













POSITION PAPER

Patient care standards for primary mitochondrial disease in Australia: an Australian adaptation of the Mitochondrial Medicine Society recommendations

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Abstract

This document provides consensus-based recommendations for general physicians and primary care physicians who diagnose and manage patients with mitochondrial diseases (MD). It builds on previous international guidelines, with particular emphasis on clinical management in the Australian setting. This statement was prepared by a working group of medical practitioners, nurses and allied health professionals with clinical expertise and experience in managing Australian patients with MD. As new treatments and management plans emerge, these consensus-based recommendations will continue to evolve, but current standards of care are summarised in this document.

Introduction

Mitochondrial diseases (MD) are the most common group of inherited metabolic diseases. At least 1 in 250 Australians carry a disease-causing mtDNA mutation that puts them at risk of MD during their lifetime.^{1–3} MD are multisystemic conditions that, in many cases are relentlessly progressive, cause a high-disease burden and

lead to premature death. MD are difficult to diagnose because their clinical features are protean and symptoms are heterogeneous – even individuals in the same family with the same causative genetic mutation may manifest varying clinical phenotypes.⁴ Many affected individuals remain undiagnosed, spend years being misdiagnosed, or are only diagnosed late in life.^{5–7} Early diagnosis and referral to specialist centres of care enables intervention and treatment that may prevent severe clinical sequelae, avoids unnecessary investigations and adverse outcomes of inappropriate therapy, and informs family planning.^{6–9}

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Given the spectrum of syndromes and wide variety of symptoms, treatment guidelines are symptom based. Patient care standards have been developed internationally to aid managing patients with MD.⁹ However, these guidelines are not always applicable in the Australian healthcare setting where the range of publicly available investigations, treatments and long-term follow up differ from that available in the USA and other international centres. Genetic diagnosis can inform precise treatment in some types of MD,^{10–12} but access to government-funded genetic testing is limited in Australia. Delays in diagnosis, whether on clinical grounds, or after genetic confirmation, may lead to lags in initiating appropriate treatments.

This document guides general physicians and primary care physicians who manage patients with MD. It builds on previous international guidelines,⁹ with particular emphasis on clinical management in the Australian setting.

Methods

A group of Australian clinicians with experience in the management of MD participated in teleconferences to discuss the international patient care standards⁹ and their application in the Australian health care setting. The group comprised neurologists (CMS, RG, CL, MN, DT, CW), paediatric neurologists (NS, MK), paediatric metabolic geneticists (SB, DB, JC, DC, CE, JL), genetic counsellors (LK), ophthalmologists (DM), allied health professionals (CB, JR), general practitioners (KC) and a specialist nurse (FEH). The Delphi method was used in formulating the Mitochondrial Medicine Society (MMS) 2017 consensus statement⁹ and therefore it was considered unnecessary to use a similar process for modifying the standards to the Australian clinical practice setting.

Recommendations

Guidelines for the standards of care for Australian patients with MD are listed in Tables 1–19. These are based on those in Parikh *et al.*⁹ Where no modifications have been recommended, text has not been altered. Additional commentary provided by our group of Australian clinicians is as follows:

Audiology

Hearing loss is a frequent clinical manifestation of MD, with half of patients affected, typically with a sensorineural aetiology.²² Hearing loss can be progressive, necessitating hearing aids and sometimes cochlear implants; regular monitoring is required. Some forms of MD, such as Leber hereditary optic neuropathy (LHON), rarely manifest auditory problems, and regular hearing tests as part of

Table 1 Australian recommendations: Audiology

- 1 Perform audiological assessment (history taking with an audiogram and/or otoacoustic emissions and auditory brainstem-evoked responses in children who cannot perform audiometry) at initial evaluation and then yearly to 2 yearly
- 2 Counsel patients to avoid environmental and other excessive noise exposure as this can exacerbate hearing loss and lead to a stepwise deterioration in hearing. This exacerbation may or may not be reversible
- 3 Aminoglycosides may exacerbate or precipitate sensorineural hearing loss in patients with MD. Avoid use unless the infection is resistant to other antibiotics
- 4 Monitor acute episodes (serious illness, stroke-like episodes, intensive care admissions) that may exacerbate or precipitate hearing loss
- 5 Address moderate to severe hearing loss with digital hearing aids to improve function
- 6 Consider cochlear implantation for profound hearing loss (>90 dB).¹³ Discuss cochlear implantation with patient and caregivers, as hearing loss may affect the development of speech and impair learning in the long term
- 7 Consider multisystemic involvement, cardiomyopathy, profound intellectual disability or cognitive impairment that may limit the benefit or patient's ability to comply with the rehabilitation process post-surgery

Specific recommendations for paediatric patients

- 1 Refer to ear nose throat surgeon for assessment if concerned
- 2 Consider differential diagnoses that exclude non-MD pathology that might contribute to hearing loss, such as recurrent middle ear disease
- 3 Refer to speech therapy for assistance with speech and language development in children with a hearing deficit
- 4 Refer to hearing support services and educational liaison regarding the management of hearing deficits for children in the classroom

MD, mitochondrial disease.

their formal management plans may not be required in patients with these specific forms of disease (Table 1).

Cardiology

A high proportion of patients with MD have cardiac involvement (50% in adults and 40% in paediatrics^{23,24}), underpinning the importance of baseline cardiac evaluation and monitoring. MMS guidelines recommend annual electrocardiograms,⁹ and our Australian consortium endorsed this, especially if there was a family history or evidence of cardiac abnormalities (Table 2).

