RECOMMENDATIONS ON EMERGENCY MANAGEMENT OF METABOLIC DISEASES
VERY LONG CHAIN ACYL CoA DEHYDROGENASE
VERY LONG CHAIN ACYL CoA DEHYDROGENASE

Please read carefully

- Meticulous treatment is important as there is a high risk of serious complications.
- Parents of children with diagnosed metabolic disorders know the early signs of decompensation in their children.
- Intervention should occur whilst the blood glucose is still normal.

INTRODUCTION

Very long Chain Acyl CoA Dehydrogenase Deficiency (VLCADD), an autosomal recessive disease, is a common disorder of fat breakdown. It is caused by an intra-mitochondrial defect in the β-oxidation of fatty acids and is a major cause of severe hypoketotic hypoglycemia. It can also cause encephalopathy, lethargy, liver dysfunction with hepatomegaly, cardiomyopathy, metabolic acidosis, hyperammonemia and sudden death.

The pathophysiological process begins with reduced glucose intake as a result of a fasting state or increased energy needs from a catabolic state (infection, stress, fever, etc...) not sufficiently provided for by caloric intake.

For most of the time patients are healthy and do not require a special diet. However metabolic stress such as fasting and/or febrile illness particularly gastro-enteritis and flu can lead to serious illness, with encephalopathy and even sudden death. This results from the accumulation of toxic fatty acids that inhibit gluconeogenesis (thus preventing endogenous glucose production), have a toxic effect on the liver and produce metabolic acidosis. Muscle, particularly myocardium, requires a lot of energy and, therefore, becomes functionally impaired resulting in lethargy, hypotonia and hypertrophic cardiomyopathy.

Note: ALL siblings of known cases should be tested for VLCADD whether or not they have a history of symptoms.
PRESENTATION

First presentation can occur in the neonatal period or when the infant is being weaned from nighttime feeds
The early signs of decompensation include:

- Marked Lethargy
- Poor appetite
- Nausea
- Vomiting: is common and should always be taken seriously
- However, some signs may be difficult to assess such as irritability or just ‘not right’. Always listen to parents carefully; their knowledge might exceed your expectations

Later signs and symptoms of decompensation may include:

- Change/Altered level of consciousness
- Hypoglycemia with lack or only ‘trace’ of urinary ketones: Hypoglycemia only occurs at a relatively late stage (or very late) so that blood glucose should not be relied on. Do not delay treatment just because the blood glucose is not low. The aim should always be to intervene whilst the blood glucose is normal. Treatment aims to prevent mobilization of fat by providing ample glucose enterally or intravenously
- Metabolic acidosis
- Hyperammonemia
- Cardiomyopathy, arrhythmias
- ‘Reye’ like syndrome
- Seizures
- Near/rescued SIDS
- Hepatomegaly
- Coma within 1-2 hours of ONSET of symptoms

NOTE that in the acute crises patients can be seriously ill WITHOUT hypoglycemia although typically FAOD crises are associated with hypoglycemia. At these times the urine typically tests ‘absent’ or ‘small’ for the presence of ketones. Liver function tests may be mildly elevated; hyperammonemia and hyperuricemia are often present during acute episodes
Initial plan and management in hospital

Almost all patients who present to hospital will require admission. If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation.

Management decisions should be based primarily on the clinical status. The first decision about therapy is whether the child can be treated orally or will need intravenous therapy.

- If the child is relatively well, may be treated orally but assess very carefully
- If the child is obviously unwell, must be treated with intravenous fluids.
- If there is any doubt at all, put up an intravenous line
- If the child is shocked or clearly very ill, arrange for admission to Intensive Care Unit

ASSESSMENT

As a rule, decompensation occurs more quickly in infants but children and adults, though more resistant, are still at risk of sudden death

a. Clinical assessment:
   - Vital signs, cardiovascular stability
   - STAT glucocheck (blood sugar) to check for hypoglycemia
   - Neurologic status (including Glasgow coma score);
   - Hydration status
   - Presence of fever; signs of infection
   - Hepatomegaly

b. Labs:
   - Blood
     - Blood gas (arterial or venous)
     - Blood glucose
→ Ammonia
→ Electrolytes (including Na+, K+, Cl−, measured CO2, Ca++, PO4, Mg)
→ Urea, creatinine
→ Creatine Kinase (CK)
→ Liver profile (including AST, ALT, AlkPO4, PT, PTT, bilirubin)
→ CBC differential

Urine
Urine dipstick for ketones

Culture
If patient is febrile, cultures of blood, urine, and/or throat are needed depending on the patient clinical presentation.

TREATMENT

1. INDICATION FOR IV (NEVER less than 10% dextrose IV infusion). One or more indication is sufficient for IV:
   - Vomiting
   - Hypoglycemia
   - Poor oral intake
   - Dehydration. Do not rely on urinary ketones as indicating dehydration!
   - Decreased alertness
   - Metabolic Acidosis

Start 10% glucose continuous infusion at 1.5x maintenance, to provide 7-8mg/kg/min.

→ Give Glucose 200 mg/kg at once (2 ml/kg of 10% glucose or 1ml/kg of 20% glucose) over a few minutes.
→ Give normal saline 10 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give 20 ml/kg normal saline instead of the 10 ml/kg. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
→ Continue with glucose 10% at 5 ml/kg/h until next solution ready. – see below
→ Quickly calculate the deficit and maintenance and prepare the intravenous fluids
  ○ Deficit: estimate from clinical signs if no recent weight available
  ○ Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children) 100ml/kg for 1st 10kg then 50 ml/kg for next 10kg then 20ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.
  ○ Give 0.45% saline/10% glucose

→ Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution. Recheck the electrolytes every 24 hours if still on intravenous fluids.

2. HYPOGLYCEMIA
Push 25% dextrose 2ml/kg and follow with a continuous 10% dextrose infusion at 1.5x maintenance, to provide 7-8 mg/kg/min glucose.
Hyperglycemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using the local diabetic protocol for treatment of DKA rather than reducing the glucose intake. Strict supervision is essential.

3. METABOLIC ACIDOSIS (Bicarbonate level <16mEq/L)
Must be treated aggressively with IV sodium bicarbonate (1mEq/kg). Treating conservatively in the expectation of a re-equilibration of acid/base balance as other biochemical /clinical parameters are normalized can lead to tragic consequences.
4. CARDIOLOGY
A cardiology assessment is necessary to properly evaluate a child with acute symptomatic VLCADD, specifically for heart failure or pericardial effusion. Should cardiology not be available the minimum evaluation required would be a CXR and EKG.

5. CARNITINE
The use of carnitine in FAODs is controversial and there are concerns that excessive long chain acyl carnitines which may be produced may induce arrhythmias. Consult with the primary metabolic physician for guidance regarding this in each individual case.

6. MEDIUM CHAIN TRIGLYCERIDE (MCT) OIL
MCT oil provides a high calorie substrate for the patient with confirmed VLCADD by bypassing the block in β-oxidation. HOWEVER, the diagnosis of VLCADD must be certain as MCT oil will exacerbate, and may be highly dangerous, to patients with other fatty acid oxidation defects.

7. PRECIPITATING FACTORS
Should be treated aggressively to help minimize further catabolism.

8. Other medications
Epinephrine may stimulate lipolysis, therefore if indicated in these children should be covered with 10% dextrose infusion. It is wise to check drug interaction and side effects such as hypoglycemia whenever prescribing for these children.
MONITORING THE PATIENT

Reassess after 4-6 hours or earlier if there is any deterioration or no improvement. If child is unable to take/maintain PO intake, start, or continue, 10% glucose continuous infusion at 1.5 x maintenance.

