A Modern Approach to the Treatment of Mitochondrial Disease

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Opinion statement

The treatment of mitochondrial disease varies considerably. Most experts use a combination of vitamins, optimize patients' nutrition and general health, and prevent worsening of symptoms during times of illness and physiologic stress. We agree with this approach, and we agree that therapies using vitamins and cofactors have value, though there is debate about the choice of these agents and the doses prescribed. Despite the paucity of high-quality scientific evidence, these therapies are relatively harmless, may alleviate select clinical symptoms, and theoretically may offer a means of staving off disease progression. Like many other mitochondrial medicine physicians, we have observed significant (and at times life-altering) clinical responses to such pharmacologic interventions. However, it is not yet proven that these therapies truly alter the course of the disease, and some experts may choose not to use these medications at all. At present, the evidence of their effectiveness does not rise to the level required for universal use.

Based on our clinical experience and judgment, however, we agree that a therapeutic trial of coenzyme Q10, along with other antioxidants, should be attempted. Although individual specialists differ as to the exact drug cocktail, a common approach involves combinations of antioxidants that may have a synergistic effect. Because almost all relevant therapies are classified as medical foods or over-the-counter supplements, most physicians also attempt to balance the apparent clinical benefit of mitochondrial cocktails with the cost burden that these supplements pose for the family.

Introduction

Treatment of mitochondrial disease is still in its infancy. Aside from symptom-based management, treatment of mitochondrial disease focuses on maintaining optimal health, using preventive measures to mitigate symptom worsening during times of physiologic stress (such as infection, dehydration, or surgery), and avoiding mitochondrial toxins.

Some evidence supports the use of antioxidant supplements aimed at reducing reactive oxygen species that are produced in increased amounts in this disease. The evidence for these and other treatments is still developing. Progress has been slow for several reasons: 1) Mitochondria have been linked to human

disease only since the 1960s, and much of the knowledge has been discovered in the past 20 years. 2) Mitochondrial diseases are classified as rare disorders, so funding for research is limited when compared with more common ailments. 3) Similarly, because most treatments for mitochondrial diseases are categorized as medical foods, the financial incentive to study and develop these compounds is small. 4) Obtaining a standardized pool of patients for trials is difficult because of continually evolving diagnostic criteria, limited ability to establish molecular genetics–based diagnosis, fluctuations in symptom severity, and an overall lack of genotype-phenotype correlations.

Scientific support for the use of vitamin-based and cofactor-based mitochondrial therapies is accumulating. Such pharmacologic supplements are intended to promote critical enzymatic reactions, reduce putative sequelae of excess free radicals, and scavenge toxic acyl coenzyme A (acyl CoA) molecules, which accumulate in mitochondrial disease. Some supplements also may act as alternative energy fuels or may bypass biochemical blocks within the respiratory chain, although these mechanisms are more widely debated. Exercise also has an important role in mitochondrial disease therapy, as it has been shown to reduce the burden of unhealthy mitochondria; increase the percentage of healthy, nonmutated mitochondrial DNA (mtDNA); and improve endurance and muscle function.

Current clinical goals for mitochondrial disease therapy are to increase energy production in the form of adenosine triphosphate (ATP) and reduce free radical production in an effort to improve, or at least stabilize, disease signs and symptoms. Among mitochondrial disease experts, there is anecdotal evidence of such improvement. A variety of scientific studies have also demonstrated some clinical improvement, although the vast majority of studies evaluating antioxidant efficacy in mitochondrial disease have been short-term, nonrandomized trials.

No definitive means of halting disease progression is yet available, and the clinical ability to predict therapeutic responsiveness, achieve optimal dosing of medications, and quantify benefits in individual patients remains limited. The long-term benefits of treatment remain unproven.

Although the diagnosis of the myriad of mitochondrial diseases may be complicated, its discussion is limited here in order to focus on treatment. Readers are referred to detailed reviews of standard diagnostic approaches for both generalists and specialists in the December 2007 issue of *Pediatrics* [1] and the May 2008 issue of *Molecular Genetics and Metabolism* [2]. Formal diagnostic criteria can be reviewed in a 2006 issue of *Neurology* [3].

Treatment

Diet and lifestyle

Healthful nutrition

Secondary mitochondrial dysfunction occurs with extreme malnutrition, including anorexia, starvation, and illness-related cachexia [4, Class III].

Mitochondrial disease patients can have altered caloric needs compared with the general population. Optimizing the number and quality of calories has been shown to improve mitochondrial health in these patients [5•, Class III]. Evaluation of resting metabolic rate may aid in establishing the ideal caloric intake needed for the patient. Though specific dietary restrictions or changes are not universally recommended, a comprehensive evaluation of a patient's nutrition and potential deficiencies is needed. Some patients may need restriction of carbohydrate, protein, or fat. Caloric supplementation, enteral feeding, limited fasting, increased meal frequency, and intravenous nutrition are all potential therapeutic avenues to consider.

Treating swallowing dysfunction, abnormal gut motility, behavioral feeding issues, and gastroesophageal reflux is recommended to allow for optimal nutritional intake.