Critical care

People with MD are vulnerable to episodes of decompensation and worsening of symptoms during intercurrent

Table 2 Australian recommendations: Cardiology

- 1 Perform baseline cardiology assessment in all patients with suspected or proven MD including:
 - a Standard 12-lead electrocardiogram (ECG)
 - b 24-h ECG (Holter monitoring)
 - c Echocardiogram (with a measure of left ventricular wall thickness and mass, and systolic/diastolic function including left ventricular ejection fraction, fractional shortening and global function score)
- 2 Perform annual ECG to monitor cardiac status in all patients with proven MD
- 3 Individualise the frequency of other methods of cardiac monitoring, taking into consideration any known evidence of cardiac involvement or family history of cardiac involvement. In patients with MD and skeletal myopathy, poor exercise tolerance and muscle fatigue, symptoms of cardiac failure may be masked and asymptomatic cardiac failure may be present
- 4 Assess other comorbidities including diabetes, hypertension and dyslipidaemia and treat accordingly to minimise disease progression from additional risk factors
- 5 For cardiac arrhythmia, consider ablation therapy for supraventricular tachycardia and Wolff–Parkinson–White syndrome
- 6 A low threshold for pacemaker implantation is needed to prevent cardiac death. Pacemakers can be combined with an implantable defibrillator if needed. An implantable cardioverter defibrillator is needed in patients at risk of sudden death, when the left ventricle wall thickness is >30 mm, and in patients with ventricular tachycardia (sustained and non-sustained)
- 7 Consider early use of angiotensinogen-converting enzyme inhibitors for cardiac failure with regular monitoring of renal function
- 8 Perform exercise testing and/or stress echocardiography in symptomatic adult patients. Consider computed tomography angiography/radionuclide myocardial perfusion imaging to assess comorbidities in patients who cannot perform exercise testing. If there is significant concern about the patient's cardiac status, the intensity of the physical activity should be reviewed in consultation with the cardiologist, according to the limitations of the individual's cardiac function
- 9 Cardiac magnetic resonance imaging, although not routinely performed in Australia, is being increasingly used to monitor cardiac function and anatomy. It is useful for diagnosing early heart failure or deterioration of cardiac function
- 10 For end-stage heart failure, consider heart transplantation in the context of other MD comorbidities

Specific recommendations for paediatric patients: In consultation with a paediatric cardiologist, consider exercise testing, or stress echocardiography in children with mtDNA mutations or MD associated with cardiac disease and arrhythmia (e.g. pre-excitation syndrome/conduction disease). Encourage physical activity including supervised graded exercise regimes. Goals should be prescribed by paediatric cardiologists and experienced physiotherapists. Note that children may not be symptomatic until the latter stages of cardiac failure.

Specific recommendations for patients confirmed to have LHON: Follow up only recommended if the patient is symptomatic or has a family history of cardiac disease

LHON, Leber hereditary optic neuropathy; MD, mitochondrial disease.

illnesses. Acute cerebral events and cardiopulmonary failure are the leading cause of mortality in patients with MD.²⁵

Table 3 Australian recommendations: Critical care

- 1 Provide diagnosed patients (especially those at risk of acute episodes or who have recurrent episodic crises) or their caregivers/parents, with an emergency management plan for their MD including diagnosis, clinical symptoms, organ-specific symptoms, baseline cardiorespiratory function, special nutritional needs, medications, allergies, and contraindicated therapies. Include guidelines for management during critical illness or emergency along with contact details for the relevant MD physician. This document should be easily available in the patient's records and widely circulated amongst all teams managing the patient. It may be useful to have the patient's records labelled as 'Mitochondrial disease' on their patient chart. Include the management plan in the patient's *My Health Record* file if it has been established
- 2 Refer critically ill patients with MD to ICU early, given the greater likelihood of multisystem dysfunction and potential for reversibility and recovery often observed in patients with MD
- 3 Assess glucose, pH, lactate, and electrolytes including sodium, potassium, calcium, magnesium, chloride and phosphate. Recurrent or persistent electrolyte imbalances should prompt an evaluation of renal tubular and adrenal function
- 4 Obtain an echocardiogram in instances of haemodynamic dysfunction. Monitor creatine kinase and troponin
- 5 Assess levels of adrenocorticotrophic hormone and cortisol immediately before administration of stress-dose steroids in patients with pressor-refractory hypotension, provided this does not delay therapy
- 6 Closely monitor lactate levels during critical care. In patients treated with L-arginine-HCl (e.g. mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)), assess blood gases and electrolytes with bicarbonate and anion gap daily
 - a Treat secondary causes of acidosis
 - b Avoid the use of intravenous solutions containing higher than 5% of dextrose
 - c Use sodium bicarbonate only for extreme acidosis
- 7 Monitor blood glucose regularly to assess for hypo- and hyperglycaemia. Consider insulin administration when required
- 8 Consider neuroimaging (magnetic resonance imaging) and electroencephalography if changes in baseline neurological state or examination occur
- 9 Consider total parenteral nutrition or intravascular lipids in patients with bowel dysmotility and severe pseudo-obstruction. In paediatric patients, intravenous 5% dextrose is usually commenced when nil-by-mouth or when patients have poor oral intake with associated vomiting and/or diarrhoea. Consider intravenous lipids (10% or 20% Intralipids 2–3 g/kg/day) if there is no evidence of associated impaired fatty acid oxidation. Introduce enteral feeds cautiously and monitor for pseudo-obstruction
- 10 Provide closer neurological monitoring for patients with bowel pseudo-obstruction, particularly in patients with MELAS or POLG-related disorders, as this may be associated with central nervous system deterioration, including stroke-like episodes
- 11 Monitor liver function, and exclude hypoglycaemia, hypoalbuminaemia or coagulopathy if liver dysfunction is present
- 12 Hepatocerebral involvement is common in infantile MD. Avoid sodium valproate, phenobarbitone, phenytoin, carbamazepine, topiramate and vigabatrin for treatment of seizures in these patients as fulminant hepatic failure and other adverse reactions may be precipitated by these medications (see neurological