Clinical assessment should include:

- Mental status (Glasgow Coma Score)
- Vital signs
- Fluid balance
- Symptoms of infection

Biochemical parameters:

- Electrolytes (including Na+, K+, Cl-, measured CO2, Ca++, PO4, Mg)
- Ammonia
- Urea, creatinine
- Blood glucose
- Blood gases

RECOVERY

- The patient should be kept NPO, while on IV infusion, until his/her mental status is more stable.
- If the patient is not significantly neurologically compromised, enteral feeds (NG/GT) with the patient special formula should be introduced as early as possible, as this allows a much higher energy intake and reduces the risk of malnutrition.
- If drinking oral fluids well, and none of the above factors present, there is no need for emergent IV infusion. But history of earlier vomiting, pyrexia, or other stressor should be taken seriously and a period of observation undertaken to ensure that PO fluids are taken frequently and well tolerated, with glucose status monitored periodically.
- Avoidance of fasting when stop IV infusion: This may include complex carbohydrate in the form of cornstarch supplementation to get through the night as the child gets older and a high carbohydrate/low fat diet is to be followed.
ACKNOWLEDGMENT

These recommendations have been compiled by Advanced Clinical Specialist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the American College of Medical Genetics (ACMG), the British Inherited Metabolic Disease Group (BIMDG), and the New England Consortium on Metabolic Programs; and have been revised by Medical Genetics Consultants in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, on August 2011

REFERENCES

→ ACT SHEET (2010), American College of Medical Genetics (ACMG), Medical Genetics Translating Genes Into Health, [on line], Accessed on 01 August 2011
→ EMERGENCY guidelines (2009), British Inherited Metabolic Disease Group (BIMDG) [on line], Accessed on 01 August 2011.
→ Emergency Treatment Protocol- New England Consortium on Metabolic Programs, [on line], Accessed in 01 August 2010
Dietary Emergency Protocol for 
Very Long Chain Co A Acyl Dehydrogenase Deficiency 
(VLCADD)

1. Discontinue regular diet/feeds
2. If your child is able to take fluids orally, start giving emergency solution every 
   2 hours during the day and every 3 hours during the night as follow :
   Add .................. Scoops Poly cose/Prophree to ..................... mls water

3. If your child has an enteral tube feeding (NGT/GT), use this tube for emer
gency solution administration for better tolerance, especially if your child is
nauseated and/or vomiting

4. When using the available tube feeding, it is preferable to give the solution
   as:
   • Small boluses : Give ........ mls of emergency solution every ........ hour
   • Or continuously if a feeding pump is available

5. If a Rehydration Solution is to be given as in case of gastroenteritis :
   Add......... Scoops Poly cose/Prophree to......... mls of Rehydration
   Solution

6. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen :
      • If the child is doing well, go back to normal diet.
      • If no improvement is seen then continue giving the emergency solution
        as instructed above if tolerated
b. Between 24 – 48 hours from starting the emergency regimen:
   • If your child appears well, reintroduce regular formula then diet.
   • If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.

c. After 48 hours from starting the emergency regimen:
   If no improvement is noticed or if the child is not taking above prescribed amounts of emergency solution, bring your child to the hospital with all medicines, special dietary products, and scoops.

7. Try to offer MCT oil during crisis to your child.

N.B:
If, at any time from starting this emergency regimen, your child is deteriorating and /or not tolerating the emergency solution due to nausea and vomiting, bring your child immediately to the hospital with all medicines, special dietary products, and scoops.

ACKNOWLEDGMENT

Dietary Emergency Protocols have been compiled by Metabolic Nutritionist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the British Inherited Metabolic Disease Group (BIMDG), and have been revised by Medical Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011
citrullinemia
CITRULLINEMIA

Please read carefully

- Meticulous and prompt treatment is important as there is a high risk of serious complications.
- Parents of children with diagnosed metabolic disorders know the early signs of decompensation in their children.

INTRODUCTION

The urea cycle converts ammonia into urea and defects of all the steps are now well documented. All cause hyperammonemia. Hyperammonemia levels appear to be extremely toxic to the central nervous system, causing cerebral edema. Hyperammonemic crises in children with urea cycle defects (UCDs) are medical emergencies and must be treated as such to avoid death or serious brain injury.

Unlike fats and carbohydrates, the body does not store protein. Excess protein is catabolized, releasing liberated nitrogen as ammonia (NH3). This additional NH3 cannot be metabolized by a defective urea cycle and so accumulates. Citrullinemia is autosomal recessive in inheritance.

In general, Decompensation is often triggered by either dietary protein intake beyond bodily requirements or secondary to catabolic processes, e.g. stresses of the newborn period, fasting, dehydration, and/or febrile illness particularly gastro-enteritis and flu. The major complication of these disorders is cerebral edema.

Treatment is aimed at reducing the production of ammonia so the patients are treated with a low protein diet and medicines that promote the removal of nitrogen by alternative pathways.

Each of the five biochemical reactions within the urea cycle is associated with a known enzyme deficiency and a related clinical disorder as shown in the diagram below.
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Each of the five biochemical reactions within the urea cycle is associated with a known enzyme deficiency and a related clinical disorder as shown in the diagram below.
PRESENTATION

The early signs of decompensation include:
- Lethargy
- Poor appetite
- Exacerbation of pre-existing neurological problems (irritability, fits, etc)
- Vomiting: is common and should always be taken seriously

However, some signs may be difficult to assess such as irritability or just ‘not right’. Always listen to parents carefully; their knowledge might exceed your expectations.

Later signs and symptoms of decompensation may include:
- Ataxia
- Protein avoidance
- Developmental delay
- Failure to thrive
- Hyperammonemia
- Coma
- Seizures
- Hepatomegaly

Note that at a very early stage the plasma ammonia concentration may not be raised, probably because there is accumulation of glutamine in the brain before ammonia increases in the blood.

Apart from arginase deficiency, which usually presents neurologically rather than as a hyperammonemnic syndrome, the other urea cycle defects often present in the newborn period with catastrophic hyperammonemia, hepatomegaly, seizures and coma secondary to cerebral edema. Typically OTC and CPS have the most severe presentation but citrullinemia and argininosuccinic acidemia may also present with severe illness. However, all the UCD disorders may present later in life with a severe acute onset or a more chronic course.
MANAGEMENT

If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation.

Initial plan and management in hospital
- If the child is shocked or clearly very ill, arrange for admission to Intensive Care Unit
- If admitted to metabolic/general ward make a careful clinical assessment including blood pressure and Glasgow Coma Scale even if the patient does not appear encephalopathic.

ASSESSMENT

Assess for cardio-respiratory instability, dehydration, fever, infection or any other physical stressor (e.g. surgery), as a potential precipitant for metabolic decompensation. Assess hepatic and neurological status.
- Blood glucose
- Electrolytes including CO2
- Blood gas
- Ammonia
- Plasma amino acids
- LFTs (AST, ALT, ALkPO4, bilirubin)

Plasma amino acids should be drawn first thing in the morning, calling the metabolic lab in advance for urgent samples. Glutamine acts as an ammonia buffer and reflects the direction of control of hyperammonemia. It is therefore essential that amino acids are checked daily in the acutely sick child with hyperammonemia secondary to a urea cycle defect.
TREATMENT

An infant/child at risk from a urea cycle disorder should be treated prospectively. The rationale of treatment includes:
1. Minimize protein intake.
2. Reverse or minimize catabolism.
3. Promote waste nitrogen excretion.

* Management decisions should be based primarily on the clinical status. It is particularly important to note any degree of encephalopathy.
* The first decision about therapy is whether the child can be treated orally or will need intravenous therapy
  → Factors that will influence the decision include how ill the child is and whether they have deteriorated suddenly in the past.
  → Can the child tolerate oral fluids?
* If the child is relatively well: may be treated orally but assess very carefully.
* If the child is obviously unwell: must be treated with intravenous fluids:
  - Give Glucose 200 mg/kg at once (2 ml/kg of 10% glucose or 1 ml/kg of 20% glucose) over a few minutes.
  - Give normal saline 5 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give up to 20 ml/kg normal saline instead of the 5 ml/kg. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
  - Continue with glucose 10% at 5 ml/kg/h until next solution ready, – see below
  - Quickly calculate the deficit and maintenance and prepare the intravenous fluids
    o Deficit: estimate from clinical signs if no recent weight available
    o Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children) 100 ml/kg for 1st 10 kg then 50 ml/kg for next 10 kg then 20 ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.
o It is assumed that the patient will be given sodium benzoate and sodium phenylbutyrate in standard doses, therefore use 0.18% saline/10% glucose. If not, use 0.45% Saline and 10% glucose
- Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.
- Recheck the electrolytes every 24 hours if still on intravenous fluids.

1. MINIMIZE/OPTIMIZE PROTEIN INTAKE

DIET SHOULD BE PLANNED IN CONJUNCTION WITH A METABOLIC DIETICIAN

In Citrullinemia, the infant can start with 0.6 grams/kg/day on day 1, using a regular formula. The administered protein is gradually increased to a maximum of 1.5-2.0 grams/kg/day.

Enteral feeds should be started as soon as practical, may even occur concomitantly with IV via NG or NJ tube if necessary. Essential amino acids should not be withheld > 24 hours, to avoid catabolic breakdown of endogenous proteins. To avoid excess amino acid load aim for 1.0 - 1.5g protein/kg body weight (50% as essential amino acids).

Once patient stabilized, feedings established and the ammonia not fluctuating may switch to oral UCD medications.

2. REVERSE OR MINIMIZE CATABOLISM

The caloric intake for these infants should run at least 120-130 kcal/g/day. Accurate records of intake and output should be kept to monitor hydration. Infection as a potential but severe catabolic stressor should be considered early (when clinical signs are apparent) and managed vigorously. Avoid valproic acid, as it decreases urea cycle function and accentuates hyperammonemia.
3. PROMOTE WASTE NITROGEN EXCRETION

To help facilitate the excretion of waste nitrogen, the following medications are employed.

a) Sodium benzoate – conjugates with glycine to form hippuric acid which bypasses the urea cycle and is excreted in urine.

b) Sodium phenylacetate – conjugates with glutamine to form phenyl acetyl-glutamine which bypasses the urea cycle and is excreted in the urine.

c) Arginine – to prevent ARG deficiency and prime any residual OTC activity but must NOT BE used in arginase deficiency where there is already an excess of arginine.