Immunizations

There is no scientific evidence that immunizations exacerbate mitochondrial disease manifestations, and most mitochondrial disease specialists strongly advocate for immunizations in an effort to protect against potentially devastating infectious diseases, which may be life-threatening for the mitochondrial disease patient.

Immunizations may be administered individually or in limited batches to reduce metabolic stress. Though there is a lack of evidence to support

Table 1. Drugs with reported mitochondrial toxicity

Medication	Symptoms	Mechanism
Valproic acid [55]	Hepatopathy; infrequently direct encephalopathy	Inhibition of fatty acid oxidation, the citric acid cycle, and oxidative phosphorylation; carnitine depletion; complex IV inhibition (contraindicated in mitochondria depletion syndromes)
Antiretrovirals [56–58]	Peripheral neuropathy, liver dysfunction, myopathy	Impairment of mtDNA replication causing mtDNA depletion; carnitine deficiency, lactic acidosis, lipodystrophy [59]
Statins [59•,60,61]	Myopathy	Multiple postulated effects, including CoQ10 depletion
Aspirin	Reye syndrome	Inhibition and uncoupling of oxidative phosphorylation
Aminoglycoside antibiotics [62,63]	Hearing loss, cardiac toxicity, renal toxicity	Impaired mtDNA translation
Aminoglycoside and platinum chemotherapeutics [64]	Hearing loss, cardiac toxicity, renal toxicity	Impaired mtDNA translation
Acetaminophen	Hepatopathy	Oxidative stress
Metformin [65]	Lactic acidosis	Inhibition of oxidative phosphorylation, enhanced glycolysis
Beta-blockers [61]	Reduced exercise tolerance	Oxidative stress
Steroids	Reports of deterioration in Kearns-Sayre syndrome	Unknown

CoQ10—coenzyme Q10; mtDNA—mitochondrial DNA.

this practice, such an option may be an acceptable alternative for parents and patients with concerns about immunizations, avoiding the risk of forgoing immunizations altogether.

A related report has focused on whether immunizations in children who appear healthy but who have a latent, predisposing mitochondrial condition may bring out autism-spectrum behaviors [6, Class IV].

Avoiding mitochondrial toxins

Many medications and environmental toxins impair mitochondrial functions. The mechanisms of action vary with individual drugs. They include direct inhibition of the electron transport chain, increased creation of reactive oxygen species, impaired mitochondrial protein transport, inhibition of mitochondrial DNA replication, or some combination of these mechanisms.

Table 1 lists drugs that are known to cause symptoms in vivo. Many other mitochondrial toxins are known to decrease mitochondrial function in vitro.

Ketogenic diet

The ketogenic diet is a high-fat diet that effectively treats some forms of medically refractory epilepsy [7,8, Class I]. Recent animal research has suggested that the ketogenic diet may be beneficial in optimizing mitochondrial function [9, Class III].

Because many mitochondrial disease patients have secondary fatty acid oxidation disorders, there are limited data on use and safety of the ketogenic diet in patients with these conditions. Only a single report has looked at the lack of efficacy of the ketogenic diet in children with electron transport chain defects and intractable seizures [10, Class IV].

The ketogenic diet is the standard of care for pyruvate dehydrogenase deficiency, but it is contraindicated in patients with known fatty acid oxidation disorders and pyruvate carboxylase deficiency.

Pharmacologic treatment

- Table 2 lists the medications most commonly used by mitochondrial medicine physicians to treat mitochondrial disease. Some of these medications are discussed in further detail below.

Coenzyme Q10

The evidence supporting the use of coenzyme Q10 (CoQ10, also known as ubiquinone) in mitochondrial disease was reviewed in 2007 [11••, Class IV]. CoQ10 is endogenously synthesized in mammalian mitochondria and is an integral component of the mitochondrial electron transport chain, shuttling electrons from complexes I or II and a number of other electron donors, including electron transfer factor, which moves electrons from fatty acid beta oxidation.

CoQ10 is found in all cell and organelle membranes, where it can participate in redox shuttling. It has an important intracellular signaling role, as well as both antioxidant and pro-oxidant roles. CoQ10 modulates the mitochondrial permeability transition pore involved in apoptosis and activates uncoupling proteins.

CoQ10 biosynthetic defects underlie several different phenotypes of human mitochondrial disease. These include neonatal encephalopathy with nephropathy (COQ2) [12, Class IV]; Leigh syndrome, lactic acidosis, and nephropathy (PDSS2) [13, Class IV]; infantile nephropathy, hepatopathy, retardation (PDSS1) [14, Class IV]; and recessive ataxia, cerebellar atrophy ± retardation, lactic acidosis, and exercise intolerance (ADCK3) [15, Class IV]. These disorders, which may respond to exogenous CoQ10 administration, represent an important group of treatable mitochondrial diseases.

Pharmacokinetics: CoQ10 is insoluble in water. Powder formulations of CoQ10 have very poor intestinal absorption. No increase in CoQ10 plasma levels was achieved when 3000 mg/d was compared with administration of 2400 mg/d, suggesting a block to gastrointestinal absorption above 2400 mg in adults [16, Class IV]. Improved bioavailability has been seen with the use of nano-particles in suspension [17].

