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Metabolic Precautions & ER Recommendations

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The catabolic state

Entering catabolism is a normal way of dealing with certain normal and abnormal stressors to the body. During these times our body is in a state of increased energy needs. There is a higher dependence on the body's stores of proteins, carbohydrates and fats to generate energy.

Catabolic stressors include prolonged fasting, fever, illness, surgery and anesthesia.

The catabolic state in metabolic disease

Metabolic disease, including mitochondrial disease, leads to a partial or complete disruption of the body's normal chemical processes. Certain chemicals are not turned over; these compounds build up and create cellular toxicity; certain chemicals are not made, which creates a cellular deficiency. When individuals with metabolic disease undergo a normal or abnormal catabolic stress, they begin turning over protein, carbohydrate and fat stores as they should - but due to the inherent chemical disruption, create more than normal levels of toxic substances and less than normal levels of the required product.

In the case of mitochondrial disease, cells are less efficient at creating adequate energy from protein, fat and carbohydrate stores. In the catabolic state, the cell's need for more cellular energy is often not met. It is during these times when the individual with mitochondrial disease is more vulnerable to cellular injury in various organs, including the brain. Certain organs can rapidly decompensate and enter a state of organ failure.

Illness as a common mitochondrial catabolic stressor

There are several catabolic stressors to the body, including prolonged fasting, illness, surgery and anesthesia. Of these, one that is faced commonly in the pediatric and adult population is illness. Viral illnesses are frequent occurrences in the growing child. And there is currently no clear way to prevent a child or adult from acquiring viral infections, though hand-washing and limiting exposures to sick contacts/contagious persons have benefits.

The patient with mitochondrial disease is not more prone to life-threatening infections. There is some anecdotal (experience-based) and small study-based evidence that mitochondrial patients have more frequent non-life-threatening viral infections such as colds, stomach-flues, bronchitis, and ear infections. This vulnerability may be due to some, yet unquantifiable, dysfunction of the immune system - though, to date, all routine measures of immune function in mitochondrial patients are normal.

There is no specific treatment for mitochondrial patients despite the potentially increased frequency of non-life-threatening infections. The precautions listed below should be followed when possible.

Precautions against catabolism

The best treatment against catabolism is preventing it from occurring. This means:

- Prevent prolonged fasting with maintaining oral fluid intake and/or IV fluids before and after a procedure/surgery
- Ensure that the fluids provided contain a source of dextrose
- Avoid medications that may be toxic to the mitochondria, such as propofol, aminoglycosides, and valproic acid, when possible
- Avoid fluids that may be toxic to the mitochondria, such as ringer's lactate
- Prevent over-sedation by volatile anesthetics
- Ensure that the patient has an illness precautions letter similar to the one outlined below

Treatment of catabolism

Once a patient is already in a catabolic state, treatment should begin immediately. This treatment includes:

- Stop the oral intake of a toxic compound, including any applicable medications (usually by making the patient NPO)
- Provide IV fluids with dextrose
- Give IV fluids at a higher than maintenance rate
- Insulin may be needed, not only to prevent hyperglycemia but also to provide the body with a hormonal signal to stop catabolism
- Monitor routine chemistries, glucose, ammonia, ketones and liver function for metabolic derangements
- Correct any metabolic derangements

- 1) Hypoglycemia - if hypoglycemic, administer 1-2 g/kg of glucose IV STAT; follow with (at least) a 10% glucose solution
- 2) Metabolic acidosis - administer NaHCO_3 as a bolus (1 mEq/kg) if acutely acidotic with $\text{pH} < 7.22$ or bicarb level < 14 , followed by a continuous infusion.
- 3) Hyperammonemia - the elevated ammonia reflects a secondary inhibition of the urea cycle. As treatment for the metabolic decompensation proceeds, the ammonia level should diminish. A level > 200 may require treatment.

- Provide medications such as IV levo-carnitine (100 mg/kg/day, divided tid) to facilitate the removal of toxic metabolic species
- Treat any underlying infection and fever

Sample Emergency/Illness Precautions Letter

To whom it may concern:

XX has a disorder of mitochondrial metabolism. Some individuals with metabolic and mitochondrial diseases are more sensitive to physiologic stressors such as minor illness, dehydration, fever, temperature extremes, surgery, anesthesia, and prolonged fasting/starvation. During such stress, rapid systemic decompensation may occur. Preventative measures are aimed at avoiding, or at very least not exacerbating such decompensation.

