

# **Patient Care Standards for Primary Mitochondrial Disease: A Consensus Statement from the Mitochondrial Medicine Society**

**Running Title:** Mitochondrial Disease Patient Care Standards

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## **ABSTRACT**

*Purpose* The purpose of this statement is to provide consensus-based recommendations for optimal management and care for patients with primary mitochondrial disease. This statement is intended for physicians who are engaged in the diagnosis and management of these patients.

*Methods* Working Group members were appointed by the Mitochondrial Medicine Society. The panel included members with several different areas of expertise. The panel members utilized surveys and the Delphi method to reach consensus. We anticipate that this statement will need to be updated as the field continues to evolve.

*Results* Consensus-based recommendations are provided for the routine care and management of patients with primary genetic Mitochondrial Disease

**KEY WORDS:** Mitochondrial disease, Care Guidelines, Consensus Criteria, Delphi Method, Mitochondrial Medicine Society, Preventative Care, Treatment

## INTRODUCTION

Primary genetic mitochondrial disorders occur due to defects in either the mitochondrial or nuclear genome impairing mitochondrial function and structure. They represent one of the most common inborn errors of metabolism with a minimum incidence of 1:5000. Advances in genomics has allowed for improved diagnosis.

Multi-system disease manifestations often occur in mitochondrial patients leading to a need for comprehensive and multi-disciplinary care. Mitochondrial specialty centers have formed over the past decade to meet this need, allowing the field of clinical mitochondrial medicine to develop. No published recommendations exist to guide patient management or clinical care decisions and standardize preventative health maintenance. Practice patterns vary considerably from center-to-center.<sup>1,2</sup> The Mitochondrial Medicine Society (MMS) developed consensus criteria to aid with the diagnosis of mitochondrial disease.<sup>3</sup> This prior publication addressed select management topics but was primarily focused on establishing diagnosis consensus guidelines.

An assessment completed by the MMS showed that 99% of 207 clinicians world-wide seeing mitochondrial patients (including neurologists, geneticists and metabolic experts) were interested in having additional guidelines available for assisting in managing their care. More than half of these respondents (51%) were aware of the Diagnostic Consensus Criteria previously published by the MMS<sup>3</sup>, with 97% finding the guidelines useful and 82% stating that the recommendations directly impacted patient management.

This statement provides consensus-based recommendations for standardized treatment and preventative health care of patients with primary mitochondrial disease. For ease of reference and use, the recommendations are organized with respect to the various organ systems

commonly involved in mitochondrial disorders, and with sections on general symptoms and presentations. This new consensus statement expands upon and is intended to complement, but does not supplant, the 2015 consensus statement "Diagnosis and Management of Mitochondrial Disease".<sup>3</sup> Importantly, our aim is not to provide an inflexible treatment protocol; the aim is to provide guidance based on an international consensus of experienced mitochondrial disease physicians.

In the interest of brevity, limited background information about the various mitochondrial disease manifestations and their comorbidities is provided here. We direct the reader who may be unfamiliar with these topics to review articles referenced within individual sections.

## **METHODS**

Working Group members were appointed by the Mitochondrial Medicine Society's Consensus Criteria Committee. An international panel included thirty-five mitochondrial medicine specialists (34 physicians and one Nurse Practitioner) from Australia (2), Canada (5), Italy (1), Netherlands (1), United Kingdom (3) and United States (23) with specialization in Biochemical Genetics, Cardiology, Clinical Genetics, Endocrinology, Neurogenetics or Pediatric Neurology. Our aim was to capture current clinical practice in these different countries and specialties.

Twenty organ or system-specific clinician-led subgroups were formed, each with at least two members, to review relevant literature and create summaries on select symptoms and comorbid conditions in mitochondrial disease. Some members served on more than one subgroup when needed. Literature summaries were created via a Pubmed Medical Subject Heading (MeSH) and keyword search of organ or system specific manifestations in mitochondrial disease. Primary literature and review articles were both reviewed for the working group summaries.

The field of mitochondrial medicine is not at a point where there is adequate high-level data to establish evidence-based clinical practice protocols. Prior classification of the level of evidence for treatment options in mitochondrial disease show that most publications are retrospective reports, case series and non-blinded, non-randomized trials.<sup>4,5</sup> Thus, the panel developed recommendations using the Delphi Method, a consensus method developed to utilize expert opinion to make a knowledge-based decision when insufficient information is available.<sup>6</sup> This method is increasingly used to develop consensus-based guidelines in medicine and rare diseases. Expert panelists review and summarize the available knowledge and answer surveys concerning the issues in question. The survey is scored to determine the variation in opinion; if consensus is not reached, these items are returned to the panelists for a second round, this time with the mean of responses from the first round available. If needed, a meeting is then held to review areas of persistent disagreement.

The survey instrument was comprised of a five-point bipolar Likert scale; the range of potential responses included strongly disagree, disagree, neutral, agree or strongly agree. Each subgroup was tasked with creating key clinical management recommendations to address within its focus area. Each response was assigned a numerical score, such that strongly disagree was scored as 1, disagree was scored as 2, neutral as 3, agree as 4 and strongly agree as 5. The mean consensus score for each item was then tallied. As per the Delphi criteria, items with a mean consensus of 80% or more (score of  $> 4$  (*Agree/Strongly Agree*) OR  $< 2$  (*Disagree/Strongly Disagree*)) were considered to reach consensus. Items that met criteria as recommendations did not necessarily have unanimous consensus.

All data summaries were reviewed and twenty-five surveys completed by all authors; one for each set of organ-system recommendations and additional surveys for added recommendations by the working group and for those items that lacked consensus. The summaries and initial survey scores are available as an online supplement.

For items that did not meet consensus, a streamlined survey was returned to the panelists for a second round, with items marked with the group's score so that each panelist was aware of the group mean when they re-scored the survey. Following completion of all surveys, a decision was reached by the working group to discard those recommendations that did not meet consensus. Only items that met consensus as defined by the Delphi process (scores of > 4) are included in the formal recommendations.

## **RECOMMENDATIONS**

To orient the reader and contextualize recommendations – brief content synopses of various disease manifestations are provided. Recent published reviews on the topic are referenced when available. Core topic areas are summarized in Figure 1 and presented in alphabetical order. A summary of recommended screening guidelines and specialist consultations to consider are placed in Tables 1 and 2. Previously published Illness, Anesthesia and Stroke Management guidelines<sup>3</sup> are summarized in Table 3. A list of medications that need to be used with caution in mitochondrial patients is summarized in Table 4.