Table 3 *Continued*

recommendations). Intravenous levetiracetam at 20–40 mg/kg can be used instead

13 In patients with bone marrow failure, transfuse packed red cells or platelets if indicated. Granulocyte colony-stimulating factor may be required for severe neutropenia and/or infections. Consult a haematologist as required

14 Supplements and cofactor therapy should be continued when possible, preferably via enteral route

ICU, intensive care unit; MD, mitochondrial disease.

In Australia, pyruvate is not routinely monitored in the critical care setting (despite this recommendation in the MMS guidelines), as assessing complex I deficiency is not the primary aim in a critical situation, and pyruvate analysis does not change clinical management. Lactate elevation may be a marker of decompensated acidosis; however, the risk of systemic acidosis is greatest if serum lactate is above 5 mmol/L. Elevated lactate may be related to the administration of 10% dextrose, which can be converted to lactate through glycolysis, or by use of lactate-containing solutions intravenously, for example Hartmann's solution (Ringer's lactate).

It should be noted that in the acute setting, thyroid function results may be misleading due to sick euthyroid syndrome (Table 3).

Endocrinology

Endocrinological manifestations of MD include diabetes, thyroid, parathyroid and short stature. Recommendations, particularly around screening, are included in Table 4. Assessment for diabetes or insulin resistance is important given insulin resistance is observed in patients without overt clinical signs (Table 4).

Gastroenterology

Gastrointestinal tract dysmotility, swallowing and bulbar muscle weakness and liver failure may all manifest in MD. Australian clinical practice closely follows the recommendations from the MMS (Table 5).

Haematology

Haematological involvement is relatively infrequent in MD, for example conditions such as sideroblastic anaemia are only seen in rare disorders such as myopathy, lactic acidosis and sideroblastic anaemia or Pearson syndrome. Recommendations for haematological management listed in Table 6 are those proposed by the MMS.

Table 4 Australian recommendations: Endocrinology

-
- 1** Assess haemoglobin A1c (HbA1c), thyroid-stimulating hormone, free thyroxine level (FT4), magnesium, phosphate, parathyroid hormone, vitamin D (25-OHD and 1,25-OHD); creatinine; and calcium, annually, particularly in patients with mtDNA deletions
 - 2** Perform fasting blood sugar levels and consider oral glucose tolerance test at the initial assessment. If the patient is already diagnosed with diabetes
 - a** Avoid metformin as a first-line treatment for diabetes as it may exacerbate lactic acidosis. If the patient is already on metformin prior to being diagnosed with MD, consider changing to an alternative agent or at least monitor lactate closely if metformin is to be continued for glycaemic control
 - b** Consider combined use of oral hypoglycaemic agents and insulin therapy, as some patients with MD may have both insulin resistance and insulin deficiency
 - 3** Investigate new onset of worsening fatigue or symptoms typically associated with adrenal insufficiency with early morning cortisol and a short synacthen test if required
 - 4** Optimise calcium and vitamin D status, encourage a good exercise regimen and avoid injuries and falls to prevent fractures. Consider bone mineral density testing (dual-energy X-ray absorptiometry and peripheral quantitative computed tomography) annually or biennially, especially in patients with nutritional deficiencies or immobility, to assess fracture risks. Consider the need for bisphosphonates in consultation with an endocrinologist

Specific recommendations for paediatric patients: Measure height, weight, body mass index and growth velocity (including an assessment of nutritional status) and monitor HbA1c. Delay in pubertal onset may occur and lead to poor bone health and necessitate a referral to a paediatric endocrinologist for hormonal therapy

MD, mitochondrial disease.

Immunology

Patients with MD often take longer to recover from infections and are at greater risk of sepsis,²⁶ particularly in those patients with Pearson or Barth syndrome. Approximately one-third of patients have a documented immunodeficiency.²⁶ However, there are no contraindications for vaccination (including live vaccines) in patients with MD (Table 7).

Nephrology

MD has been associated with asymptomatic kidney disease as well as reduced glomerular filtration rate, proteinuria and/or haematuria, (with and without hypertension), metabolic acidosis, renal tubular acidosis, focal segmental glomerulosclerosis, progressive renal and rapid progression to renal failure.²⁷ Because MD may play a significant role in the development of or acceleration of pre-existing renal disease, recommendations were made as listed in Table 8.

