Newcastle Mitochondrial Disease Guidelines

Anaesthesia & Peri-Operative Care in Adult Patients:

Screening and Subsequent Management

December 2014 Updated September 2015

Contents

Introduction

Mitochondrial disease is the commonest group of inherited neuromuscular disorders and characterised by variable multisystem involvement throughout a range of phenotypes. Associated co-morbidities increase the likelihood of anaesthetic and/or surgical intervention where unfortunately guidance is lacking; often leading to delays or suboptimal management. Very little evidence exists regarding the safest and most effective anaesthetic regimes, in part because of limited reporting and publication bias, but also because it is hard to consider the mitochondrial disorders as a single entity; severity ranging from asymptomatic carriers to those fully dependent on carers with severe multi-organ failure. In this respect we try to provide guidance regarding risk stratification, but also highlight problems specific to certain genotypes or phenotypes**.** In general, most mitochondrial patients tolerate anaesthetics well, with most risk attributable to the severity of associated comorbidities such as cardio-respiratory involvement or severe lactic acidosis reflecting a profound mitochondrial respiratory chain defect. The need for anaesthetic or surgical intervention may not always be predictable, but planning for such an eventuality is possible and advantageous. Referral to a specialist mitochondrial centre is advised and the screening programmes recommended for mitochondrial patients (see published mitochondrial guidelines) should ensure that important baseline information regarding current cardiac and respiratory function in particular are already known. Wherever possible, and especially in elective surgery, efforts should be made to obtain all relevant information regarding comorbidities and multisystem involvement. Early liaison with a specialist mitochondrial centre is encouraged so that specific advice or recommendations can be offered in a timely fashion. In some cases, surgical tissue handling and specimen preparation requires fresh frozen tissue sections rather than fixed tissue processing to facilitate subsequent mitochondrial studies. This may also be the case for cardiac or renal biopsies where mitochondrial disease is felt to enter the differential diagnosis. Failure to do so may render the tissue sample uninterpretable.

Pre-operative and post-operative care is an important consideration in the mitochondrial patient. Following the guidelines below can help prevent potential complications by raising awareness of common issues that are often overlooked or identified late in many patients. Appropriate hydration and calorific intake are important, as well as ensuring all relevant drugs are delivered during any periods

of planned or unavoidable fasting. Gastrointestinal dysmotility and pseudo-ileus can be a major problem postoperatively and should be addressed both pre and post-operatively.
In summary, liaison with a specialist mitochondrial centre and achieving as full an understanding as possible of a patient's disease will help limit any risks or complications arising from anaesthetics or surgery. For most patients the major contributor to risk appears to be cardio-respiratory status as it is with non-mitochondrial patients. For most patients the risks appear low and necessary surgical interventions should not be unduly delayed or withheld unless there is evidence for an unacceptable risk-benefit ratio.

Patient-centred Care

This guideline offers expert consensus advice on the care of patients with mitochondrial disease. The care of these patients and their treatment should take into account patients' needs and preferences. People with mitochondrial disease should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines –'Reference guide to consent for examination or treatment' (2001), available from www.dh.gov.uk. Healthcare professionals should also follow the code of practice accompanying the Mental Capacity Act (a summary of this code is available from www.dca.gov.uk/menincap/bill-summary.htm).

Good communication between healthcare professionals and patients is essential. It should be supported by the best available information tailored to the patients' needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English. If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care. Families and carers should also be given the information and support they need.

Key Priorities for Implementation

In view of the diverse phenotypes of mitochondrial disease, we recommend that all patients diagnosed with mitochondrial disease should be discussed with a mitochondrial specialist prior to any proposed, planned surgery – assuming there is time to do so without creating a clinically disadvantageous delay. Early planning is helpful in avoiding complications and both the surgeon and anaesthetist should be aware of the diagnosis and its implications. Risk stratification can be a useful way of guiding the level of caution and preparation required. Fasting should be minimized and calorific and fluid intake maintained. Structured care planning in the post-operative period is important and early reaction to complications is beneficial. This document is intended for guidance only, and should not replace patient-specific management plans influenced by other factors such as patient preference and pragmatism.

