Newcastle Mitochondrial Disease Guidelines

Gastrointestinal Involvement in Adult Mitochondrial Disease:

Screening and Initial Management

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Introduction
Mitochondrial disease is now recognized as the commonest form of inherited neuromuscular disease. Multisystem disease is a hallmark of these disorders yet gastrointestinal involvement is often overlooked. Diseases defined by a gastrointestinal phenotype (eg. mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)) are extremely rare, but gastrointestinal involvement is a frequent feature of more common forms of mitochondrial disease such as that due to the m.3243A>G mutation, where constipation, chronic intestinal pseudo-obstruction (CIPO) and significant dilatation of small and large bowel often complicate the clinical course. The severity of symptoms may go unrecognised in these patients until they present in crisis. CIPO is now increasingly recognized in several mitochondrial disorders and successful management can prove difficult. Gross faecal loading, CIPO, or commonly both may contribute to anorexia, nausea and vomiting, making administration of aperients and other drugs difficult, as well as hampering adequate fluid and calorific intake in a metabolically vulnerable group. Achieving bowel clearance and regularity of defaecation can be slow and is often associated with significant morbidity and sometimes mortality. In less severely affected patients, symptoms may be non-specific such as anorexia, nausea, abdominal pain and constipation. It is common for these symptoms to have been labelled as ‘irritable bowel syndrome’ prior to presentation. Patients who harbour a mutation in the MTTL-1 gene (m.3243A>G) are more commonly affected by gastrointestinal dysmotility compared to most other genotypes. Importantly, gastrointestinal involvement in mitochondrial disease is treatable, yet no current guidelines exist. Treatment is more likely to be effective if initiated early and for this reason it is important to screen all patients with mitochondrial disease at the point of diagnosis.
**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](http://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](http://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 have a gastrointestinal assessment at baseline. This should include a clinical assessment (history and examination) utilizing the Bristol Stool Scale (BSS) where possible. Further investigation and follow-up should be based on the initial evaluation and reports of significant gastro-intestinal dysmotility will usually require a more comprehensive assessment including specialist advice, education and derivation of an individualized treatment plan.

This document is intended for guidance only, and should not replace patient-specific management plans influenced by other factors such as patient preference.
1. **Gastrointestinal Screening in Patients with Mitochondrial Disease**

   Initial assessment should be made through directed history taking at the time of diagnosis and at regular intervals (e.g. annual review and opportunities arising from unrelated GP visits), or if clinical status changes with development of symptoms suggestive of gastro-intestinal involvement. Upper and lower GI involvement usually coexist and both need to be considered. The assessment should include the following:

1.1 **Constipation**: review of daily bowel function aiming for normal stool consistency at least once every day. The Bristol stool scale (BSS)\(^1\) should be used for assessment where possible. Patients with mitochondrial disease often fail to report constipation despite fulfilling diagnostic criteria - some patients not passing stools for more than five days. Common symptoms of early satiety, abdominal discomfort, bloating, and poor appetite are frequently experienced. Often these symptoms can lead to hospital admission and occasionally result in unnecessary surgical procedures, particularly where the association with mitochondrial disease is not appreciated. Overflow faecal incontinence due to constipation is also a common feature, which is often mistaken for diarrhoea (see below).

1.2 **Diarrhoea**: true diarrhoea is rarely due to mitochondrial disease and other causes should be excluded. Small volume loose stool can be due to overflow faecal incontinence as a result of constipation and rectal loading. This is best confirmed with a plain abdominal x-ray. Other treatable causes should be excluded and if diarrhoea is persistent small bowel bacterial overgrowth should be considered and discussed with a specialist mitochondrial unit or gastroenterology specialist.
1.3 **Upper GI dysmotility**: symptoms of early satiety, poor appetite, gastric reflux, upper abdominal discomfort and bloating may all be pointers toward upper GI dysmotility. Unless self-limiting, referral to a gastroenterologist is advised. Scintography and/or radio-opaque marker studies may be employed to help confirm a diagnosis of gastroparesis or slow transit constipation.

