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Treatment of Mitochondrial Disorders

Sreenivas Avula[1], **Sumit Parikh, MD**[1], **Scott Demarest, MD**[2], **Jonathan Kurz, MD**[2], and **Andrea Gropman, MD**[2]

[1]Department of Neurology, Cleveland Clinic, Cleveland, OH

[2]Department of Neurology, Children's National Medical Center and the George Washington University of the Health Sciences, Washington, DC

Opinion statement

While numerous treatments for mitochondrial disorders have been suggested, relatively few have undergone controlled clinical trials. Treatment of these disorders is challenging, as only symptomatic therapy is available. In this review we will focus on newer drugs and treatment trials in mitochondrial diseases, with a special focus on medications to avoid in treating epilepsy and ICU patient with mitochondrial disease, which has not been included in such a review. Readers are also referred to the opinion statement in A Modern Approach to the Treatment of Mitochondrial Disease published in Current Treatment Options in Neurology 2009. Many of the supplements used for treatment were reviewed in the previous abstract, and dosing guidelines were provided. The focus of this review is on items not previously covered in depth, and our discussion includes more recently studied compounds as well as any relevant updates on older compounds. We review a variety of vitamins and xenobiotics, including dichloroacetate (DCA), arginine, coenzyme Q10, idebenone, EPI-743, and exercise training. Treatment of epilepsy, which is a common feature in many mitochondrial phenotypes, warrants special consideration due to the added toxicity of certain medications, and we provide a discussion of these unique treatment challenges. Interesting, however, with only a few exceptions, the treatment strategies for epilepsy in mitochondrial cytopathies are the same as for epilepsy without mitochondrial dysfunction. We also discuss intensive care management, building upon similar reviews, adding new dimensions, and demonstrating the complexity of overall care of these patients.

Keywords

Mitochondria; Mitochondrial disorders; Treatment; Energy metabolism; Coenzyme Q10; Thiamine; Riboflavin; Carnitine; Creatine; Idebenone; Dichloroacetate (DCA); Cysteine; Lipoic

Corresponding author: Andrea L. Gropman, MD, Department of Neurology, Children's National Medical Center, 111 Michigan Avenue NW, Washington, DC 20010, Phone: 202-476-2120, Fax: 202-476-5226, agropman@childrensnational.org.
Sreenivas Avula, MD, Phone: 216-444-4934; Fax: 216-445-9139, mail:avulas@ccf.org
Sumit Parikh, MD, Phone: 216-444-1994; Fax: 216-445-9139, parikhs@ccf.org
Scott Demarest, MD, Phone: 202-476-2120; Fax: 202-476-5226, sdemares@childrensnational.org
Jonathan Kurz, MD, Phone: 202-476-2120; Fax: 202-476-5226, jkurz@childrensnational.org

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Sreenivas Avula, Scott Demarest, and Jonathan Kurz declare that they have no conflict of interest.

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Introduction

Mitochondrial disorders are a group of rare inherited diseases of energy metabolism caused by impairment of the mitochondrial oxidative phosphorylation system [1]. Mitochondria perform a multitude of tasks, including combating the production of reactive oxygen species, initiating apoptosis, and generating energy as adenosine triphosphate (ATP) by means of the electron-transport chain and the oxidative phosphorylation system. Mitochondria house a variety of metabolic reactions such as pyruvate oxidation and metabolism of amino acids, fatty acids, and steroids. Defects in any of these mitochondrial functions can lead to primary mitochondrial diseases.

With a limited base of evidence and little data from randomized trials, the treatment of mitochondrial diseases is still anecdotal. And because they are classified as rare disorders, research funding has been limited. Most treatments are considered medical foods, and there is little financial incentive to study these compounds. There are hundreds of mitochondrial diseases, each individual grouping rare, resulting in a heterogeneous study population.

With the recent advances in molecular diagnostics, mitochondrial disorders are now being increasingly identified, and more controlled trials are expected. While case studies and series have reported treatment effects, there is scant evidence to support most pharmacological interventions (exceptions are coenzyme Q10 supplementation in primary genetic defects of coenzyme Q10 synthesis and L-arginine for metabolic stroke). Aside from symptom-based management, treatment of mitochondria 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 [2]. Agents that have been used include respiratory chain cofactors, other metabolites secondarily decreased in mitochondrial disorders, antioxidants, and agents acting on lactic acidosis.