Recently, reduced CoQ has become commercially available in the form of ubiquinol. This formulation is three to five times better absorbed when compared with the oxidized form of CoQ, ubiquinone.

CoQ is carried in the blood in white cells and platelets. In plasma, CoQ is largely (95%) bound to lipoproteins in the reduced ubiquinol form.

The plasma half-life of administered CoQ10 is about 36 hours. Following 1 month of oral administration of two relatively bioavailable CoQ10 formulations (a liquid and a wafer), blood levels returned to baseline 2 weeks following CoQ10 cessation (Haas, unpublished data, Class IV).

Catabolic pathways for CoQ have not yet been characterized.

CoQ levels in blood and tissues fall with normal aging. CoQ levels in a 70-year-old are about 50% of those in a 20-year-old.

Standard dosage   Ubiquinol doses of 2 to 8 mg/kg per day (administered twice daily with meals) seem prudent; this form of CoQ10 in a solubilized, bioavailable form is preferred over ubiquinone. Ubiquinone doses of 5 to 30 mg/kg per day (administered in two divided doses daily with meals) is an available alternative.

Contraindications   None known.

Main drug interactions   May lower warfarin concentrations.

Main side effects   Wakefulness.

Special points   CoQ10 has been approved by the US Food and Drug Administration (FDA) for treatment of mitochondrial disease. Although animal and human experience with CoQ10 treatment has shown no toxicity, it is not known whether supratherapeutic blood levels are safe. Pro-oxidant and physiologic signaling roles of CoQ are a concern [18].

Table 2. Mitochondrial medications and supplements*

Medication	Dosage (pediatric)	Dosage (adult)	Monitoring	Adverse effects	Comments
CoQ10 as ubiquinol (preferred)	2–8 mg/kg po daily divided in two doses	50–600 mg po daily	May obtain pretherapy level and monitor CoQ10 level in leukocytes or plasma	Wakefulness, sleep disruption; may reduce warfarin concentration	Solubilized bioavailable formulation preferred. Absorption may be improved when taken with meals
CoQ10 as ubiquinone	10–30 mg/kg po daily divided in 2 doses	300–2400 mg po daily divided 2–3 times a day	May obtain pretherapy level and monitor CoQ10 level in leukocytes or plasma	Wakefulness, sleep disruption; may reduce warfarin concentration	Less potent than ubiquinol and less well absorbed; solubilized bioavailable formulation preferred. Absorption may be improved when taken with meals
Riboflavin (B$_2$)	50–400 mg po daily	50–400 mg po daily	Not usually done	High doses may cause anorexia and nausea	Changes urine color and smell; effects may be minimized by giving at bedtime
L-Creatine	0.1 g/kg po daily; maximum 10 g/d	5 g po daily, given 1–2 times per day	Renal function	GI upset	Primarily used in myopathy patients, though evidence exists for routine use in all mitochondrial disease patients; converted to creatinine in the gut
L-Arginine	*Acute stroke:* 500 mg/kg IV per day for 1–3 days; *Maintenance:* 150–300 mg/kg po or IV daily divided 2–3 times a day	*Acute stroke:* 500 mg/kg IV per day for 1–3 days; *Maintenance:* 150–300 mg/kg po or IV daily divided 2–3 times a day	Plasma arginine in amino acid profile	Hypotension (with IV loading), hyponatremia, headache, nausea, diarrhea. Myelinolysis reported with high dose in single case	Used with metabolic strokes, especially in MELAS or in those with low-normal plasma arginine; citrulline is used in urea cycle defects as an alternative to arginine
L-Carnitine	10–100 mg/kg per day IV or po divided 3 times a day	100–1000 mg per dose, given IV or po 2–3 times a day	Pretherapy free and total plasma carnitine levels	GI upset, fishy odor (due to bacterial degradation; may be improved with antibiotic). Reports of cardiac rhythm disturbances in long-chain fatty acid oxidation defects	FDA-approved for metabolic diseases; available as prescription generic and brand. Only 10%–20% absorbed. Acetyl-carnitine is an alternative
B50 or B100 (B vitamin complexes)	1 tab po given 1–2 times a day	1 tab po given 1–2 times a day	Not usually done	Toxic neuropathy may occur with chronic use of larger doses than recommended	Poorly palatable
Vitamin E	1–2 IU/kg po daily	100–200 IU po daily	Not usually done	Possible adverse cardiac risks at doses > 400 IU/d	Absorption may be improved when taken with meals
Vitamin C	5 mg/kg po daily	50–200 mg po daily	Not usually done	Increases iron absorption; high doses may cause renal insufficiency (single case report)	Easily absorbed water-soluble vitamin

*CoQ10 and a B vitamin are the most commonly used medications in a starting "mitochondrial treatment cocktail."
CoQ10—coenzyme Q10; FDA—US Food and Drug Administration; GI—gastrointestinal; IV—intravenous; MELAS—mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; po—by mouth.

