodium phenylbutyrate. (11) It has been approved by the US Food and Drug Administration (FDA) for children aged 2 years and older, but recent studies have demonstrated tolerance in patients with UCD who are as young as 2 months. (12) In times of acute illness, sodium phenylbutyrate and sodium phenylacetate

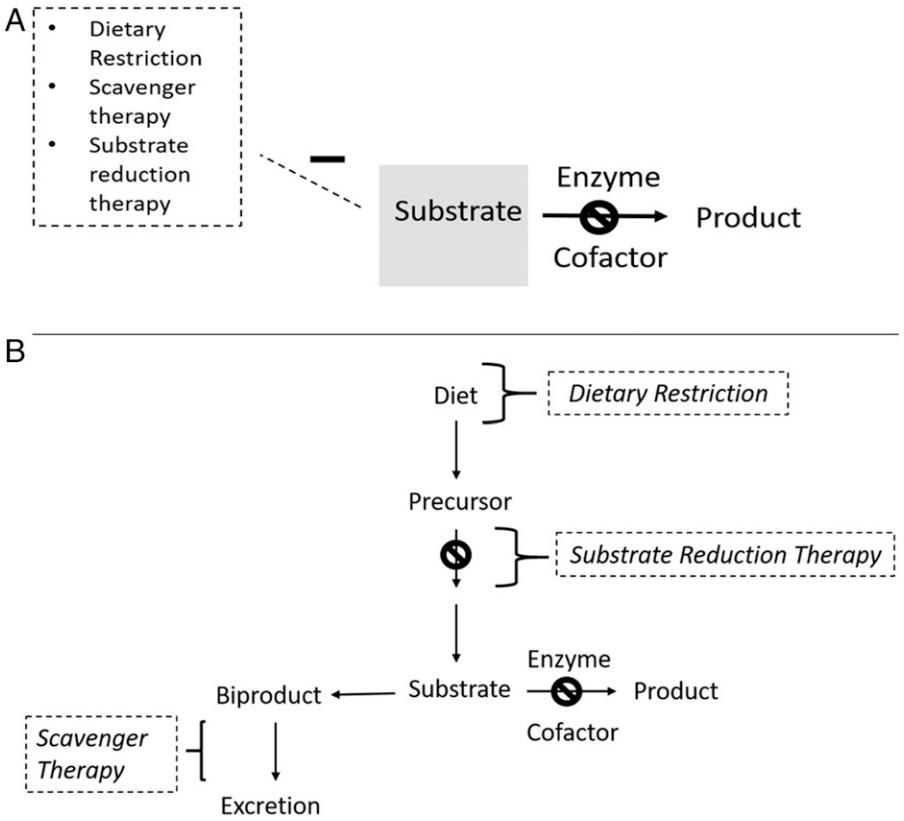

Figure 2. A. Substrate reduction (denoted with a minus [–] sign) can be achieved via dietary restriction, scavenger therapy, or substrate reduction therapy. B. The site of action of each of these approaches in more detail. Dietary restriction involves limiting disease-specific substrate in the diet. Substrate reduction therapy acts upstream of the enzymatic block. Scavenger therapy allows for excretion of toxic byproducts that resulted from substrate accumulation.