1.4 **Weight loss/difficulty gaining weight**: anorexia, early satiety and either weight loss or clear difficulty in gaining or regaining weight is very common in mitochondrial disorders. Weight loss and/or change in bowel habits usually needs reasonable exclusion of other causes. Dietetic assessment is important and patients should be screened for under-nutrition using MUST (adults) and STAMP (children) nutritional screening tools. Early liaison with a dietician is recommended for nutritional management plans and prevention of further under-nutrition.

2. **Gastrointestinal Investigations in Symptomatic Patients**

2.1 **Exclude other/contributing causes**

2.1.1 **Routine bloods**: FBC, U&Es, Ca2+, Glucose, HbA1c, TFT. Consider coeliac screen.

2.1.2 **Drugs**: numerous medications are associated with gastrointestinal side effects (eg. opiate analgesics). Risk/benefit ratios and available alternatives need to be considered.

2.1.3 **Diet**: High fibre diets can worsen constipation in many patients with mitochondrial disease – particularly those with more severe symptoms. It may, in part, be due to weakened peristalsis. Dietetic assessment is helpful in identifying contributing dietary factors.
2.2 Directed Investigations

2.2.1 Abdominal examination (including rectal examination): this is important to exclude masses, organomegaly, painless urinary retention (accompanying bowel involvement in some patients affected by m.3243A>G mutation), and to assess the degree and location of faecal loading.

2.2.2 Abdominal X-ray (AXR): this is helpful as a baseline investigation for future comparison in all cases presenting with gastrointestinal symptoms. Even in mild cases the AXR provides useful information and a baseline for future comparison. In some patients both small and large bowel can be chronically dilated and recognition of this can sometimes prevent unnecessary surgical intervention. Advanced abdominal imaging such as contrast CT abdomen and pelvis, or barium studies may need to be considered.

2.2.3 Bladder assessment: painless urinary retention can occur particularly in m.3243A>G patients with advanced multi-system disease. Clinical examination should detect this but ultrasound may be required. In some cases there may be associated hydroureret/hydronephrosis.

2.2.4 Specialist Opinion: except in mild and well-controlled cases we recommend discussion with a mitochondrial specialist and consideration of referral to a gastroenterologist. It is important that recognition of gastrointestinal dysmotility as part of the mitochondrial disorder spectrum is highlighted as otherwise unnecessary investigations may occur.
2.3 **Specialist Investigations**: Gastric emptying studies should be reserved for those patients in whom vomiting is prominent. Investigation of GI transit time may be employed to help confirm a diagnosis of slow transit constipation. Detailed discussion regarding the range of investigations available to the gastroenterologist is beyond the scope of this guideline but liaison with a specialist mitochondrial centre is advised.

3. **Gastrointestinal Management in Patients with Mitochondrial Disease**

3.1 **Prevention**

Maintaining a regular bowel habit is much easier to achieve than treating established constipation. Early advice and recommendations are encouraged – even in asymptomatic individuals.

3.1.1 **Nutrition**: Advice on healthy and well balanced diets is advocated for asymptomatic patients or those with only minor symptoms (Further details on healthy eating are available at British Dietitian Association’s webpage, [https://www.bda.uk.com/foodfacts/HealthyEating.pdf](https://www.bda.uk.com/foodfacts/HealthyEating.pdf)). Those with constipation will require additional nutritional advice and may benefit from a low fibre diet, when constipation is refractory to other conventional measures such as increased fluid intake and macrogol or other osmotic laxatives. Referral to a gastroenterology dietitian is recommended for advice on preparation of a balanced, low fibre diet (avoiding seeds, pips, skins and stalks) containing adequate calorific/nutritional content and meal planning to optimize calorific intake to combat fatigue associated with mitochondrial dysfunction.

3.1.2 **Fluid intake**: good hydration is advised – taking into account the needs regarding any other comorbidities (eg. cardiac or renal disease). Strict attention should be paid to fluid balance during inpatient hospital stays.
Patients are often of low body mass (with lower intravascular volumes) and may have existing cardiomyopathy or renal dysfunction. It is therefore important to be wary of fluid overload and cumulative volume of feeds, IV fluids, and IV medications (eg. anti-epileptic drugs) should be closely monitored.