1. Risk Stratification in Patients with Mitochondrial Disease

The following guidance aims to identify those patients at highest risk of complications during anaesthesia or the post surgical period. Other risk factors including comorbidities unrelated to mitochondrial disease need to be considered and an opinion from a mitochondrial specialist is advised. The final decision regarding the appropriateness of surgery and type of anaesthesia should remain with the surgeon/anaesthetist.

1.1. **Advanced Cardiac Disease**:

1.1.1. Cardiomyopathy (especially if reduced left ventricular function)

1.1.2. Risk of tachyarrhythmia (eg known WPW syndrome or cardiomyopathy (most common in m.3243A>G and m.8344A>G))

1.1.3. Risk of bradyarrhythmia (eg heart block on ECG (most common in single large-scale mtDNA deletions – e.g. Kearns Sayre Syndrome))

1.2. **Advanced Myopathy** (and therefore potential respiratory muscle weakness and/or bulbar dysfunction/issues of airway protection):

1.2.1. Respiratory muscle weakness (possible type 2 respiratory failure or deterioration with post surgical abdominal splinting)

1.2.2. Diaphragmatic weakness (possible type 2 respiratory failure and/or deterioration when supine or with post surgical abdominal splinting)

1.2.3. Bulbar dysfunction (perioperative aspiration of gastric contents, swallowing issues and/or obstructive sleep apnoea)

1.2.4. Immobility (relevant to post-operative care and DVT risk)

1.3. **Significant Lactic Acidosis**:

1.3.1. At Rest: those patients known to produce a significant lactic acidosis at rest are probably at a higher risk proportionate to the level of that rise. A patient with a resting pre-operative lactate of 7.0 mmol/L is probably at greater risk than a patient with a lactate of 3.0 mmol/L for example. This is probably because this rise is a marker of greater overall cellular dysfunction – albeit it does not identify which tissues in addition to skeletal muscle are compromised or at risk of dysfunction. This is most commonly seen in patients with m.3243A>G, m.8344A>G and patients with complex 1 deficiencies. An appreciation of the baseline pre-operative lactate is helpful when interpreting post-operative results. Arterial or venous samples may be used. Venous samples are less invasive and felt to be representative as most data in adult mitochondrial patients is derived from venous sampling. In order to obtain reliable results it is important that venous samples are taken uncuffed (ie taken without a tourniquet) and transported and analysed without delay. Arterial samples are more invasive but studies in non-mitochondrial patients suggest a good correlation with venous lactate but are usually slightly lower.

1.3.2. Post Exercise: markedly elevated lactate levels after exercise are more sensitive to disease but probably less likely to predict increased risks during surgery.

1.3.3. During Metabolic Stress: markedly elevated lactate levels in the context of sepsis or immediately after a seizure can be hard to interpret and may not be a particularly helpful indicator.

1.4. **Seizures**:

1.4.1. *POLG* related epilepsy: patients carrying autosomal recessive mutations in the polymerase gamma gene are probably at the highest risk of morbidity/mortality due to seizures in the peri-operative period. **It is vital that their case is discussed with a mitochondrial specialist unless the urgency of surgery prevents this.**

1.4.1.1. **Sodium Valproate is absolutely contraindicated** due to potentially fatal hepatotoxicity.

1.4.1.2. Other anti-epileptic drugs (AEDS) should be administered as prescribed but in some cases alternative methods of administration may be necessary.

1.4.1.3. Potential drugs interactions should be taken into account.

1.4.1.4. Seizures of any type developing in the perioperative period need to be treated as a matter of urgency and a specialist involved at the earliest opportunity. Focal motor/sensory/occipital seizures may progress to intractable status epilepticus with a high morbidity/mortality. Early control is essential. For this reason we recommend aggressive treatment with sequential administration of anticonvulsants in line with the NICE guidelines for the acute management of generalized epilepsy. Our own experience is that the urgency of such situations is often underestimated and the narrow window for effective therapeutic intervention can be missed. Patients often appear well and fully conscious, with focal motor seizures (eg finger/thumb twitching) or occipital seizures (often manifesting with positive visual phenomena such as flashing lights/phosphenes and progressing to homonymous hemianopia. In this respect differentiation from migraine can be difficult, but

fortification spectra do not usually occur, and headache is not usually severe). Reference should be made to the published Epilepsy Guidelines in Mitochondrial Disease.