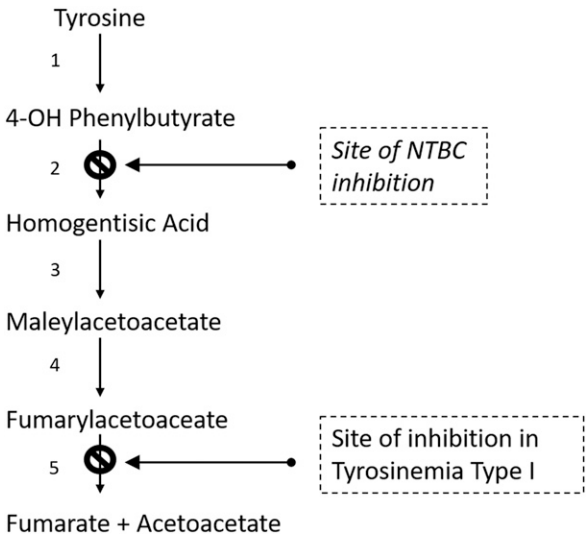

Figure 3. Substrate reduction therapy for hereditary tyrosinemia type 1 (HT-1) with 2-[2-nitro-4-(trifluoromethyl)benzoyl]cyclohexane-1,3-dione (NTBC). The enzymes in the tyrosine degradation pathway are labeled 1 through 5. 1: Tyrosine aminotransferase; 2: 4-OH hydroxyphenylpyruvate dioxygenase (HPD); 3: homogentisic acid dioxygenase; 4: maleylacetoacetate isomerase; 5: fumarylacetoacetate hydrolase (FAH). HPD (2) is the site of inhibition by NTBC. HT-1 is caused by FAH deficiency. (5)

can be given intravenously. If hyperammonemia is severe and nonresponsive to medical management, hemodialysis or continuous venovenous hemofiltration is used for emergent removal of ammonia. (10)

Scavenger therapy is also widely applied in the treatment of methylmalonic acidemia (MMA) and propionic acidemia (PA). These inherited disorders of amino acid metabolism result in significant morbidity and mortality, along with metabolic acidosis, failure to thrive, and varying degrees of cardiac dysfunction and renal disease. (13) MMA and PA result in accumulation of toxic short-chain acyl-coenzyme A (CoA) compounds. The administration of L-carnitine allows urinary excretion of these short-chain acylcarnitines and is an important component of treatment. (13)(14)

Short-chain CoA species also mediate secondary hyperammonemia in patients with MMA and PA, by reducing N-acetylglutamate (NAG) synthesis. NAG is a stimulator of

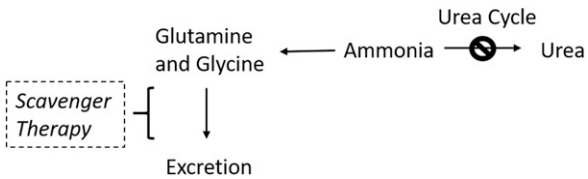

Figure 4. In urea cycle disorders, waste nitrogen accumulates in the form of ammonia, with secondary accumulation of glutamine and glycine. Ammonia scavengers facilitate excretion of nitrogen by conjugating with glutamine and glycine, which is then excreted in the urine.

carbamoyl phosphate synthetase (CPS), the first and rate-limiting step in the urea cycle. With insufficient NAG, CPS activity is decreased and hyperammonemia develops. (15) Currently, there are no treatments available in the United States for hyperammonemia in patients with organic acidemias. N-carbamylglutamate (carglumic acid) is a synthetic analog of NAG. (16) It is approved for the treatment of NAG synthetase deficiency; clinical trials are currently under way to evaluate the use of carglumic acid for the management of hyperammonemia in patients with PA and MMA. (17)

PROVIDING PRODUCT

Insufficient product distal to the biochemical block causes its own set of physiologic perturbations. For many disorders, administration of product is necessary to achieve metabolic control or restore homeostasis (Fig 5). This is well-illustrated by the practice of supplying tyrosine in the treatment of PKU. Tyrosine has various physiologic responsibilities, including the synthesis of epinephrine, norepinephrine, and dopamine, as well as melanin. In patients with PKU, phenylalanine is not converted to tyrosine because of PAH deficiency and tyrosine becomes conditionally essential. PKU-specific formulas are enriched with tyrosine to meet this need. (3) Similarly, in UCDs, arginine becomes an essential amino acid and it, or its precursor citrulline, is supplemented, provided the primary defect is not in arginine or citrulline metabolism. (10)

Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is a disorder of very-long-chain fatty acid metabolism, characterized by varying degrees of hypoketotic hypoglycemia, cardiomyopathy, and myopathy. In this disorder, there is deficiency of the enzyme VLCAD, which catalyzes β-oxidation of fatty acids of 14 to 20 carbons in length. With each turn of the β-oxidation spiral, 2 carbons are cleaved. The relevant dehydrogenase changes based on carbon length, with chains of 10 to 14 fatty acyl-CoAs being processed by long-chain acyl-CoA dehydrogenase, 6 to 10 by medium-chain acyl-CoA dehydrogenase, and 4 to 6 by short-chain acyl-CoA dehydrogenase. (18) Patients with long-chain defects such as VLCAD deficiency are given a long-chain fat-restricted diet, with supplementation of medium-chain triglycerides (MCTs), which bypasses the enzymatic block in long-chain fatty acid oxidation disorders. (5) Triheptanoin is an investigational treatment for long-chain fatty acid oxidation disorders that also provides MCT as an energy source. However, unlike MCT, it also provides propionyl-CoA which serves to replace deficient tricarboxylic acid

intermediates by conversion to succinyl-CoA. This investigational drug is still under study, but a phase II open-label trial showed some benefits in exercise tolerance. (19)

ENHANCED CONVERSION OF SUBSTRATE TO PRODUCT

Treatments that enhance the conversion of substrate to product are desirable because they most directly address the underlying biochemical defect. This has historically been approached with cofactor therapies. However, with advances in medicine, we have begun to more precisely correct the biochemical perturbation with enzyme replacement and gene therapies (Fig 6).

Cofactor Therapy

Cofactors are compounds that assist in enzymatic activity. Some IEMs are caused by a primary cofactor deficiency; others are not caused by cofactor deficiency but show clinical improvement with cofactor supplementation. Some subtypes of MMA, for example, are B_{12} responsive. These subtypes have defects in the transport or synthesis of B_{12} and related cofactors and can be treated with hydroxocobalamin with favorable prognosis. For this reason, testing for B_{12} responsiveness is recommended as part of the evaluation for patients newly diagnosed with MMA. (20)

An example of cofactor supplementation without deficiency is sapropterin treatment in PKU. Tetrahydrobiopterin (BH4) is a cofactor for PAH, the enzyme deficient in PKU. In 2007, sapropterin dihydrochloride was approved by the FDA for the treatment of PKU. Sapropterin is an orally administered synthetic BH4. Despite normal BH4 levels, approximately 25% to 50% of PAH-deficient patients are sapropterin-responsive. (21)(22)(23)(24) Sapropterin is hypothesized to act as a chaperone for residual enzyme. Patients who are sapropterin-responsive may have a 2- to 3-fold increase in protein intolerance, and are found to have improved neuropsychiatric symptoms and positive impact on quality of life. (25)

Enzyme Replacement Therapy

Enzyme replacement therapy (ERT) involves the periodic infusion of deficient enzyme to patients with eligible diseases. Lysosomal storage diseases have been the focus of ERT development because of the ability to target the drug to the lysosome with mannose-6-phosphate tagging. The first effective ERT was developed in the 1980s for Gaucher disease, when researchers demonstrated that weekly infusions of exogenous macrophage-targeted human placental glucocerebrosidase was of clinical benefit for type 1 Gaucher disease. (26) Since then, many more ERTs have become clinically available for the treatment of lysosomal storage diseases, including Fabry disease, Pompe disease, lysosomal acid lipase deficiency, mucopolysaccharidoses (MPS) type I, II, IV-A, VI, and VII. Clinical trials are currently under way for the use of ERT for acid sphingomyelinase deficiency (Niemann-Pick disease type B) and MPS IIIB. (27) Despite the overall success of ERT, there remain a few key challenges. These include the time commitment and financial burden inherent to lifelong infusion therapies. Safety concerns also exist, including the risk of an antidrug antibody response with hypersensitivity reactions. For diseases with neurologic symptoms, another major challenge is the inability of the drug to cross the blood-brain barrier. (28) Intraventricular ERT has been FDA approved for the treatment of neuronal ceroid lipofuscinosis type 2 disease. This lysosomal disorder causes neurodegeneration in early childhood, with loss of motor, language, and

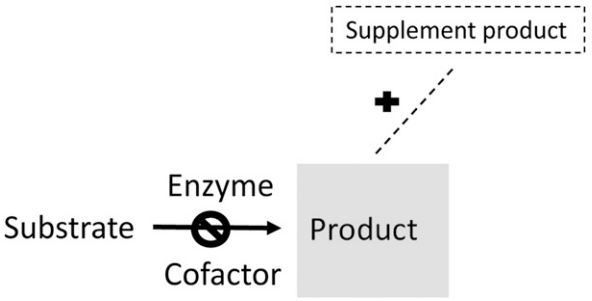

Figure 5. Insufficient conversion of substrate to product results in product deficiency. For many inborn errors of metabolism, supplementation of product (denoted with a plus (+) sign) is an important component of restoring homeostasis.