Table 2. Mitochondrial medications and supplements* (*Continued*)

Medication	Dosage (pediatric)	Dosage (adult)	Monitoring	Adverse effects	Comments
Alpha-lipoic acid	50–200 mg/d	50–200 mg/d	Not usually done	None known	None
Folinic acid as leucovorin, containing both D and L isomers	0.5–1.5 mg/kg po daily, given 1–2 times per day (higher doses are used in folinic acid–responsive epilepsy)	2.5–25 mg po daily given 1–2 times per day	May assess spinal fluid folate and plasma/urine pipecolic acid	Rash and pruritus	Cerebral folate can also be replenished with Isovorin (L-isomer, active form) or 5-methyl-tetrahydrofolate (Deplin), the natural transport form of folate across the blood-brain barrier. Consider for patients with symptom worsening or with proven cerebral folate deficiency

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Cost/cost-effectiveness	CoQ treatment is expensive (about $200/mo for 400 mg/d of ubiquinol). However, the prevalent expert view is that CoQ supplemental therapy is beneficial in mitochondrial disease.

Riboflavin

	Riboflavin is a water-soluble B vitamin (B$_2$) that serves as a flavoprotein precursor. It is a key building block in complex I and II and a cofactor in several other key enzymatic reactions involving fatty acid oxidation and the Krebs cycle.
	Multiple acyl CoA dehydrogenase deficiency (MADD), typically caused by electron-transport flavoprotein dehydrogenase (*ETFDH*) gene mutations, is a known inborn error of metabolism involving several of these enzymatic reactions; riboflavin supplementation using moderate to high doses can lead to amelioration of symptoms and slowing of disease progression [19••, Class II].
	Several non-randomized studies have shown riboflavin to be efficacious in treating mitochondrial diseases, specifically complex I and/or complex II disease [20–22, Class III–IV].
Standard dosage	50–400 mg/d.
Contraindications	None known.
Main drug interactions	None known.
Main side effects	High doses may cause anorexia and nausea.
Special points	Can change urine odor and color.
Cost	60 tablets of 50 to 100 mg cost $5.

L-Creatine

	Creatine, a compound present in cells, combines with phosphate in the mitochondria to form phosphocreatine. It serves as a source of high-energy phosphate, released during anaerobic metabolism. It also acts as an intracellular buffer for ATP and as an energy shuttle for the movement of high-energy phosphates from mitochondrial sites of production to cytoplasmic sites of utilization.
	The highest concentrations of creatine are found in tissues with high energy demands, such as skeletal muscle and brain. Creatine is continuously replaced through a combination of diet and endogenous synthesis.
	A reduction in phosphocreatine in skeletal muscle in patients with mitochondrial myopathies has been reported by direct measurement [23, Class IV]. Patients with mitochondrial encephalomyopathies may also have a reduction in brain creatine [24, Class IV].
	A randomized, controlled trial in adult patients with mitochondrial cytopathies showed benefits from creatine taken as an initial dose of 5 g twice a day for 2 weeks followed by 2 g twice a day for 1 week [25, Class II]. Treatment resulted in an increase in high-intensity, isometric, anaerobic, and aerobic power. No effects were observed on aerobic cycle-ergometry exercise variables, body composition, 2-minute walk, or activity of daily living scores. Similar results were reported in four pediatric patients with mitochondrial encephalomyopathies [26, Class IV]. Other studies have failed to show benefit of creatine treatment in mitochondrial disease.
Standard dosage	*Adult*: 10 g/d, divided into two doses. *Pediatric*: 0.1 g/kg per day, divided into two doses.
Contraindications	None known.
Main drug interactions	None known.
Main side effects	Gastrointestinal distress.
Special points	L-Creatine supplementation may produce elevation of serum creatinine and should be used with caution in patients with renal or hepatic disease. Crystals may form in the urine with high doses (single case report).
Cost	$20 for a 1000-g container (powder).

L-Arginine

Arginine is a semi-essential amino acid involved in growth, urea detoxification, and creatine synthesis. L-arginine produces nitric oxide, which has neurotransmitter and vasodilatory properties.

An initial small study demonstrated that intravenous (IV) administration of L-arginine (500 mg/kg/dose) quickly decreased the severity of strokelike symptoms, enhanced the dynamics of microcirculation, and reduced tissue injury from ischemia in patients with mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) [27, Class III]. In a larger study, a decrease in clinical severity and frequency of strokelike events was demonstrated in MELAS patients treated prophylactically with oral L-arginine (150–300 mg/kg/d) [28, Class III]. Responsive individuals tended to have baseline plasma arginine levels in the lower limits of normal.

We have successfully used L-arginine for metabolic strokes in patients with MELAS and other types of mitochondrial disease, both as an IV medication in the acute setting and as a daily oral medication to reduce the frequency of events.

Standard dosage	*Acute stroke*: 500 mg/kg IV per day for 1–3 days. *Maintenance dose*: 150–300 mg/kg orally or IV daily, divided into two or three doses.
Contraindications	None known.
Main drug interactions	None known.
Main side effects	Gastrointestinal upset.
Special points	Electrolyte disturbances and hypotension may be seen with high IV doses. In a single reported case, fatal overdosing of IV arginine led to marked hyponatremia and natriuresis with secondary central pontine and extrapontine myelinolysis.