1.4.2. *POLG* disease without epilepsy (including pre-symptomatic carriers of homozygous or compound heterozygous mutations): these patients should be considered at risk of seizures and any arising treated actively along with rapid liaison with a mitochondrial specialist. Focal motor/sensory/occipital seizures may progress to intractable status epilepticus with a high morbidity/mortality. Early control is essential. Use of prophylactic AEDS is controversial but may be indicated in certain circumstances. Discussion with a mitochondrial specialist is advised prior to any proposed surgery.

1.4.3. MELAS phenotypes: patients who have previously suffered stroke-like episodes seem surprisingly tolerant of general anaesthesia and the major risks appear related to epilepsy and the comorbidities listed above (1.1, 1.2 and 1.3). Focal seizures (often non-convulsive) are often a driving factor in stroke-like episodes and should be suspected where focal signs develop or patients remain obtunded/encephalopathic. Urgent treatment is required as for POLG related epilepsy (see 1.4.1 above). The commonest causative mutations are m.3243A>G, m.13513A>G and AR *POLG* disease (see notes above).

1.4.4. Other epileptic phenotypes: for most other mitochondrial patients with epilepsy the major risks appear related to the other comorbidities listed above (1.1, 1.2 and 1.3) rather than the epilepsy itself – so long as AEDS are administered and usual care applied. This group includes patients with MERRF (m.8344A>G).

1.5. **Gastrointestinal Dysmotility manifesting as Paralytic Ileus**: this is most commonly a clinical issue in patients with severe disease due to the m.3243A>G mutation but can affect other genotypes too. It may be the presenting complaint in the very rare Mitochondrial NeuroGastroIntestinal Encephalomyopathy (MNGIE). Paralytic ileus may develop post-operatively or during illness and can commonly contribute to morbidity/mortality through anorexia, vomiting of oral or NGT/PEG delivered feeds, fluids, and medications, immobility and occasionally surgical intervention. Dilated loops of small and large bowel may be chronic. Raised lactate levels ordinarily taken as a surrogate marker for small bowel perforation or intra-abdominal sepsis may simply represent background lactic acidaemia and comparison should be made with pre-operative levels. Surgical intervention should be avoided unless absolutely necessary. Conservative management and liaison with a specialist centre usually suffices. Awareness and pre-operative assessment can minimise these risks.

1.6. **Exceptions and Disease Specific Notes:**

1.6.1. Healthy Carriers: risks to apparently healthy carriers of mtDNA or nuclear DNA mutations depend on the individual mutation and, in the case of many mtDNA mutations, the level of heteroplasmy (proportion of mutated vs wild-type mtDNA) in relevant tissues. In most cases the risks are low but some disease specific considerations are listed below. Discussion with a mitochondrial specialist is advised.

1.6.1.1. High heteroplasmy levels: for many mtDNA mutations – most notably the m.3243A>G and m.8344A>G mutations – the higher the heteroplasmy level (mutated vs wild-type mtDNA) in relevant

tissues the higher the risk of a predisposition to significant multisystem disease. For the care of mitochondrial patients and their families we recommend directed screening programmes for those at risk of disease (see published mitochondrial guidelines - www.newcastle-mitochondria.com). In the context of proposed surgery – diabetes, cardiac or respiratory disease should have been identified or excluded as a result of these programmes in many cases. In the absence of documented multisystem involvement we feel it reasonable to consider those with high heteroplasmy levels to be at higher risk of perioperative complications (eg lactic acidosis, seizures, gastrointestinal dysmotility) than those with lower levels. It is important to note however that low heteroplasmy levels in blood may offer false reassurance in certain mutations (eg m.3243A>G) where levels in other tissues (eg skeletal or cardiac muscle) may be present at high levels. It is important to acknowledge that this is a spectrum and accurate predictions are not always possible. Because risks relating to heteroplasmy levels are genotype, phenotype and tissue specific, we advise discussion with a mitochondrial specialist as part of any pre-operative work-up.