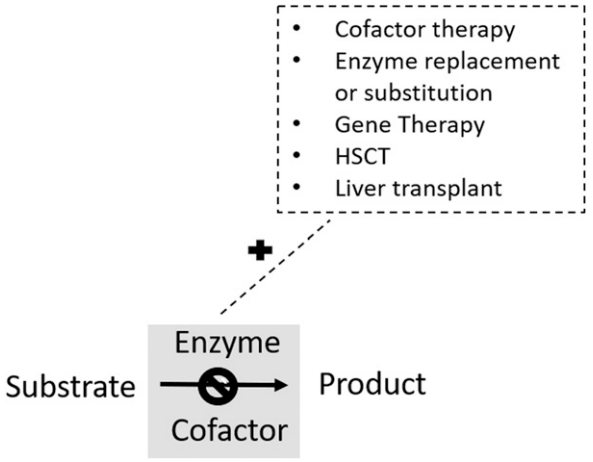

Figure 6. Treatments that enhance the conversion of substrate to product include cofactor therapy, enzyme replacement and substitution therapies, gene therapy, hematopoietic stem cell transplantation (HSCT), and liver transplantation.

TABLE. **Multipronged Approach to Treatment of Select IEMs**[a]

	DECREASE SUBSTRATE			PROVIDE PRODUCT	ENHANCE CONVERSION OF SUBSTRATE TO PRODUCT	
DISEASE	DIETARY RESTRICTION	SCAVENGER THERAPY	SUBSTRATE REDUCTION THERAPY	DIETARY SUPPLEMENT	COFACTORS	ENZYME REPLACEMENT
PKU	Phenylalanine-restricted diet			Tyrosine enriched formula	Sapropterin	Pegvaliase
MSUD	Branched chain amino acid–restricted diet				Thiamine	Liver transplant
HT-1	Phenylalanine- and tyrosine-restricted diet		NTBC			Liver transplant
MMA	Methionine-, threonine-, valine-, and isoleucine-restricted diet	Carnitine			B12	Liver transplant
PA	Methionine-, threonine-, valine-, and isoleucine-restricted diet	Carnitine			Biotin	Liver transplant
UCDs	Essential amino acid formulas	Nitrogen scavengers		Arginine or citrulline		Liver transplant, gene therapy

HT-1=hereditary tyrosinemia type 1; IEM=inborn error of metabolism; MMA=methylmalonic acidemia; MSUD=maple syrup urine disease; NTBC=2-[2-nitro-4-(trifluoromethyl)benzoyl]cyclohexane-1,3-dione; PA=propionic acidemia; PKU=phenylketonuria; UCDs=urea cycle disorders.
[a]*Often treatments from each category (decreasing substrate, providing product, and enhancing conversion) are provided in concert to optimize metabolic control.*

visual function. Intraventricular ERT has been shown to slow disease progression but requires an intraventricular device, which poses a risk for central nervous system infections and device malfunction. (29)

A novel enzyme substitution therapy, pegvaliase, was approved by the FDA in 2019 for the treatment of adults with PKU. Pegvaliase is a PEGylated form of phenylalanine ammonia lyase, a bacterial enzyme that converts phenylalanine to transcinnamic acid and ammonia, resulting in clinically significant reduction of phenylalanine levels. (30)(31)

HEMATOPOIETIC STEM CELL TRANSPLANTATION

When ERT is not available or desirable, hematopoietic stem cell transplantation (HSCT) can serve as an indirect method of enzyme delivery. Transplanted donor cells offer a continuous source of enzyme and may even deliver enzyme within the central nervous system by the passage of donor-derived cells across the blood-brain barrier to become microglia. (32) HSCT has been performed for inborn errors with neurologic manifestations, including X-linked adrenoleukodystrophy, metachromatic leukodystrophy, and Krabbe disease.