Table 5 Australian recommendations: Gastroenterology

- 1 Regularly screen for symptoms of upper and lower gastrointestinal tract dysmotility including nausea, early satiety, abdominal distension and constipation. Consider further investigations such as gastric emptying and colonic transit studies. Persistent symptoms, physical examination or radiological findings of impacted stool should prompt intervention
- 2 Diarrhoea is not a common symptom in MD (besides overflow incontinence from constipation). Investigate its aetiology, including pancreatic insufficiency
- 3 Manage acute pseudo-obstructive presentations aggressively. Water-soluble contrast enemas may relieve obstruction and allow for exclusion of alternate aetiologies such as volvulus. Patients should be nil-by-mouth at these times; provide intravenous hydration with dextrose and electrolytes. Onset of pseudo-obstruction in MELAS patients may be a harbinger of neurologic decline, including new stroke-like episodes, and patients should be closely monitored to avoid neurological deficits
- 4 Evaluate cases with suspected aspiration or bulbar dysfunction with a video fluoroscopic/fibreoptic endoscopic evaluation of swallowing and seek advice on feeding strategies from a speech pathologist
- 5 Monitor malnourished patients including measuring weight and body mass index, not less than every 6 months (or 3–4 monthly in the paediatric population)
 - a Refer all patients identified on anthropometric examination as at risk for malnutrition to a dietitian
 - b In addition to monitoring body mass and growth patterns, assessing standard markers of nutritional status, vitamin levels and trace elements can help guide therapy
 - c Encourage diet/exercise programmes that promote lean muscle mass over those that simply increase body mass index
 - d In the rare circumstance that the patient is obese, encourage carefully monitored weight loss that may improve functional ability without exacerbating underlying symptoms
- 6 In the presence of severe bulbar dysfunction with risk of aspiration, gastroesophageal reflux or chronic malnutrition that does not respond to dietary intervention including use of nasogastric tube consider gastrostomy or jejunostomy tube insertion in consultation with a gastroenterologist or surgeon. Consider risk of general anaesthesia and use precautionary measures
- 7 If patients have symptoms or laboratory values indicative of exocrine pancreatic insufficiency, refer to a gastroenterologist
- 8 Assess liver function including synthetic liver function and CK. Refer to a gastroenterologist if there is evidence of deranged liver enzymes or serum markers of hepatic synthetic deficiency emerge
- 9 In severe cases of acute or acute on chronic liver failure, consider liver transplantation after carefully excluding significant MD in other organs, particularly brain. Additional caution regarding liver transplantation may be needed in patients with *POLG* mutations owing to the potential of increased morbidity and mortality

CK, creatine kinase; MD, mitochondrial disease; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes.

Neurology

Patients with MD may have a wide spectrum of neurological manifestations including seizures, stroke-like episodes, encephalopathy, headaches, movement disorders,

Table 6 Australian recommendations: Haematology

Australian recommendations: Haematology

- 1 Consider a complete blood count with differential cell counts annually for patients with primary MD. Patients with MD at higher risk of anaemia or bone marrow suppression (MLASA or Pearson syndrome) should undergo testing immediately if symptoms occur
- 2 Consider iron studies, vitamin B12 and folate in patients at risk of nutritional deficits and/or concomitant symptoms of fatigue
- 3 For patients with sideroblastic anaemia, blood transfusions and iron chelation therapy may be necessary

MD, mitochondrial disease; MLASA, myopathy, lactic acidosis and sideroblastic anaemia.

Table 7 Australian recommendations: Immunology

Australian recommendations: Immunology

- 1 Evaluate immune function early in any patient with MD experiencing recurrent or severe infections†
 - a Investigations to consider include quantitative immunoglobulin levels, vaccine-specific immunoglobulin G (IgG) titres and lymphocyte subset levels (T cell, B cell, switched memory B cell compartment, natural killer cells). Immune function evaluation and management may be conducted assisted by an immunologist
 - b Consider prophylactic treatment strategies including antibiotic prophylaxis, immunoglobulin replacement therapy, or granulocyte colony-stimulating factor therapy in patients with documented immune deficiencies
- 2 Offer patients with MD age-appropriate vaccination including an annual influenza vaccine
- 3 In patients with human immunodeficiency virus and MD, consider combinations of antiretroviral agents, for example integrase inhibitors and newer protease inhibitors with dual nucleoside reverse transcriptase inhibitors. These are less toxic to mitochondrial function^{14–16}

†Recurrent or severe infections are defined as those that are complicated, in multiple locations, resistant to standard treatment, caused by uncommon organisms, or recur more than 10 times a year.

MD, mitochondrial disease.

muscle weakness and neuropathy. Some of these may be life-threatening. Developmental delay or neurological regression may also be observed in children. Here we have incorporated recommendations for stroke-like episodes into the overall recommendations for neurology (Table 9).

Ophthalmology

Progressive visual loss may be the predominant phenotype in some MD such as in LHON or dominant optic atrophy. The use of idebenone (a co-enzyme Q10 analogue) in patients with LHON was strongly recommended in the MMS guidelines.⁹ In Australia, idebenone is approved for

Table 8 Australian recommendations: Nephrology

- 1 Screen all patients with suspected MD for renal dysfunction with baseline measurement of blood pressure, anthropometry, serum urea, sodium, potassium, chloride, anion gap (normal anion gap acidosis) calcium, magnesium, phosphate and creatinine
- 2 If suspected renal involvement, consider
 - a urine microscopy, pH and urinary chemistry including glucose, beta 2 microglobulin and albumin/creatinine ratio
 - b Nuclear medicine GFR scans (chromium EDTA GFR and diethylenetriamine pentaacetic acid) and as required in consultation with a nephrologist
 - c In children, consider measurement of cystatin C (a more sensitive marker of GFR than serum creatinine in children with muscle dysfunction) and baseline renal ultrasound to monitor growth of kidneys followed by annual or biennial testing as needed
 - d Monitor renal function parameters (urine albumin/creatinine ratio, serum creatinine, UEC with HCO₃ and other metabolic parameters) at 6–12 monthly intervals. Those with significant abnormalities should be referred to a nephrologist with experience in the management of MD
 - e Monitor and optimise bone health with established renal disease in consultation with nephrologists and endocrinologists
 - f Replace electrolytes (e.g. potassium, HCO₃, calcium, magnesium and/or phosphate) as needed. In paediatric patients, consider early placement of a gastrostomy tube to assist with compliance, aiming for partial or complete correction, where possible to optimise growth and development
 - g Consider dialysis and renal transplantation for end-stage renal disease, in context of quality of life and survival with other comorbidities

DTPA, diethylenetriamine pentaacetic acid; EDTA, ethylenediamine tetraacetic acid; GFR, glomerular filtration rate; MD, mitochondrial disease; UEC, urea, electrolytes and creatinine.