Due to our focus on treatment, we do not review details on the evaluation and diagnosis of mitochondrial disease. For those interested in learning more about the evaluation of mitochondrial disease, we refer the reader to the Mitochondrial Medicine Society diagnostic tool kit, available at www.mitosoc.org/blogs/diagnosis.

Current treatment options

Most mitochondrial treatments aim at either enhancing mitochondrial function or treating the consequences of mitochondrial dysfunction. Select therapies are aimed at increasing the respiratory chain substrate, enhancing electron transfer within the respiratory chain, or attempting a biochemical bypass of specific respiratory chain complexes. Others attempt to reduce toxic metabolites, increase ATP storage, or produce adaptations in mitochondria that improve oxidative capacity.

Many of the mainstays of treatment, including dosing regimens for these compounds, were recently reviewed in an article in this journal [2] and are not discussed here unless new information is available. In this update, we will focus on newer drugs and treatment trials in mitochondrial diseases. Table 1 summarizes the information covered in the previous article.

There has been considerable discussion regarding whether these supplements should be provided individually or as a "cocktail." In addition, there is no clear consensus on which supplements should be used in the cocktail, with choices of supplements that vary from provider to provider.

Augmentation of respiratory chain components

Some mitochondrial treatments are aimed at augmenting respiratory chain components and thereby enhancing electron transfer. Agents known to enhance electron transport at different levels of respiratory chain include coenzyme Q10, idebenone, and riboflavin.

Coenzyme Q10

CoQ10 is an integral component of the mitochondrial electron transport chain, shuttling electrons from complexes I and II and a number of other electron donors. It is important to identify primary CoQ10 deficiency, as this condition often responds to supplementation. CoQ10 has been used to treat other mitochondrial disorders, although treatment protocols have not been standardized. Clinical improvement after CoQ10 supplementation has been selectively documented in many of these patients, albeit with mixed results. While CoQ10 was discussed extensively in the previous review [2], there is one new publication of note. A total of 30 mitochondrial disease patients were included in a double-blind placebo-controlled crossover trial. The mean age was 48 6+/−3 years for the MELAS group and 56 6+/−3 years for the remaining participants [3].

Dosage—The intervention with 60 days of moderate- to high-dose (1200 mg/day) CoQ10 supplementation transiently attenuated the post-exercise rise in lactate and increased oxygen consumption/lean body mass in a subset of participants, but there was no effect on grip strength or lactate production during a non-ischemic isometric forearm exercise protocol. Gray matter choline-containing compounds were lower with CoQ10 supplementation [3]. Ubiquinol doses of 2–8 mg/kg/day (administered twice daily with meals) are commonly used; this form of CoQ10 in a solubilized bioavailable form is preferred to use of ubiquinone. Ubiquinone, typically administered in doses of 5–30 mg/kg/day (administered in two divided doses daily with meals), is an available alternative.

Idebenone

Idebenone, an analog of coenzyme Q, has a more favorable pharmacokinetic profile than other Co Q analogs [4]. However, idebenone may represent an inhibitor of both the redox and proton-pumping activity of complex I [5] and may cause mitochondrial depolarization and reduced nicotinamide adenine dinucleotide (NADH) depletion [4, 6]. Most recently, idebenone has been shown to be effective in improving recovery after the onset of vision loss in Leber's hereditary optic neuropathy (LHON).

A multicenter double-blind randomized placebo-controlled trial (Klopstock et al., 2011) [7] was conducted in 85 patients with LHON optic neuropathy due to mitochondrial DNA mutations. Inclusion criteria were patients between 14 and 64 years of age who harbored m.3460G>A, m.11778G>A, or m.14484T>C mitochondrial DNA mutations, and described vision loss due to LHON within 5 years. The primary endpoint did not reach statistical significance in the intention-to-treat population, although notable improvement was observed in vision in one eye for patients who had bilateral vision loss [7].A separate randomized double-blind placebo-controlled intervention [8] in LHON patients demonstrated that treatment with idebenone protected from loss of color vision, particularly in patients at imminent risk of further vision loss. The mean age of patients was 28.1 years; 87.2% were men, 76.9% carried the m.11778G>A mutation, and mean duration since onset was 2 years [8].