3.1.3 Avoid fasting where possible: If nausea, anorexia, or encephalopathy prevent adequate enteral hydration then IV fluids (usually 5% dextrose) should be commenced. Nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered for sedated/encephalopathic patients whose oral calorific intake is inadequate (for those without a pre-existing PEG or other form of percutaneous feeding tube in situ). Low residue feeds are required. Regular low volume continuous administration is recommended as large boluses are often poorly tolerated due to gastric dysmotility and may result in vomiting of feeds. It is important to recognise gastroparesis however (see management below). Vomiting following feeds should be a ‘red flag’ symptom and lead to the patient being placed ‘nil by mouth’ (NBM). Sedated patients are at greater risk of aspiration and airway protection should be assessed.

3.1.4 Immobility: this can contribute to constipation so regular physical activity is recommended. Specific advice can be provided for those in whom disability limits their activities or in whom severe fatigue requires measures for energy conservation. Even in those with severe disability, regular changes in posture/positioning (eg. sitting out rather than remaining supine) is beneficial. This should be addressed during hospital admissions and intercurrent illness.
3.2 Treatment of upper GI dysmotility

3.2.1 Acute presentations (e.g. mimicking mechanical obstruction)

This can occur in isolation or more frequently during inter-current illness or following surgical procedures. These events are seen most commonly in patients carrying the m.3243A>G mutation and often accompany stroke-like episodes or hospitalisation for other reasons. Prompt recognition of clinical symptoms and radiological findings is crucial so that drainage of the stomach and small bowel content can be achieved with the insertion of wide-bore nasogastric (NG) tube (‘Drip and suck’). Prominence of vomiting, particularly projectile vomiting or vomiting of bilious or faecal matter in the setting of a distended abdomen following oral intake should alert the clinician to this as a possible serious acute complication of CIPO. This can be particularly dangerous in patients unable to adequately protect their own airway – such as those with encephalopathy, seizures, or bulbar dysfunction. Administration of gastrograffin is sometimes useful for both diagnostic and therapeutic purposes (excluding mechanical intestinal obstruction but also treating the pseudo-obstruction). Patients should be kept nil by mouth and enteral feeding is contra-indicated until the pseudo-obstruction has resolved. IV fluids (with avoidance of Ringers lactate solution) should be commenced to provide adequate fluid intake. Total parenteral nutrition (TPN) should be considered early if prolonged fasting is likely. Concomitant faecal impaction should be treated as outlined in the section below (see section 3.3.3).

3.2.2 Chronic upper GI dysmotility: effective treatment of upper GI symptoms is difficult so it is important to treat existing lower GI issues (eg. constipation) prior to considering the use of prokinetic agents such
as erythromycin. Metoclopramide and domperidone are no longer advised as per MHRA guidelines (due to risks of extrapyramidal and cardiac side-effects respectively). In patients with refractory and intrusive symptoms, referral to a gastro-enterologist is recommended for further advice on pharmacological management or consideration of other treatment modalities (eg. jejunostomy). In patients with severe GI dysmotility symptoms and in whom percutaneous gastrostomy or jejunostomy insertion is considered, nasojejunal feeding should be trialled for 6 weeks to identify the best artificial feeding modality to help alleviate symptoms and maximise nutritional absorption. For patients who already have a gastrostomy in situ, and have ongoing upper GI dysmotility symptoms that are unresponsive to prokinetic agents and modulation of their nutritional feeding regime, conversion to a jejunostomy tube is recommended as jejunal feeds in this instance are likely better tolerated and better absorbed. Alternative diagnosis such as peptic ulcer should be considered and investigated accordingly.

3.2.3 Small bowel bacterial overgrowth: If diarrhoea remains protracted after exclusion of overflow diarrhoea and treatment of faecal impaction, the possibility of small bowel bacterial overgrowth should be considered. Discussion with a gastroenterology specialist is advised as further tests (such as lactulose breath test and glucose breath test)\(^{12}\) and eradication therapies (antibiotics eg rifaximin, metronidazole, ciprofloxacin, amoxicillin-clavulinate)\(^{12,13}\) may be warranted. Note, prokinetic agents may have a role in the treatment of small bowel overgrowth.
3.3 Management of Lower GI dysmotility

3.3.1 **Mild Constipation**: For general short-term use stimulant laxatives such as docusate sodium or bisacodyl are a rational choice if the stool is hard. Early review of efficacy is important to avoid development of chronic issues. Some evidence suggests that docusate on its own may not be effective.