LHON by the Therapeutic Goods Administration; however, it is not subsidised under the Pharmaceutical Benefits Scheme. There have also been reports of spontaneous improvement of vision in patients with LHON without treatment, especially in those with m.14484T>C and m.3460G>A mutations.^{28–31} Recommendations for the management of non-specific ophthalmological manifestations of MD are listed in Table 10.

Orthopaedics and rehabilitation medicine

In Australia, evaluation and care for patients is not always conducted by a rehabilitation medicine specialist. Patients are often cared for by physiotherapists or other allied health professionals (Table 11).

Pregnancy

Family planning for patients with MD is best managed in consultation with a physician with expertise in

Table 9 Australian recommendations: Neurology

- For all neurological manifestations
- 1 Monitor clinical condition closely and regularly
 - 2 Avoid valproic acid, especially in patients with *POLG*-related disease as it exacerbates seizures and may precipitate liver failure
 - 3 Use vigabatrin with caution, particularly in patients with optic atrophy or mtDNA-depletion syndromes
 - 4 Use topiramate and zonisamide with caution as they may worsen acidosis
 - 5 Neurobehavioural (e.g. autism and attention deficit disorder) and psychiatric comorbidities occur frequently in patients with MD. Manage in line with standard clinical approaches
- Epilepsy
- 1 In patients with MD who develop altered levels of consciousness, episodes of behaviour arrest or alterations of cognition and change in seizure frequency from baseline, there should be a low threshold to obtain electroencephalogram (EEG) monitoring
 - 2 EEG in association with seizure semiology can aid in diagnosis and classification of epilepsy; however, a normal EEG does not exclude the presence of seizure activity
 - 3 For treating seizures, levetiracetam and benzodiazepines are preferable
 - 4 Use levetiracetam for status epilepticus. Benzodiazepines like midazolam or clonazepam can be used as rescue medications. For treatment of epilepsy, levetiracetam, lamotrigine, clonazepam and clobazam are known to be safe
 - 5 When epilepsy partialis continua is present, investigate to exclude a metabolic stroke-like episode, metabolic encephalopathy or other secondary metabolic crisis
 - 6 Consider use of ketogenic diet in refractory epilepsy in MD with careful monitoring
- Headaches
- 1 Treatment for migraines in MD is similar to that in patients without MD, noting that treatments such as valproate are contraindicated. Consider prophylactic oral L-arginine in MELAS-related migraine headaches
 - 2 Sudden onset, focal neurological features or worsening severity of migraines in MD may herald the onset of stroke-like episodes or seizures, requiring prompt evaluation
 - 3 Watch for irritability and altered personality in children, especially those with intellectual disability, as this may be how headache presents
- Movement disorders and altered tone
- 1 Perform routine neurologic assessment of movement disorders and spasticity. Consider other causes, and medical, procedural, and surgical treatments to improve quality of life
 - 2 Evaluate sudden onset or new movement disorders for disease progression and/or acute insult. Conduct neuroimaging (MRI with MRS), electrophysiological testing and baseline laboratory investigations as indicated. Consider performing cerebrospinal fluid folate and neurotransmitter assays to exclude treatable causes of movement disorders
 - 3 Use medications that alter tone cautiously as they can selectively worsen cognitive status, decrease muscle strength and secondarily respiratory effort, and impact gastrointestinal motility and urinary function
 - 4 Although botulinum toxin can be of benefit in assisting with spasticity and dystonia, use it with caution because of potential side-effects such as exacerbating muscle weakness

Table 9 Continued

- 5 Recommend physical therapy and assessments to maximise mobility, prevent contractures, joint dislocations and alleviate discomfort and pain
- 6 Consider deep brain stimulation when appropriate for treatment of mitochondrial movement disorders, taking into account the patient's long-term prognosis and level of morbidity

Myopathy

- 1 Evaluate muscle function at initial assessment, including assessment of strength, CK level measurement. Consider baseline electromyography if symptomatic muscle involvement is present
- 2 Monitor serum CK, lactate and FGF21 and/or GDF15 levels annually, in patients with a myopathy or as clinically indicated, with symptom worsening or a decline in function
- 3 Assess for secondary causes of a myopathy, especially if CK levels are above 1000 U/L (other than in TK2-related disease) and consider a complete blood count, inflammatory markers, thyroid function tests, autoimmune and toxicology screen when appropriate
- 4 Follow standard rhabdomyolysis treatment protocols for recurrent rhabdomyolysis and myoglobinuria, triggered by exercise or illness
- 5 Submaximal aerobic exercise may improve muscle function to benefit patients with MD; consider an individualised programme.¹⁷ Evaluate cardiac function before the initiation of an exercise programme (Table 2)
- 6 Use agents such as statins, corticosteroids, metformin and antiretrovirals with caution and monitor patients closely since these agents may exacerbate the underlying myopathy
- 7 Consider co-enzyme Q10 (10–30 mg/kg/day in two divided doses)¹⁸ to treat primary co-enzyme Q10 deficiency, riboflavin (50–200 mg daily)¹⁹ for myopathy associated with *ACAD9* deficiency and a combination of co-enzyme Q10 and riboflavin for *ETFDH*-related myopathy (see other considerations section and Table 18)

