Overview of Approaches to Mitochondrial Disease Therapy

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Abstract
Mitochondrial respiratory chain diseases are the most prevalent group of inherited neurometabolic disorders and are clinically, biochemically, and genetically heterogeneous. They may present at any stage of life and often manifest with severe multisystem disease, although single organ involvement is characteristic of some conditions such as Leber hereditary optic neuropathy. As a result of these complexities, the diagnostic pathway is often challenging, so too is further advice, guidance, and therapy following diagnosis. Difficulties also occur with regard to genetic counseling, prognostic assessment, and treatment; there is still no cure or even agreed standards of treatment available for these debilitating diseases. Limited therapeutic options and a lack of curative treatment have led to physicians prescribing individual “trials of therapy” for which no evidence-based recommendations are available. However, new therapeutic options are the focus of active molecular genetic, biochemical, and clinical research, and some medicinal compounds have achieved international governmental approval. In this chapter, we summarize these advances and provide a broad overview of the treatment and novel approaches to preventing transmission of mitochondrial disease.

Keywords
mitochondrial disease, phenotype, genetic, therapy, mtDNA

Introduction
Mitochondrial disorders are frequently multisystemic and the most prevalent group of inherited neurometabolic diseases (prevalence: 1:4300).¹ The diseases are clinically, biochemically, and genetically heterogeneous so that recognition and diagnosis are often difficult. However, recent advances in next-generation sequencing (NGS) technology have led to vast improvements in genetic diagnosis for these patients. Improved diagnostic algorithms and the use of NGS have enabled an earlier diagnosis for many and, in rare cases, the early instigation of effective therapy. Due to the variability of clinical features and the particular nature of some of the biochemical or genetic defects, it is not easy for the lay practitioner to identify and screen for treatable aspects of mitochondrial disease and early referral to a specialized center is therefore recommended. There is still no cure available for the vast majority of these conditions, and though liver or hematopoietic stem cell transplant may offer hope for a few, clinical care is largely confined to managing the complications of these diseases (Newcastle Care Guidelines: www.newcastle-mitochondria.com) or assisting prevention through prenatal testing, preimplantation genetic diagnosis (PGD), and mitochondrial donation therapy. The limited therapeutic options and the lack of curative treatment options have led to increased individual therapy trials, particularly focused on optimizing oxidative phosphorylation (OXPHOS) and improving antioxidant capacity. Mostly, a combination of vitamins, commonly including coenzyme Q10 (ubiquinone), thiamine, and riboflavin is recommended. However, there are trials ongoing worldwide investigating potential therapeutic approaches.

Background of mtDNA and nDNA Mutations and Mitochondrial Disease
Primary mitochondrial diseases are genetic conditions that impair the process of intracellular energy conversion known

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as OXPHOS and may occur as a result of mutations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA). Mitochondrial DNA is a maternally inherited, circular double-stranded molecule of 16 569 base pairs, encoding 37 genes (13 proteins of the OXPHOS system, 2 rRNAs, and 22 tRNAs). The remaining mitochondrial proteins are nuclear-encoded and imported into the mitochondria. Mutations of mtDNA can be classified into (1) structural rearrangements (eg, large-scale single deletion of mtDNA), (2) quantitative disorders of mtDNA (reduction in mtDNA copy number, mtDNA depletion), and (3) point mutations.

All eukaryotic cells contain, depending on their lineage and differentiation, a variable number of mitochondria, which carry numerous copies of the mitochondrial genome (>100 000 copies in mature oocytes). During mitosis, wild-type mtDNA and mutant mtDNA are randomly distributed to the daughter cells (replicative segregation). A cell is deemed to be homoplasmic if all mtDNA copies are identical. However, a heteroplasmic state exists if wild-type and mutant mtDNA are coexistent in a cell. The level of heteroplasmacy describes the percentage of mutant mtDNA and may vary over time. In general, the proportion of mutated mtDNA has to exceed a certain percentage (threshold) to cause biochemical defects leading to clinical symptoms and, above this threshold, the higher the level of heteroplasmacy the greater the risk of disease. One clear exception occurs in the form of homoplasmic mutations where biochemical and clinical phenotype can be variably expressed.