DO NOT DELAY STARTING MEDICATION. The medicines should be given as continuous intravenous infusions, except in the mildest of cases (see table 1). In an emergency the doses given should always be an increase from those used routinely (see table 2). These sodium benzoate and sodium phenylbutyrate can be given together: the maximum concentration for infusion being no more than 1 gram of each drug to 50ml of 5 or 10% dextrose.

Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Emergency Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium benzoate</td>
<td>Up to 250 mg/kg/d</td>
</tr>
<tr>
<td>Sodium phenylbutyrate</td>
<td>Up to 500 mg/kg/d</td>
</tr>
<tr>
<td>Arginine</td>
<td>Up to 600 mg/kg/d</td>
</tr>
</tbody>
</table>

In an emergency the loading dose should be given initially followed by the maintenance.
Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading over 90 minutes</th>
<th>Followed by maintenance dose over 24 hours</th>
<th>Maximum daily dose (every 24 hours thereafter)</th>
<th>Sodium content of maximum maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium benzoate</td>
<td>250 mg/kg</td>
<td>250 mg/kg</td>
<td>Up to 500 mg/kg*</td>
<td>3.5 mmol/kg/d</td>
</tr>
<tr>
<td>Sodium phenylbutyrate</td>
<td>250 mg/kg</td>
<td>250 mg/kg</td>
<td>Up to 500 mg/kg*</td>
<td>3.5 mmol/kg/d</td>
</tr>
<tr>
<td>Arginine</td>
<td>300 mg/kg</td>
<td>300 mg/kg</td>
<td>600 mg/kg</td>
<td>3.5 mmol/kg/d</td>
</tr>
</tbody>
</table>

* Use of the maximum doses would be exceptional and usually 250 mg/kg/d would be sufficient.

Avoid carnitine as it has not been shown to be helpful. Although UCD infants are often low in carnitine, it is known to conjugate with sodium benzoate.

Also avoid citrulline as it will further exacerbate citrullinemia and ASA in which there already is an excess of citrulline.

If an IV is required, that solution should NOT contain sodium as plenty will be provided by the sodium benzoate and sodium phenylacetate.

- Treat any infection and constipation (which increases ammonia absorption from the gut). Lactulose is recommended as theory suggests this will be beneficial although, as yet, this is unproven.

MANAGEMENT OF PROGRESSIVE HYPERAMMONEMIA

If the blood ammonia is elevated, repeat the level. If confirmed:

- Discontinue oral feedings and oral medication
- Administer a 10% (or higher) glucose solution and Intralipid.
- Administer the urea cycle medications as an IV bolus.
For Citrullinemia
- Sodium benzoate (250 mg/kg/day or 5.5g/m2)
- Sodium phenylacetate (250 mg/kg/day or 5.5g/m2)
- 10% Arginine HCL (600 mg/kg/day)
(Surface area for the benzoate and phenylacetate should provide a more accurate dose in adolescents and adults)

Mix this in 35 cc/kg of 10% dextrose (no sodium) and run as a bolus over 90 minutes. This is then followed by the same solution administered as a 24 hour infusion.

- These infusions should begin during acute illness regardless of the amount of oral UCD medication already provided. Monitor ammonia levels every 4 hours, amino acids daily. Electrolytes, acid-base status and the anion gap should be monitored regularly. If another IV is required, that solution should not contain sodium.

- Glucose levels should be kept between 120-170 mg/dl. If necessary for control of hyperglycemia can use insulin (remains controversial) bearing in mind that wide swings in glucose levels affect brain osmolarity.

- Cerebral edema; Oncotic agents such as albumin will increase the overall nitrogen load but may in selected cases be considered. Mannitol has not been found to be helpful for edema secondary to hyperammonemia and steroids should not be used. Hyperventilation is recommended, but only under close appropriate supervision.

Potential side effects of sodium benzoate/phenylacetate regime
Increased incidence of nausea and vomiting with bolus.
Overdoses (3-5x recommended dose) can lead to symptoms reminiscent of hyperammonemia, specifically agitation, confusion and hyperventilation. Death has occurred (associated with cerebral edema, hypotension and cardiovascular collapse)
If the ammonia continues to rise:
Suggest transfer to PICU with metabolic and hemodialysis facilities and alert pediatric nephrology team. Remember placement of access lines for dialysis takes time so do not delay.
If dialysis is not immediately available, give a loading dose of sodium benzoate/phenylacetate, to slightly retard ammonia rise and in anticipation of dialysis ASAP.

If the ammonia continues to rise, CONSIDER DIALYSIS
Dialysis will clear ammonia at:
- 170-200ml/min for ECMO based dialysis. Osmotic shifts have NOT been observed with this rapid rate of clearance. Additionally a hemofilter in the circuit will continue to remove ammonia between dialysis cycles.
- 10-30 ml/min hemodialysis
- 3-5 ml/min peritoneal dialysis (this rate will however take several days to significantly reduce the ammonia load, at a time when brain damage is related to duration of hyperammonemia toxicity)

*note that dialysis itself is associated with significant morbidity/mortality, particularly in the neonate, and decisions to consider using dialysis must balance the risk:benefit ratio for each child.

MONITORING THE PATIENT

If there is any hint of incipient encephalopathy (lethargy, unusual behaviour, etc) start neurological observations - at least hourly - & seek specialist help. Under these circumstances, fluid volumes should be reduced and given via a central line as concentrated solutions to minimize the risk of cerebral edema.

Reassess after 4-6 hours or earlier. Clinical assessment should include a Glasgow coma score and blood pressure.

Blood tests
- Blood gases
- Ammonia
- Urea & electrolytes
RECOVERY

As ammonia falls and clinical status returns to baseline, patient can switch to oral medications and gradual reintroduction of diet in conjunction with the metabolic dietician as described in “treatment” section. The use of oral sodium benzoate and sodium phenylbutyrate (the much less odiferous oral form of sodium phenylacacetate) is determined, dependent on the patient, either on body weight or body surface area. The dose should be decided in conjunction with a metabolic physician if the patient does not have an up to date regimen.

NOTE that there may be a rebound hyperammonemia initially with the efflux of intracellular ammonia into the ‘relatively’ ammonia depleted blood. THUS it is important to continue closely monitoring ammonia levels until they remain stable in the normal range.

ACKNOWLEDGMENT

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- Emergency Treatment Protocol- New England Consortium on Metabolic Programs, [on line], Accessed in 01 August 2010
Dietary Emergency Protocol for
Urea Cycle Disorders (UCD)

1. Discontinue regular diet/feeds
2. If your child is able to take fluids orally, start giving emergency solution every 2 hours during the day and every 3 hours during the night as follow: Add ................ Scoops Polycose/Prophree to ................. mls water
3. If your child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if your child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the solution as:
   • Small boluses: Give ........ mls of emergency solution every ........ hour
   • Or continuously if a feeding pump is available
5. If a Rehydration Solution is to be given as in case of gastroenteritis: Add ........ Scoops Polycose/Prophree to ............ mls of Rehydration Solution
6. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen:
      ➔ If the child is doing well, go back to normal diet.
      ➔ If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
   b. Between 24 – 48 hours from starting the emergency regimen:
      ➔ If your child appears well, reintroduce amino acid mix excluding natural protein source.
      ➔ If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
   c. After 48 hours from starting the emergency regimen:
      ➔ If the child is doing well and amino acid mix is well tolerated, start introducing natural protein in the diet gradually over few days starting with half amount.
      ➔ If no improvement is noticed or if the child is not taking above prescribed amounts of emergency solution, bring your child to the hospital with all medicines, special dietary products, and scoops.
N.B:
If, at any time from starting this emergency regimen, your child is deteriorating and/or not tolerating the emergency solution due to nausea and vomiting, bring your child immediately to the hospital with all medicines, special dietary products, and scoops.

ACKNOWLEDGMENT

Dietary Emergency Protocols have been compiled by Eman Megdad, Metabolic Nutritionist - Medical Genetics, KFSH&RC- Riyadh based on protocols and guidelines of the British Inherited Metabolic Disease Group (BIMDG), and have been revised by Medical Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011
MAPLE SYRUP URINE DISEASE (MSUD)
MAPLE SYRUP URINE DISEASE (MSUD)

Please read carefully

- Meticulous and prompt treatment is important as there is a high risk of serious complications.
- Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children.