Dosage—In the LHON study, a dose of 900 mg/day (300 mg three times daily during meals) was administered. In other trials, a dose of 90–270 mg/day was used.

Riboflavin

Riboflavin is a water-soluble B vitamin (B2) that serves as a flavoprotein precursor. It is a key building block in complexes I and II and a cofactor in several other key enzymatic reactions involving fatty acid oxidation and the Krebs cycle This compound was also discussed in detail in the prior review [2]. Since then, a new disorder with complex I deficiency due to mutations in acyl-CoA dehydrogenase 9 (ACAD9) was described. ACAD9 is a flavin adenine dinucleotide-containing flavoprotein, and treatment with riboflavin was advised [9].The effect of riboflavin in cell cultures with mutations in ACAD9 [10] in two cases showed that supplementation of riboflavin for 3 days resulted in a significant increase in complex I activity, whereas the activity of complex IV remained unchanged [10].

Dosage—Standard dosage is from 50–400 mg/day in divided doses; the average dose is 100 mg/day.

Bypass of respiratory chain components

Succinate, vitamin C, and vitamin K were discussed in our previous review, [2] and are all agents known to cause bypass of respiratory chain components. Succinate is a citric acid cycle intermediate that donates electrons directly to FAD, thus partially bypassing complex I. Administration of vitamin K in the form of menadione and vitamin C increased the recovery rate of ATP synthesis in a patient with a deficiency in a cytochrome b-containing complex III.

Agents known to increase substrate supply to the respiratory chain

Agents aimed at increasing respiratory chain substrate availability include thiamine, carnitine, and the synthetic agent dichloroacetate (DCA). Thiamine enhances pyruvate dehydrogenase activity, thereby increasing the availability of pyruvate for oxidation. DCA

keeps the pyruvate dehydrogenase complex in an active state and reduces the accumulation of lactate in body tissues. Carnitine was previously discussed in detail [2].

Dichloroacetate (DCA) was discussed in the previous review, and there has been one new study since then. DCA is a potent lactate-lowering drug that 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 [2]. 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 did not lead to conclusive evidence of the benefits of DCA in patients with mitochondrial disorders [2]. An open-label chronic safety study on patients who had originally participated in randomized controlled trials of DCA showed that chronic DCA administration was generally well-tolerated in patients with congenital causes of lactic acidosis and was effective in maintaining normal blood lactate levels, even in pyruvate dehydrogenase complex (PDC)-deficient children not consuming a strict ketogenic diet. The age of participants ranged from 16.9 to 49.9 years (mean ± SD: 23.5 ± 10.9 years) [11].

Dosage—DCA has been used in clinical trials at a dose of 25 mg/kg/day in two divided daily doses.

Thiamine: A case report described clinical recovery with thiamine usage in mitochondrial disorder in a patient 24 years of age with adult-onset Leigh disease presenting as severe brainstem encephalopathy of subacute onset. A marked clinical recovery was seen after administration of high doses of thiamine, coenzyme Q, L-carnitine, and vitamins C and E, combined with effective treatment with continuous positive airway pressure for the underlying severe obstructive sleep apnea [12].

Dosage—Thiamine has been used in doses up to 900 mg/day.

Energy buffering

Creatine

Creatine, which combines with phosphate in the mitochondria to form phosphocreatine, acts as buffer for ATP. It serves as a source of high energy phosphate released during anaerobic metabolism [2]. There have been no new trials since the last publication.

Dosage—Start with 0.1 g/kg po daily; maximum 10 g/day.

Agents with antioxidant activity

Some of the agents that have been used in the treatment of mitochondrial disorders have focused on decreasing the toxic metabolites by using antioxidants. They include cysteine, vitamin E, lipoic acid, and N-acetyl-cysteine (NAC).