### **Audiology**

Hearing loss is a frequent manifestation of mitochondrial disease though the prevalence is not yet known. A recent comprehensive review article on the topic is not available though some aspects were recently reviewed.<sup>7,8</sup> Progressive sensorineural hearing loss (SNHL), typically of a cochlear origin<sup>9</sup>, is the most common form, although congenital forms and auditory neuropathy can occur. SNHL is believed to mainly result from reduced energy production within both stria vascularis and hair cells and increased reactive oxygen species leading to apoptosis. The health of both the auditory nerve and central auditory system are impacted by mitochondrial disease as well, especially when there is central nervous system (CNS) involvement. In

addition, patients may have hearing loss caused, precipitated or exacerbated by aminoglycosides, such as gentamicin. SNHL usually affects the higher frequencies first, then progresses to involve the middle, and then lower frequencies.<sup>7,8</sup>

### *Recommendations*

1. Formal audiology testing should be performed at time of diagnosis and then every 1-2 years to monitor progression. A sensorineural or auditory neuropathy pattern of hearing loss should be confirmed.
2. Patients should be counseled to avoid environmental and other excessive noise exposure since this can exacerbate hearing loss and even lead to a step-wise deterioration in hearing ability. This exacerbation may or may not be reversible.
3. Aminoglycosides may exacerbate or precipitate the development of hearing loss and should be used with caution.
4. Moderate to severe hearing loss should be treated with digital hearing aids to improve function; when profound, cochlear implantation should be considered.

### **Cardiology**

The cardiac muscle is a high-energy dependent tissue and both cardiomyopathy and arrhythmias are frequently encountered in mitochondrial diseases. A recent retrospective study of more than 200 patients with genetically confirmed mtDNA or nDNA mutations found cardiac involvement in 30%.<sup>10</sup> Recent reviews of cardiac manifestations in primary mitochondrial disease have been published.<sup>11,12</sup>

The frequency of cardiomyopathy in patients with mitochondrial disease has been estimated to be 20% - 40% in older studies though not all had genetically confirmed disease. More recent work has reported cardiac anomalies such as impaired left ventricular ejection-fraction (LVEF),

left-ventricular hypertrophy (LVH) or late-gadolinium-enhancement in up to 53% of their cohort of patients with Mitochondrial Encephalopathy, Lactic Acidosis and Stroke (MELAS), Chronic Progressive External Ophthalmoplegia (CPEO) or Kearns Sayre Syndrome (KSS).<sup>13</sup> While hypertrophic cardiomyopathy seems to be more prevalent, dilated, restrictive, left ventricular non-compaction and histiocytoid cardiomyopathies have been described.<sup>12</sup>

Cardiac conduction abnormalities with an unpredictable course are also a frequent manifestation and arrhythmias are a common cause of death, particularly in KSS and those with the m.3243A>G mutation. Patients are at-risk for sudden death or major cardiac event. In some studies cardiac conduction defects were reported in greater than 10% of patients with mitochondrial disease.<sup>10</sup> Wolf-Parkinson-White (WPW) syndrome, incomplete bundle branch or atrio-ventricular blocks, premature ventricular contractions, and pre-excitation resulting in supraventricular arrhythmias have all been noted.<sup>14</sup> Intra-ventricular conduction block is a significant independent risk factor for major adverse cardiac events in patients with mitochondrial disease.<sup>10</sup>

### *Recommendations*

1. Care at a tertiary center with cardiology expertise in mitochondrial diseases is preferred.
2. Baseline assessments should include
  - a. Standard 12-lead electrocardiogram (ECG) and echocardiogram (with measurement of left ventricular mass and systolic/diastolic function).
  - b. 24-hour ECG (Holter monitoring) in patients with palpitations, paroxysmal events or in high risk patients including patients with cardiomyopathy.

- c. Screening tests should include asymptomatic mutation carriers at significant risk of developing cardiac disease, especially those with maternally inherited mtDNA mutations known to be associated with cardiac disease.
3. Follow-up evaluation should include clinical assessment, blood pressure measurement, ECG and echocardiography every 12 months for at least 3 years.
  - a. Earlier follow-up is suggested for those with new onset cardiac symptoms or those at higher risk.
  - b. Extension of this 12-month interval should be considered only after discussion with a clinician experienced in the management of cardiac involvement; however, if the patient is stable for 3 years, ECG and echocardiography may be extended to every 2-3 years with return to yearly follow-up (or more frequently) if ECG or echocardiography suggests cardiac deterioration.
  - c. In asymptomatic mutation carriers, the interval of follow-up should be according to their risk of developing disease.
4. 24-to-48-hour ECG monitoring should be obtained every 1-2 years for all patients at high-risk of pre-excitation syndrome/conduction disease, patients with severely impaired LV systolic function (LVEF < 35%), patients with paroxysmal symptoms suggestive of cardiac involvement (palpitations) and patients with left ventricular systolic or diastolic dysfunction.
  - a. More frequent monitoring is needed in patients with large-scale mtDNA deletions due to the high risk of heart block and either of two of the more common pathogenic mtDNA mutations (m.3243A>G and m.8344A>G) owing to the high risk of ventricular pre-excitation.
  - b. Ablation should be considered in supraventricular tachycardia, Wolf-Parkinson-White or any arrhythmias potentially treatable by this technique.

- c. A low threshold for pacemaker implantation is needed to prevent cardiac death. Pacemakers can be combined with implantable defibrillator if needed. An implantable cardioverter-defibrillator (ICD) is needed in patients at risk of sudden death, when the LV wall thickness is  $\geq 30$  mm and in patients with ventricular tachycardia (sustained and non-sustained).
5. Cardiac magnetic resonance imaging is needed for patients with inconclusive echocardiographic images to identify structural remodeling, to quantify abnormalities more precisely prior to starting a treatment and when invasive therapies like septal myectomy are considered.
6. Other comorbidities should be assessed, including high blood pressure, diabetes and dyslipidemias and should be treated accordingly.
7. Exercise testing and-or stress echocardiography should be performed under close monitoring to assess functional capacity, response to therapy and exercise-induced dynamic left-ventricular outflow tract obstruction. This test should not be performed in all patients; the potential health risks (exercise intolerance, metabolic decompensation) should be weighed against the expected benefits of such a test.
8. If physical activity is possible, the intensity of the physical activity should be prescribed by the cardiology team, according to the limitations of their cardiac function.
9. In the setting of end-stage heart failure, transplantation may be an option. Decisions to list a patient for transplant should be taken in the light of other comorbidities and the known natural history of the specific mitochondrial disease.

### **Critical Care**

Patients with metabolic diseases, including mitochondrial disease, are vulnerable to episodic decompensation and worsening of symptoms during inter-current illness. These episodes of

critical illness may be precipitated by catabolism and increased systemic energy demands during times of infection, fasting, anesthesia and surgery. In some cases, no acute precipitating events are apparent. Prompt intervention is essential as many patients respond to timely intervention.