INTRODUCTION

Maple syrup urine disease (MSUD) is an organic acid disorder but is often classified as an amino acid disorder because of increased levels of branched chain amino acids as well as the organic acids.

MSUD is disorder affecting the breakdown of branched chain amino acids (BCAA = Leucine, Isoleucine & Valine). In classical (severe) MSUD the only significant pathway for the removal of BCAA is via protein synthesis as there is very little renal excretion. The encephalopathy is the result of accumulation of the BCAA (particularly leucine), which are toxic at high concentrations. There may be no hypoglycaemia, hyperammonemia or acidosis. Plasma amino acids can seldom be measured urgently, so management has to be based on the clinical state.

The central emergency features of MSUD are profound metabolic ketoacidosis and brain edema with lethargy progressing to coma. Decompensation is often triggered by metabolic stress such as fasting and/or febrile illness particularly gastro-enteritis and flu.

PRESENTATION

Well at birth but, symptoms may develop quite rapidly within 4-7 days. Later in childhood similar symptoms develop during acute illness.
Poor suck, disinterest in feeding
Lethargy
Weight loss
Neurological deterioration with alternating hypertonia and hypotonia
Dystonic “decerebrate-like” extension of the arms
Seizures
Coma
Pseudotumor cerebri and/or bulging fontanels occasionally seen
Maple syrup/burnt sugar like odor (from urine, bodily secretions & ear wax)

Presentation varies depending on the severity of the metabolic defect. The neonatal form presents in the first week of life with a life-threatening illness. Survivors of severe neonatal episodes are often neurologically devastated, when treatment was delayed. The infantile or late-onset form has a more insidious presentation with failure to thrive, developmental delay, and perhaps other neurologic features. Intermittent forms of MSUD are also described. All forms can have acute severe life-threatening decompensatory episodes.

Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children. Always listen to parents carefully; their knowledge might exceed your expectations.

ASSESSMENT

a. Clinical assessment :
   → Vital signs, cardiovascular stability
   → Hydration status
   → Neurologic status (including Glasgow coma score); evidence of increased intracranial pressure
   → Presence of fever; signs of infection
   → Glucocheck (blood sugar) to check for hypoglycemia

a. Labs :
   Blood
   → Plasma amino acids
   → Newborn screening (via tandem mass spectrometry or ‘Guthrie testing’
b. LABS:

Blood
- Blood gas
- Electrolytes, glucose
- CBC differential
- Serum amylase, lipase (pancreatitis can accompany metabolic episodes)
- Ammonia if diagnosis not certain
- Actate if diagnosis not certain

Urine
- Urinalysis for ketones

Culture
If patient is febrile, cultures of blood, urine, and/or throat are needed depending on the patient clinical presentation.

Warning: avoid lumbar puncture unless absolutely necessary – brain edema may be present and LP could cause herniation

Neonatal MSUD may not display marked abnormalities on routine tests and may not have metabolic acidosis. If hyperammonemia is present it is usually mild (<130 µ mol/L).

CBC and blood lactate are usually normal. The MAIN abnormalities found are in plasma amino acids and urine organic acids. The DNPH test (2,4 dinitrophenylhydrazine) detects elevated 2-oxoacids in the urine and is a useful rapid screening test.

IMMEDIATE TREATMENT

Almost all patients who present to hospital will require admission. If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation

> Immediate management decisions should be based primarily on the clinical status. The first decision about therapy is whether the child can be treated orally or will need intravenous therapy.
Factors that will influence the decision include, how ill is the child and have they deteriorated suddenly in the past?

Can the child tolerate oral fluids?
- If the child is relatively well: may be treated orally but assess very carefully.
- If the child is obviously unwell: must be treated with intravenous fluids.

In MSUD enteral feeds should be used wherever possible to promote anabolism and protein synthesis. It is easier to give more energy as well as the aminoacid mixture. If the peripheral circulation is compromised give intravenous fluids, but may still be possible to give the aminoacid mixture and some energy orally.

1. Discontinue natural protein.
2. Provide the large amount of calories needed (120-140 kcal/kg/day).
3. Provide fluids and sodium to treat dehydration, reestablish normal perfusion and urine output, and avoid hyponatremia.
4. Enteral therapy with special formula that contains all required amino acids but is free of the branched chain amino acids.
5. Identify and treat the infection or other causes of the metabolic stress.

SPECIFICS OF TREATMENT

1. IV fluid therapy

D10/normal saline with 20 meq KCL at 1 ½ times maintenance for 1-2 hours.

If the child is unwell:
- Give Glucose 200 mg/kg at once (2 ml/kg of 10% glucose or 1 ml/kg of 20% glucose) over a few minutes.
- Give normal saline 10 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give 20 ml/kg normal saline instead of the 10 ml/kg. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
- Continue with glucose 10% at 5 ml/kg/h until next solution ready. – see below.
- Quickly calculate the deficit and maintenance and prepare the intravenous fluids.
→ Deficit: estimate from clinical signs if no recent weight available
→ Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children) 100ml/kg for 1st 10kg then 50 ml/kg for next 10kg then 20ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.
→ Give 0.45% saline/10% glucose
  o Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.
  o Recheck the electrolytes every 24 hours if still on IV fluids.

2. Stat laboratory tests
As described above

3. Branched chain amino acid-free formula
There are a number of other medical product formulas (see below). The only major differences are the amount of protein equivalents and calories per 100 grams of powder.
For instance, Ketonex-1 has only 15 grams protein equivalents but 480 calories per 100 grams powder. Certain of these medical product formulas are appropriate only for infants and others for both children and adults. The table below lists the pertinent information about each of the products.

<table>
<thead>
<tr>
<th>Product</th>
<th>Supplier</th>
<th>Designation</th>
<th>Nutrition Prot Eq (g)</th>
<th>Energy (kCal)</th>
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<tr>
<td>Ketonex 1</td>
<td>Ross</td>
<td>Infant</td>
<td>15</td>
<td>480</td>
</tr>
<tr>
<td>MSUD 1</td>
<td>Mihupa*</td>
<td>Infant</td>
<td>41</td>
<td>280</td>
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<td>Child/Adult</td>
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</table>
If one of the special formulas is unavailable, BUT ONLY IF ONE OF THEM IS UNAVAILABLE, pedialyte orally or Pro-Phree in water can be given to provide calories as a temporary measure until the child can be transferred to a metabolic center or the special medical product formula obtained. The standard recipe for Pro-Phree is to add 125 grams Pro-Phree to water for total volume of 960 ml, providing a 20 kcal/oz solution. If the infant/child does not feed, pass NG or J tube for feeding.

4. Calories
Achieve a caloric intake of 120-140 kcal/kg/day with combination of enteral formula and IV glucose and Intralipid. Approximately 40-50% of the calories should be as Intralipid and formula. Intra-lipid may be added 2g/kg/d (0.4ml/kg/hour of 20% solution).

5. Evaluate the lab results, intake and clinical status. Aims are :
   a. Provide 120-140 kcal/kg/day and sufficient protein as amino acids free of the branched chain amino acids
   b. Eliminate ketoacidosis as determined by:
      - Serum bicarbonate level of 24 meq/L
      - Absence of ketones in urine
      - Negative urine DNPH test
   c. Maintain serum sodium at 140-145 meq/L. Monitor urine sodium output to establish loss and replacement requirement
   d. Measure plasma amino acids q24 hours. Levels should be reduced to:
      - leucine < 300 umol/L
      - isoleucine 300 umol/L
      - valine 400 umol/L
It is important to realize that isoleucine and valine levels may drop rapidly and that very low levels (isoleucine < 100 umol/L and valine < 200 umol/L ) will keep the leucine level from dropping by limiting protein synthesis. Low levels will also allow more leucine to enter brain by providing less transport competition and thus will produce or enhance brain edema and neurological complications. Add isoleucine and valine at 100-150 mg/kg/day to maintain these levels.
   e. Less irritability, increased alertness, no vomiting, reduced hyperreflexia
6. As serum sodium approaches 140-145 meq/L, reduce IV fluids to D10/0.45 normal saline and monitor serum sodium closely (hyponatremia enhances brain edema in MSUD). After 24 hours, adjust sodium intake to provide 4 meq/kg/day. Too much sodium will complicate fluid management.

7. If serum bicarbonate is below 14 meq/L and blood pH < 7.2, give IV bolus NaHCO₃ as 2.5 meq/kg over 30 minutes, then 2.5 meq/kg/day until serum bicarbonate is 24-28 meq/L.

8. If blood glucose rises > 200 mg/dL after one hour of IV infusion, begin insulin infusion at 0.05-0.1 unit/kg/hr using the local diabetic protocol for treatment of DKA rather than reducing the glucose intake until blood glucose is controlled. Strict supervision is essential.