L-Carnitine

L-Carnitine is a cellular compound that plays a critical role in the process of mitochondrial β-oxidation of fatty acids and the esterification of free fatty acids that may otherwise be sequestered by CoA. Carnitine transfers long-chain fatty acids across the mitochondrial inner membrane as acylcarnitine esters. These esters are oxidized to acetyl CoA, which enters the Krebs cycle and results in subsequent generation of ATP via oxidative phosphorylation.

Certain tissues, such as skeletal muscle, heart, and liver, largely depend on β-oxidation for ATP production. Carnitine may prevent CoA depletion and remove excess, potentially toxic, acyl compounds; at this time there is no pharmacologic method to increase CoA levels.

Diet is the source of 75% of carnitine; 25% is synthesized in the body, predominantly within muscle, liver, and kidneys. Skeletal muscles contain 90% of total body carnitine [29]. Plasma concentration of carnitine is regulated by its active reabsorption in the proximal renal tubules.

Primary carnitine deficiency due to defective carnitine synthesis or transport is not a typical feature of mitochondrial disorders. However, patients with respiratory chain defects tend to have lower than average free carnitine levels in plasma and increased esterified carnitine levels. This shift may reflect partial β-oxidation impairment [30••, Class IV]. L-carnitine supplementation for mitochondrial disorders is a common practice aimed at restoring free carnitine levels and removing accumulating toxic acyl compounds.

Carnitine is available as a generic or brand-name prescription (Carnitor; Sigma-Tau Pharmaceuticals, Gaithersburg, MD) for oral or IV use in mitochondrial disease. It is commonly used empirically in combination with other vitamins and cofactors (Table 2) [31, Class IV]. No studies have confirmed a benefit of isolated use of carnitine in patients with primary mitochondrial disorders.

Standard dosage	*Oral:* Children: 20–100 mg/kg/d divided into two or three doses; higher doses have been used. Adults: 330–990 mg/dose two or three times per day; 3 g/d is the usual maximum. *IV:* Children and adults: 50–100 mg/kg/d divided every 4–6 hours, increased as needed to a maximum of 300 mg/kg/d.
Contraindications	Hypersensitivity to carnitine.
Main drug interactions	None.
Main side effects	Body odor due to bacterial breakdown of carnitine in the gut, which is often dose-related and may be treated by dose reduction; a short course of metronidazole or neomycin also can help. Gastrointestinal upset (particularly flatulence and diarrhea) also may occur. Allergic reactions are rare. Tachyarrhythmia occurred in an animal model of very long chain acyl CoA dehydrogenase deficiency. Chronic administration of high doses of oral carnitine in patients with severely compromised renal function may result in accumulation of potentially toxic metabolites [32, Class IV].
Cost	$70: 90 generic tablets (330 mg). $35: 118 mL of 1 g/10 mL generic suspension.

Other redox agents

Thiamine (B₁), vitamins C and E, and alpha-lipoic acid also have been used in mitochondrial disease patients, individually or as part of an antioxidant cocktail. These therapies have less scientific data available regarding treatment of mitochondrial disease than the medications discussed here in more detail.

Folinic acid

Folinic acid is a reduced form of folic acid, a water-soluble B vitamin (B₉) involved as a cofactor in multiple metabolic reactions. It is most commonly available as leucovorin, containing the D (inactive) and L (active) isomers of the chemical. It is also available as Deplin (5-methyl-tetrahydrofolate, 5-MTHF; PamLab, Mandeville, LA), which is the natural transport form of folate across the blood-brain barrier, and Isovorin (levofolinic acid; Spectrum Pharmaceuticals, Irvine, CA), containing only the L-isomer (active) form.

A few case reports [33, Class IV] and one small case series [34, Class IV] have suggested that mitochondrial disease may lead to secondary cerebral folate deficiency, defined by low cerebrospinal fluid (CSF) folate, especially of the C1 donor, 5-MTHF. The mechanism of cerebral folate deficiency in mitochondrial disease is unclear; it is postulated to result from a failure to produce adequate ATP for active folate transport across the blood-brain barrier.

Most cases of proven 5-MTHF CSF deficiency in mitochondrial disease have occurred in patients with Kearns-Sayre syndrome. Studies in other forms of mitochondrial disease have been less consistent in demonstrating cerebral folate deficiency.

Standard dosage	*Pediatric*: 0.5–2.5 mg/kg daily, given once or twice a day. *Adult*: 2.5–25 mg daily, given once or twice a day.
Contraindications	None known.
Main drug interactions	None known.
Main side effects	None known.

Historical treatments now less commonly used

Dichloroacetate

Dichloroacetate (DCA) is a potent lactate-lowering drug. It activates the pyruvate dehydrogenase complex by inhibiting the activity of pyruvate dehydrogenase kinase, which normally phosphorylates and inhibits the enzyme. The ability of DCA to keep the pyruvate dehydrogenase complex in an active state reduces the accumulation of lactate in body tissues.