Initial triage stratification of critically ill mitochondrial patients should include a systemic assessment of all body systems since the disease is multisystemic and patients may develop new organ system involvement during an acute decompensation. Cardiopulmonary failure and acute cerebral events have been described as the leading cause of mortality in adult mitochondrial patients.<sup>15</sup> Patients with mitochondrial disease are more likely to have underlying myopathy, immobility, dysphagia, chronic intestinal pseudo-obstruction (CIPO), cardiomyopathy, cardiac arrhythmias including WPW – all increasing their risk of cardiorespiratory compromise during illness or medical stress. Renal dysfunction with alterations in fluid and electrolyte homeostasis and impairment of acid base balance is a potential cause of morbidity and mortality. Tubulo-interstitial disease is the most common acute renal manifestation. Focal segmental glomerulosclerosis, steroid resistant nephrotic syndrome and end stage renal disease during acute illness have also been described.<sup>16</sup> Endocrinopathies can manifest during critical illness in mitochondrial patients. Diabetes mellitus due to insulin insufficiency secondary to islet cell dysfunction or insulin resistance<sup>17-19</sup>, primary adrenal insufficiency, thyroid dysfunction, hypoparathyroidism and hypogonadism are also seen.<sup>20,21</sup> Patients with mitochondrial diseases may be chronically malnourished with deficiencies of both macro and micronutrients. Decreases in nutritional intake due to poor oral or enteral tolerance, in the setting of gastrointestinal (GI) dysmotility and paralytic ileus may further compromise nutrition in ill states. A recent study has shown a higher burden of strokes following acute worsening of CIPO in MELAS patients.<sup>22</sup>

*Recommendations:*

The recommendations below are in addition to routine intensive-care management that might be undertaken for any critically ill patient. They are in addition to routine illness consensus guidelines published previously<sup>3</sup> and summarized in Table 3.

1. Patients should be provided a summary document by their mitochondrial disease care center of clinical symptoms, organ specific symptoms, baseline cardiorespiratory function, special nutritional needs, medications, allergies and contraindicated therapies. The document should include anticipatory guidelines for management during critical illness. The document must be updated at each follow up visit and be readily available for review in an emergency.
2. Critically ill mitochondrial disease patients must be carefully triaged at presentation and referred to a center equipped to manage multisystem dysfunction when necessary.
3. Ventilatory assessment should include evaluation for aspiration, atelectasis, infection and account for underlying issues of abnormal tone, nerve and muscle disease.
4. An echocardiogram should be obtained in instances of hemodynamic dysfunction.
5. In patients with pressor-refractory hypotension, empiric administration of stress-dose steroids should be considered; blood levels of adrenocorticotrophic hormone and cortisol can be collected immediately prior to facilitate the diagnostic evaluation but their collection should not delay therapy.
6. Electrolyte assessment should include sodium, potassium, calcium, magnesium and phosphate. Recurrent or persistent electrolyte imbalances should prompt an evaluation of renal tubular and adrenal function.
7. Patients may acutely develop elevations in lactate or pyruvate resulting in decompensated acidosis and should be monitored closely particularly during introduction of feeds or weaning from respiratory support.

8. Thyroid and adrenal function should be assessed in patients at times of critical illness and reassessed during a prolonged ICU stay. Hypo- and hyper-glycemia can occur and regular blood glucose monitoring is needed.
9. Any change in baseline neurological exam warrants consideration for repeat neuroimaging.
10. MELAS patients with pseudo-obstruction should receive closer neurologic follow-up as the symptom may represent a harbinger of stroke.
11. Nutritional support must be provided with enteral feeds if tolerated or with peripheral or central parenteral nutrition that is calculated with the help of a trained dietician. Nutritional support should be started as soon as medically safe to do so (preferably within 48 hours of admission) to avoid a prolonged catabolic state that may lead to further metabolic decompensation.
12. Hypoglycemia, hypoalbuminemia or coagulopathy must be excluded if liver dysfunction is suspected. Importantly, hepatocerebral involvement is common in infantile mitochondrial disease; the use of valproate for seizure control must be avoided in these patients as fulminant hepatic failure has been associated with this medication.
13. In patients with marrow failure, transfusions with packed red cells or platelets may be necessary. Granulocyte colony stimulating factor (GCSF) may be required in the setting of severe neutropenia and/or infections. Additional studies and interventions may require the services of a hematologist.
14. Supplements and cofactor therapy should be continued when possible.

## **Endocrinology**

Mitochondrial disease patients are at risk for a variety of endocrine diseases. Recent reviews on the topic are available.<sup>20,21</sup> Diabetes mellitus has long been a well-recognized potential endocrine consequence of mitochondrial disease.<sup>23</sup> Clinical presentations suggestive of either

“typical” Type I or II diabetes mellitus can both be caused by primary mitochondrial impairment (mitochondrial disease-associated diabetes mellitus). Mitochondrial-related diabetes mellitus may present insidiously, clinically similar to more “typical” age- and weight-related Type 2 diabetes mellitus with both insulin resistance and inadequate pancreatic beta-cell insulin production. Children may present with more features of insulin deficiency. Diabetes mellitus is one of the most common findings in patients with the m.3243A>G mutation, typically manifesting as maternally-inherited diabetes and deafness (MIDD).<sup>17-19</sup>

Both hypothyroidism and, to a far lesser extent, hyperthyroidism have been reported in patients with primary mitochondrial diseases and may coexist with other endocrinopathies.<sup>20,21</sup> Short stature is common. There may be failure of sufficient growth hormone (GH) production and some children may benefit from GH supplementation.<sup>24</sup> Hypoparathyroidism has been reported in some sub-types of mitochondrial diseases, most notably KSS. Concurrent renal tubulopathy in KSS can make both diagnosis and management more challenging.<sup>25</sup> Individuals with mitochondrial disorders may also be at risk for poor bone health, particularly if they are chronically ill, malnourished, and immobile. Certain medications, such as antiepileptic drugs, may compound the issue.

Adrenal insufficiency can also occur in primary mitochondrial diseases and consists mostly of either primary adrenocortical insufficiency, due to diminished cortisol secretion (Addison disease), or to hyperaldosteronism. Most described cases have been associated with Pearson or KSS, MELAS and *POLG*-related disease.<sup>20,21</sup> Primary hypoglycemia is not a common occurrence in mitochondrial disease and is usually related to hepatic impairment. The presence of hypoglycemia should prompt screening for reversible causes (e.g., adrenal insufficiency, GH deficiency, hyperinsulinism). Primary or hypergonadotropic and hypogonadotropic

hypogonadism have been observed, in particular in *POLG*-related disease<sup>26</sup> and myopathies presenting with progressive external ophthalmoplegia.<sup>21,27</sup>

### *Recommendations*

1. An annual Hemoglobin A1c (HgbA1c), thyroid-stimulating hormone (TSH), free thyroxine level (FT4), vitamin D and screening for hypoparathyroidism (serum calcium, magnesium, phosphate, parathyroid hormone, vitamin D (25-OHD and 1,25-OHD); urine: creatinine, calcium and phosphate) can be considered in individuals with mitochondrial diseases.
  - a. In those with mtDNA deletions, which are more strongly associated with secondary endocrinopathies, annual screening is recommended.
2. Biguanides such as Metformin may need to be avoided or used with caution in mitochondrial disease because they may exacerbate lactic acidosis.
3. Multi-agent therapy may be needed, including insulin, for patients with mitochondrial diabetes as they may have both insulin resistance and insulin deficiency.
4. Growth and maturation in children with mitochondrial disorders should be measured consistently at routine well-child primary care physician visits. If short stature and/or sub-optimal growth and weight gain occur, a comprehensive evaluation should be undertaken, guided by the history and physical examination, and with attention to treatable causes, including GH deficiency.
  - a. Nutritional status should be assessed in all children with decreased linear growth velocity.
  - b. In patients with GH deficiency, treatment with GH should be considered.
  - c. Atypical patterns of sexual maturation should prompt investigation for hypogonadism.