9. If neurological signs worsen (vomiting, lethargy, hyperreflexia, clonus), suspect severe cerebral edema. Critical edema most often occurs during IV therapy, either due to serum sodium below 135 meq/L or continued ketosis and vomiting. Brain edema with brain stem herniation is the most frequent cause of death in MSUD. If suspected, obtain brain CT or MRI. If severe edema confirmed, infuse mannitol at 1-2 grams/kg over 30-40 minutes. Add lasix for diuresis but carefully monitor serum sodium to maintain concentration in the 140-145 meq/L range. Can infuse hypertonic saline to maintain the level.

10. Vomiting is the nemesis of MSUD. It provokes a ketoacidotic episode and complicates enteral therapy. Zofran at 2-4 mg every 6-8 hours can be effective in controlling vomiting.

11. Hemodialysis should be a last resort but may be lifesaving in a neonate who presents with coma and seizures and in whom IV therapy may not correct the profound metabolic derangements in time to prevent death from cerebral edema with brain stem compression. This could also be true for an older infant or child (or even adult). The Renal Service should be alerted as soon as hemodialysis is considered, well before the decision to hemodialyze is made, so that adequate preparations can be made in advance.
MONITORING THE PATIENT

Reassess after 4-6 hours or earlier if there is any deterioration or no improvement. Clinical assessment should include:

- Mental status (Glasgow Coma Score)
- Vital signs specifically BP and temperature
- Fluid balance
- Symptoms of infection

Biochemical parameters:

- Electrolytes (including Na+, K+, Cl-, measured CO2, Ca++, PO4, Mg)
- Aminoacids (quantitative)
- Urea, creatinine, glucose
- Blood gases
- CBC differential
- Urine for ketones and specific gravity
  - If improving, continue intravenous fluids (please refer to the previous section)
  - If deteriorating (clinical state, fluid overload), seek specialist help. Hemofiltration (hemodialysis) may need to be considered urgently. Note peritoneal dialysis is less efficient. Exchange transfusion is dangerous and should not be used.

RECOVERY

Once the patient is stable and accepting enteral feeding, the plasma amino acids must be monitored daily to reestablish amino acid homeostasis. On the basis of these levels, the branched chain amino acid-free medical formula with added source of branched chain amino acids and the low protein foods are adjusted to aim for plasma levels as follows:

- Leucine 175 umol/L
- Isoleucine 200 umol/L
- Valine 300 umol/L
- Other amino acids within normal limits
This will require careful attention to the amount of medical formula ingested, the amount of protein added to the formula, the amount of low protein foods ingested and the amount of supplemental isoleucine and valine added to the formula (each supplement should be available in the pharmacy as a 100 mg/10 ml solution)

ACKNOWLEDGMENT

These recommendations have been compiled by Advanced Clinical Specialist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the American College of Medical Genetics (ACMG), the British Inherited Metabolic Disease Group (BIMDG), and the New England Consortium on Metabolic Programs; and have been revised by Medical Genetics Consultants in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011

REFERENCES

- ACT SHEET (2010), American College of Medical Genetics (ACMG), Medical Genetics Translating Genes Into Health, [on line], Accessed on 01 August 2011
- EMERGENCY guidelines (2009), British Inherited Metabolic Disease Group (BIMDG) [on line], Accessed on 01 August 2011.
- Emergency Treatment Protocol- New England Consortium on Metabolic Programs, [on line], Accessed in 01 August 2010
Dietary Emergency Protocol for Maple Syrup Urine Disease (MSUD)

1. Discontinue regular diet/feeds
2. If your child is able to take fluids orally, continue giving your child the branched chain amino acids free formula as ………………+……… every 2 hours during the day and every 3 hours during the night as follow:
   Add ……… Scoops of …………. + ……….. scoops of …………. to ……… mls water

3. If your child has an enteral tube feeding (NGT/GT), use this tube for feeding for better tolerance, especially if your child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the prepared formula as:
   • Small boluses: Give …….. mls of emergency of formula every ……. hour
   • Or continuously if a feeding pump is available

5. If a Rehydration Solution is to be given as in case of gastroenteritis:
   Add……….. Scoops Polycose/Prophree + Scoops……….. to……….. mls of Rehydration Solution

6. If possible, send a blood sample (Dry Blood Spot) for Tandem MS.

7. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen:
      If the child is doing well, go back to normal diet after consulting your dietician
      If no improvement is seen then continue giving the formula as instructed above if tolerated.
   b. Between 24 – 48 hours from starting the emergency regimen:
      • If your child appears well, do the following
• If a blood sample was NOT sent: Reintroduce gradually the natural protein at ¼ normal intake for the first day, then ½ normal intake for the second day, then full normal intake on the third day.
• If a blood sample was sent, contact your dietician to adjust the diet/formula according to lab results. Supplements of Isoleucine and/or Valine from hospital pharmacy might be needed.

**c. After 48 hours from starting the emergency regimen:**
If no improvement is noticed or if your child is not taking adequate amounts of formula or not tolerating the formula, bring your child to the hospital with all the medications, special dietary products and scoops.

**N.B:**
If, at any time from starting this emergency regimen, your child is deteriorating and/or not tolerating the formula due to nausea and vomiting, bring your child immediately to the hospital with all medicines, special dietary products, and scoops.

**ACKNOWLEDGMENT**

Dietary Emergency Protocols have been compiled by Metabolic Nutritionist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the British Inherited Metabolic Disease Group (BIMDG), and have been revised by Medical Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011.
3-HYDROXYMETHYLGLUTARYL-CoA
3-HYDROXYMETHYLGLUTARYL-CoA

Please read carefully

- Meticulous and prompt treatment is important as there is a high risk of serious complications.
- Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children.
- Intervention should occur whilst the blood glucose is still normal.

INTRODUCTION

3-HMG CoA Lyase deficiency is one of several defects in the degradation pathway of leucine (a major branched-chain amino acid).
Most of the defects produce metabolic ketoacidosis but ketones are absent or low despite acidosis and hypoglycemia in 3-HMG CoA Lyase deficiency.
Thus, this is a cause of hypoketotic hypoglycemia.
In the presence of catabolism or substantially reduced food intake (e.g. infection, severe exertion), the combination of an increased cellular requirement for energy and reduced glucose intake results in proteolysis with release of amino acids and fatty acids. Enhanced leucine and fatty acid degradation is an attempt by the body to produce the needed energy in the form of ketones. When 3-HMG-CoA lyase is deficient, the increased fluxes in both leucine degradation and fatty acid oxidation result in an accumulation of 3-hydroxymethylglutararyl-CoA.
The accumulated substrate produces metabolic acidosis, inhibits gluconeogenesis resulting in hypoglycemia, and inhibits the urea cycle resulting in hyperammonemia.

PRESENTATION

The early signs of decompensation include:
→ Lethargy
→ Poor appetite
→ Vomiting: is common and should always be taken seriously
→ However, some signs may be difficult to assess such as irritability or just ‘not right’. Always listen to parents carefully; their knowledge might exceed your expectations.

Later signs and symptoms of decompensation may include:
→ Encephalopathy
→ Hypotonia
→ Failure to thrive
→ Hepatomegaly
→ Reye syndrome picture
→ Developmental delay
→ Seizures
→ Sudden death

ASSESSMENT

Clinical decompensation can occur rapidly in an infant and may be more gradual in older children.

a. Clinical assessment:
   → Vital signs
   → STAT glucocheck (blood sugar)
   → Neurologic status (including Glasgow coma score)
   → Hydration status
   → Presence of fever, signs of infection

b. LABS:
   BLOOD:
   → Blood gas (arterial or venous)
   → Blood glucose
   → Ammonia
   → Electrolytes (including Na+, K+, Cl-, measured CO2, Ca++, PO4, Mg)
   → Urea, creatinine
   → Liver profile (including AST, ALT, AlkPO4)
   → CBC differential
   → Lipase
Urine
→ Urine dipstick for ketones
→ Urinalysis for specific gravity

Culture
If patient is febrile, cultures of blood, urine, and/or throat are needed depending on the patient clinical presentation.

ASSESS BIOCHEMICAL PARAMETERS REGULARLY AND FREQUENTLY WHILE SICK

TREATMENT

1. INDICATION FOR IV (NEVER less than 10% dextrose infusion)
   (One or more indication is sufficient for initiating IV therapy)
   → Vomiting
   → Hypoglycemia
   → Poor oral intake
   → Dehydration. Do not rely on ketones as indicating dehydration
   → Decreased alertness
   → Metabolic acidosis
   Start 10% glucose continuous infusion at 1.5 x maintenance to provide 7-8mg/kg/min

2. DO NOT ADMINISTER LIPIDS IN ANY FORM

3. HYPOGLYCEMIA
   Push 25% dextrose 2ml/kg and follow with a continuous 10% dextrose infusion at 1.5x maintenance to provide 7-8mg/kg/min glucose
4. **METABOLIC ACIDOSIS** (Bicarbonate level<16)
Must be treated aggressively with IV Sodium bicarbonate (1 mEq/kg). Treating conservatively in the expectation of a re-equilibration of acid/base balance as other biochemical/clinical parameters are normalized can lead to tragic consequences.