Difficulties in “Genotype–Phenotype Correlations”

Defects of OXPHOS are one of the most common groups of inherited neurometabolic diseases, and with the advent of NGS technology, opportunities to make a genetic diagnosis in these disorders continue to grow. However, studying this disease remains problematic for a number of reasons. Firstly, the clinical manifestations of mitochondrial disease are protean and may present at any stage of life. Disease may involve a single (Leber hereditary optic neuropathy [LHON]) or multiple (Kearns Sayre Syndrome) organs, often with intermittent acute exacerbations punctuating a slowly progressive disease with extended periods of relative stability. Moreover, the genotype–phenotype relationship in mitochondrial diseases can exhibit remarkable overlap, with the same clinical phenotype being caused by mutations in several different genes, and in contrast, the same genetic mutation can give rise to several distinct phenotypes. For example, the m.3243A>G mutation is associated with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), maternally inherited diabetes and deafness (MIDD), chronic progressive external ophthalmoplegia (CPEO), and nonsyndromic clinical presentations. Aggravating the problem of “genotype–phenotype” correlations, there is a historical lack of genetic diagnosis and reliance on biochemical abnormalities detected in affected tissue.

Improvements in Clinical Research

During recent years, there has been an immense improvement in genetic diagnosis of patients with mitochondrial diseases due to advanced technologies including whole exome sequencing and whole genome sequencing. Improved diagnostic algorithms and the use of these new technologies have enabled an earlier diagnosis for many, and in rare cases, the early instigation of effective therapy. The establishment of “orphan drug status” and other incentives, including tax respite and voucher exchange schemes, has made clinical research in mitochondrial disease rather more attractive to the pharmaceutical industry. A directive from the European Government requiring each member state of the European Union to produce a national strategy for rare diseases has also been helpful in mobilizing support from national governments. This area of research has been further assisted by the development of national cohorts and registries of patients, facilitating “deep” phenotyping and collection of natural history data. These initiatives have undoubtedly improved the “trial readiness” of the mitochondrial disease population in some countries at least.

Previous Therapeutic Approaches

Treatable Aspects

Due to the wide variability of phenotypes in mitochondrial diseases, early identification and screening for treatable aspects are necessary. If possible, the patient should be referred to a specialized mitochondrial center for initial diagnosis and coordination of investigation and treatment. Depending on the patient/parent preferences, subsequent care may be provided locally with input from the specialized center. Clinical care guidelines for managing various aspects of mitochondrial disease are available from the Wellcome Centre for Mitochondrial Research in Newcastle upon Tyne, United Kingdom. These clinical guidelines are updated every 2 years and can be found online: http://www.newcastle-mitochondria.com/clinical-professional-home-page/clinical-publications/clinical-guidelines/. Furthermore, handbooks for patients and parents of affected children are available for download from the Mitochondrial Medicine Society: http://www.mitosoc.org/toolkit/. Recently, the clinical guideline on management of stroke-like episodes in MELAS has been updated.

Cardiac involvement is a common feature in mitochondrial diseases. Both, conduction abnormalities and cardiomyopathy are observed in mitochondrial disease patients. Recent studies show an association of specific cardiac phenotypes with pathogenetic mtDNA mutations (eg, heart block associated with large-scale mtDNA deletions, hypertrophic cardiomyopathy with mtDNA point mutations, and adult sudden death syndrome with the m. 3243A>G mutation). General assessment of patients and seemingly asymptomatic carriers for possible cardiac involvement should include a standard 12-lead electrocardiogram and transthoracic echocardiogram. Cardiomyopathy can be managed with the use of angiotensin-converting
enzyme inhibitors, which may prevent early hypertrophic remodeling, while coadministration of β-adrenergic receptor antagonists (β-blockers) or calcium channel blockers will slow the heart rate and improve diastolic filling. Pacemaker implantation should be considered if patients are at risk of atrioventricular (AV) block (including first-degree AV block >300 milliseconds) or any fascicular block with or without symptoms. Clinical vigilance to identify heart block and prompt action with regard to implanting a pacing device can be life-saving in mitochondrial disease.