5. Adrenal insufficiency should be considered in mitochondrial patients with new onset of worsening fatigue or symptoms typically associated with adrenal insufficiency.
6. Optimization of calcium and vitamin D status and attention towards injury/fall prevention are reasonable steps to prevent occult and/or atraumatic fracture. Bone density testing should be considered in patients with encephalopathy or immobility to assess for fracture risks.

### **Gastroenterology**

Mitochondrial diseases often feature GI system involvement including intestinal dysmotility, constipation, poor weight gain, obesity, swallowing dysfunction and pancreatic and hepatic dysfunction. A comprehensive review has recently been published.<sup>28</sup>

GI dysmotility (including CIPO in severe cases) is a relatively common feature of many mitochondrial diseases and may present with early satiety, weight loss, nausea, constipation or overflow incontinence/diarrhea. Constipation can also present without dysmotility due to underlying myopathy, neuropathy, medication effects, dietary alterations, decreased fluid intake and decrease in patient mobility. CIPO is characterized by more than six-months of severe symptoms of intestinal obstruction such as abdominal distention and pain, nausea and vomiting with clinical/radiographic evidence of dilated bowel in the absence of mechanical obstruction.<sup>29</sup> CIPO may be caused by neurologic or myopathic defects or secondary to medications.<sup>30,31</sup> A recent study has shown a potential higher burden of strokes following acute worsening of CIPO in MELAS patients.<sup>22</sup>

Any combination of dysmotility, constipation and/or dysphagia can lead to chronic nausea, vomiting, poor appetite and exacerbate poor weight gain and ongoing malnutrition seen as a metabolic consequence of mitochondrial disease. Obesity is a less common feature of

mitochondrial disease. Patients with primary mitochondrial disease are also at risk of aspiration pneumonia, due to oropharyngeal weakness or discoordination, compounded by gastro-esophageal reflux disease (GERD). The use of a gastrostomy- or gastrojejunal- tube and consideration for fundoplication can improve nutritional status and decrease aspiration and GERD-related risks.

Exocrine pancreatic insufficiency can occur, especially in Pearson syndrome, KSS and patients with the m.3243A>G mutation.<sup>32,33</sup>

Patients with mitochondrial disease are at risk for liver dysfunction and liver failure. While typically presenting with multi-system manifestations, isolated liver disease is most frequently caused by defects of mtDNA maintenance such as mtDNA deletion and depletion, especially in those with *POLG*, *DGUOK* and *MPV17* mutations.<sup>28</sup> Patients with mutations in *POLG* are at a higher risk of developing valproate induced liver failure. Antipyretic therapy and induction of anabolism including glucose and parenteral lipids may ameliorate the course of liver crises in certain patients as has been noted in *NBAS* deficiency.<sup>34</sup>

Liver transplantation may be indicated in some cases and has been performed in patients with mitochondrial disease. Survival after liver transplantation in some mitochondrial patients approaches that of transplanted patients without mitochondrial disease – although some patients may fare worse (*POLG*-related disease).<sup>35-37</sup>

### *Recommendations*

1. Mitochondrial patients should be screened for symptoms of upper and lower tract dysmotility including nausea, early satiety and constipation. Persistent symptoms or physical examination or radiologic findings of impacted stool should prompt referral.

2. Diarrhea is not a common symptom in mitochondrial disease (outside of overflow incontinence from constipation) and should lead to an investigation as to the etiology including pancreatic insufficiency.
3. Acute pseudo-obstructive presentations should be managed aggressively. Water soluble contrast enemas may relieve obstruction and allow for exclusion of alternate etiologies such as volvulus. Patients should be nil-by-mouth at these times; Intravenous (IV) hydration with dextrose and electrolytes should be provided. Onset of pseudo-obstruction in MELAS patients may be a harbinger of neurologic decline including new strokes and patients should be closely monitored at these times.
4. Any cases with suspected aspiration or bulbar dysfunction should be evaluated with a swallow study and advise on feeding strategies by a speech therapist.
5. Decisions regarding gastrostomy or jejunostomy tube insertion should be made in close consultation with a gastroenterologist and in some cases, palliative care.
6. All patients with a mitochondrial disease diagnosis should undergo surveillance for malnutrition including measurement of weight and weight for height no less often than every 6 months.
  - a. Mitochondrial patients with growth failure should be screened for pancreatic insufficiency.
  - b. All patients identified on anthropometric examination as at risk for malnutrition should be seen by a dietician with experience in the management of patients with neuromuscular or mitochondrial disease.
  - c. Standard markers of nutritional status, vitamin levels and trace elements can help guide therapy in addition to monitoring body mass.
  - d. Diet/exercise programs that promote lean muscle mass should be promoted over simply increasing body mass index.

- e. If obesity is present, careful management is indicated to ensure weight loss that may improve functional ability without exacerbating other underlying symptoms.
7. If patients have symptoms or laboratory values indicative of exocrine pancreatic insufficiency, referral to a gastroenterologist is indicated.
8. Patients with mitochondrial disease should have an annual transaminase level assessed; synthetic liver function should be evaluated if transaminases are elevated or if the patient is symptomatic. Elevated liver enzymes or laboratory markers of hepatic synthetic deficiency should prompt referral to a hepatologist.
9. In the setting of acute or acute on chronic liver failure, liver transplantation may be an option. Decisions to list a patient for transplant should be taken in the light of other comorbidities and the known natural history of the specific mitochondrial disease. Additional caution regarding liver transplantation may be needed in patients with *POLG* mutations owing to the potential of increased morbidity and mortality.

## **Hematology**

Hematologic disease is not a common occurrence in mitochondrial patients although mild anemia is observed relatively frequently. Sideroblastic anemia is a known classical feature of several rare mitochondrial diseases, including Pearson syndrome. Other types of anemia, leukopenia, neutropenia, thrombocytopenia and pancytopenia have also been described although these are not seen frequently. A review on the topic is available.<sup>38</sup> Anemia and/or iron deficiency may also occur due to feeding or GI issues potentially compounding symptoms of fatigue.

## *Recommendations*

1. A complete blood count (CBC) with differential should be considered annually in patients with primary mitochondrial disease. Patients with mitochondrial diseases at higher risk of anemia or bone marrow suppression (such as Pearson syndrome) should have CBCs checked more frequently with the interval based on the patient's clinical course.
2. Iron studies should be considered in patients at risk of nutritional deficits and/or concomitant symptoms of fatigue.