Since its discovery in 1973, DCA has been used to treat conditions associated with lactic acidosis, including mitochondrial disorders. Most published reports about the use of DCA are individual case reports. Several controlled trials have not led to conclusive evidence of the benefits of DCA in patients with mitochondrial disorders [35, Class II].

An open-label trial of DCA used for up to 7 years in patients with mitochondrial disorders demonstrated a variable response, consistent with the genetic heterogeneity and the intermittent nature of these disorders. The study's conclusion was that DCA may provide at least temporary benefit for some patients with mitochondrial disorders [36, Class III].

A randomized double-blind, placebo-controlled, 3-year crossover trial of DCA in patients with MELAS had to be terminated because of DCA toxicity, consisting of peripheral neuropathy that overshadowed the assessment of potential benefit [37, Class II].

DCA has "orphan drug" status. It is used on a compassionate basis or as a part of research protocols in several centers in the United States. Its use declined after the publication of the results from the MELAS trial.

Standard dosage	10–50 mg/kg/d divided into two doses.
Contraindications	DCA induces dose-dependent and exposure-dependent reversible peripheral neuropathy. Patients with certain mitochondrial disorders (eg, MELAS) are probably more prone than others to the toxic effects of DCA.
Main drug interactions	None known.
Main side effects	DCA may induce mild elevation of liver transaminase.

Succinate and menadione

Succinate may be used as an anaplerotic compound in specific patients.

Menadione has been banned by the FDA because of toxicity, including hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD) deficiency and neonatal hepatopathy.

Interventional procedures

For most patients with mitochondrial disease, typical acute interventions are limited to preventing worsening of the disease and symptoms. Some individuals with metabolic and mitochondrial diseases are more sensitive to physiologic stressors such as minor illness, dehydration, fever, temperature extremes, surgery, anesthesia, and prolonged fasting or starvation. During such stress, rapid systemic decompensation may occur. Preventive measures are aimed at avoiding (or at least not exacerbating) such decompensation.

Mainstays of treatment during or prior to acute metabolic decompensation in mitochondrial disease include keeping patients well hydrated, providing sufficient anabolic substrate, correcting secondary metabolic derangements, avoiding pharmacologic mitochondrial toxins, and providing cofactor and/or salvage therapies.

A supplementary table available online at the website of The Mitochondrial Medicine Society (http://mitosoc.org/blogs/diagnosis/illness-management) lists the basic assessment and management steps to take during times of catabolic stress. Pertinent details are noted below.

Intravenous fluids and substrate therapy

No single protocol is optimal for every mitochondrial disease patient. Dextrose/electrolyte therapy should be considered if a patient is unable to maintain oral fluid intake in the face of a catabolic stressor, including fever, illness, or vomiting. Any underlying infection and fever should be aggressively treated [38, Class III].

Hospital admission should be considered, not exclusively for dehydration, but to prevent catabolism by providing an anabolic food in the form of dextrose. To prevent catabolism, total parenteral nutrition should be offered at an early stage. The use of intravenous lipids may be limited because of the frequent occurrence of impaired fatty acid oxidation in mitochondrial disease.

Assessment of the patient's cardiac and renal status must be performed prior to aggressive fluid therapy. Hydration and substrate therapy involves providing 5% or 10% dextrose-containing IV fluids, given at 1.25 to 1.5 times the maintenance rate. IV fluids should not contain lactated Ringer's solution. Fluids should be weaned based on laboratory parameters, oral intake, and resolution of the underlying metabolic stressor.

If the patient is acutely acidotic (pH < 7.22 or bicarbonate level < 14 mM), metabolic acidosis can be controlled by administering sodium bicarbonate as a bolus (1 mEq/kg) followed by a continuous infusion.

Hyperammonemia can occur because of secondary inhibition of the urea cycle. As treatment for the metabolic decompensation proceeds, the ammonia level should diminish. A level less than 200 µM may require salvage therapy or dialysis.

A high dextrose delivery with D10 or D20 may be needed, especially if fluids containing 5% dextrose are not correcting acidosis or metabolic derangements. When higher dextrose delivery is given, insulin may also be required. Insulin controls hyperglycemia and serves as a potent anabolic hormone, promoting protein and lipid synthesis, removal of plasma free fatty acids, and improved adenosine translocase activity. Insulin is typically given in the intensive care unit, with the initial dose in the range of 0.05 to 0.1 U/kg per hour, and is titrated accordingly.

Once the initial crisis passes, enteral feeding should be considered. Protein, lipids, or both can be added if there are no concomitant disorders of protein or fat catabolism. Once the patient's laboratory parameters begin to normalize, restarting the patient's home-based diet is advised.

Antioxidant therapy during acute illness

L-Carnitine therapy during an acute illness may be beneficial. It should be given intravenously at a dosage of at least 100 mg/kg per day. Doses of up to 300 mg/kg per day have been used. If the patient has been taking a higher oral dose, that dose should be used intravenously for treatment.