Some mitochondrial diseases are defined by a severe gastrointestinal phenotype (eg, mitochondrial neurogastrointestinal encephalomyopathy [MNGIE]). Others, such as those caused by the m.3243A>G mutation, have significant gastrointestinal involvement which is often unrecognized and may lead to chronic intestinal pseudo-obstruction (CIPO), a potentially life-threatening complication in these patients. Acute presentations of CIPO can mimic mechanical obstruction of both, the upper gastrointestinal (GI) and the lower GI. In the acute phase, intravenous (IV) fluids (with avoidance of Ringers lactate solution) should be provided. Vomiting associated with CIPO can lead to serious complications, especially in patients who are not able to adequately protect their own airways. In any case of CIPO, surgical intervention should be the last option due to its high mortality rates.

Furthermore anorexia, nausea, and vomiting can cause difficulties in taking oral medication or even hamper fluid and calorie intake. Patients having chronic constipation may benefit from a low fiber diet and institution of simple measures such as increasing fluid intake and the use of osmotic laxatives. If these interventions are unsuccessful, then consideration should be given to referral for gastroenterological and dietetic opinions. Some patients with mitochondrial disease experience significant dysphagia or severe gastroesophageal reflux and surgical placement of a gastrostomy (with or without fundoplication) or jejunostomy may be necessary.

Diabetes Mellitus is one of the most common features in mitochondrial diseases and female patients harboring one of the commonest mtDNA mutations (m.3243A>G) appear to have an increased risk of gestational diabetes. Although a large proportion of patients with the m.3243A>G mutation have clinical features that do not conform with a specific syndrome, many do have a syndromic presentation that includes MELAS, CPEO, and MIDD. The clinical presentation ranges from ketone positive, insulin-dependent diabetes to classical non-insulin-dependent diabetes. Progression to insulin dependency as a result of pancreatic islet cell dysfunction is common and often rapid (<4 years).

Epilepsy is a regular feature of many mitochondrial diseases and particularly common in myoclonic epilepsy with ragged-red fibers (MERRF), MELAS, and POLG1-associated syndromes such as Alpers-Huttenlocher. The MELAS and MERRF seem to respond well to Levetiracetam and/or Clozapam, and early initiation/escalation of anticonvulsant therapy is crucial in managing stroke-like episodes with the aim of preventing cortical damage due to seizure activity. Sodium valproate should be avoided due to potential hepatotoxicity, particularly in patients with mutations in POLG1.

Central nervous system (CNS) involvement is a recognized feature of mitochondrial disease, with spasticity and dystonia being common CNS manifestations in both children and adults. Medical intervention with conventional treatments for spasticity and dystonia should be tailored to the individual and initiated early, in conjunction with appropriate physiotherapy. Baclofen or botulinum toxin injections should be considered in cases of spasticity while those having dystonia should be offered a trial of l-Dopa.

Exercise is known to improve functional capacity in patients with mitochondrial disease, and although exercise does not provide a cure for mitochondrial disease, it can greatly improve quality of life, prevent complications, and help with the management of ataxia.

Respiratory impairment, as a consequence of diaphragmatic weakness, is a common occurrence in mitochondrial myopathies though is often overlooked by both physicians and patients. Affected patients may develop chronic respiratory insufficiency or decompensate acutely as a result of cardiopulmonary disease, general anesthesia, or postoperative complications. Diaphragmatic weakness may also lead to nocturnal hypoventilation, which can be effectively treated by noninvasive positive pressure ventilation. Swallowing difficulties (usually due to bulbar weakness) can lead to aspiration pneumonia, and repeated episodes may contribute to chronic respiratory failure. Paradoxically, coughing can causeatelectasis, reduced lung volumes, and predispose to recurrent chest infections. Patients with respiratory involvement should be offered access to all relevant vaccinations (eg, influenza vaccine, pneumonia vaccine).

Otolaryngology and Psychological Support

Swallowing and speech difficulties can often be significantly improved by speech therapy. Hearing disorders can be improved with a hearing aid, and in individual cases, a cochlear implant may also be indicated. Many patients have difficulty coping with mitochondrial disease, and aspects such as fatigue are particularly challenging. Perhaps not surprisingly, the prevalence of psychological problems such as depression is high in this patient group, and psychotherapy is often appropriate.