1.6.1.2. *POLG*: asymptomatic carriers of homozygous or compound heterozygous mutations carry a risk of seizures that is important to recognise (see above). Carriers of heterozygous mutations (whether AR or AD disease) do not appear at risk.

1.6.2. Specific mutations: it is important to consider the organs at risk in individual mutations. Most of the common and/or relevant mutations have already been discussed above. Others worthy of note are:

1.6.2.1. Leber's Hereditary Optic Neuropathy (LHON): Low risk. For most patients there is no multisystem involvement.Toxic agents such as alcohol and tobacco increase the risks of optic neuropathy but evidence regarding the risks of surgery or anaesthetic agents in LHON is lacking. No specific precautions are advised. Rare dystonic/CNS phenotypes should be discussed with a specialist. Evidence for cardiac involvement is limited and pre-operative ECG sufficient unless symptoms/signs of cardiomyopathy exist. Common mutations are m.11778G>A, m.3460G>A, and m14484T>C.

1.6.2.2. Aminoglycoside Induced deafness: Low risk. For most patients there is no multisystem involvement. Aminoglycosides should be avoided and appropriate alerts documented in the medical record and anaesthetic notes. Genetic causes include m.1555A>G, m.1494C>T, m.1095T>C, m.827A>G, m.7444G>A, and m.961T>C mutations

1.6.2.3. Leighs Syndrome in Adulthood: in most cases the risk of multisystem disease is high. Full assessments are recommended including uncuffed lactate measurements. Seizures, lactic acidosis, bulbar dysfunction and cardiac issues represent possible complications. In general the risk of CNS deterioration is probably lower than in infantile cases of Leigh Syndrome. New cranial nerve dysfunction or difficulty weaning from respiratory support should raise suspicion of brainstem pathology. Common causes include

recessive nuclear mutations and the m.8993T>G/C mtDNA mutation.

1.6.2.4. Peripheral Neuropathy: Certain mitochondrial phenotypes include a clinically significant neuropathy. MERRF, NARP, *POLG* and MNGIE are best known. Risks mainly relate to other comorbidities. Significant autonomic neuropathy is rare. Evidence is lacking for worsening of the neuropathy in the perioperative period but it seems sensible to avoid malnutrition and drugs that are notable for peripheral nerve toxicity. Anecdotal reports of the demyelinating neuropathy of MNGIE worsening in this context exist so specialist advice should be sought.

2. Pre-Operative Care

2.1. **Planning and preparations**: with the exception of emergency surgery it is usually possible to liaise with mitochondrial specialists and ensure all relevant information is available prior to any planned procedure. Because the potential for perioperative complications is generally higher in mitochondrial disease; we recommend preoperative discussion with the critical care unit to either pre-plan admission in the post-operative period or to ensure beds are available if unexpected complications develop. Patients requiring ventilatory support may benefit from elective surgery being undertaken in a specialist centre. In addition:

2.1.1. Assessing known multisystem involvement: it is important to clarify the extent of relevant multisystem involvement using the recommendations in this guideline (some existing results from screening programmes (see published mitochondrial guidelines) may be sufficiently recent as to avoid the need for repetition). Ideally all

results should be available but some specialist investigations (eg ECHO, PFTs, mutation heteroplasmy levels) may need retrieval from a local specialist centre or distant mitochondrial centre. Most patients should have up to date cardiac and respiratory assessments as well as an annual screen for diabetes.

2.1.2. Baseline investigations (for comparison): certain investigations are helpful not only for clarification of which systems may be involved, but also as a point of reference for later comparison. A raised lactate, creatine kinase (CK), abnormal ECG or an abdominal X-Ray (AXR) showing dilated loops of bowel may cause unnecessary concern unless it is appreciated that they are unchanged from the pre-operative state. CK measurements in particular can fluctuate (usually between 50 and 1000 U/L – up to 4 x normal range) and this may be apparent from previous results.