CoQ10 and other antioxidants such as vitamin C and E are also given at the doses listed in Table 2. Any other supplements and antioxidants being given at home should be continued by mouth if possible. There is no intravenous formulation of CoQ10.

IV L-arginine therapy should be considered for a patient with a possible metabolic stroke.

Medication contraindications

Individuals with mitochondrial disease generally should avoid valproic acid, statins, aminoglycoside antibiotics, and erythromycin. There are no absolute contraindications, however, and these medications can be given if no appropriate alternative is available, as long as a prior adverse reaction to the medication has not occurred.

If a medication such as valproate is to be used for the first time during an acute illness, liver enzymes, ammonia, and synthetic liver function should be closely monitored.

Anesthesia

Questions remain about anesthetic sensitivity in mitochondrial disease patients. Some individuals with mitochondrial metabolic diseases are more sensitive to volatile anesthetics and need a much lower dose to

achieve a bispectral index (BIS) value less than 60. This effect has been seen more often in patients with reduced complex I capacity. Sevoflurane may be better tolerated than isoflurane or halothane [39, Class IV].

The potential risk of propofol in mitochondrial disease patients is debated, but propofol has been used routinely in many of these patients for brief periods of sedation (less than 30–60 minutes) without apparent clinical problems. Limiting propofol use to short procedures and brief periods of sedation is currently advised.

Surgery

- During preoperative and postoperative fasting, catabolism can be prevented by using dextrose-containing IV fluids, which should not contain lactated Ringer's solution. Routine chemistries, a complete blood count, liver function (synthetic and cellular), ammonia, glucose, ketosis, and lactic acidosis should be monitored and any derangements should be corrected. IV fluids are continued until the time of discharge, because they are intended to deter catabolism and not simply to treat dehydration.

Vagus nerve stimulation

Children with mitochondrial disease often have seizures that are not responsive to antiepileptic drugs. Therapy using vagus nerve stimulation (VNS) has been reported only in a single small series ($n = 5$) of children with electron transport chain dysfunction. Duration of VNS and seizure frequency was followed over a period of 3.4 to 10.75 years. None of the children had reduced seizure activity with VNS placement [40, Class IV]. There is also anecdotal evidence among the coauthors of this article that VNS devices have been unsuccessful in decreasing epilepsy in mitochondrial disease patients.

Organ transplantation

Most mitochondrial diseases involve multiple organ systems, so the transplantation of single organs is not therapeutically appropriate, but there are uncommon circumstances in which specific organ transplantation may be considered. There is also some evidence that patients with electron transport chain deficiencies may be candidates for liver transplants, given the correct clinical circumstances (mostly in children with isolated liver involvement and normal neurologic examinations). Long-term data and outcomes are lacking.

Some of the authors have personal experience with beneficial effects of cardiac transplantation in cardiomyopathy due to mitochondrial disease. Some of these patients have been observed for 5 years.

Two specific mitochondrial depletion syndromes, one involving the liver and the other involving gastrointestinal function, may represent exceptions to the rule. Patients having the hepatocerebral syndrome produced by mutations in deoxyguanosine kinase are currently considered for liver transplantation, which has led to long-term survival in some cases with a lack of neurologic involvement. Liver transplantation in patients with neurologic disease was not associated with improved survival [41, Class IV].

The second depletion syndrome, mitochondrial neurogastrointestinal encephalopathy (MNGIE), may be the single mitochondrial disorder for which stem cell transplantation may replete the missing enzyme activity and result in long-term clinical improvement. MNGIE is a disorder of nucleotide utilization that results in severe gastrointestinal malabsorption, encephalopathy, leukodystrophy, and myopathy. The compromised enzyme activity of thymidine phosphorylase increases the pool of deoxythymidine triphosphate and produces an imbalance in

the purine pools, thereby altering mitochondrial DNA replication and repair. Enzyme replacement using platelets or other hematopoietic cells has provided limited disease treatment. Stem cell transplantation has proven to be highly efficacious, both in symptom relief and in duration of treatment effects [42, Class III]. The number of patients who have received stem cell transplants is limited, but the results in these few have been extremely encouraging, with the longest-living survivor now more than 40 months past transplantation and making a good recovery (Hirano, personal communication).

Assistive devices

Cochlear implants

Sensorineural hearing loss occurs in many mitochondrial disorders, most notably in association with specific mtDNA mutations. The A1555G mutation is seen in individuals who have extreme susceptibility to hearing loss upon aminoglycoside exposure. Spontaneous hearing loss is associated with the A3243G mutation in MELAS and the mtDNA deletions seen in Kearns-Sayre syndrome. Sensorineural hearing loss also can be seen in other nuclear and mitochondrial DNA disorders.

Cochlear implants consist of an external component, which includes a microphone and speech processor with a radiofrequency transducer, and an intracranial portion consisting of another coil (positioned beneath the radiofrequency coil) connected to electrodes placed within the cochlea of the inner ear. Following surgical implantation, the patient and therapist adjust the speech processor to best suit the person's specific pattern of hearing loss, and the additional auditory information can be useful to regain some degree of hearing. Efficacy depends on the degree of hearing loss and the individual's premorbid ability to process auditory information. In some patients, the device allows only the detection of environmental sounds, such as a doorbell or the presence of speech, whereas it allows other patients to decipher language in a quiet environment [43, Class II].