## **Immunology**

The immune system and its interplay with mitochondria remains poorly understood<sup>39</sup>, although *in vitro* studies have repeatedly demonstrated that mitochondria are crucial for proper function of both the cellular and humoral immune systems.<sup>40-42</sup> Certain conditions such as pancytopenia or neutropenia have been well described in disorders such as Barth and Pearson syndromes.<sup>43,44</sup>

The most comprehensive study investigating immune function and/or risk of infections in patients with mitochondrial disease included a large cohort without genetically confirmed disease.<sup>45</sup> Patients in this cohort seemed to be at a higher risk of recurrent infections and sepsis and some showed abnormalities on immune testing including hypogammaglobulinemia, low vaccine titers, and low switched memory B-cell compartment.<sup>45</sup>

Specific studies have not investigated the safety of vaccine administration in children with mitochondrial disease, although reviews of patient outcomes in other inherited metabolic disorders show that vaccines are generally safe.<sup>46</sup> The MMS recommends vaccination for all patients with mitochondrial disease since risk of their mitochondrial disease worsening from life-threatening infections is likely to be greater than the theoretical risk of decompensation following vaccination.<sup>47</sup>

## Recommendations

1. Immune function should be evaluated early in any mitochondrial disease patient experiencing recurrent or severe infections\*. Investigation should include quantitative immunoglobulin levels, vaccine-specific IgG titers and lymphocyte subset levels (T cell, B cell, switched memory B-cell compartment, Natural Killer cells). Immune evaluation and management should be conducted with the assistance of an immunologist familiar with mitochondrial disease.

*\*Recurrent or severe infections are defined as those that are complicated, in multiple locations, resistant to treatment, caused by unusual organisms or consisting of > 10 upper respiratory infections a year.*

2. Immune testing may be useful to identify patients that may benefit from prophylactic treatment strategies including antibiotic prophylaxis, immunoglobulin replacement therapy, and GCSF.
3. Patients with mitochondrial diseases should be offered age appropriate vaccination including the influenza vaccine as well as other relevant vaccines when there is an underlying pulmonary pathology (i.e. pneumococcal vaccine).

## Nephrology

Kidneys contain a high density of mitochondria, particularly in the cortical tubules, and all sections of the nephron may be affected by mitochondrial disease. In general, renal tubular dysfunction is more frequently seen in childhood-onset mitochondrial disease, whilst glomerular disease is more frequent in adults, although exceptions do occur. The prevalence of renal dysfunction in mitochondrial disease is not known, since the published literature consists largely of single case reports and small case series. Recent reviews on the topic are available.<sup>16,48</sup>

Mild tubular dysfunction is one of the most common findings in a variety of mitochondrial disease patients,<sup>49</sup> especially those with mtDNA deletion disorders. Fanconi-type proximal

tubulopathy with severe electrolyte losses, tubulo-interstitial nephritis, Bartter-like syndrome, renal tubular acidosis and a Gitelman-like hypomagnesaemia have all been described and are seen in a range of mitochondrial diseases.<sup>16</sup>

Glomerular dysfunction, including steroid-resistant nephrotic syndrome, which may progress to focal segmental glomerulosclerosis (FSGS), may also occur in mitochondrial disease and has been associated with a variety of mtDNA and nDNA defects. The common m.3243A>G pathogenic variant, often associated with MELAS, has most commonly been associated with FSGS.<sup>16</sup> Chronic tubulointerstitial nephritis has also been noted in some.

Patients have at times needed dialysis and renal transplantation. Most reported cases with mitochondrial disease undergoing renal transplantation have fared well and survival in mitochondrial patients match national averages.<sup>36</sup>

### *Recommendations*

1. All patients with suspected mitochondrial disease should be screened for renal dysfunction at presentation, including blood urea, creatinine, sodium, potassium, calcium, magnesium, phosphate and urinary albumin/creatinine ratios.
2. Patients with significant renal dysfunction should be referred to a nephrologist, preferably with experience of mitochondrial disease, who can guide measurement of glomerular filtration rate and need for renal replacement therapy.
3. Electrolyte replacement – large volumes of potassium, calcium, magnesium and/or phosphate - may be needed, and consideration should be given to the early placement of a gastrostomy tube if the patient struggles to take these supplements orally.

4. Dialysis for end stage renal disease should be considered palliative, and patients receiving dialysis should ideally also be considered for renal transplantation.
5. Renal transplantation should be offered after careful multidisciplinary review and discussion with the affected family and consideration of the full clinical picture.

## **Neurology**

### *Developmental Disability*

Since mitochondrial diseases frequently cause neurologic impairment as well as vision and/or hearing impairment, patients with mitochondrial diseases are at risk for global developmental disability (GDD) and intellectual disability (ID). Mitochondrial diseases can cause a variety of developmental disabilities in isolation or in various combinations, including ID, autism, cerebral palsy, or isolated learning disabilities. Attention deficit disorder (ADD) with or without hyperactivity (ADHD) can be seen. Concomitant or isolated language or motor disability can also be present. Mitochondrial diseases due to point mutations in nDNA or mtDNA, large scale mtDNA deletions or mtDNA depletion can all present with isolated or global developmental delay and/or ID. For a given disease within the same family, the severity of intellectual and developmental delays or disabilities can be quite broad. One affected family member may have preserved cognition while another affected individual in the same family may have significant ID.

Many mitochondrial diseases can also cause loss of developmental and cognitive skills, referred to a “neuroregression” or “psychomotor regression.” Neuroregression is a semiologically distinct entity from GDD/ID. Regression can occur at any age and frequently leads to life-limiting neurologic impairment. Such regression warrants a thorough and expedited evaluation for a treatable etiology.

### *Recommendations:*

1. As patients with mitochondrial disease are at risk of developmental disabilities every patient deserves a formal neurodevelopmental screen appropriate for age.
2. Baseline neuropsychological testing should be considered for mitochondrial patients with CNS disease. Testing should be repeated for cognitive, behavioral or personality change and to allow for optimal tracking of their function and development of personalized care plans.
3. If DD/ID is confirmed, then one should consider referrals to a developmental specialist, appropriate therapists and for community and school support services. Anticipatory guidance should be provided to parents, siblings and family.
4. Concomitant symptoms such as autism, ADD/ADHD and psychiatric disease should be addressed and treated.
5. Neurodevelopmental and cognitive status should be closely monitored at each follow-up since mitochondrial patients can be at risk of neurologic regression.
6. Developmental regression at any age warrants a thorough evaluation for a potential treatable condition as well as an assessment for disease progression; testing may need to include repeat neuroimaging and an EEG.

### *Epilepsy*

The prevalence of epilepsy in mitochondrial disease is not accurately known although seizures may be a presenting or late feature.<sup>50</sup> Seizures are reported to occur in 35% – 60% of infants, children and adolescents with biochemically or genetically confirmed disease.<sup>50-53</sup> The prevalence in adults is potentially lower with one study reporting a general prevalence of 23%; certain genotypes such as the m.3243A>G and m.8344A>G mutations may have a higher prevalence.<sup>54</sup> Focal and generalized seizures, epilepsia partialis continua (EPC), myoclonus

and infantile spasms have all been noted. Patients may also have progressive myoclonic epilepsy or recurrent status epilepticus. EEG findings vary.<sup>55</sup>

Treatment of epilepsy is similar to non-mitochondrial disease patients with seizures. However, valproic acid should be avoided, especially in patients with *POLG* mutations, due to the risk of fulminant hepatic failure and worsening of neurologic symptoms, including seizures. Vigabatrin may also need to be avoided in patients with mtDNA depletion because it inhibits the conversion of deoxyribonucleoside diphosphate to deoxyribonucleoside triphosphate in the mitochondrial nucleoside salvage pathway and may worsen mtDNA depletion.<sup>56</sup> Topiramate may worsen acidosis.<sup>57</sup> Epilepsy may be refractory to treatment. No specific combination of medications has been shown to be more beneficial.