Cysteine

A whey-based oral supplement (WBOS) with a relative abundance of glutamylcysteine has been shown to augment intracellular glutathione concentrations [13]. Supplementation of healthy young adults with such a nutritional formulation augmented lymphocyte glutathione concentrations and increased muscle performance [13]. A randomized placebo-controlled crossover in mitochondrial diseases (7 women, 6 men; mean age 52.5 ± 15.2 years) showed that treatment did not modify lactate concentration, clinical scale, or quality of life, but significantly reduced oxidative stress levels [14].

Dosage—In clinical trials, a dose of 10 g/day was administered.

Lipoic acid

Lipoic acid is found naturally within the mitochondria and is an essential cofactor for pyruvate dehydrogenase and ketoglutarate dehydrogenase [15, 16]. Lipoic acid acts as a potent antioxidant and decreased a marker of oxidative stress in healthy volunteers aged 37.5 +/− 7.7 years [17].

Dosage—Typical range is 50–200 mg/day, and up to 600 mg/day has been reported.

N-acetyl cysteine (NAC)

Glutathione is a major intracellular antioxidant, and its biosynthesis depends on the intracellular availability of cysteine [13]. Oral N-acetyl cysteine prevents glutathione depletion in the brain by systemically increasing cysteine and synthesis of glutathione [21]. Supplementation with N-acetyl cysteine enhanced muscle cysteine and glutathione availability and attenuated fatigue during prolonged exercise in endurance-trained individuals [18, 19]. However, there were significant adverse effects with this treatment, possibly related to elevations in extracellular cysteine [20].

Viscomi et al. (2010) [22] treated five patients (ages 10–32 months) carrying a homozygous mutation in ETHE1 with daily therapy consisting of oral metronidazole (30 mg/kg body weight) and NAC (105 mg/kg body weight). ETHE1 impairment accumulates H2S that inhibits cytochrome c oxidase and short-chain acyl-CoA dehydrogenase (COX, also known as SCAD) [22]. After >3 months of therapy, these patients showed clinical, biochemical, and MRI improvement. MRI at 36 months of age showed a reversion of brain atrophy and a reduction in leukodystrophy, although the lesions in the neo-striatum had become more evident. Ethylmalonic acid (EMA) in urine and plasma dropped significantly and persistently, as did the concentrations of C4 acylcarnitines [22].

Agents with mechanism of action on nitric oxide (NO) metabolism

Arginine

Arginine, a semi-essential amino acid involved in growth, urea detoxification, and creatine synthesis [2], produces nitric oxide, which has neurotransmitter and vasodilatory properties. It has been studied in mitochondrial disease primarily in the treatment of metabolic strokes. Since the last review, a study was performed assessing arginine, citrulline, and NO

metabolism in control subjects and subjects with MELAS syndrome. Patients were 18–57 years of age, diagnosed clinically with MELAS syndrome, and harbored the m.3243A>G mutation in the MT-TL1 gene; control subjects were healthy adults aged 20–46 years [23]. The results showed that arginine and, to a greater extent, citrulline supplementation increased the de novo arginine synthesis rate, plasma concentrations and flux of arginine and citrulline, and NO production. De novo arginine and NO synthesis increased markedly with citrulline supplementation [23]. The effect of arginine and citrulline supplementation may extend beyond improvement in stroke-like episode to improvement in other clinical features associated with MELAS syndrome, including migraine headaches, muscle weakness, exercise intolerance, and diabetes [23]. These compounds are undergoing further study.

Dosage—Standard dosage in acute stroke is 500 mg/kg IV per day for 1–3 days. Maintenance dose is 150–300 mg/kg orally or IV daily, divided into two or three doses.

Improvement in oxidative capacity

Exercise and training has been shown to increase oxidative capacity. This was discussed in the previous review [2], and there is a new publication available since last update. After 10-week aerobic training in 7 patients (6F e 1 M, mean age 44.9 ± 12.1 years) affected by mitochondrial disease, there was a decrease in the occurrence of oxidative stress as indicated by significant decrease in the circulating levels of lipoperoxides, These data indicate that oxidative stress occurs in mitochondrial patients, and that aerobic training is useful in partially reverting this condition [24].