In one study of 12 patients with profound postlingual hearing loss associated with mitochondrial disease (10 with > 90 dB hearing loss over the frequencies used for speech), 7 regained the ability to use the telephone and 10 regained useful speech recognition [44, Class IV].

An MRI cannot be obtained after receiving some models of cochlear implants.

The cost of the procedure (including evaluation, hardware, surgical and hospital fees, and rehabilitation) ranges from $45,000 to $105,000, with an average of about $60,000 per ear.

Cardiac pacemakers and defibrillators

Cardiac conduction defects with or without associated cardiomyopathy are part of the spectrum of illness in some mitochondrial disorders, most notably in patients with Kearns-Sayre syndrome. Cardiac manifestations may also occur in patients with mtDNA disorders, fatty acid oxidation defects, and disorders due to nuclear genes, such as seen in Friedreich's ataxia and Barth syndrome [45, Class III].

The newer automatic internal cardiac defibrillators (AICDs) are implantable medical devices that monitor the cardiac rhythm, function as a pacemaker if necessary, can determine whether or not a rhythm disturbance is pathogenic, and override the pacing to perform a synchronized cardioversion or an unsynchronized shock in the case of ventricular defibrillation. Less sophisticated external devices are available, often as a bridge to AICD.

Limited literature (mainly case reports and small, uncontrolled series) supports some efficacy, so the use of an AICD may be considered for patients with mitochondrial cardiac conduction defects with or without

cardiomyopathy. AICD success in other disease states adds support for their consideration in the population of patients with mitochondrial cardiac conduction disorders [46, Class IV].

The cost of the procedure (including evaluation, hardware, surgical and hospital fees, and 4 years of follow-up) is estimated to be $98,000 (1997 data). Newer data suggest that the device itself costs about $28,000, with a cost of $34,000 to $74,000 per quality-adjusted life year [47, Class II].

Physical/speech therapy and exercise

Exercise

Exercise is one of the few proven methods for improving mitochondrial functioning and decreasing the burden of unhealthy mitochondria [48, Class III].

Patients with mitochondrial cytopathy may have a low maximal oxygen uptake (peak VO_2), which can lead to exercise intolerance, even with activities of daily living [49, Class III].

Whenever possible, exercise regimens should be supervised by a therapist, trainer, or kinesiologist. A 12-lead electrocardiogram should be obtained prior to beginning an exercise regimen. Patients should start at a very low intensity and brief duration and should progress gradually. Use of a recumbent exercise bicycle and/or pool therapy may be better tolerated than other regimens in those with gait instability or excessive fatigue. A simple carbohydrate–containing drink or meal prior to exercising may increase endurance.

Graded endurance exercise can improve exercise tolerance as well as biochemical enzyme activity and mutation burden [50•, Class III]. Resistance exercise (using weights) can be performed by many patients and can increase strength.

The exercise regimen should be halted during an illness or fasting state.

Therapies

The goal of therapy is not to change the underlying mitochondrial disease, but to preserve and maximize strength, mobility, and functioning. In addition to the more widely known physical, occupational, and speech therapies, respiratory therapy and hippotherapy should also be considered [51, Class III].

Other treatments

Hyperbaric oxygen

There is no evidence that hyperbaric oxygen therapy is beneficial for patients with mitochondrial disease, and there is a theoretical concern about oxygen toxicity in these patients.

Emerging therapies

Sirtuins

Sirtuin compounds (SIRT 1–7) modulate histone deacetylases (at lysine residues), which affect the activity of multiple metabolic enzymes via stimulation of the peroxisome proliferator–activated receptor (PPAR) family, the PPAR-γ coactivator 1α (PGC-1α), and insulin signaling pathway. PPAR signaling regulates gene expression of multiple metabolic pathways, including gluconeogenesis, metabolism of fatty acids, adipocyte differentiation, cell survival, and ubiquitination [52, Class II].

A known pharmacologic PPAR pan-agonist (bezafibrate), which is FDA-approved for diabetes, was recently demonstrated to improve lifespan and ameliorate muscle disease manifestations by increasing mitochondrial biogenesis and tissue ATP levels in a skeletal muscle conditional knockout mouse [53, Class IV].

SIRT-1 agonists are currently being developed for a variety of conditions, including mitochondrial disease, and are currently entering phase 2 clinical trials. No clinical trials have been completed to guide their use or determine their risks and benefits in primary mitochondrial disease.

Resveratrol

Resveratrol, an agent found in red wine, is an antioxidant, an apoptosis inhibitor, and an SIRT-1 agonist. Resveratrol has been studied for its potential role in the treatment of diabetes, cardiovascular disease, neurodegenerative disease, cancer, obesity, and aging [54, Class IV]. No clinical trials have been completed to guide its use or determine its risks and benefits in primary mitochondrial disease.

Disclosure

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