### *Recommendations*

1. In mitochondrial patients with recurrent stereotypical spells, episodes of behavior arrest or alterations of state from baseline there should be a low threshold to obtain EEG monitoring, especially in those with underlying cognitive disability or dementia.
2. Avoid the use of valproic acid, especially in patients with *POLG*-related disease. Vigabatrin may need to be avoided in patients with mtDNA depletion syndromes. Topiramate may worsen acidosis.
3. EPC, when present, should raise the concern of a metabolic stroke.

### *Headaches*

Headaches are seen more frequently in several mitochondrial diseases than in the general population and can represent a manifesting feature of select mitochondrial diseases (MELAS, MERRF, Alpers-Huttenlocher, and carriers of m.3243A>G).<sup>58-60</sup>

Severe headaches in MELAS patients have been associated with stroke-like episodes and seizures.<sup>58</sup> There are no studies looking at the treatment of headache in patients with mitochondrial disease. Most typical migraine therapies, including triptans, can be used. There are some medications that may need to be avoided or used with caution; butterbur products contain pyrrolizidine alkaloids, which are strong oxidants, and theoretically may induce liver damage.<sup>61</sup> Long term acetaminophen use can reduce hepatic reduced-glutathione and potentiate oxidative hepatic damage. Topiramate may worsen acidosis.<sup>57</sup> Valproate should be avoided due to the risk of liver failure, especially in *POLG*-related diseases.

*Recommendations:*

1. Sudden onset or worsening severity of migraines in mitochondrial disease may represent underlying strokes or seizures, requiring further evaluation for these conditions at that time.
2. Treatment for migraines in mitochondrial disease is similar to that in patients without mitochondrial disease.
  - a. Caution may be needed with use of topiramate, butterbur and chronic acetaminophen for headache management in mitochondrial disease patients. Valproic acid should be avoided; it is contraindicated in patients with *POLG* mutations.

*Movement Disorders and Altered Tone*

Patients with primary mitochondrial disease are vulnerable to injury to the basal ganglia, cerebellum, cortex or corticospinal tracts, and are thus at risk of developing movement disorders and abnormalities of tone. Patients can have a mixed movement and tone disorder that includes hyper- and hypo-kinetic or cerebellar types of movements, hypotonia, spasticity, rigidity

and dystonia.<sup>62</sup> Myoclonus, ataxia, gait disturbance, Parkinsonism, and rigidity have also been noted. Patients with *POLG* mutations or mtDNA depletion syndromes are at a higher risk for Parkinsonian symptoms.<sup>59,62-66</sup>

### *Recommendations*

1. Routine neurologic assessment for disorders of movement and tone is needed.
2. Sudden onset of a new disorder of movement or tone should lead to an evaluation of disease worsening and potential secondary causes; neuroimaging, electrophysiological testing and baseline laboratory investigations are recommended. Assays of CSF neurotransmitter and folate levels should be considered and treatable causes should be excluded.
3. Management of movement and tone disorders in mitochondrial disease is similar to that in patients with movement disorders of other causes. Medical, procedural and surgical treatments should be considered. Treatment can improve quality of life.
  - a. Caution should be used with medications that alter tone as they can selectively worsen cognitive status, decrease muscle strength and secondarily respiratory effort and impact GI motility and urinary function.
  - b. Valproic acid should be avoided as a treatment, especially in *POLG* disease.
  - c. Botulinum toxin should be used with caution in view of potential systemic effects.
4. Physical Medicine and therapy assessments are recommended to maximize mobility, prevent contractures and alleviate discomfort and pain.
5. Deep brain stimulation should be considered when appropriate for treatment of mitochondrial movement disorders, rigidity and dystonia, considering the patient's long term prognosis and level of morbidity.

### *Myopathy*

Myopathy is a common manifestation of some mitochondrial diseases and may include ophthalmoplegia and ptosis. Early onset myopathy may present with profound hypotonia in infancy. Patients are at risk of associated dysphagia, respiratory insufficiency, cardiomyopathy, exercise intolerance, myalgia, fatigue and infrequently rhabdomyolysis. Mitochondrial myopathies do not typically lead to marked baseline elevations in creatine kinase (CK) (with the exception of the myopathic form of *TK2*-related mitochondrial disease).

### *Recommendations*

1. An initial evaluation of muscle function is routinely needed including assessment of strength, CK measurement and consideration of an electromyogram (EMG).
2. Annual CK levels should be considered in patients with a myopathy, especially with symptom worsening or a decline in function.
3. Secondary causes of a myopathy should be considered and assessed for, especially if CK levels are above 1000 (other than in *TK2*-related disease) and include at least a CBC, TSH and toxicology screen when appropriate.
4. Management for recurrent rhabdomyolysis and myoglobinuria, at times triggered by exercise or illness, should follow general treatment recommendations; acylcarnitine and urine organic acid analysis may be needed to exclude fatty acid oxidation defects in new cases.
5. Exercise may benefit patients with mitochondrial myopathies (see prior exercise recommendations).<sup>3</sup>
6. Agents such as statins, corticosteroids, metformin and antiretrovirals should be used with caution since they may exacerbate the underlying myopathy.
7. Riboflavin should be considered for myopathy associated with *ACAD9* deficiency; a combination of Coenzyme Q<sub>10</sub> and riboflavin should be considered for *ETFDH*-related myopathy.

### *Neuropathy*

Mitochondrial diseases can lead to primary neuropathy. Large and small fiber, axonal and demyelinating neuropathies have all been described, often presenting subclinically.<sup>67-71</sup>

Peripheral neuropathy may be more common in *POLG*, *TYMP*, *MPV17* and *SURF1* related mitochondrial diseases and in patients with the m.8993T>G and m.8993T>C mtDNA mutations.

Neuropathy can also occur secondarily as a complication of mitochondrial diabetes, renal insufficiency, or side effects from treatments.

### *Recommendations*

1. Mitochondrial disease patients should be screened for peripheral neuropathy when clinical symptoms/signs suggestive of peripheral nerve dysfunction are present. A comprehensive EMG and Nerve Conduction Velocity (NCV) study should be considered and should include both upper and lower extremities with evaluation of both sensory and motor nerves.
2. Screening for treatable causes of peripheral neuropathies should be obtained, especially when the findings are atypical for the underlying mitochondrial disease. As diabetes may be more common in certain mitochondrial diseases including MELAS and MIDD, optimal glycemic control may help a sensory polyneuropathy.
3. Treatment of mitochondrial neuropathies is symptomatic and follows guidelines established for the care of non-mitochondrial neuropathies. Caution and close monitoring is needed if medications causing mitochondrial toxicity are used. Valproate should be avoided as a potential treatment, especially in patients with *POLG* mutations.

### *Stroke*

The data for the management of mitochondrial stroke were previously reviewed with recommendations published by the MMS.<sup>3,72</sup> These recommendations are summarized in Table 3.

