

Nav Bar - About Mitochondrial Disease- Mito Physicians Manual

MitoAction is proud to support the efforts of clinicians who are interested in empowering patients and families with mitochondrial disease. MitoAction is also committed to improving awareness and education about Mito, including patient advocacy and education tactics for pediatricians and primary-care physicians.

A reference guide is currently being developed to support these objectives. The complete manual will be available online in the Fall of 2007. To learn more about this project, please read our clinical project summary below.

Thank you for supporting MitoAction!

A RESOURCE MANUAL FOR MITOCHONDRIAL DISEASE MANAGEMENT

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INTRODUCTION

Mitochondrial diseases represent a group of metabolic diseases associated with defective cellular energy production. They are progressive in nature and their phenotypes typically involve multiple systems. The age of onset can be prenatal or any age from the neonatal period through adulthood. In some cases, a maternal inheritance pattern identifies multiple affected cases within the same family. The incidence of mitochondrial disease is not known but estimated to be at least 1:4000 to 1:7500; in its many forms, it is among the more common metabolic disorders.

Because of the multi-system nature of mitochondrial disease, patient care demands the integration of treatment provided by multiple caregivers. Optimally, a patient's primary care provider works closely with some clinician knowledgeable about mitochondrial disease. The primary provider local to the patient's home helps to provide basic health care support and helps to manage the patient to keep the patient stable in his/her own community. The mitochondrial disease expert acts as a resource for other sub specialists involved in the patient's care, and participates in care coordination.

At present, the care and wellbeing of mitochondrial patients are threatened at many levels. Mitochondrial diseases are medically complex and chronic in nature. There is a general lack of knowledge about mitochondrial disease within the medical community, and there are too few clinicians considered expert in the diagnosis and management of mitochondrial disease (i.e., metabolic clinicians or biochemical geneticists). Insurance coverage for appropriate diagnostic testing and management services is often inadequate and/or inaccessible. Professional advocacy is essential to enable patients to get suitable care within the health care system and the proper attention within the educational system. It is generally agreed that most patients and families affected by mitochondrial disease

regularly encounter medical and paramedical providers unfamiliar with mitochondrial disease or its issues. As an unfortunate result, patients and families are often left to fend for themselves, and parents too frequently act as the primary providers for their children. The lack of adequate medical resources also places a huge burden on metabolic and other clinics that care for these patients to regularly intervene and compensate for shortcomings elsewhere in the health care system. Unfortunately, with few young physicians entering biochemical genetics (and pediatric neurology), this situation is only expected to worsen over time.

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In order to improve the quality and accessibility of care for patients with mitochondrial disease (and reduce the growing, unacceptable burden on metabolic clinics), the following objectives are suggested:

1. To increase awareness about mitochondrial disease at all levels within the medical community;
2. To empower non-metabolic clinicians to participate more in the management of mitochondrial disease.

The objective is to engage non-metabolic clinicians (in primary care and non-metabolic subspecialties) to participate more in the care of mitochondrial patients. In order to support these efforts, we propose developing a **Mitochondrial Disease Management Manual**.

THE MITOCHONDRIAL DISEASE MANAGEMENT MANUAL

The Mitochondrial Disease Management Manual would provide the following information:

1. ***Protocols for different clinical scenarios***, e.g., management during general infections, peri-operative care, routine preventive care (e.g., immunizations);
2. ***General medical guidelines*** for a number of paramedical and educational settings, e.g., for schools;
3. ***Medical considerations for a wide range of clinical symptoms*** that patients develop, taken from a mitochondrial perspective.

1. Protocols for different clinical scenarios:

A patient's mitochondrial disorder needs to be considered in many routine and special medical circumstances. For example, patients with muscle weakness can develop prolonged and often debilitating fatigue in association with significant infectious illnesses and routine and seasonal immunizations are indicated in most patients. However, the

fever that often follows certain inoculations might not be tolerated well, and proactive treatment with antipyretics can be beneficial along with attention to fluids.