Newly studied medications with antioxidant activity

EPI-743

EPI-743, a synthetic analog of vitamin E, targets repletion of reduced intracellular glutathione [25]. In an open-label study (Enns et al., 2012) in 13 children (ages 2–27 years) with mitochondrial diseases, EPI-743 modified disease progression in >90% of patients as assessed by clinical, quality-of-life, and noninvasive brain imaging parameters [26]. In another open-label study, a single-arm clinical trial was performed in 10 children with genetically defined Leigh syndrome. Patients (ages 1–13 years) were treated for 6 months with EPI-743 and had improved clinical outcomes [25]. In a small open-label trial, EPI-743 arrested disease progression and reversed vision loss in all but 1 of the 5 consecutively treated patients (8–54 years of age) with Leber hereditary optic neuropathy (LHON). Dosage of EPI-743 orally 3 times daily (100–400 mg per dose) was used in this trial. [27].

Dosage—Not established.

Possible upcoming therapies

Drugs such as benzafibrate, resveratrol, and AICAR target the master regulator of mitochondrial biogenesis, PGC-1α, either directly or indirectly, and manipulate mitochondrial metabolism [28].

Bezafibrate

Like the other fibrates, bezafibrate is an agonist of PPARα and is commonly used for the treatment of dyslipidemia. Bezafibrate is known to induce mitochondrial biogenesis and to control the expression of antioxidant enzymes and uncoupling proteins. In an animal murine model of COX deficiency [29], bezafibrate administration improved mitochondrial protein production and mitochondrial ATP-generating capacity. Bezafibrate treatment also attenuated astrogliosis and decreased the level of inflammatory markers in the affected tissues. Overall, bezafibrate had a neuroprotective effect in this mouse model of mitochondrial encephalopathy. The clinical trial of BEZ treatment for a boy with the intermediate form of glutaric acidemia type 2 (GA2) showed that daily administration dramatically improved his motor and cognitive skills, accompanied by sustained reduction of C4, C8, C10, and C12 acylcarnitines in blood and normalized urinary organic acid profile. No major adverse effects have been observed. These findings imply that bezafibrate may be a promising therapeutic agent for the treatment of neurodegenerative disease associated with mitochondrial dysfunction, although further study is warranted [29, 30].

Resveratrol

Resveratrol (3, 5, 4’-trihydroxy-trans-stilbene, RSV) is a natural component present in low concentrations in the skin of red grapes and is well-studied for its capability to activate sirtuins, including SIRT1, in mammals [28]. Sirtuins play an integral role in mitochondrial proliferation by increasing PGC-1a activity. In the majority of these studies, the pharmacological activation of the PGC-1α axis showed true potential as therapy, but the compound has not been studied specifically in mitochondrial disease [28].

Dimethylglycine (DMG)

DMG is a component of pangamic acid; the mechanism by which it may improve respiratory chain function is unclear. DMG is oxidized by a flavine adenine dinucleotide-dependent dehydrogenase, and its electrons enter the respiration chain at the level of coenzyme Q, upstream of COX. It is transformed to sarcosine by dimethylglycine dehydrogenase, another mitochondrial enzyme [31, 32]. A randomized double-blind study on 5 children (9–17 years of age) with Saguenay-Lac-Saint-Jean cytochrome c oxidase (SLSJCOX) deficiency showed that the mean VO2 (measurements of venous lactate and oxygen consumption) in 5 participants was lower after administration of both DMG and placebo, although neither value reached statistical significance. There was no detectable effect on blood lactate, pyruvate, bicarbonate, or pH. No significant side effects were noted [31].

Other future therapies

Gene therapy

In the future, therapy for mitochondrial disorders may also include germ-line and gene therapy. Tachibana et al. (2009) reported in Nature that the mitochondrial genome could be efficiently replaced in mature nonhuman primate oocytes by spindle chromosomal complex transfer from one egg to an enucleated mitochondrial-replete egg. The reconstructed oocytes with the mitochondrial replacement were capable of supporting normal fertilization and

embryo development and produced healthy offspring. Genetic analysis confirmed that nuclear DNA in the 3 infants born thus far originated from the spindle donors, whereas mtDNA came from the cytoplast donors [33, 34].