5. **CARNITINE**
Should be provided PO (100-200 mg/kg/day divided TID) or IV 100 mg/kg/day in divided doses every 8 hours.

6. **PRECIPITATING FACTORS**
Should be treated aggressively to help minimize further catabolism

**MONITORING THE PATIENT**

Reassess after 4-6 hours or earlier if there is any deterioration or no improvement. Clinical assessment should include Glasgow coma score and blood pressure.
Blood tests:
> Blood gases
> Glucose check
> Urea & electrolytes

**RECOVERY**

Restart oral feeds as soon as possible; once the child is alert and has stopped vomiting.
If drinking oral fluids well and none of the above factors present, there is no need for emergent IV infusion. But history of earlier vomiting, pyrexia, or other stressor should be taken seriously and a period of observation undertaken to ensure that PO fluids are taken frequently and well tolerated, with glucose status monitored periodically.
ACKNOWLEDGMENT

These recommendations have been compiled by Advanced Clinical Specialist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the American College of Medical Genetics (ACMG), the British Inherited Metabolic Disease Group (BIMDG), and the New England Consortium on Metabolic Programs; and have been revised by Medical Genetics Consultants in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011

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→ Emergency Treatment Protocol- New England Consortium on Metabolic Programs, [on line], Accessed on 01 August 2010
Dietary Emergency Protocol for 3-HYDROXYMETHYLGLUTARYL-CoA (3-HMG CoA) LYASE DEFICIENCY

1. Discontinue regular diet/feeds
2. If your child is able to take fluids orally, start giving emergency solution every 2 hours during the day and every 3 hours during the night as follow:
   Add ............... Scoops Polycose to ................. mls water
3. If your child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if your child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the solution as:
   • Small boluses: Give ........ mls of emergency solution every .......... hour
   • Or continuously if a feeding pump is available
5. If a Rehydration Solution is to be given as in case of gastroenteritis:
   Add .......... Scoops Polycose/Prophree + Scoops ........... to .......... mls of Rehydration Solution
6. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen:
      → If the child is doing well, go back to normal diet.
      → If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
   b. Between 24 – 48 hours from starting the emergency regimen:
      → If your child appears well, reintroduce all amount of amino acid mix excluding natural protein source.
      → If no improvement is seen then continue giving the formula as instructed above if tolerated.
c. After 48 hours from starting the emergency regimen:
   ➔ If the child is doing well and amino acid mix is well tolerated, start introducing natural protein in the diet gradually over few days starting with half amount especially if ammonia level is known to be elevated.
   ➔ If no improvement is noticed or if the child is not taking above prescribed amounts of emergency solution, bring your child to the hospital with all medicines, special dietary products, and scoops.

N.B:
If, at any time from starting this emergency regimen, your child is deteriorating and/or not tolerating the emergency solution due to nausea and vomiting, bring your child immediately to the hospital with all medicines, special dietary products, and scoops.

ACKNOWLEDGMENT

Dietary Emergency Protocols have been compiled by Metabolic Nutritionist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the British Inherited Metabolic Disease Group (BIMDG), and have been revised by Medical Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011.
METHYLMALONIC ACIDEDEMIA (MMA)
METHYLMALONIC ACIDEMIA (MMA)

Please read carefully

- Meticulous and prompt treatment is important as there is a high risk of serious complications.
- Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children.

INTRODUCTION

Methylmalonic acidemia, an autosomal recessive disorder, is caused by a deficiency of a specific enzyme on the catabolic pathway of certain amino acids (isoleucine, valine, threonine and methionine). The co-factor for the enzyme is a derivative of vitamin B12 (hydroxocobalamin). Decompensation is often triggered by metabolic stress such as fasting and/or febrile illness particularly gastro-enteritis and flu. The central emergency features of the MMA are profound metabolic ketoacidosis and hypoglycemia.

Treatment is aimed at reducing the sources of the precursors so the patients are treated with a low protein diet and medicines. Some patients respond to pharmacological doses of vitamin B12.

PRESENTATION

The early signs of decompensation include:
- Lethargy
- Poor appetite
- Vomiting: is common and should always be taken seriously
- However, some signs may be difficult to assess such as irritability or just ‘not right’.

Always listen to parents carefully; their knowledge might exceed your expectations.
Later signs and symptoms of decompensation may include:

- Change/Altered level of consciousness
- Rapid and deep breathing (Kussmaul breathing)
- Seizures
- Hepatomegaly

Later signs and symptoms of decompensation may include:

- Ketoacidosis
- Hypoglycemia
- Neutropenia
- Hyperammonemia
- Hypocalcemia/hypokalemia

The ketoacidosis, hyperammonemia and hypoglycemia can explain the lethargy and obtundation. The ketoacidosis also produces vomiting. Mobilization of free fatty acids from stores to the liver produces a fatty liver. The increased organic acids may also be toxic to hepatocytes.

**ASSESSMENT**

**a. Clinical assessment**

- Vital signs, cardiovascular stability
- STAT glucocheck (blood sugar) to check for hypoglycemia
- Neurologic status (including Glasgow coma score); evidence of increased intracranial pressure
- Hydration status
- Presence of fever; signs of infection
- Hepatomegaly

**b. LABS:**

Blood

- Blood gas (arterial or venous)
- Blood glucose
- Ammonia
- Electrolytes (including Na+, K+, Cl-, measured CO2, Ca++, PO4, Mg)
→ Urea, creatinine
→ Liver profile (including AST, ALT, AlkPO4)
→ CBC differential
→ Lipase

**Urine**
→ Urine dipstick for ketones
→ Urinalysis for specific gravity

**Culture**
If patient is febrile, cultures of blood, urine, and/or throat are needed depending on the patient clinical presentation.

**NOTE:** Organic acids and ammonia are toxic to the brain and accumulations of these may result in cerebral edema. Caution should be exercised when considering the need for a lumbar puncture. If meningitis/encephalitis is a possibility, then CT of brain should be considered before lumbar puncture.

**TREATMENT**

The treatment for acute metabolic decompensation in these disorders includes:
1. Hydration
2. Correction of the biochemical abnormalities (metabolic acidosis, hyperammonemia, hypoglycemia)
3. Reversal of catabolism/promotion of anabolism
4. Elimination of toxic metabolites
5. Treatment of the precipitating factor when possible (e.g. infection, excess protein ingestion)
6. Cofactor supplementation
7. Consider hemodialysis
1. HYDRATION

→ Give 20 ml/kg normal saline as a bolus immediately. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.

→ Continue with normal saline 10 ml/kg/hour until next solution ready. – see below

→ Quickly calculate the deficit and maintenance and prepare the intravenous fluids

- Deficit: estimate from clinical signs if no recent weight available
- Maintenance: The formula for calculating maintenance fluid (This is the BNF recommendation for children with 20% added because of the increased requirement in methylmalonic acidaemia) 120ml/kg for 1st 10kg then 60 ml/kg for next 10 then 25ml/kg thereafter using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.

- Note: Many patients with methylmalonic acidaemia have a renal tubular defect so that they cannot concentrate or acidify their urine normally. The recommended volumes have been adjusted to take account of this. Additional water, sodium and sometimes bicarbonate may be necessary but beware of oliguria in those with very poor renal function.

- Give 10% dextrose with normal saline 0.45%:
  - Intravenous fluids should be administered with enough glucose to prevent further catabolism and sufficient alkali to treat the acidosis
  - Consider running 10% dextrose with a piggybacked bicarbonate infusion of 1.25-1.5 X times the maintenance rate. Piggybacking allows individual Adjustment/titration of the IV solutions. Add KCl if renal function is not compromised

→ Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.

→ After the initial 24 hours, continue with glucose 10% with saline 0.45% (unless evidence of continuing sodium depletion or hypematraemia). Monitor the urea and electrolytes regularly 6 hourly particularly the plasma potassium concentration. Treat hypokalemia as necessary.
N.B: Ringer's lactate should NEVER be used for fluid/electrolyte therapy in a child with a known/suspected metabolic disorder.

2. CORRECTION OF BIOCHEMICAL ABNORMALITIES

   a. Hypoglycemia: if hypoglycemic, give Glucose 200 mg/kg at once (2 ml/kg of 10% glucose or 1ml/kg of 20% glucose) over a few minutes; follow with (at least) a 10% glucose solution

   b. Metabolic acidosis: administer Sodium Bicarbonate (NaHCO₃) as a bolus (1 mEq/kg) if acutely acidic with pH < 7.22 or bicarb level < 14, followed by a continuous infusion. If hypernatremia becomes a problem, reduce the rate of the NaHCO₃ drip; replace with K acetate.