Patient Groups

Patients, families, and carers affected by mitochondrial disease in many countries in Europe, North America, and Australasia have formed their own patient support groups. These, usually charitably funded groups provide practical and emotional support to families and often help with access to expert assessment and opinion. An international mitochondrial patient organization has been formed from representatives of individual mitochondrial patient groups across many different countries and, like the United Mitochondrial Disease Foundation (United States) and the Lily Foundation (United Kingdom), has campaigned for patients with mitochondrial disease at the highest levels of government.
Specific Therapies: Vitamins

Due to the clinical, biochemical, and genetic heterogeneity of mitochondrial diseases, there is still no standardized treatment available. Another limiting factor is the inaccessibility of the mitochondrion as a target for possible drugs: a potential treatment needs to enter the mitochondrial matrix, surrounded by 2 mitochondrial lipid membranes, having already traversed the cell membrane. A variable combination of vitamins, commonly including coenzyme Q10 (ubiquinone), thiamine, and riboflavin among others is often recommended on the basis that these may be helpful in optimizing OXPHOS and are very unlikely to cause harm at the doses prescribed.

Vitamin cocktails: Coenzyme Q10 (ubiquinone) acts as a mobile electron carrier (complex I/II to complex III) and has, in addition, antioxidative properties. Although ubiquinone deficiency is a clear indication for treatment with high dose (500-1000 mg/d) coenzyme Q10, this compound is also tried in many other mitochondrial diseases usually with more modest doses, in the range of 90 to 300 mg/d. The side-effect profile of coenzyme Q10 is remarkably benign with even high doses producing few, if any, problems. Riboflavin (vitamin B2) is a precursor of flavoprotein. It serves as a key building block in complex I and II and as cofactor in several other key enzymatic reactions involving fatty acid oxidation and the Krebs cycle. The main indication for treatment (50-100 mg/d orally) is complex I or complex II deficiency in relation to ubiquinone deficiency caused by ETFDH mutations. Recently, a neonatal case of complex I deficiency (including hypotonia, cardiac hypertrophy, lactic acidosis) due to an ACAD9 mutation has been reported. After treatment with large doses of Riboflavin, a favorable clinical response was observed. The patient had no cognitive impairment and normal psychomotor development at the age of 5 years.

Carnitine transfers long-chain fatty acids across the mitochondrial inner membrane into the mitochondrial matrix where there are necessary for the mitochondrial β-oxidation. Carnitine is available for oral or intravenous use in mitochondrial diseases. Individual therapy with acetyl-L-carnitine is often suggested; however, there is limited evidence to support this recommendation.

Some vitamins, are mainly used as part of an antioxidant cocktail, for example, thiamine, vitamin C, and vitamin E. Thiamine, often used to treat patients with pyruvate dehydrogenase (PDH) deficiency, is known to enhance the activity of PDH and increase the availability of pyruvate for oxidation. Biotin is a water-soluble vitamin that serves as an essential coenzyme for 5 carboxylases. Both, biotin and thiamine are used in treatment of biotin-responsive basal ganglia disease caused by mutations in SLC19A3 gene. Furthermore, biotin is also used in patients with biotinidase deficiency mutations, which is known to mimic Leigh syndrome.

Many patients with mitochondrial disease are at risk of vitamin D deficiency due to their chronic ill health, lack of sun exposure (immobility), or and dietary insufficiency. For this reason, frequent measurement of vitamin D levels in blood is recommended, and if applicable, vitamin D substitution should be ensured.

Idebenone

Leber hereditary optic neuropathy is most frequently caused by one of the following mtDNA mutations: m.11778G>A, m.3460G>A, and m.14484T>C though a number of “secondary” mutations have been described. Most LHON patients remain asymptomatic until early adulthood when visual loss may be sudden and profound. Often asymmetric in onset, the visual loss can be triggered by smoking and possibly alcohol. The marked decrease in visual acuity experienced during the acute phase of LHON is thought to be a consequence of respiratory chain dysfunction in viable, but inactive, retinal ganglion cells. Idebenone is known to preserve or reestablish retinal ganglion cell function during the acute phase and thus protects from irreversible retinal ganglion cell loss. The first complete randomized, placebo-controlled, double-blind clinical trial in LHON, including 85 unselected patients with LHON ≥14 years of age, receiving 900 mg/d of idebenone or placebo in a 2:1 ratio for 24 weeks, provided clear evidence supporting the beneficial effects of idebenone in LHON. Accordingly, the European Medicines Agency has subsequently licensed Raxone (idebenone) to treat adults and adolescents aged 12 years and older at a recommended daily dose of 900 mg. Treatment should begin immediately after diagnosis and continue, if possible, for at least 2 years.