Neuropathy

- 1 Screen patients with MD for symptoms and clinical signs of peripheral large and small fibre neuropathy at baseline and annually; consider a comprehensive nerve conduction study and electromyogram that includes both upper and lower extremities with evaluation of sensory and motor nerves
- 2 Screen for treatable causes of peripheral neuropathy including deficiencies in vitamin B6, vitamin B12, folate or vitamin E, especially when the findings are atypical for the underlying MD
- 3 Diabetes mellitus is more common in certain MD, including MELAS and maternally inherited diabetes and deafness. Ensure optimal glycaemic control to minimise diabetes associated small fibre neuropathy
- 4 Treatment of mitochondrial neuropathies is symptomatic and follows guidelines established for the care of non-mitochondrial neuropathies. Caution and close monitoring are needed if medications causing mitochondrial toxicity are used

Stroke-like episodes

- 1 Acute stroke-like episodes in primary MD typically have anatomically consistent visible MRI and CT scan abnormalities, even if they do not conform to a single vascular territory. MRS to measure elevated intracerebral lactate levels may be helpful in confirming the diagnosis although is not pathognomonic of MD associated stroke. Clinical symptomatology usually correlates with the lesion distribution but does not necessarily correlate with the severity of the neuroradiological abnormalities

Table 9 Continued

- 2 Administer intravenous anti-convulsant therapy (first-line: levetiracetam 40 mg/kg) early in the acute setting of a stroke-like episode, especially if the patient has MELAS m.3243A>G or other mutations in the *MTTL1* gene
- 3 Administer intravenous L-arginine for stroke-like episodes as soon as possible to reduce severity or duration of stroke-like episodes in patients with MELAS syndrome. Recommended doses are: 500 mg/kg for children²⁰ preferably within 3 h of symptom onset followed by the administration of similar dosage of intravenous arginine as continuous infusion over 24 h for 3–5 days. In adults, administer an initial loading dose of 0.5 g/kg in 10% solution intravenously over 30 min,²¹ followed by same intravenous dosage per day in divided doses until clinical improvement (often over 3–7 days). Admit patients to the intensive care unit (ICU) for close monitoring if there is drowsiness, ongoing seizures or acute neurological deterioration
- 4 Consider prophylactic oral L-arginine to reduce the risk of recurrent stroke-like episodes in MELAS patients. A daily dose of 150–300 mg/kg/day (probably up to 24 g/day)²¹ oral arginine in 2–3 divided doses is recommended
- 5 The role of monitoring plasma arginine and citrulline levels and oral citrulline supplementation in the treatment of MELAS is unclear and requires further research

Specific recommendations for paediatric patients

- 1 Because these patients may regress neurologically, closely monitor neurodevelopmental and cognitive status at each follow up. Regular neurodevelopmental assessments (3–4 monthly) are recommended especially in younger children
- 2 Perform a comprehensive neurodevelopmental screen on paediatric patients with MD. This can include Griffiths scales for the younger children
- 3 Consider baseline formal neuropsychological testing for paediatric patients with MD over the age of 6 years with central nervous system disease. Consider repeat testing biennially or earlier in the presence of cognitive, behavioural and/or personality change to allow for optimal tracking of patient function and development of personalised care plans
- 4 Consider referral to a developmental paediatrician and appropriate therapist (including community support services and liaison with educational services) if developmental disability/ID is confirmed
- 5 Evaluate developmental regression at any age for a potential treatable condition or disease progression; testing may need to include repeat neuroimaging and an EEG

CK, creatine kinase; ID, intellectual disability; MD, mitochondrial disease; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy.

MD. Prenatal or pre-implantation genetic diagnosis is available in Australia, but mitochondrial donation is only legal in the United Kingdom. During confinement, patients should be referred to a high-risk pregnancy unit and a specialised mitochondrial disease clinic or clinician, especially if there are multiple systemic features (Table 12).

Table 10 Australian recommendations: Ophthalmology

- 1 A comprehensive clinical evaluation for eye disease should include visual acuity, visual fields, ocular motility, documentation of ptosis, slit lamp examination and fundoscopy regardless of reported symptoms
- 2 At the time of diagnosis, refer patients to an ophthalmologist for detection of visual, retinal, macular, intraocular pressure and optic nerve changes, supported by optical coherence tomography. Electrophysiology, including visual evoked potentials and electroretinography, can be considered. Consider annual ophthalmology exams thereafter
- 3 Refer patients with visual impairment to a low-vision specialist
- 4 Surgery may be indicated to treat strabismus, ptosis or cataracts
- 5 Recommend ocular lubrication with methylcellulose eye drops or ointments for patients with inappropriate closure of palpebral fissures due to ptosis or after ptosis repair
- 6 Encourage LHON carriers to limit alcohol consumption (<2 drinks/day) and avoid smoking as these have been associated with increased risk of visual loss. Patients with LHON who participate in sports with a risk of eye or head injury should wear recommended eye or head protection
- 7 Patients with LHON should undergo periodic neurologic and cardiac evaluations, particularly if there is a family history of other neurological or cardiac problems
- 8 Monitor patients with the m.3243 A>G mutation for maculopathy with fundus autofluorescence

LHON, Leber hereditary optic neuropathy.