Adeno-associated virus-mediated gene therapy

Yu et al. (2013) demonstrated the feasibility of directly targeting AAV to the mitochondria by fusing a mitochondrial targeting sequence to the AAV2 VP2 capsid protein to achieve ND4 expression in the mitochondria. The vector was used to transduce hybrid cell lines containing mitochondria with a human ND4 mutation. Results showed that not only was the mutant AAV capsid localized within the mitochondria, but that the delivered ND4 protein was properly translated in cells. ATP synthesis was increased 48% in treated cells. This study demonstrated that mitochondrial gene delivery by AAV is achievable [35].

Special considerations

Treatment of epilepsy in mitochondrial disease

Epilepsy is a common feature in many mitochondrial phenotypes and can present as any type of seizure. Reduced mitochondrial function leads to neuronal hyperexcitability by reducing sodium-potassium ATPase activity, disruption of intracellular calcium homeostasis, and glutamate disturbances [36–40]. This can lead to a destructive positive feedback loop in conditions such as POLG and MELAS, where the increased metabolic demand of seizure contributes to further neuronal injury and epileptogenesis [41]. Myoclonic and focal are the most common seizure types, and there is a significant risk of either generalized or focal status epilepticus. In conditions such as MELAS, focal seizures are often preceded by migraines with aura-like phenomena. Mitochondrial respiratory chain defects have also been identified in more classic epileptic encephalopathies, including Ohtahara syndrome, West syndrome, Lennox-Gastaut syndrome, and Landau-Kleffner syndrome [42]. Mitochondrial dysfunction as a cause or contributor to epilepsy is likely significantly clinically underappreciated [43].

With only a few exceptions, the treatment of epilepsy in mitochondrial cytopathies, while challenging, utilizes the same strategies as that of epilepsy with any other etiology. The most notable difference is in avoiding drugs that can potentially worsen mitochondrial function. POLG-related disorders are an absolute contraindication to the use of valproate due to the risk of hepatic failure [44–45] (Table 1). It may be reasonable to complete POLG testing prior to starting valproate treatment in any patient who develops intractable epilepsy and has a history of developmental delay [46]. Valproate has been associated with worsening of MELAS and seizures [47–50], and should be used with caution in any patient thought to have mitochondrial dysfunction. However, it was shown to bring status under control, improving overall disease control, in at least one case [51]. It is unclear if valproate was better tolerated due to concomitant treatment with creatine in this case.

While a combination of sodium channel drugs and benzodiazepines with the addition of topiramate or levetiracetam generally appears to be effective, it has not been rigorously tested [52]. Carbamazepine was reported to gradually control electroclinical status in a patient with MELAS [53], while phenytoin, on the other hand, was reported to cause

intestinal pseudo-obstruction in a MELAS patient [54]. It is highly likely that other antiepileptic drugs also interact with the mitochondrial respiratory chain and ATP production. One in vivo study found that while carbamazepine decreased ATP, lamotrigine may increase the production of ATP [55], which could explain the potential neuroprotective effects that have been observed [56]. Levetiracetam may be a reasonable first-line drug for MERRF [57].

There is growing evidence supporting the use of the ketogenic diet in the treatment of epilepsy related to mitochondrial disease. Although the mechanism of the diet remains poorly understood, it is thought that in mitochondrial disease it may partially bypass complex I [58]. Laboratory studies have shown that it may alter disease progression of mitochondrial cytopathies. In humans, data includes individual case reports [59–60] and three retrospective studies involving more than 60 patients in total. One study assessed safety only, reporting no serious adverse effects [61]. The other two, with a combined total of 38 patients with various mitochondrial cytopathies and refractory epilepsy, reported that as many as half of the patients became seizure-free and up to 75% had a 50% reduction in seizures [42, 62]. Reported side effects included hypoglycemia and persistent acidemia requiring cessation of the diet for two patients [62]. No serious or life-threatening side effects have been reported with the use of ketogenic diet in mitochondrial disease. The long-term effectiveness of the diet has not been reported, and it remains unclear whether it modifies the course of mitochondrial diseases.