L-Arginine and Citrulline

Stoke-like episodes in MELAS syndrome usually occur before the age of 40 years and are 1 cardinal clinical feature of this condition. Hemianopsia or cortical blindness are often the first focal neurological disturbances, and the episodes are often accompanied by migraine-like headaches with vomiting and epileptic seizures. Nitric oxide (NO) donors, such as L-arginine and citrulline, may be a therapeutic option for MELAS-related stroke-like episodes, and research studies are ongoing. These NO donors may reduce the severity of stroke-like episodes and reduce the frequency of the episodes. However, there are only a few clinical trials investigating L-arginine, and the window of opportunity for treatment with L-arginine is limited (within 12 hours of onset).

Dichloroacetate

Dichloroacetate (DCA) is a synthetic agent aimed to increase the respiratory chain substrate availability, so as to keep the PDH complex in an active state and reduce the accumulation of lactate in body tissues. Dichloroacetate is used to treat lactic acidosis, a common problem in mitochondrial disorders. However, treatment with DCA leads to irreversible peripheral neuropathy. Controlled trials did not lead to conclusive evidence of the benefits of DCA in patients with mitochondrial disorders,
but individual case reports suggest some benefit from using DCA as a treatment option.9

EPI-743 is a synthetic analogue of vitamin E (para-benzoquinone), targeting the repletion of reduced intracellular glutathione.26 There are some studies showing that treatment with EPI-743 in patients with Leigh syndrome (subacute necrotizing encephalopathy) improved the clinical outcome.25–27 EPI-743 is known to be a potent antioxidant (about >100× higher than CoQ10), but it failed to reach the end point in a recent double-blind randomized controlled trial, although an unblinded extension phase of the study is currently ongoing.

**Potential Therapies**

**Heteroplasmy Shift**

Mitochondrial DNA mutations tend to be present in a heteroplasmic state. Therefore, one therapeutic approach is the elimination or reduction of mutated mtDNA amount below the threshold at which the disease biochemically or clinically manifests. Several groups have recently developed cellular models by targeting to mitochondria recombinant restriction endonucleases,29–31 zinc finger endonucleases,32 or transcription activator-like effector nucleases (TALENs).32 Bacman et al were able to reduce the level of heteroplasmy in cell lines of patients harboring a mtDNA deletion (human osteosarcoma cells heteroplasmic for the large 5 kb “common deletion”) and a point mutation (osteosarcoma cybrids heteroplasmic for 14459G>A [LHON] in the MT-ND6 gene).32 The group engineered mitochondrial-specific TALENs. The expression of mitoTALENs led to permanent reductions in heteroplasmy levels in both cell lines. However, one limitation was the severe cellular depletion of mtDNA before repopulation with favorable heteroplasmy ratio.

**Hypoxia**

According to cell and zebra fish model studies, a genetic or small molecule activation of hypoxia response is protective against mitochondrial toxicity.33 Limiting oxygen availability has been found to be a protective factor during respiratory chain inhibition. In a genetic mouse model of Leigh syndrome, it could be shown that chronic hypoxia leads to a marked improvement in survival, body weight, body temperature, behavior, neuropathology, and disease biomarkers.33

**Bone Marrow and Liver Transplantation**

MNGIE is clinically characterized by CPEO, severe gastrointestinal dysmotility leading to cachexia, peripheral neuropathy, and leukoencephalopathy, usually leading to death in early to mid-adulthood.34 The genetic basis of this disease is a loss-of-function mutation in the TYMP gene encoding for the cytosolic enzyme thymidine phosphorylase (TPase), which leads to severe elevations of thymidine and deoxyuridine in blood and other tissues, likely disrupting the dinucleotide pool available for mtDNA synthesis and causing instability of the mtDNA that results in multiple deletions, depletion, and point mutations.35,36 Approaches to eliminate thymidine and deoxyuridine in blood and other tissues only showed positive results transiently.37–39 However, permanent restoration of TPase activity has been achieved by allogeneic hematopoietic stem cell transplantation.40 Another approach of treatment to restore the TPase activity may be liver transplantation as a cellular source of TP.41 A recent study investigated 11 patients who underwent hepatic resection for focal disorders. The overall results of Western blot, ELISA, immunohistochemistry, and qPCR showed that TYMP messenger RNA was expressed in the liver. Consequently, liver transplantation may be considered as a therapeutic alternative for patients with MNGIE.41