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A more serious situation involves surgical or diagnostic procedures requiring anesthesia. These raise a number of issues including:

- The safety of fasting beforehand (potentially a problem for patients with secondary fatty acid oxidation dysfunction);
- Precautions regarding the type of anesthesia to be used;
- Complications during the post-operative period such as vomiting and loss of appetite, related in part to slowed gut motility.

[The “Protocol for Anesthesia in the Mitochondrial Disease Patient” can be found here.](#)

2. General medical guidelines:

Medical guidelines for mitochondrial disease can enhance education plans with recommendations that promote a safe classroom space for mitochondrial patients (e.g., temperature control) along with suggestions that can help maximize productivity (introducing regular rest periods). These have applications for adult patients and workplaces as well. Similarly, specialized guidelines can be developed for physical therapists, occupational therapists, behavioral therapists, and so on.

[Sample guidelines for use in the school setting can be found here.](#)

3. Medical considerations for a wide range of clinical symptoms:

Typically, the situation of a mitochondrial patient who presents to her/his primary care provider with a new symptom or with an increased intensity to a previously-known symptom prompts a call to the mitochondrial clinic or clinician for assistance or referral. In many situations the primary provider does not feel comfortable or competent in thinking through the potential causes for the new symptom or participating in its management. This is unfortunate because often the issue is not a complex one and does not require a "mitochondrial expertise." Furthermore, referring out questions on a regular basis can create a situation where patients or families learn to bypass the primary provider altogether, posing questions directly to the mitochondrial clinician. Over time there is a risk that the primary pediatrician will be excluded more and more from patient care. This arrangement is not beneficial to the patient and family, to the pediatrician, or to the overburdened mitochondrial clinic.

This section of the manual describes common symptoms found in mitochondrial patients, reviews for each a practical differential diagnosis, suggests testing that can help tease out the cause, and in some cases recommends a plan for treatment. Such outlines help to empower the primary pediatrician (or any non-mitochondrial sub specialist) to play more of a role in managing patients with energy disorders. The section will be indexed and cross-referenced to facilitate easier use.

Among the range of symptoms to be considered are the following (and others will be added) –

- Constitutional - failure to thrive, excessive weight gain, short stature, sleeping problems, irregular body temperature, heat and cold intolerance, sweating abnormalities;
- Infections – frequency, severity, pneumonia, urinary tract infections, central line infections;
- GI/Nutrition - anorexia and poor feeding, vomiting, bloating, abdominal pain, constipation, diarrhea;
- Neuromuscular - developmental delays, loss of skills (regression), autistic features, behavioral issues, fatigue, headache, limb pain, numbness/tingling, dizziness, lethargy, balance issues, periodic worsening of neurologic symptoms;
- Autonomic symptoms;
- Cardio-Pulmonary - heart rate abnormalities, dizziness, shortness of breath/difficulty breathing, sleeping problems;
- Renal/bladder - difficulty with voiding;
- Endocrine - precocious puberty;
- Hematologic - bruising;
- Immunologic - frequent infections;
- Dermatologic - pallor, flushing, mottling, rashes;
- Eyes/vision - blurry vision;
- Hearing loss.

[An example of a discussion of “Fatigue: Symptom Management for the Mito Patient” can be found here.](#)

Margaret Klehm, PNP, will be the primary author of the Mitochondrial Disease Management Manual. Ms. Klehm has worked with Mark Korson, MD, and the Metabolism Service for 15 years, until 2000 at Children’s Hospital Boston and since then at Tufts-New England Medical Center. She has worked with dozens of mitochondrial patients (pediatric and adult) and their families over several years and has considerable experience in diagnosing mitochondrial complications and participating in their management. In addition, she has extensive familiarity with the coordination of patient care in community and medical center settings.