Various other therapies have shown promise in isolated case studies. One patient with Kearns-Sayre syndrome and low CSF/serum folate ratio suggestive of concomitant folate transporter disruption was reported to benefit from folinic acid supplementation [63]. Status epilepticus refractory to benzodiazepines, thiopental, phenytoin, and propofol resolved with the addition of ketamine in a 22 year-old with a POLG mutation [64]. A patient with PDH-E1α gene mutation resulting in Leigh syndrome showed marked overall improvement, including epilepsy control, with the addition of sodium pyruvate 0.5 g/kg/day [30]. L-arginine infusion or a cocktail of folic acid, riboflavin, and coenzyme Q10 may be he helpful for status epilepticus associated with MELAS [65, 66]. There is a noticeable paucity of reliable treatment data in mitochondrial disease. Future data should focus on high-quality treatment trials [67].

Perioperative considerations

General principles of perioperative and intraoperative management of patients with mitochondrial disease include supportive care to avoid metabolic decompensation and acidosis, anticipation of the potential need for additional ventilatory or circulatory support, and caution with regard to potential adverse effects of anesthetics and other medications. Typical preoperative fasting may provide undesirable physiologic stress. Intravenous dextrose-containing fluids should be initiated preoperatively to avoid catabolism during fasting. Although some practitioners have reported use of lactated Ringer’s without serious complication [68], it remains prudent to avoid the use of lactate-containing fluids due to the potential for exacerbation of lactic acidosis as a result of impaired lactate metabolism.

Preoperative and perioperative electrolyte abnormalities including hyperkalemia and hyponatremia have been described in MELAS [68, 69], supporting the need for careful monitoring of electrolytes. Preoperative evaluation should include routine chemistries, complete blood count, liver function, ammonia, glucose, and baseline serums lactate. Cardiomyopathy may be present, and cardiac conduction abnormalities are a feature of several mitochondrial disorders [70, 71]. A 12-lead EKG should be obtained, with the potential addition of an echocardiogram.

Physiologic stressors such as surgery have the potential to induce catabolism and exacerbate mitochondrial disease. Furthermore, a degree of suppression of mitochondrial function has been suggested in studies of numerous anesthetic agents, including opiates, propofol, and inhalational and local anesthetics [72]. Nonetheless, there are numerous reports of safe, effective general anesthesia and procedures in patients with mitochondrial disease [68, 73–75]. Physiologic and laboratory parameters should be monitored intraoperatively, including liver function, routine chemistries, ammonia, lactate, and ketosis. Normothermia should be maintained.

The choice of anesthetic agents and dosing regimens requires additional caution and careful titration. These patients may have increased sensitivity to inhalational anesthetics and other induction agents [76, 77]. Sevoflurane may be an agent of choice among the volatile anesthetics due to decreased arrhythmogenicity [75]. There is not sufficient evidence to suggest that patients with mitochondrial disease have an increased susceptibility to malignant hyperthermia [68]. Several authors describe the use of propofol without adverse effects [68, 74, 78], although its use has generally been limited to short-term administration. The data regarding neuromuscular blocking agents are mixed, with case reports describing instances of unchanged, increased, or decreased sensitivity to non-depolarizing agents. [75, 79–84]. In general, care should be taken in the titration and monitoring of neuromuscular blockade in patients with mitochondrial disorders due to the possibility of underlying myopathy and the potential for increased drug sensitivity and altered drug metabolism.

Postoperatively, additional attention is necessary to ensure safe recovery. Opioid analgesia should be titrated carefully to avoid respiratory depression and acidosis. Dextrose-containing fluids should be continued until patients have returned to their full preoperative diet. Pre-existing myopathy, hepatorenal dysfunction, and interaction with other medications may prolong the effects of neuromuscular blockade, and patients may require increased respiratory support. Similarly, pre-existing skeletal muscle weakness may compromise postoperative ventilation. Bulbar weakness secondary to myopathy may increase the risk for aspiration of gastric contents, and ongoing additional ventilatory support should be available if needed.

Intensive care in mitochondrial disease

Mitochondrial dysfunction has been implicated in the pathogenesis of critical illness, including sepsis [72, 85, 86], response to traumatic injury [87], and progression to multi-system organ dysfunction [88]. Restoration of mitochondrial function may be an important step in recovery from critical illness [89, 90]. Patients with a baseline impairment in mitochondrial function are thus at particular risk for decompensation in the setting of an

acute illness. Underlying mitochondrial disease may predispose critically ill patients to multiple organ-system dysfunction as well as neurologic complications, including seizures and metabolic stroke [91]. Current treatments are largely supportive, and are aimed at avoidance or mitigation of metabolic decompensation and treatment of specific organ-system dysfunction.