2.1.3. Bowel care: some patients (in particular those with high heteroplasmy levels and/or severe disease due to the m.3243A>G mutation) are prone to gastrointestinal dysmotility. This is rarely volunteered but can be problematic particularly in the post-operative period. It is advised to identify constipation early and to initiate a bowel management plan to ensure regular bowel opening (at least once every 2 days) in the pre-operative period (see published Gastrointestinal guidelines).

2.1.4. Surgical specimens: Surgical tissue handling and specimen preparation requires fresh frozen tissue sections rather than fixed tissue processing to facilitate subsequent mitochondrial studies. This may also be the case for cardiac or renal biopsies where mitochondrial disease is felt to enter the differential diagnosis. Failure to do so may

render the sample uninterpretable. Confirming these requirements, ensuring the local pathology department is prepared, and obtaining the patient's/carer's consent all takes time and is best arranged well in advance. In cases where the diagnosis of mitochondrial disease has not been confirmed it is also wise to obtain consent for a stored blood sample for later DNA analysis if required.

2.2. **Pre-Operative Investigations:**

2.2.1. Routine bloods: FBC, U&Es, LFTS, Ca^{2+}, Mg^{2+}, glucose, HbA1c, and CK.

2.2.2. An uncuffed venous lactate (see earlier notes re: collection) is recommended for most patients but especially those whose mitochondrial disease presented before the age of 30, if there is a significant myopathy, or a history of exercise intolerance.

2.2.3. ECG and ensure availability of other relevant cardiac data according to published cardiac guidelines. Updating cardiac investigations before the recommended interval (eg ECHO or 24 hour Holter monitor) is left to the discretion of the anaesthetist)

2.2.4. FVC (erect *and* supine)

2.2.5. AXR: consider pre-operative abdominal X-ray – especially if abdominal surgery is planned. Some patients (especially m.3243A>G) have chronically dilated loops of bowel that can appear alarming if the chronicity is not appreciated.

2.3. **Pre-Operative Management**:

2.3.1. Ensure hydration and calorific intake: prolonged fasting or dehydration can be harmful for patients with mitochondrial disease. Pre-operative fasting should therefore be minimised. We recommend

non-diabetic patients receive 50g carbohydrate in liquid form 2 hours prior to surgery. Oral carbohydrate may have an additional benefit to gastrointestinal motility in the perioperative period but this is unproven in mitochondrial patients. An IV 5% dextrose infusion is recommended where ileus or vomiting is likely to prevent absorption.

2.3.2. Mitochondrial diabetes can be managed pre-operatively in the same way as non-mitochondrial diabetes. Metformin is generally avoided however due to potential for worsening lactic acidosis (see published diabetic guidelines).

2.3.3. Ensure patients are not severely constipated (see 'early preparations')

2.3.4. Consider the need for DVT prophylaxis in 'at risk' patients according to local protocols

2.4. **Emergency Surgery**: the extent of the preparation and investigation possible pre-operatively depends on the urgency of the necessary surgery and the associated risk-benefit ratios to any potential delay incurred. Routine bloods and ECG are usually possible, and if existing guidelines have been followed important information regarding existing multisystem involvement should be readily available. In our own centre we are encouraging patient held records (Mitochondrial Disease Patient Logbook) to help ensure that this information can travel with the patient. Discussion with a specialist mitochondrial centre is advised if time allows.

3. Anaesthesia

No good evidence exists regarding the safety or efficacy of routinely used anaesthetic techniques in adult mitochondrial disease. Importantly there is no

evidence to suggest that particular agents are contraindicated. No good case series exist and rare case reports are difficult to interpret and likely influenced by publication bias. Case series of anaesthesia used in paediatric cohorts are published however, and although the underlying genetics and clinical presentations are inherently different from adult cases it is never the less reassuring that no evidence was found for any increase in risk relating to the anaesthesia itself (Driessen et al 2006, Footitt et al 2008).