## **Ophthalmology**

The ophthalmologic involvement in mitochondrial disease is diverse and may be the dominant feature, such as ophthalmoplegia and ptosis in various CPEO conditions; or specific for a syndrome, such as optic nerve disease in Leber Hereditary Optic Neuropathy (LHON). Alternatively, the ophthalmologic manifestations may be nonspecific, such as cataracts, retinal disease, nystagmus, strabismus or decreased visual acuity. Involvement of the iris and ciliary body, choroid and uvea are rare in mitochondrial disease, compared to involvement of the lens (refractive errors and cataracts), retina (pigmentary retinopathy or macular degeneration), optic nerve (optic nerve atrophy), extraocular muscles (ophthalmoplegia) and levator palpebrae (ptosis). The reported frequency of ophthalmologic manifestations in mitochondrial disease is variable ranging from 35-81%<sup>73-75</sup> and has been described in multiple types of mitochondrial diseases.

LHON is mentioned separately owing to its relatively high prevalence and several unique features of the disease. The disorder is a common mitochondrial optic neuropathy leading to an acute onset of painless, bilateral central vision loss, often developing in the young adult years. Heavy alcohol and moderate nicotine/tobacco exposure increase the risk of symptoms developing and avoidance of these environmental triggers is recommended. Some patients with LHON appear to develop additional neurologic symptoms or cardiac conduction defects.<sup>76</sup> Idebenone is a potential treatment.<sup>77,78</sup>

*Recommendations:*

1. A thorough clinical evaluation for eye disease should include visual acuity, visual fields, eye motility exam, documentation of ptosis and fundoscopy regardless of reported symptoms.
2. Patients should be referred to a neuro-ophthalmologist for detection of visual, retinal, macular and optic nerve changes at the time of diagnosis, supported by Optical Coherence Tomography (OCT) and Electroretinography (ERG). If symptomatic, an assessment of intraocular pressure is indicated. Annual ophthalmology exams should be conducted thereafter.
3. Patients with visual impairment should be referred to a low vision specialist.
4. Surgery may be beneficial for strabismus or cataracts. Surgery for ptosis may be needed and should be conducted by a surgeon experienced in treating patients with mitochondrial disease.
5. Lubrication of the eyes may be needed due to inappropriate eye lid spread of tears in patients with ptosis or after ptosis repair.
6. Heavy alcohol use and smoking should be avoided among LHON carriers as these are strongly associated with increased risk of visual loss.
7. LHON patients should receive periodic neurologic evaluations and annual ECG.

## **Orthopedics**

Orthopedic complications occur in mitochondrial disease due to a variety of causes including underlying myopathy, neuropathy, abnormalities of tone, strokes, basal ganglia or cerebellar disease. Orthopedic interventions may be necessary for contractures, scoliosis, hip dislocation, and limb deformities. Regular orthopedic examination of patients with mitochondrial diseases may be indicated. Treatment is symptomatic and peer reviewed data is lacking for the efficacy of specific orthopedic interventions in mitochondrial diseases. Recommendations are based on those made for similar issues for patients with non-mitochondrial diseases.

## *Recommendations*

1. Patients should be examined annually for orthopedic complications including scoliosis, contractures, dislocations and limb deformities, especially if the patient has underlying abnormalities in tone, muscle strength or neurologic functioning.
2. Evaluation and care by a rehabilitation medicine specialist and therapy are used to maintain safety, mobility and an active lifestyle.
3. Inpatient rehabilitation may improve function in some patients and should be considered when needed.
4. Orthopedic interventions, both operative and non-operative, for scoliosis, dislocations and limb deformities may be beneficial to selected patients. As with all procedures, life expectancy should be weighed against risks of discomfort and recovery time when considering an orthopedic procedure.

## **Pregnancy**

There are mostly only single case reports published on the clinical course of pregnancy in mitochondrial disease patients. As a time of extreme physiologic change, pregnancy theoretically represents a period of potential risk in several areas for the pregnant woman with mitochondrial disease and her fetus. Mitochondrial patients are at risk of developing or exacerbating comorbid systemic symptoms, increasing the risk of complications during pregnancy.

Several prior case reports of women with MELAS or carriers of MELAS-related mtDNA mutations showed a risk of premature rupture of membranes, preterm labor, gestational diabetes, preeclampsia, worsening acidosis, myopathy, neuropathy, status epilepticus and stroke.<sup>79-83</sup> A recent retrospective analysis<sup>84</sup> showed that obstetric complications did occur more

frequently in carriers of the common m.3243A>G mutation associated with MELAS. Of 96 pregnancies reviewed, 25% had a preterm delivery (5.5% extremely premature), 12% had preeclampsia and 11% had gestational diabetes. 13% of the children born had a birthweight < 5<sup>th</sup> %ile. Four fetal deaths were reported.

Pregnancy in mitochondrial disease also elicits the concern of transmission of a genetic disorder. Appropriate preconception genetic counseling and discussion of options of prenatal testing are needed. A fetus affected by mitochondrial disease may also be at higher-risk for prenatal morbidity. Finally, premature ovarian failure is a feature of several mitochondrial disorders and affected women should be referred for assisted reproductive technologies if they wish to have children.<sup>21,85</sup>

### *Recommendations*

1. Pregnant women with mitochondrial disease require closer monitoring by their specialists.
2. Pregnancies should ideally be managed by an obstetrician with expertise in the management of high-risk pregnancies since affected women may be at higher risk for preterm labor and preeclampsia.
3. Women with mitochondrial disease should be counseled about a potential increased risk of gestational diabetes; glucose tolerance testing should be obtained early and later in the pregnancy.
4. Patients should be counseled about continuation or dose changes of current medications (e.g. antiepileptics, antihypertensives).
5. Women with or at risk of mitochondrial disease should receive preconception genetic counseling and be offered prenatal testing where this is feasible.

6. Closer fetal monitoring may be required for a prenatal onset of symptoms when there is a concern of genetic transmission of a mitochondrial disorder (especially in cases of mtDNA-mediated or autosomal dominant disease).

## **Psychiatry**

There appears to be a potential higher prevalence of psychiatric disorders in individuals with mitochondrial disease,<sup>86,87</sup> however, all but one study used healthy controls as a reference group. Thus, although it is important to screen for psychiatric symptoms in individuals with mitochondrial disease, more research is needed to understand whether psychiatric symptoms are specifically related to mitochondrial disease or to other factors that are common in chronic disease conditions.

Mood disorders, especially major depression, appear to be the most prevalent psychiatric disorder reported across studies. The prevalence of anxiety disorders varies and psychotic disorders are less common.<sup>86-88</sup>

### *Recommendation*

1. A standardized screening tool for depression and anxiety symptoms should be routinely used.

## **Pulmonology**

The lungs are not usually directly involved in the clinical manifestations of primary mitochondrial disease; however neuromuscular and CNS involvement may affect the lungs and breathing in patients with primary mitochondrial disease. Patients with mitochondrial disease can have either central brainstem dysfunction and/or a myopathy, with or without dysphagia. Respiratory insufficiency, aspiration and infection may also occur. Respiratory symptoms may include noisy

breathing, hoarseness, stridor, congestion, cough, abnormal breathing, snoring, sleep disturbances, daytime hypersomnolence, and exercise intolerance. Case reports have outlined worsening following respiratory tract infections.<sup>89,90</sup> Respiratory hypoventilation may also occur.<sup>91</sup> Pulmonary hypertension has been described.<sup>85</sup> Anesthesia may worsen respiratory symptoms and precipitate respiratory failure. Primary cardiomyopathy may lead to congestive heart failure and associated pulmonary edema, especially in the setting of respiratory muscle weakness. Polysomnography may show findings of central apnea, obstructive sleep apnea and decreased ventilatory drive in response to hypoxia and/ or hypercapnia.<sup>92</sup>

Children with more severe diseases such as Leigh syndrome tend to have more severe, early and chronic respiratory complications compared to later onset mitochondrial diseases where respiratory problems may only arise during acute decompensations.