3.3.2 **Moderate Constipation**: bulk forming laxatives (eg fybogel) are generally unsuitable for patients with mitochondrial disease (See Appendix B). Therefore treatment should be:

3.3.2.1 First line treatment: macrogols - eg Movicol 1-3 sachets daily in divided doses usually for up to 2 weeks. A maintenance dose of 1-2 sachets daily may be given.

3.3.2.2 Second line treatment: Bisacodyl or glycerol suppositories should be administered when the rectum is empty, but the colon is still loaded. They may still have a stimulant effect. Oral bisacodyl and combination therapy can also be considered.

3.3.2.3 Other drugs used in constipation: If gastrointestinal symptoms persist despite treatment with 2 laxatives for a period of 6 months then referral should be made to a gastroenterologist for consideration of treatment with prucalopride (2mg once daily) or Lubiprostone (start at 24 microgram once daily with food - and titrate up to 24 microgram twice daily if necessary) as per NICE guidance. EMA have recently approved the use of prucalopride in men; UK license imminent.

3.3.2.4 Trans-anal Irrigation: referral to a gastroenterology team experienced in the use of colonic irrigation should be considered
both in the acute and chronic situations. In either scenario the relative risks and benefits need to be carefully considered. Colonic irrigation as a maintenance therapy may prevent hospital admission if available through local community nursing teams, but needs to be considered on a case by case basis.

3.3.2.5 Surgical Intervention: this should be considered as a last resort and only after discussion with a mitochondrial specialist. In rare circumstances it is necessary to consider surgical evacuation and/or formation of a functioning ileostomy/colostomy. In those scenarios we recommend reference to published guidelines for ‘Anaesthesia and Peri-Operative Care in Adult Mitochondrial Disease’. Clinically relevant tissue samples (eg bowel wall) may be available at operation but mitochondrial studies will be hampered or impossible if samples are not collected fresh (not fixed) and frozen appropriately. Certainly examples exist where such interventions have improved quality of life where other treatment options had failed.

3.3.2.6 Other therapies: Abdominal massage as an adjunctive therapy may be useful in certain clinical scenarios.

3.3.3 Faecal loading/impaction: Use of phosphate enemas should be the first line management in cases of impaction to ensure rectal clearance followed by use of macrogols - eg Movicol 8 sachets daily dissolved in 1 litre of water and drunk within 6 hours, usually for a maximum of 3 days. Reduce to maintenance dose once desired effect realised. Phosphate enema is not suitable for regular use without the supervision of a gastroenterologist.
3.4 Subacute large bowel pseudo-obstruction
The immediate treatment for subacute large bowel pseudo-obstruction is similar to that of subacute small bowel obstruction mimicking mechanical obstruction (please see section 3.2.1) and faecal impaction (see section 3.3.2.3). In addition, for refractory cases of large bowel pseudo-obstruction, we would advise early liaison with a gastroenterologist/colorectal surgeon with experience in the management of pseudo-obstruction and a mitochondrial disease specialist. Surgical intervention is rarely necessary and should be considered a last resort after discussion with mitochondrial experts. Although the patient may have a markedly distended abdomen and dilated bowel loops on AXR, the clinical picture is not that of the ‘acute abdomen’. Additional treatments to consider include:

3.4.1 Placement of a flatus tube: this may be of benefit when colonic dilatation extends to the rectum.

3.4.2 Endoscopic colonic decompression: this may be considered for refractory cases in the hands of an experienced gastroenterologist/colorectal surgeon.

3.5 Specific Scenarios

3.5.1 Peri-Operative Care: Intestinal pseudo-obstruction may develop during illness and in the post-operative period and this commonly contributes to morbidity/mortality through anorexia, vomiting of oral or NGT/PEG delivered feeds, fluids, and medications, immobility and occasionally surgical intervention. Awareness and pre-operative assessment can minimise these risks (see published ‘Anaesthetic and Per-Operative Care’ guidelines). It is vitally important to maintain hydration and calorific intake during these episodes.

3.5.2 Pregnancy: antenatal care should include advice regarding bowel care, with a focus on prevention where possible. Obstetricians should be
made aware of the diagnosis of mitochondrial disease at the booking appointment (see published ‘Pregnancy in Mitochondrial Disease’ guidelines). Laxatives that are considered safe in pregnancy include docusate, lactulose, macrogols, senna and bisacodyl.