Mark Korson, MD, will co-author the Manual. Dr. Korson served as director of the Metabolism Clinic at Children's Hospital Boston between 1990 and 2000, and currently directs the Metabolism Service at Tufts-New England Medical Center.

SUMMARY

There is a severe shortage of providers familiar with mitochondrial disease. This impacts significantly the quality of care that patients and families with energy disorders receive. Metabolic clinics and their staff are a resource for medical and other providers who follow mitochondrial cases. However, the demand is already high and expected to grow. The Mitochondrial Disease Management Manual can serve as an information resource for primary providers and non-metabolic specialists, allowing them to play a greater role in the management of patients with mitochondrial disease.

SAMPLE PROTOCOL FOR PERI-OPERATIVE CARE

(DATE)

Re: (NAME)

D.O.B.: (DATE)

(NAME) is a patient with mitochondrial disease with symptoms that include:

Patients with mitochondrial disease can tolerate surgery and anesthesia safely. However, precautions to reduce further any risk from the procedure include:

1. Elective procedures should be postponed if the patient develops any signs of intercurrent infection prior to the procedure date;
2. Minimize the time necessary for fasting. The patient should be encouraged to take some fluids (orally or enterally) just before becoming NPO;
3. An intravenous line should be placed pre-operatively and fluids provided postoperatively until the patient is eating/drinking well, or able to tolerate fluids through a g- or j-tube if present;
4. IV fluids should contain dextrose and electrolytes; do not administer Ringer's Lactate since patients with mitochondrial disease may have disturbed lactate metabolism; providing extra lactate may be harmful;
5. If the patient takes any vitamins as part of his/her mitochondrial management, these can be provided once PO fluids are tolerated;
6. If the patient has a problem with vomiting post-operatively, s/he should be admitted and continued on intravenous fluids until able to tolerate fluids/food.

Some patients have some degree of fasting intolerance due to disturbed fatty acid oxidation as a secondary complication of their primary mitochondrial disease. If there are concerns about fasting tolerance, the IV fluids should contain 10% dextrose with electrolytes to run at 1.25x maintenance or higher. The higher glucose solution is necessary to minimize catabolism, i.e., flux through a defective fatty acid oxidation pathway; 10% dextrose is more effective than 5% dextrose at accomplishing this goal.

If there are any questions regarding the safety of induction agents or other anesthetic medications, please consult *Anesthesia and Mitochondrial Cytopathies*, by Cohen, Shoffner, and DeBoer. It can be downloaded from the United Mitochondrial Disease Foundation web-site: <http://www.umdf.org/pdf/mitoane.pdf>

Please call with any questions.

(Doctor's Name)
Phone and Pager Number

SAMPLE GUIDELINES FOR SCHOOLS

(Date)

Re: (___NAME___)
D.O.B. _____

(___NAME___) is a (____) year old boy with a diagnosis of mitochondrial disease, a defect in energy metabolism. His symptoms include: (______). His diagnosis was confirmed based on (______).

Mitochondrial disorders may involve any combination of a variety of body systems including the brain and muscles (causing poor stamina, seizures, altered muscle tone, muscle weakness, strokes); autonomic nervous system (temperature dysregulation, heart rate abnormalities, blood pressure dysregulation, poor heat tolerance, increased sweating, skin pallor and blotching); eyes (vision loss); hearing deficit; endocrine disease (diabetes mellitus, hypothyroidism, hypoparathyroidism, adrenal insufficiency); heart (cardiomyopathy); liver (dysfunction, cirrhosis); kidneys (renal tubular acidosis); metabolic issues (lactic acidosis). Symptoms become especially severe during ordinary infections, often with ordinary exercise, with significant psychological stress, and sometimes with excessive heat or humidity. The disease is progressive, and organ dysfunction can become more apparent with time.

There is no specific therapy for mitochondrial disease in that one cannot provide energy therapeutically in a direct way. Treatment focuses on vitamin and cofactor therapy, nutrition support, developmental/educational stimulation, prevention of unnecessary infections, and monitoring for potential, treatable complications.