Hypersialorrhea is common in patients who have CNS involvement affecting oropharyngeal strength or coordination, but it can also be caused by GERD, constipation and side effects of medicines. Treatment may be necessary to prevent aspiration pneumonia, improve hygiene, and reduce social stigma.

### *Recommendations*

1. Baseline evaluation of respiratory status to assess for muscle weakness and other cardiopulmonary comorbidities. The history should guide screening for additional comorbidities including obstructive sleep apnea, bulbar weakness, risks for aspiration, gastroesophageal reflux, asthma, and chronic obstructive lung disease.
2. Initial and follow-up evaluation should include routine pulse oximetry with vital signs.

3. Polysomnograms should be considered at baseline in every patient at diagnosis to assess for sleep disturbances, central or obstructive apnea and nocturnal hypoventilation.
4. Patients even with mild abnormalities should be referred to a pulmonary specialist for follow up and management.
  - a. Spirometry in both the supine and upright positions should be considered; if appropriate seal with a mouth piece cannot be achieved, a nasal clip or a face mask needs to be used.
  - b. Additional testing may be required at the discretion of a pulmonologist familiar with neuromuscular diseases which can affect the pulmonary system.
  - c. If initial tests are normal, repeat testing should be deferred until new symptoms arise or if there is a suspicion of disease deterioration.
  - d. For patients with a well characterized respiratory involvement, testing should be repeated periodically to follow progress and predict the pulmonary function over time to guide management.
5. Neuromuscular weakness predisposes to respiratory issues in the peri-operative period due to poor airway tone, clearance of secretions and chronic aspiration.
  - a. Prior to surgery, pulmonary assessment should be performed, with pulse oximetry as a minimum. If SpO<sub>2</sub> is <95% a blood gas should be obtained to assess carbon dioxide levels.
  - b. For patients with neuromuscular weakness, preoperative use of noninvasive positive-pressure ventilation (NPPV) should be considered, especially if there is a weak cough, recurrent pneumonia, or low maximum expiratory pressure.
  - c. Post-operatively, those with neuromuscular weakness can be extubated to NPPV to prevent prolonged intubation, with weaning as tolerated since recovery may be prolonged.

- d. Postoperative atelectasis may require aggressive pulmonary toilet with cough assist, airway clearance, and chest physiotherapy.
  - e. Pain management should limit use of narcotics which can further suppress adequate cough and recovery.
6. Pulmonary testing should also be considered during acute disease decompensations with exacerbated symptoms. If the disease is rapidly progressive and respiratory weakness evident on testing, a pulmonary specialist referral and more frequent monitoring is warranted.
- a. Incentive spirometry is commonly used in hospitals but manual compression, glossopharyngeal breathing and insufflations should also be attempted by a respiratory therapist in hospital or at home during the recovery period.
  - b. Chest X-ray and computed tomography are recommend in the acute setting to identify diaphragm abnormality, collapsed lungs, aspiration and any other pulmonary pathology.

## **Other considerations**

### ***Altitude***

There is a theoretical concern that mitochondrial disease patients may be at risk of deterioration with high-altitude travel due to associated acute to sub-acute hypobaric hypoxia and associated physiologic changes. Hypoxia brought on by altitude changes is known to produce oxidative damage in cells, increase generation of reactive oxygen species, inhibit mtDNA transcription and translation, decrease mitochondrial muscle fiber content, and down-regulate the electron-transport-chain and fatty acid oxidation capacity.<sup>93-95</sup> It is known that mtDNA variations may also play a role in the ability to tolerate rapid changes to higher altitudes and that mitochondrial changes stabilize and decrease or resolve under chronic high-altitude conditions. High-altitude sickness brings a risk of associated cerebral edema, pulmonary hypertension and retinopathy –

although there is no concrete evidence yet that these conditions occur in a higher prevalence in mitochondrial disease patients exposed to altitude changes. Chronic conditions, such as underlying pulmonary and cardiovascular disease can be exacerbated at high altitudes in any patient.

### *Recommendations*

1. Careful consideration and planning are needed for high altitude travel as patients may be susceptible to medical worsening during these times. Rapid recognition and treatment of complications is important.
2. Due to a lower pO<sub>2</sub> during air travel, patients with cardiomyopathy or respiratory weakness need to consider oxygen saturation monitoring en route and potentially have access to supplemental oxygen.

### ***Fatigue***

Fatigue is a common complaint in mitochondrial patients. As mitochondrial diseases can cause a combination of neuromuscular disease and systemic symptoms, there are often a multitude of causes for fatigue and worsening of baseline fatigue. The consensus recommendations for the evaluation of fatigue due to a system-specific issue are outlined in several of the individual sections above and summarized below.

### *Recommendations*

1. The evaluation of notable or worsening fatigue in mitochondrial patients should include an evaluation for treatable etiologies including consideration of cardiac insufficiency, anemia, an endocrinopathy (specifically thyroid and adrenal disease), worsening myopathy, pulmonary insufficiency, sleep disorder, nutritional and iron deficiencies and deconditioning.

### ***Care Coordination***

Mitochondrial diseases are complex and chronic. Multiple physician visits and frequent hospitalizations are needed at times in a patient's disease course. The diagnosis carries an emotional, psychosocial and financial burden for the patient and their family. Additional support and care coordination is routinely needed.

- A social work consult should be considered for resource and support planning and to assess for social risk factors that may impact care

### **SUMMARY**

The practice of mitochondrial medicine remains challenging due to a paucity of high-quality evidence to guide clinical patient care and management. The MMS used the Delphi method to generate consensus recommendations based on the current knowledge to-date along with the experience of mitochondrial specialists to help begin the process of standardization of care. We hope that these recommendations also raise awareness of the complete spectrum of symptoms and findings in mitochondrial disease and aid in the diagnosis, management and monitoring of co-morbid conditions.

Consensus guidelines are not meant to apply to all cases or conditions and require clinical judgment when used. Recommendations should be adjusted with advances in the field, data from clinical trials and evidence from future studies.

Due to the rarity of each individual mitochondrial disease, large-scale clinical trials may remain elusive. Networked centers in the US, through organizations such as the MMS and the North American Mitochondrial Disease Consortium, supported by patient advocacy groups, may serve as an opportunity to allow for gathering of high-quality evidence. Colleagues in other countries

have already formed such networks allowing for systematic phenotyping and analysis of this very complex group of patients. The MMS hopes to continue to foster these relationships to advance education, research and collaboration in the field.

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