Anecdotal evidence from adult patients undergoing general anaesthesia in our own cohort, and a general paucity of case reports to the contrary would suggest that in most cases general anaesthesia in adult mitochondrial disease occur without incident and for the most part anaesthetic risk is primarily influenced by cardiopulmonary disease and the severity of other comorbidities. Although no specific anaesthetic agents are contraindicated, some are generally avoided because of potential complications. Some of the issues regularly raised are addressed below:

3.1. **Propofol**: this is generally considered safe in the induction of anaesthesia. There is a however potential for worsening pre-existing lactic acidosis with prolonged use in the maintenance of anaesthesia so propofol is generally avoided for that purpose. It should be stressed however that most reports of lactic acidosis in mitochondrial patients are in children, and often in genotypes/phenotypes where lactate rises are known to occur in the context of metabolic stress (eg sepsis or surgery) making the causation difficult to establish in many cases.

3.2. **Rhabdomyolysis**: there is no evidence to suggest a significantly increased risk of rhabdomyolysis relating to surgery in adult mitochondrial disease. Modest CK elevation (<2000 U/L) may be observed post-operatively but is unlikely to be clinically significant or directly related to anaesthesia.

Comparison with pre-morbid levels is helpful and repeat bloods advised to exclude clinically significant rises.

3.3. **Malignant hyperthermia**: it is important to clarify that **there is no evidence to suggest that the risk of malignant hyperthermia (MH) in adult mitochondrial patients is any different to the general population.** Non-depolarising neuromuscular relaxants are generally used without complication – taking into account pre-existing myopathy and bulbar disease. Genotypes (eg. m.3243A>G) and phenotypes (e.g. MELAS) associated with lactic acidosis are prone to increased lactic acid levels and tachycardia at times of stress (including surgery), but it is important that this picture together with a modest CK elevation is not misinterpreted (or reported) as malignant hyperthermia without good supporting evidence for this. Historically it is also possible that on occasion myopathies associated with malignant hyperthermia (central core disease or King-Denborough Syndrome) were misdiagnosed as mitochondrial myopathies because of the shared features of ophthalmoplegia and myopathy.

3.4. **Intravenous fluids**: depending on circumstances fluids from 0.9% saline to 10% dextrose are commonly used (usually 5% dextrose). Lactate buffers (eg Ringer's solution) are discouraged because of the risk of exacerbating lactic acidosis. Careful attention to fluid balance is important as many mitochondrial patients have a low body mass and are at risk of both cardiomyopathy and renal impairment. There is therefore a risk of fluid overload.

4. **Post-Operative Care**:

4.1. **Recovery Room:**

4.1.1. Cognitive recovery: return to pre-operative levels of alertness may be mildly delayed in patients with clinically evident encephalopathy. Focal neurological deficits (including visual field defects) or obtundation/confusion that persists should raise suspicion of non-convulsive focal status epilepticus and investigated/treated as an emergency (see published epilepsy and/or stroke-like episodes guidelines). Main groups at risk are MELAS phenotypes, m.3243A>G, and POLG mutations.

4.1.2. Motor recovery: some patients with myopathic phenotypes or existing bulbar disease may be slightly slower than other patients to recover full bulbar and motor function. This is usually short-lived.

4.1.3. Respiratory recovery: in Leigh Syndrome, rare reports exist of brainstem necrosis following metabolic stressors (sepsis/ anaesthesia/surgery). These are predominantly paediatric cases and the risks are probably lower in adult disease. Failure to wean should prompt consideration of cerebral imaging (preferably MRI).

4.2. **Post-Operative Management**

4.2.1. Ensure hydration and calorific intake: fasting or dehydration can be harmful for patients with mitochondrial disease. Post-operative fasting should therefore be minimised and a 5% dextrose IV infusion is recommended if oral intake is delayed.

4.2.2. Hyponatraemia: MELAS and m.3243A>G patients in particular are prone to mild/moderate hyponatraemia (125-135mmol/mol). Any necessary fluids should be chosen accordingly. Management depends on the cause. SIADH and/or renal tubular acidosis (RTA) type 4 are both

recognised. Fluid restriction in cases of SIADH is not usually necessary and dehydration should be avoided. Rapid correction of hyponatraemia should be avoided. If chronic and mild, correction is not usually required.