Despite the availability of ERT, HSCT remains the standard of care for children with severe MPS I who are younger than 2 years and have minimal cognitive impairment. (33)(34) Although ERT has not been shown to prevent neurocognitive decline, early treatment with HSCT may be neuroprotective. (35)(36)(37)(38)(39)(40)(41)(42) However, HSCT is not curative and has been shown to have limitations in preventing and treating other disease manifestations, including orthopedic and ophthalmologic symptoms. (32)(43) Any benefits must be carefully weighed against the morbidity and mortality of transplantation.

LIVER TRANSPLANTATION/HEPATOCYTE TRANSFER

Orthotopic liver transplantation (OLT) is used as a treatment for many IEMs with prevalent enzyme expression in the liver. For such diseases, the donor liver serves as a source of gene therapy in the recipient. IEMs now account for 19% of pediatric liver transplantations in the United States; a 6-fold increase in liver transplantation for IEMs was seen between 1987 and 2017. (44) Transplantation is now considered standard of care for children with ornithine transcarbomylase deficiency and other proximal urea cycle defects. (10) Transplantation before age 2 years is recommended for these conditions because of

the high risk for life-threatening metabolic decompensation before transplantation. After transplantation, patients are effectively cured, though they may require ongoing citrulline repletion. Maple syrup urine disease is also cured by liver transplantation. Many other conditions, including PA and MMA, have significant improvements in metabolic stability but require ongoing protein restriction; affected patients remain at risk for metabolic stroke. (45)

Despite the overall success of OLT for patients with hepatic IEMs, transplantation invites its own set of risks and complications. Data from the Scientific Registry for Transplant Recipients and United Network for Organ Sharing demonstrate that children younger than 2 years have a lower 5-year survival compared with children aged 2 to 9 years. (44)(46) Human heterologous liver cell transplantation (LCT) is a lower-risk procedure that has been proposed as a bridge to transplantation. (47) In LCT, cells from human donor organs are cryopreserved and infused through the portal vein. They then engraft into the recipient liver and compete for growth. (48) In a prospective clinical trial of 12 patients with severe UCDs, LCT was found to have a favorable safety profile. Hepatocyte transfer has the added advantage of sharing a single donor organ among several recipients. (49) However, metabolic stability from this procedure is transient. (47)

GENE THERAPY

Recent advances in gene replacement therapy and genome editing offer hope for nonsurgical cures for IEMs. Gene replacement therapy involves delivery of the therapeutic gene using a viral vector. Because of the safety and efficacy benefits, adeno-associated viral vectors are currently favored for liver-directed gene therapies. (48) Lentiviral and retroviral vectors are being explored for central nervous system disease. (50)

Adenoviral and lentiviral therapies are being evaluated in preclinical and clinical trials for a variety of disorders including several UCDs, metachromatic leukodystrophy, X-linked adrenoleukodystrophy, and MPS IIIa, to name a few. Ongoing research will need to continue to evaluate safety and efficacy of these treatments.

Genome editing encompasses a group of technologies that allow alteration of the DNA sequence in the recipient. Genome editing with the CRISPR-Cas9 system successfully corrected a mouse model of tyrosinemia type 1, and more recently a mouse model of PKU. (51)(52) This new technology is promising for the future of hepatic IEMs but will require rigorous study of safety and efficacy before clinical application.

CONCLUSION

Over the past several decades, the treatment of children with IEMs has been at the forefront of scientific progress. Medications like NTBC for HT-1, sapropterin dihydrochloride for PKU, and ERTs for children with lysosomal storage diseases have changed the course of previously devastating illnesses. Emerging gene therapy and editing technologies offer hope for a single, curative therapy for many IEMs. Nonetheless, the paradigm of restricting substrate, providing product, and enhancing conversion of substrate to product, remains the basis of present treatment for many of these diseases. These therapies are often provided in concert with one another, as illustrated in the Table. Titrating such interventions is complex and should be done in coordination with clinicians specializing in IEMs whenever possible.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of fatty acids.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of amino acids.
- Know the clinical manifestations, laboratory features, and treatment of organic acid disorders.
- Know the clinical manifestations, laboratory features, and treatment of disorders in the metabolism of the urea cycle.

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