Given the increased sensitivity to physiologic stress in acutely ill patients with mitochondrial cytopathies, increased metabolic support should begin before systemic decompensation becomes apparent. This includes maintaining hydration, providing sufficient calorie intake, correction of metabolic and electrolyte abnormalities, and treatment of the underlying precipitating condition. Medications toxic to mitochondria should be avoided if possible. Normothermia should be maintained. Intravenous dextrose-containing fluids should be given to prevent dehydration and to provide anabolic substrate. Fluid therapy should take into account the patient's clinical situation and any underlying cardiac or renal dysfunction. Where appropriate, aggressive fluid therapy with dextrose-containing fluids should be provided at 1.25 to 1.5 times maintenance. Lactate-containing fluids should be avoided. If enteral nutrition is not possible, parenteral nutrition should be considered early, with resumption of enteral nutrition as soon as is practical.

Laboratory values including electrolytes, acid-base status, and serum lactate should be monitored closely. Cardiac monitoring should be maintained throughout the acute illness, given the potential for arrhythmias and other cardiac abnormalities. Continuous EEG monitoring should be considered for any encephalopathic critically ill patient due to the risk for subclinical status epilepticus [92, 93]. Seizures are common in many mitochondrial cytopathies and may exacerbate ongoing metabolic decompensation. Common treatment protocols for status epilepticus are generally appropriate in mitochondrial disease unless contraindicated by specific organ-system dysfunction. Caution should be exercised with the use of valproate in mitochondrial disease due to its inhibition of mitochondrial beta-oxidation of fatty acids [94].

One disease-specific therapy that does have limited supportive evidence is L-arginine for stroke-like episodes in MELAS. Energy failure and/or mitochondrial angiopathy are possible mechanisms for these episodes. Based on a potential angiopathic mechanism and the observation that patients with MELAS have lower serum concentrations of L-arginine, several small studies investigated the acute use of L-arginine in stroke-like episodes [95, 96]. Intravenous arginine dosed at 500 mg/kg/day, given acutely at the onset of stroke-like symptoms, ameliorated acute stroke symptoms and improved serum lactate levels [95]. Daily oral arginine at 150–300 mg/kg/day may provide prophylaxis against further stroke-like episodes [96]. The proposed mechanism of action is nitric oxide-mediated vasodilation [97]. Blood pressure should be monitored for hypotension with intravenous arginine dosing.

Conclusions

Classification of therapies for mitochondrial disorders has evolved from the empirical therapies targeting residual respiratory chain to acting at the molecular level to alter expression of mutated mtDNA genes within the cell nucleus. This report discusses older as

well as newer pharmacological agents, many of which are in clinical trials. However, in the future, treatment strategies may employ a combination of pharmacological treatments that have undergone rigorous clinical trials targeting OXPHOS, as well as newer strategies at the molecular level. The identification of quantifiable disease-specific biomarkers will aid in the quest for rational treatment strategies in the future.

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References and Recommended reading

Papers of particular interest, published recently, have been highlighted as:

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•• Of major importance

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Table 1

Select drugs with reported mitochondrial toxicity

Medication	Symptoms	Mechanism (if known)
Valproic acid	Hepatopathy	Inhibits fatty acid oxidation, the citric acid cycle, and oxidative phosphorylation; depletes carnitine and inhibits complex IV. This drug is contraindicated in mitochondrial depletion syndromes such as POLG
Antiretrovirals	Peripheral neuropathy Liver dysfunction and myopathy	Impairs mtDNA replication, leads to mtDNA depletion, carnitine deficiency, lactic acidosis, lipodystrophy
Aminoglycoside antibiotics	Hearing loss, cardiac toxicity, and renal toxicity	impaired mtDNA translation
Steroids	Reports of deterioration in Kearns-Sayre syndrome	

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 (B2)	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), hypernatremia, 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

Mitochondrial medications and supplements					
Medication	**Dosage (pediatric)**	**Dosage (adult)**	**Monitoring**	**Adverse effects**	**Comments**
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
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

* 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 stroke like episodes; po=by mouth