3.5.3 **Aspiration pneumonia**: treatment should be in accordance with the local hospital guidelines but there should be a low threshold for appropriate step-up in treatment (eg. antibiotics and/or transfer to a high dependency unit) to reflect the increased risks associated with the metabolic issues and multisystem disease.
4. **Notes on the scope of this guidance**
The guideline was developed by experts in mitochondrial disease and gastrointestinal disease based at the Wellcome Trust Centre for Mitochondrial Research, Newcastle University, the Newcastle upon Tyne Hospitals NHS Foundation Trust and County Durham and Darlington NHS Foundation Trust. This group specified which aspects of the screening, diagnosis and management of gastrointestinal involvement in patients with mitochondrial disease was to be included and excluded.

4.1 **Audience**
These guidelines are intended for use by the following people or organisations:
- all healthcare professionals
- commissioning organisations
- service providers

4.2 **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.
- 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.
5. 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 NHS Highly Specialised Services. The accumulation of experience within these centres, and access to focussed multidisciplinary 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 potential gastrointestinal involvement and the role of early recognition and good bowel care in preventing future complications and morbidity.
- Access to specialist clinics allows relevant genetic counselling and family tracing to facilitate the identification of those at risk of developing disease, or to formally diagnose those who may already be affected.
- Close liaison is required between the specialist centre itself and local services. We recommend local gastroenterology follow up where frequent or emergency central review is impractical.
6. Research recommendations

6.1 Natural history studies
Comprehensive assessment of a large cohort of mitochondrial disease patients is required to document the effects of gastrointestinal dysmotility on morbidity and mortality within different genotypes/phenotypes.

6.2 Pharmacological agents and dietary supplements
Further research involving randomised controlled trials of therapeutic agents efficacious for the treatment of gastrointestinal dysmotility in other disease states is needed to establish safety and efficacy data in mitochondrial cohorts.

7. Updating the guidelines
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.

Last updated December 2015
Appendix A

Management of chronic upper and lower gastrointestinal symptoms in mitochondrial disease

Clinical Assessment

Upper GI symptoms
• Bloating and abdominal pain
• Gastric reflux
• Decreased appetite
• Early satiety and/or post-prandial nausea/vomiting

Consider Gastroparesis
• Review diet/medications
• Bloods & AXR
• Refer to gastroenterologist for consideration of scintography and/or radio-opaque examination

Treatment options
• Implement low fibre diet
• Consider prokinetic agent (e.g. erythromycin)
• Parenteral or Enteral feeding (preferably jejunostomy) may be considered if refractory symptoms/weight loss

Lower GI symptoms
• Bloating and abdominal pain
• Difficult/infrequent defaecation
• Abnormal Bristol Stool Chart
• Clinical evidence of faecal loading

Consider Constipation
• Review diet/medications
• Bloods & AXR

Treatment options
• Implement low fibre diet
• See Appendix B for treatment of:
  ➢ Mild constipation
  ➢ Moderate constipation
  ➢ Severe constipation/Faecal impaction/loading

Treatment Failures
• Refer to Mitochondrial Centre
• Refer to gastroenterologist
• Consider colonic irrigation
• Consider other newer agents – e.g. prucalopride, lubiprostone
Appendix B: Treatment of Constipation

Mild Constipation

1st Line Treatment
Docusate sodium
100mg twice daily. This can be increased to 500mg daily on divided doses.

2nd Line Treatment
Bisacodyl or Glycerol suppositories

Moderate Constipation

1st Line Treatment
Macrogols 1-3 sachets daily for 2 weeks and followed by 1-2 sachets daily as maintenance therapy.

2nd line Treatment
Bisacodyl or Glycerol suppositories

Severe/Faecal Impaction

1st Line Treatment
Phosphate enema

2nd Line Treatment
Macrogol up to 8 sachets daily for 3 days Review daily

NOTE: 1. Adopt low-fibre diet. Avoid bulk-forming laxatives e.g. Fybogel
2. All medications mentioned above should only be administered as prescribed.
Appendix C: The Guideline Development Group

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