Table 11 Australian recommendations: Orthopaedics and rehabilitation medicine

- 1 Patients should be examined annually for musculoskeletal complications including kyphoscoliosis, contractures, dislocations and limb deformities, especially if the patient has underlying abnormalities in tone, muscle strength or neurologic functioning
- 2 Evaluation and care by allied health professionals or rehabilitation specialists can help maintain safety, mobility and an active lifestyle
- 3 Inpatient intensive rehabilitation may improve function in some patients especially with recent regression of motor skills and should be considered
- 4 Orthopaedic interventions, both operative and nonoperative, 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 orthopaedic procedure

Psychiatry

Depression and anxiety are very common in adult patients with MD. In Australia, there is no standardised screening tool for depression and anxiety in paediatric or adult MD populations. However, it is recommended that clinical assessment should be undertaken using validated general instruments such as the Beck Depression Inventory³² or the Beck Anxiety Inventory³³ (Table 13).

Table 12 Australian recommendations: Pregnancy

- 1 Ensure pregnant women with MD are medically reviewed by their MD specialist throughout their pregnancy in conjunction with their obstetric management
- 2 Ideally, consult an obstetrician with expertise in managing high-risk pregnancies as affected women may be at higher risk for preterm labour and preeclampsia
- 3 Counsel women with MD about a potential risk of gestational diabetes; oral glucose tolerance test should be obtained early and later in the pregnancy
- 4 Provide access for prospective parents with or at risk of MD with preconception genetic counselling and offer prenatal or pre-implantation genetic testing where this is feasible. Offer genetic counselling promptly to women diagnosed during pregnancy
- 5 Closer foetal 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)
- 6 Encourage early involvement of the neonatologist especially in transmissible MD and develop a care plan to be followed during labour and after birth of the baby. Monitoring of the neonate in ICU may be required and options for labour in a maternal and neonatal centre may alleviate maternal anxiety

ICU, intensive care unit; MD, mitochondrial disease.

Table 13 Australian recommendations: Psychiatry

- 1 Routinely screen for depression and anxiety symptoms
- 2 Evaluate psychiatric symptoms promptly as they can be a manifestation of encephalopathy or other change in neurological status
- 3 In the paediatric population, screen for low self-esteem and anxiety due to lack of active participation in sports and physical activities

Respiratory

Respiratory function may be impaired due to neuromuscular or central causes, and be exacerbated by diaphragmatic weakness, obstructive sleep apnoea, intermittent aspiration or infection. Cardiac failure, anaesthetics, aspiration pneumonia and respiratory tract infections may precipitate respiratory failure (Table 14).

Surgery/anaesthesia/perioperative care

Many surgical procedures may be needed including muscle biopsy and gastrostomy placement, and managing musculoskeletal complications. The stress of surgery and anaesthesia may lead to unexpected complications. It is important to avoid prolonged fasting, hypothermia, hypoglycaemia, acidosis and nausea and vomiting in the postoperative period. Malignant

Table 14 Australian recommendations: Respiratory

- 1 Routinely screen for symptoms of respiratory muscle weakness and additional comorbidities including obstructive sleep apnoea, bulbar weakness, risks for aspiration, gastroesophageal reflux, asthma and chronic obstructive pulmonary disease
- 2 Perform baseline assessment with respiratory function tests and if clinically indicated (e.g. evidence of diaphragmatic or respiratory muscle weakness), perform overnight pulse oximetry
- 3 Have a low threshold to refer patients with clinically significant abnormalities to a respiratory specialist for follow up and management
 - a Consider referral to a respiratory specialist for respiratory function tests and spirometry in both the supine and upright positions. If an appropriate seal with a mouthpiece cannot be achieved, use a nasal clip or a face mask. Additional testing may be performed at the discretion of a respiratory specialist familiar with neuromuscular diseases
 - b If initial tests are normal, repeat testing may be deferred until new symptoms arise or if there is a suspicion of disease deterioration
 - c For patients with well characterised respiratory involvement, repeat testing periodically to follow progress and predict the pulmonary function
- 4 Consider overnight sleep studies if clinically indicated to assess for sleep disturbances, central or obstructive apnoea, and nocturnal hypoventilation
- 5 Neuromuscular weakness predisposes to respiratory issues in the perioperative period due to poor airway tone, clearance of secretions, and chronic aspiration. Prior to any surgical intervention, perform a thorough pre-anaesthetic evaluation and respiratory assessment. Assessment of lung function (spirometry) and pre-anaesthetic evaluation with additional investigations such as blood gases and polysomnography if indicated should occur 2–3 months prior to anaesthetic to allow initiation of non-invasive ventilation if appropriate
 - a Before surgery, a pre-anaesthetic evaluation should be performed. If SpO₂ is <95%, a blood gas should be obtained to assess carbon dioxide levels. For patients with neuromuscular weakness, preoperative use of non-invasive positive pressure ventilation should be considered, especially if there is a weak cough, recurrent pneumonia or low maximum expiratory pressure
 - b Postoperatively, those with neuromuscular weakness can be extubated to non-invasive positive pressure ventilation to prevent prolonged intubation, with weaning as tolerated since recovery may be prolonged
 - c Postoperative atelectasis may require aggressive pulmonary toilet with cough assist, airway clearance and chest physiotherapy
 - d Limit use of opioids, which can further suppress adequate cough and recovery
- 6 Strongly consider respiratory referral during acute disease decompensation with exacerbated symptoms
 - a Incentive spirometry is commonly used in hospitals, but manual compression, glossopharyngeal breathing and insufflations should also be attempted by a respiratory clinical nurse consultant or physiotherapist in hospital or at home during the recovery period
 - b Obtain chest X-ray and/or CT chest in the acute setting to identify diaphragm abnormality, collapsed lungs, aspiration and any other pulmonary pathology

CT, computed tomography.