      - WARNING severe acidosis (pH < 7.2 or base deficit > 10 mmol/l) is potentially very dangerous.
      - Initially give a half correction [0.15 x weight x base deficit (mmol/l)] mmol sodium bicarbonate over at least 30 minutes. 1 ml of sodium bicarbonate 8.4% contains 1 mmol of sodium and bicarbonate and must be diluted at least 1ml to 5ml of 5% glucose. Then review and check plasma urea and blood gases. Repeat as clinically needed.
      - If further doses of sodium bicarbonate appear to be needed, ask why? Is perfusion normal? What is the blood pressure, capillary refill time and urine flow? Could the patient have pancreatitis or cardiomyopathy? The treatment that will need to be considered is haemofiltration (possibly peritoneal dialysis), assisted ventilation and inotropes. Such treatment should be under metabolic specialist supervision.

   c. Hyperammonemia: the elevated ammonia reflects a secondary inhibition of the urea cycle. As treatment for the organic acidemia proceeds, the ammonia level should diminish.

      - If hyperammonaemic (> 200 μmol/l in first 24 hours or >250 μmol/l thereafter) consider N-carbamylglutamate 250 mg/kg as a single oral dose if available. Alternatively give sodium benzoate 250 mg/kg/day enterally
      - For extremely elevated ammonia or persistently elevated levels, dialysis should be considered (see Dialysis- Part 7).
3. REVERSAL OF CATABOLISM / PROMOTION OF ANABOLISM

a - GLUCOSE: Catabolism can be diminished by providing large amounts of glucose (10% dextrose at maintenance or above), thereby surpassing hepatic glucose production. This therapy should be started as soon as possible after the patient presents to the emergency room.

b - PROTEIN: Amino acid therapy may be very beneficial in facilitating clinical improvement but should be implemented only under the supervision of a metabolic nutritionist or physician with expertise in metabolic management.

- All natural protein (containing all amino acids) should be withheld for 48-72 hours while the patient is acutely ill.
- Providing specialized diet which includes only "non-offending amino acids" (i.e., avoiding isoleucine, valine, threonine, and methionine) during the initial crisis period may not only stimulate anabolism but help prevent significant weight loss.
- If the patient is not significantly neurologically compromised, these formulas can be provided enterally (NG or GT).
- If enteral feeding is contra-indicated, consideration should be given to providing TPN.

c - LIPID: If TPN considered, intralipid may be given to supply extra calories; intralipid is composed of even chain fatty acids, so it should not increase concentrations of propionate (a 3- carbon organic acid), a precursor of methylmalonate, or methylmalonate.

Intra-lipid of 20% solution may be added at 2g/kg/day (0.4ml/kg/hour)

d - CALORIES: A goal for calories during a period of decompensation, in order to support anabolism, would be about 20% greater than ordinary maintenance needs. One must remember that withholding natural protein from the diet also eliminates this source of calories and should be replaced by other dietary or nutritional sources.
e. **INSULIN**: Insulin is a potent anabolic hormone, promoting protein and lipid synthesis. Hyperglycemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using the local diabetic protocol for treatment of DKA rather than reducing the glucose intake. Strict supervision is essential.

f. **TREAT CONSTIPATION**: which increases propionate absorption from the gut. Do not use lactulose as this can be fermented to propionate by gut bacteria.

**Medicines to be avoided**: Sodium Valproate, Lactulose

4. **ELIMINATION OF TOXIC METABOLITES**:
Correction of acute metabolic perturbations (acidosis, hypoglycemia) may help clear some of the factors contributing to the encephalopathy associated with acute metabolic crises. However, the presence of large quantities of toxic metabolites, believed to be toxic to the brain as well, is not cleared with glucose or bicarbonate, or rapidly with hydration. Consideration should be given to providing the means to help facilitate the excretion of these compounds:

a. **L-CARNITINE**: Free carnitine levels are low in the organic acidemias. L-Carnitine should be given intravenously - 200 mg/kg/24h given as a bolus of 100 mg/kg in 30 minutes and then 50 mg/kg every 6 hours intravenously. When oral fluids are tolerated, carnitine may be administered PO at a dose of 100 mg/kg/day.

b. **ANTIBIOTICS**: Administering broad-spectrum antibiotic may speed recovery in a patient in acute crisis.

c. **DIALYSIS**: When a patient is comatose, dialysis is indicated to facilitate a more rapid clearance of metabolic toxins (see 7. DIALYSIS)
5. TREATMENT OF PRECIPITATING FACTORS
Infection should be treated vigorously when possible. Note that neutropenia (and thrombocytopenia) frequently accompany metabolic decompensation. Bone marrow recovery is expected once the levels of toxic metabolites diminish significantly.

6. COFACTOR SUPPLEMENTATION FOR METHYLMALONIC ACIDEMIA
Cobalamin (B12) 1mg intramuscularly might be useful in cases of vitamin responsive enzyme deficiencies. In children with established diagnoses, parents will often know whether or not their child is a responder.

7. DIALYSIS
Dialysis (i.e., Peritoneal Dialysis, Hemodialysis, Continuous Renal Replacement Therapy) is indicated in cases with:

- Intractable metabolic acidosis
- Unresponsive hyperammonemia
- Coma
- Severe electrolyte disturbances (usually iatrogenic)

The Renal Service should be alerted early on in the hospital course.

MONITORING THE PATIENT
Clinical parameters:

- Mental status (Glasgow Coma Score)
- Vital signs specifically BP and temperature
- Fluid balance
- Evidence of bleeding (if thrombocytopenic)
- Symptoms of infection (if neutropenic)

Biochemical parameters:

- Electrolytes (including Na+, K+, Cl-, measured CO2, Ca++, PO4, Mg)
- Urea, creatinine, glucose, ammonia
- Lipase
- Blood gases
- CBC differential
- Urine for ketones and specific gravity
RECOVERY

• The patient should be kept NPO until his/her mental status is more stable.
• If the patient is not significantly neurologically compromised, enteral feeds (NG/GT) with the patient special formula containing all but the offending amino acids should be introduced as early as possible, as this allows a much higher energy intake and reduces the risk of malnutrition (see THERAPY, Part 3).
• If enteral feeds cannot be introduced within 48 hours start total parenteral nutrition (TPN) early to avoid malnutrition. (Note only moderate protein restriction when using TPN is necessary. Discuss with metabolic specialist team)

ACKNOWLEDGMENT

These recommendations have been compiled by Advanced Clinical Specialist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the American College of Medical Genetics (ACMG), the British Inherited Metabolic Disease Group (BIMDG), and the New England Consortium on Metabolic Programs; and have been revised by Medical Genetics Consultants in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011

REFERENCES

→ ACT SHEET (2010), American College of Medical Genetics (ACMG), Medical Genetics Translating Genes Into Health, [on line], Accessed on 01 August 2011
→ EMERGENCY guidelines (2009), British Inherited Metabolic Disease Group (BIMDG) [on line], Accessed on 01 August 2011.
→ Emergency Treatment Protocol - New England Consortium on Metabolic Programs, [on line], Accessed in 01 August 2010
Dietary Emergency Protocol
Methylmalonic Acidemia (MMA)

1. Discontinue regular diet/feeds
2. If your child is able to take fluids orally, start giving emergency solution every 2 hours during the day and every 3 hours during the night as follow:
   Add .................. Scoops Polycose/Prophree to .................. mls water
3. If your child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if your child is nauseated and/or vomiting.
   
4. When using the available tube feeding, it is preferable to give the solution as:
   • Small boluses: Give ........ mls of emergency solution every .......... hour
   • Or continuously if a feeding pump is available

5. If a Rehydration Solution is to be given as in case of gastroenteritis:
   Add............ Scoops Polycose/Prophree + Scoops.......... to.......... mls of Rehydration Solution
6. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen:
      If the child is doing well, go back to normal diet.
      If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
   b. Between 24 – 48 hours from starting the emergency regimen:
      If your child appears well, reintroduce all amount of amino acid mix excluding natural protein source.
      If no improvement is seen then continue giving the formula as instructed above if tolerated.
c. After 48 hours from starting the emergency regimen:
   → If the child is doing well and amino acid mix is well tolerated, start introducing natural protein in the diet gradually over few days starting with half amount especially if ammonia level is known to be elevated.
   → If no improvement is noticed or if the child is not taking above prescribed amounts of emergency solution, bring your child to the hospital with all medicines, special dietary products, and scoops.

N.B:
If, at any time from starting this emergency regimen, your child is deteriorating and/or not tolerating the emergency solution due to nausea and vomiting, bring your child immediately to the hospital with all medicines, special dietary products, and scoops.