Ethylmalonic encephalopathy is caused by ETHE1 mutations and leads to toxic accumulation of hydrogen sulfide and its metabolites, including thiosulphate. Clinical features include diffuse microvasculature damage (petechial purpura, multiple necrotic brain lesions), orthostatic acrocyanosis, and hemorrhagic effusions of intestinal mucosa associated with chronic diarrhea. The early-onset brain damage leads to severe psychomotor delay with spastic tetraparesis.42 Recently, the development of a liver-specific, adenovirus-mediated expression of human wild-type ETHE1 as a therapy in an Ethe1−/− mouse model led to the hypothesis that liver transplantation could also ameliorate human ethylmalonic encephalopathy.43 Recently, a 9-month-old girl underwent liver transplantation, with her mother as a living donor.4 Eight months after liver transplantation, striking neurological improvement with remarkable achievements in psychomotor development, along with dramatic reversion of biochemical abnormalities, has been observed.

**PGC1α**

PGC1α is known to have neuroprotective effects by increasing mitochondrial biogenesis and its functioning.44 Due to its role in regulation of mitochondrial function, PGC1α is emerging as an important player in ageing and neurodegenerative disorders.44 Bezaflibrate and resveratrol are known to be PGC1α stimulators, and the former already has supportive data from preclinical studies (cellular and mouse models) showing improvement in mitochondrial function and is already licensed as a treatment for high blood fat and has a well characterized side-effect profile. Currently, there is a phase II study of bezafibrate in people with mitochondrial myopathy ongoing in Newcastle upon Tyne, United Kingdom (Newcastle-upon-Tyne Hospitals NHS Trust).

**MitoQ—Antioxidant Delivery**

One major source of reactive oxygen species (ROS) are mitochondria. Consequently, the development of antioxidants, decreasing mitochondrial oxidative damage is one major approach in therapies of mitochondrial diseases.45 To date, MitoQ is the best characterized mitochondria-targeted antioxidant, consisting of a quinone moiety linked to a
The transmission of mitochondrial disease is dependent on the proportion of mutated mtDNA carried by the affected mother’s egg. Homoplasmic mutations will be transmitted to each child in a homoplasmic state. However, in women with heteroplasmic mutation loads, the level transmitted to their children is more difficult to predict. The only methods to avoid transmission of mutated mtDNA are dependent on egg donation, including mitochondrial donation where there remains a small risk of mutation carryover (see below). Other methods such as PGD are risk reduction procedures and are unlikely to completely prevent transmission of the mutated mtDNA. Preimplantation genetic diagnosis and/or prenatal diagnosis are offered to women who have heteroplasmic mtDNA mutations, but are aiming to use their own eggs to have a baby, and women having a mitochondrial disease due to a nuclear mutation. Preimplantation genetic diagnosis may be offered as part of an in vitro fertilization (IVF) cycle prior to the pregnancy. Prenatal diagnosis will be carried out when the pregnancy has been established for some time (chorionic villus sampling at 11-12 weeks’ gestation or amniocentesis at 15-17 weeks). However, none of these techniques can be offered to clinical trials with more severe disabilities are necessary to evaluate the long-term efficacy of this treatment. 

Prevention of Mitochondrial Diseases

The transmission of mitochondrial disease is dependent on the proportion of mutated mtDNA carried by the affected mother’s egg. Homoplasmic mutations will be transmitted to each child in a homoplasmic state. However, in women with heteroplasmic mutation loads, the level transmitted to their children is more difficult to predict. The only methods to avoid transmission of mutated mtDNA are those dependent on egg donation, including mitochondrial donation where there remains a small risk of mutation carryover (see below). Other methods such as PGD are risk reduction procedures and are unlikely to completely prevent transmission of the mutated mtDNA. 

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