The following recommendations should help support (___NAME___)'s good health and enable him to be more productive in a school environment:

POOR STAMINA AND THE NEED FOR FLEXIBILITY:

Children with mitochondrial disease often suffer from a chronically low level of energy. They fatigue easily compared to other children, even with ordinary activity or play. Prolonged reading and writing can fatigue the eyes and hands respectively. Furthermore, even emotional distress, since it too increases a person's metabolic rate, can be challenging for a patient with an energy disorder.

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A mitochondrial patient's energy level can often be very fluctuant, in an unpredictable way. It is therefore important that (____NAME____)'s school day schedule be flexible enough to accommodate this unpredictable variability. On "good days", he may need only a few breaks or rest periods mixed in with his more active subjects (physical education and recess are considered active times). On "bad days", most of the day may need to be a "low activity" day with expectations for learning that day dropped to a more realistic, manageable level; learning may have to be more passive. This kind of flexibility may, in the long run, allow (____NAME____) to be productive and able to demonstrate better what he knows and what he is capable of learning. Some children do even better if their school day is shortened, others if they attend school two or three days a week with home tutoring during "home days". At times, it is important to introduce a child slowly to a particular routine to determine how he tolerates it. Mornings are usually the most productive time for patients with energy disorders; as the day goes on they are often less able to attend or maintain the stamina to stay on task. Whatever approach is begun, it is important that it be re-evaluated from time to time to make sure it is the most appropriate plan for (____NAME____).

Consideration should be given to having (____NAME____) participate in an *adaptive* physical education program.

Activities involving reading and writing should include regular breaks, and could be augmented by services which reduce fatigue. For reading, someone could read part of the work to (____NAME____). Using a computer keyboard may reduce energy demands on the muscles of the hand while also contributing to a higher quality of finished product.

Fatigue can have a direct bearing on behavior. If a child's behavior deteriorates significantly primarily during periods of fatigue, s/he might not have the energy to control her behavior at those times. A general approach that reduces fatigue can help reduce the frequency and severity of such "melt-downs". Measures to help the child control behavior are useful in reducing the "energy drain" caused by those behaviors.

PREVENTION OF INFECTIONS:

Because (____NAME____) can become unusually weak during infectious illnesses, precautions should be taken to help reduce the number of infections that (____NAME____) contracts. Such precautions by caregivers, teachers and therapists who care for or work with the children include:

- reducing the number of exposures to other children with infections

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- proper handwashing technique, especially at home and at school
- keeping vaccinations up to date (including seasonal vaccinations, e.g., to influenza)
- implementing any reasonable routine that helps promote improved personal hygiene

AUTONOMIC DYSFUNCTION:

Abnormal regulation of autonomic functions can be among the most problematic issues for a mitochondrial patient. Autonomic dysfunction can include abnormal regulation of heart rate and/or blood pressure, abnormal gut motility (usually constipation, sometimes diarrhea), intolerance of heat and cold and therefore fluctuating temperature, due in part to an impaired sweating mechanism and skin temperature regulation. (____NAME____) may have problem tolerating significant heat and humidity. The following recommendations can help improve (____NAME____)'s performance in school:

- The ambient temperature should be kept constant and comfortable. Excessive heat or cold will directly impact his health and ability to learn and perform;
- Summer learning programs should be in an air-conditioned environment;
- He should be provided the opportunity to drink fluids during the day, as needed.

Children with mitochondrial disease can be a challenge medically. Their needs are complex. However, with adequate support, they can often shine academically. Without support, they are frequently unable to achieve their full educational potential. Please call with any questions or concerns you may have about (____NAME____) or his mitochondrial disease.