4.2.3. Mitochondrial diabetes can be managed post-operatively in the same way as non-mitochondrial diabetes with the exception that metformin is usually avoided – see published diabetic guidelines.

4.2.4. Urine output: this should be closely monitored in all patients. Absent or reduced urine output should prompt rapid assessment of possible causes. In cases of acute renal failure a CK should be checked and compared to pre-operative levels to exclude rhabdomyolysis. Asymptomatic urinary retention may occur due to detrusor failure (mainly in advanced cases of MELAS) and is diagnosed by palpation +/- ultrasound. This rarely requires a permanent urinary catheter.

4.2.5. Bowel Care: some patients (in particular those with high heteroplasmy levels and/or severe disease due to the m.3243A>G mutation) are prone to gastrointestinal dysmotility. This is rarely volunteered but can be problematic particularly in the post-operative period where paralytic ileus may develop. It is advised to identify constipation early and to initiate a bowel management plan to ensure regular bowel opening (aiming for a good bowel motion per day) in the pre-operative period (see published gastrointestinal guidelines). Good pre-operative bowel care and judicious use of opiates should minimise risks. Consider post-operative AXR if ileus or pseudoileus suspected. Comparison with pre-operative AXR is often helpful.

4.2.6. DVT prophylaxis: consider the need for DVT prophylaxis in ‘at risk’ patients according to local protocols. Immobility should be anticipated and addressed.

5. Notes on the scope of this guidance

The guideline was developed by experts in mitochondrial disease and anaesthesia based at the Newcastle Mitochondrial Centre and the Newcastle upon Tyne Hospitals NHS Foundation Trust. This group specified which aspects of peri-operative management in patients with mitochondrial disease was to be included and excluded.

5.1. Audience

These guidelines are intended for use by the following people or organisations:

- all healthcare professionals
- commissioning organisations
- service providers

5.2. Guideline Limitations

Limitations of these guidelines include:

- Lack of a firm evidence base for reference. Guidelines in mitochondrial disease are currently unable to adopt the evidence-based approach used by organisations such as NICE, and at present are predominantly based on consensus expert opinion.
- Overall, the evidence review identified no randomized controlled trials or high quality case-control or cohort studies in adult mitochondrial disease.
- Further studies are needed (see research recommendations below).
- Specialist Mitochondrial Centres are located in Newcastle, London, and Oxford. The development of these centres represents an important advance in the care of patients with mitochondrial disease.

6. Implementation

Integral to this guideline is publication of the benefits of access to a specialist clinic with experience in mitochondrial disease.

- Specialist mitochondrial clinics are provided by selected centres with the support of the Highly Specialised Service. The accumulation of experience within these centres, and access to focussed multi-disciplinary team input is designed to offer the best available care for patients with mitochondrial disease.
- Centres are currently located in Newcastle, London and Oxford.
- Patient education is an important aspect of the initial consultation, but also as a vital component of future care. We aim to provide an understanding of the underlying disorder, the potential risks relating to anaesthesia or surgery, and the importance of informing doctors of the diagnosis and seeking a specialist opinion.
- Access to specialist clinics allows relevant genetic counselling and family tracing to facilitate the identification of those at risk of developing disease. The potential for complications to arise in symptomatic or asymptomatic carriers during anaesthesia or surgical intervention highlights the importance of this programme.
- Regular review at a specialist clinic ensures that the extent and relevance of any multisystem disease is well documented and available, even in the event of emergency surgical procedures. For elective procedures it is beneficial to implement the preparations outlined in this guideline as early as possible and arrangements made to facilitate liaison with a specialist unit throughout the peri-operative period if required.

7. Research recommendations

7.1. Safety of Anaesthetic Agents in Adult Mitochondrial Patients: Comprehensive assessment of anaesthetic outcomes in a large cohort of mitochondrial disease patients from a variety of genotypes and clinical groups where pre-operative data is comprehensively documented and full anaesthetic, operative and post-operative data is available.

8. Updating the guideline

The Newcastle Mitochondrial Guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence every 2 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may update the guidance prior to any scheduled changes.

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Appendix A: The Guideline Development Group

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