Mainstays of treatment during or prior to acute metabolic decompensation in mitochondrial and metabolic disease includes keeping patients well-hydrated, providing sufficient anabolic substrate, correcting secondary metabolic derangements, avoiding pharmacological mitochondrial toxins, and providing cofactor and/or salvage therapies.

IV fluids and substrate therapy

- Dextrose/electrolyte therapy should be considered if a patient is unable to maintain oral fluid intake in the face of a catabolic stressor, including fever, illness or vomiting.
- A hospital admission should be considered, not exclusively for dehydration, but to prevent catabolism by providing an anabolic food in the form of dextrose.
- Routine chemistries, CBC, liver function (synthetic and cellular), ammonia, glucose, ketosis and lactic acidosis should be monitored and any derangements corrected.
- Assessment of the patient's cardiac and renal status must be performed prior to aggressive fluid therapy
- Hydration and substrate therapy involves providing 5 or 10% dextrose containing IV fluids given at 1.25-1.5X times the maintenance rate. A high dextrose delivery with D10 or D20 might be needed, especially if acidosis or metabolic derangements are not correcting with 5% dextrose containing fluids. When a higher dextrose delivery is given, insulin may also be needed. Insulin not only controls hyperglycemia but also serves as a potent anabolic hormone, promoting protein and lipid synthesis. Insulin is typically given in the intensive-care-unit setting with the initial dose in the 0.05-0.1 U/kg/hour range, and titrated accordingly
- IV fluids should never contain Lactated Ringers solution
- Fluids should be weaned based on laboratory parameters, oral intake and resolution of the underlying metabolic stressor
- Once the initial crisis passes, enteral feeding should be considered. Protein can be added if hyperammonemia has resolved and there is no concomitant disorder of protein catabolism. If there is no primary or secondary fatty acid oxidation dysfunction, lipids may also be added
- Once the patient's laboratories begin to normalize, restarting the patient on their home-based diet is advised

Laboratory Parameters

- If acutely acidotic with a pH < 7.22 or bicarbonate level < 14 mM, metabolic acidosis can be controlled by administering sodium bicarbonate as a bolus (1 mEq/kg) followed by a continuous infusion
- Hyperammonemia can occur due to secondary inhibition of the urea cycle. As treatment for the metabolic decompensation proceeds, the ammonia level should diminish. A level > 200 uM may require salvage therapy or dialysis
- Any underlying infection and fever should be aggressively treated

Antioxidant therapy

- Levo-carnitine therapy during an acute illness may be beneficial. It should be given intravenously at a dose of at least 100 mg/kg/day. Doses of up to 300 mg/kg/day have been used. If the patient is on a higher oral dose, that dose should be used intravenously for treatment

- Any other home-based supplements and antioxidants being given should be continued by mouth if possible.

Medication contraindications

- Medications that should generally be avoided during times of illness in individuals with mitochondrial disease include valproic acid, statins, aminoglycoside antibiotics, and erythromycin
- There are no absolute contraindications and these medications can be given if an alternative medication is not available or appropriate as long as a prior adverse reaction to the medication has not occurred
- Should a medication such as valproate be used for the first time during an acute illness, liver enzymes, ammonia and synthetic liver function should be closely monitored

Anesthesia

- Questions on anesthetic sensitivity in mitochondrial patients remain
- Some individuals with mitochondrial metabolic diseases are more sensitive to volatile anesthetics and need a much lower dose to achieve a bispectral (BIS) index of <60. This effect has been seen more in patients with reduced complex 1 capacity. Sevoflurane might be better tolerated than isoflurane and halothane
- Debate remains as to the potential risk of propofol administration in mitochondrial disease patients. However, propofol has been routinely used in many mitochondrial patients for brief periods of sedation (less than 30-60 minutes) without apparent clinical problems. Limiting propofol use to short procedures and brief periods of sedation is advisable for now

Fasting with surgery

- During pre- and post-operative fasting, catabolism can be prevented by using dextrose-containing IV fluids. IV fluids are continued until the time of discharge, since they are intended to deter catabolism and not simply treat dehydration
- IV fluids should never contain Lactated Ringers solution
- Routine chemistries, a complete blood count, liver function (synthetic and cellular), ammonia, glucose, ketosis and lactic acidosis should be monitored and any derangements corrected

Please contact my office if you have any questions regarding this letter

Sincerely,