Yours sincerely,

(Doctor's Name)

SAMPLE SYMPTOM MANAGEMENT DISCUSSION - FATIGUE

FATIGUE

Patients with mitochondrial diseases have issues with creating energy at the cellular level. They might be able to muster adequate energy for periods of time but then lose it rapidly. Affected children fatigue easily on the playground relative to their peers and siblings, and often tend to more sedentary activities. A period of rest or sleep is generally required before energy levels are restored.

CAUSES OF INCREASED FATIGUE

Patients can become more fatigued as a result of ***EXCESSIVE PHYSICAL EXERTION***, and the degree of exertion can vary from day to day.

Assessment:

1. Consider any change in recent activity out of the routine.

Recommendation:

1. Ensure a routine that allows regular rest periods during the day and which is flexible to accommodate a patient's higher-energy and lower-energy days ("good days" and "bad days"). Adequate time must be allowed for patients to rest up in preparation for or to recover from a higher-energy activity or situation.

INFECTIONS can be associated with fatigue. Patients can display fatigue as an early sign of an emerging infection. The significant fatigue might exacerbate the symptoms (e.g., poor respiratory muscle effort with development of pneumonia) and be part of a prolonged recovery time that can last days or weeks.

Assessment:

1. Evaluate for infection and infectious contacts.

Recommendation:

1. Assess for signs of infection. Treat aggressively.
2. See INFECTION, page ...

EXCESSIVE EMOTIONAL DISTRESS can also be a significant energy drain over time. Anyone with chronic anxiety, depression, and/or obsessive/compulsive behaviors can become fatigued; this is particularly true for patients with limited energy reserve.

Assessment:

1. Assess for causes for chronic anxiety or other persistent mood or behavioral abnormality.

Recommendation:

1. A formal evaluation is indicated to identify correctly a psychiatric cause for emotional distress. Aggressive therapy should be considered

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including medication if appropriate. The goal of treatment is to reduce the energy loss due to an abnormal chronic emotional state, and allow this energy to be used in more productive ways.

TEMPERATURE AND HUMIDITY CHANGES (ESPECIALLY EXCESSIVE HEAT are also associated with increased fatigue. Some patients with mitochondrial disease appear to have some problems with autonomic regulation including regulating body temperature at higher or lower ambient temperatures (see ***HEAT AND COLD INTOLERANCE***, page...). This also occurs when temperatures turn warm and conditions become more humid and patients are active but have not yet acclimated to the temperature change. Some patients react similarly to cold temperatures.

Assessment:

1. Monitor the temperature in the patient's environment outdoors, at home, and wherever the patient spends the day (day-care, school, and so on).

Recommendation:

1. Patients or their caregivers should monitor the ambient temperature and take appropriate precautions. Some cannot tolerate being outside in the summer beyond a few minutes unless they are in water (and sometimes even then for limited periods of time because they become chilled if the water temperature is too cold). Air-conditioning might be needed at home or in the classroom to keep temperatures within a comfortable range.

Fatigue is described in patients with ***VASCULAR DYSAUTONOMIA*** (due to autonomic dysregulation). Other autonomic symptoms are generally present as well (see ***AUTONOMIC SYMPTOMS***, page...).

Assessment:

1. Assessment for vascular dysautonomia includes monitoring for orthostatic changes in blood pressure and heart rate; some patients will demonstrate excessive changes depending on their posture. In some, the urine specific gravity or urine osmolality will be remarkably high (spec grav > 1.015 or urine osmolality > 400) despite what appears to be adequate fluid intake.
2. The patient should be referred to a specialist (usually a cardiologist or

neurologist) who assesses autonomic dysregulation.

Recommendation:

1. When autonomic dysregulation is present, extra fluids, at a maintenance fluid rate or above, can be helpful in reducing symptoms and improving overall energy levels.

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Patients who have **ALLERGIES** are also fatigued. The fatigue might appear to come on rather suddenly when allergies are seasonal.

Assessment:

1. Assessment for evidence of environmental allergies.

Recommendation:

1. Treat symptomatically.