Table 15 Australian recommendations: Surgery/anaesthesia/perioperative care

- 1 Individualise surgical care according to the underlying MD, comorbidities and indication for surgery. Consider pre-surgical anaesthetic evaluation (also see Table 14, Surgery/anaesthesia/perioperative care section)
- 2 When possible, admit the patient the night before any elective surgery
- 3 Avoid fasting for longer than required and, if possible, place the patient with MD first on the list
- 4 Avoid volatile anaesthetics and propofol
- 5 Avoid lactate-containing agents when there is risk of lactic acidosis
- 6 In patients on ketogenic diets for epilepsy, avoid glucose infusions

MD, mitochondrial disease.

Table 16 Australian recommendations: Altitude

- 1 Consideration and careful planning are needed for high altitude travel as some patients, especially those with cardiopulmonary involvement, may be susceptible to clinical deterioration during these times. Complications are infrequent but require rapid recognition and treatment
- 2 Due to a lower pO₂ during air travel, patients with cardiomyopathy or severe respiratory weakness need to consider oxygen saturation monitoring *en route* and potentially have access to supplemental oxygen

hyperthermia-like reactions have been reported in MD (Table 15).

Other considerations

Altitude

There is no anecdotal evidence of patients with MD experiencing high altitude sickness, although it is reasonable to suspect there is a higher risk for those patients with cardiorespiratory compromise (Table 16).

Fatigue and exercise

Fatigue is a common symptom in patients with MD. To date, exercise therapy is the main treatment option to improve this symptom (Table 17).

Supplements and nutrition

Always encourage a healthy nutritious diet. A high-fat and high-protein diet may be useful in children, but there is limited evidence to suggest using it on a regular basis in all patients with MD. The benefits of ketogenic diets are unclear, and there is concern about their long-term use and the potential risks versus benefits of inducing ketosis. There is some anecdotal evidence for their use in patients with MD and epilepsy, although no

Table 17 Australian recommendations: Fatigue and exercise

Fatigue

- 1 Evaluate notable or worsening fatigue in patients with MD, including for treatable aetiologies: cardiac insufficiency, nutritional anaemia, an endocrinopathy (specifically thyroid and adrenal disease), worsening myopathy, respiratory insufficiency, sleep disorder, nutritional and iron deficiencies, and deconditioning
- 2 Recommend graded, regular physical activity to improve symptoms of exercise intolerance and fatigability, given the evidence that aerobic exercise in patients with MD increases energy production¹⁷
- 3 When required, allow easy access to scooters or wheelchairs to allow participation in family activities
- 4 In the paediatric population consider use of alternative learning strategies like typing instead of writing and regular periods of rest in the classroom

Exercise

- 1 Recommend moderate intensity aerobic exercise at 70% of the patient's maximum heart rate to improve baseline levels of fitness, except in those patients with cardiac arrhythmia and/or cardiopulmonary involvement
- 2 Evidence to support the benefit of resistance or concentric training is still limited
- 3 Studies have suggested that high-intensity interval training could stimulate mitochondrial biogenesis. However, to date, there is limited evidence for the clinical benefits for this intervention in patients with MD
- 4 In consultation with an exercise therapist, physiotherapist, allied health professional, or sports medicine physician, recommend a tailored exercise programme

MD, mitochondrial disease.

randomised controlled trials have been performed to date (Table 18).

Care coordination

In Australia, care coordination varies between hospitals. However, in all tertiary hospitals the management of patients with MD often involves a multidisciplinary team. Social support of patients should also be part of care (Table 19).

Conclusion

The MMS standards of care⁹ provided an excellent basis to these Australian recommendations. We hope that

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Table 18 Australian recommendations: Supplements and nutrition

- 1 All patients should follow a well balanced nutritional diet with advice from a qualified dietitian, where appropriate
- 2 There is limited evidence of the benefits of the ketogenic and high-fat diets in MD. Consider high-fat diet in patients with intractable epilepsy, complex I deficiency or in the acute setting after excluding β -oxidation defects
- 3 There are anecdotal reports that supplements such as co-enzyme Q10 (CoQ), carnitine, thiamine, riboflavin, magnesium orotate, alpha-lipoic acid could be helpful. There is not enough evidence to prove their benefit, apart from in specific conditions including thiamine, with ketogenic diet in pyruvate dehydrogenase deficiency and CoQ in primary CoQ deficiency
- 4 Treat specific nutritional deficiencies in patients with MD
- 5 Monitor nutritional status annually in children, including iron studies, vitamin D, zinc and other micronutrients
- 6 Supplement carnitine (50–100 mg/kg/day in 2–3 divided doses) in patients with carnitine deficiency

MD, mitochondrial disease.

Table 19 Australian recommendations: Care coordination

- 1 Ideally involve a social worker for resource and support planning and to assess for social risk factors that may affect care
- 2 An experienced case manager is recommended to assist patients in their applications for the national disability support scheme

adapting these original standards aids in the diagnosis and management of patients with MD in Australia. Clinical judgement, however, should guide all decisions for individual patient care. In addition, emerging evidence may justify treatment practices (or evidence against such practices) that have been outlined in this document.

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