ACKNOWLEDGMENT

Dietary Emergency Protocols have been compiled by Metabolic Nutritionist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the British Inherited Metabolic Disease Group (BIMDG), and have been revised by Medical Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011.
ISOVALERIC ACIDEMIA
ISOVALERIC ACIDEMIA

Please read carefully

- Meticulous and prompt treatment is important as there is a high risk of serious complications.
- Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children.

INTRODUCTION

Isovaleric acidemia, an autosomal recessive, is caused by a deficiency of isovaleryl CoA dehydrogenase, an enzyme on the catabolic pathway of leucine. It is often referred to as the “sweaty foot syndrome” due to the characteristic odor body and body fluids odor produced by it.
Decomposition is often triggered by metabolic stress such as fasting and/or febrile illness particularly gastro-enteritis and flu but an obvious cause is not always apparent.
The central emergency features of the organic acid disorders are profound metabolic ketoacidosis and hypoglycemia.
Treatment is aimed at reducing production of isovaleric and increasing its removal. The patients are treated with a low protein diet, glycine and carnitine.

PRESENTATION

The early signs of decompensation include:
- Lethargy
- Poor appetite
- Vomiting: is common and should always be taken seriously
- However, some signs may be difficult to assess such as irritability or just ‘not right’. Always listen to parents carefully; their knowledge might exceed your expectations.
Later signs and symptoms of decompensation may include:
- Change/Altered level of consciousness
- Hypoglycemia
- Metabolic acidosis
- Hyperammonemia
- Neutropenia
- “sweaty foot” odor
- Seizures
- Hepatomegaly

There are two types of presentation, depending on the severity of the metabolic defect. The neonatal form presents within the first days of life with a life threatening picture of severe lethargy progressing to obtundation. The infantile or late-onset form has a more insidious presentation with failure to thrive, developmental delay, and perhaps other neurologic features such as seizures and spasticity. These children can decompensate acutely during catabolic stress, usually brought on by infection. In both presentations, the pungent odor may be prominent on the body and in the blood.

The constellation of laboratory findings in these organic acid disorders:
- Ketoacidosis
- Hypoglycemia
- Neutropenia
- Hyperammonemia
- Hyperglycinemia

The ketoacidosis, hyperammonemia and hypoglycemia can explain the lethargy and obtundation. The ketoacidosis also produces vomiting. Mobilization of free fatty acids from stores to the liver produces a fatty liver. The increased organic acids may also be toxic to hepatocytes.
INITIAL MANAGEMENT IN HOSPITAL

If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation. Management decisions should be based primarily on the clinical status. The first decision about therapy is whether the child can be treated orally or will need intravenous therapy.
- If the child is relatively well, may be treated orally but assess very carefully
- If the child is obviously unwell, must be treated with intravenous fluids.
- If there is any doubt at all, put up an intravenous line
- If the child is shocked or clearly very ill, arrange for admission to Intensive Care Unit

ASSESSMENT

a. Clinical assessment:
   → Vital signs, cardiovascular stability
   → STAT glucocheck (blood sugar) to check for hypoglycemia
   → Neurologic status (including Glasgow coma score);
   → Hydration status
   → Presence of fever; signs of infection
   → Hepatomegaly

b. Labs:
   Blood
   → Blood gas (arterial or venous)
   → Blood glucose
   → Lipase
   → Ammonia
   → Electrolytes (including Na+, K+, Cl-, measured CO₂, Ca++, PO₄, Mg)
   → Urea, creatinine
   → Liver profile (including AST, ALT, AlkPO₄)
   → CBC differential
Urine
→ Urine dipstick for ketones
→ Urinalysis for specific gravity

Culture
If patient is febrile, cultures of blood, urine, and/or throat are needed depending on the patient clinical presentation.

NOTE: organic acids and ammonia are toxic to the brain and accumulations of these may result in cerebral edema. Caution should be exercised when considering the need for a lumbar puncture. If meningitis/encephalitis is a possibility, then CT of brain should be considered before lumbar puncture.

TREATMENT

The treatment for acute metabolic decompensation in these disorders includes:
1. Hydration
2. Correction of the biochemical abnormalities (metabolic acidosis, hyperammonemia, hypoglycemia)
3. Reversal of catabolism/promotion of anabolism
4. Elimination of toxic metabolites
5. Treatment of the precipitating factor when possible (e.g. infection, excess protein ingestion)
6. Cofactor supplementation
7. Consider dialysis

1. HYDRATION
Intravenous fluids should be administered with enough glucose to prevent further catabolism and sufficient alkali to treat the acidosis.
Consider running 10% dextrose with a piggybacked bicarbonate infusion of 1.25 - 1.5 X times the maintenance rate. Piggybacking allows individual Adjustment/titration of the IV solutions. Add KCl if renal function is not compromised.
INITIAL MANAGEMENT IN HOSPITAL

- Give normal saline 10 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give 20 ml/kg normal saline instead of the 10 ml/kg. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
- Continue with glucose 10% at 5 ml/kg/h until next solution ready. – see below
- Quickly calculate the deficit and maintenance and prepare the intravenous fluids
  - Deficit: estimate from clinical signs if no recent weight available
  - Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children) 100ml/kg for 1st 10kg then 50 ml/kg for next 10kg then 20ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.
  - Give 0.45% saline/10% glucose.
- Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.
- Recheck the electrolytes every 24 hours if still on IV fluids.

Ringer’s lactate should NEVER be used for fluid/electrolyte therapy in a child with a known/suspected metabolic disorder.

2. CORRECTION OF BIOCHEMICAL ABNORMALITIES

a. Hypoglycemia: If hypoglycemic, Give Glucose 200 mg/kg at once (2 ml/kg of 10% glucose or 1 ml/kg of 20% glucose) over a few minutes; follow with (at least) a 10% glucose solution

b. Metabolic acidosis: Administer NaHCO3 as a bolus (1 mEq/kg) if acutely acidotic with pH < 7.22 or bicarb level < 14, followed by a continuous infusion. If hypernatremia becomes a problem, reduce the rate of the Na bicarb drip; replace with K acetate.

  - If acidosis persists after correction of blood glucose and perfusion, sodium bicarbonate may be needed if the pH < 7.1 or the pH is deteriorating rapidly or the base deficit is greater than 15 mmol/l.
- Initially give a half correction [0.15 x weight x base deficit (mmol/l)] mmol sodium bicarbonate over at least 30 minutes. 1 ml of sodium bicarbonate 8.4% contains 1 mmol but this solution should be diluted at least 1ml to 5ml of 5% glucose. Then review and check U&E and pH & blood gases. The acidosis normally corrects fairly quickly so that repeat doses of sodium bicarbonate should only occasionally be needed. Before doing so ask why? Is perfusion normal? What is the blood pressure, capillary refill time and urine flow? Could the patient have pancreatitis or cardiomyopathy? The treatment that will need to be considered is hemofiltration (possibly hemodialysis), assisted ventilation and inotropes.

b. Hyperammonemia: the elevated ammonia reflects a secondary inhibition of the urea cycle. As treatment for the organic acidemia proceeds, the ammonia level should diminish.

If hyperammonemic (> 200 µmol/l in first 24 hours or >250 µmol/l thereafter) consider N-carbamylglutamate 250 mg/kg as a single oral dose if available. Alternatively give sodium benzoate 250 mg/kg/day enterally For extremely elevated ammonia or persistently elevated levels, dialysis should be considered (see Dialysis; Part 4-c).

3. REVERSAL OF CATABOLISM / PROMOTION OF ANABOLISM

a. GLUCOSE: Catabolism can be diminished by providing large amounts of glucose (10% dextrose at maintenance or above), thereby surpassing hepatic glucose production. This therapy should be started as soon as possible after the patient presents to the emergency room. Hyperglycemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using local diabetic protocol for treatment of DKA rather than reducing the glucose intake. Strict supervision is essential.

b. PROTEIN: All natural protein (containing all amino acids) should be withheld for 48-72 hours while the patient is acutely ill.

Amino acid therapy may be very beneficial in facilitating clinical improvement. Provide an amino acid preparation which includes only "non-offending amino acids" (i.e., avoiding leucine) during the initial crisis period may not only stimulate anabolism but also help prevent significant weight loss.
If the patient is not significantly neurologically compromised, these preparations can be provided enterally. Specialized formula preparations for isovaleric acidemia provide the appropriate mix of amino acids. Where there exists a high risk for aspiration or a contraindication to enteral feeding, consideration should be given to providing a specialized parenteral amino acid solution available through specific TPN pharmacies.

c. LIPID: Intralipid may be given to supply extra calories.

d. CALORIES: A goal for calories during a period of decompensation, in order to support anabolism, would be about 20% greater than ordinary maintenance needs. One must remember that withholding natural protein from the diet also eliminates this source of calories and should be replaced by other dietary or nutritional sources.

e. INSULIN: Insulin is a potent anabolic hormone, promoting protein and lipid synthesis. While large scale or objective studies do not exist to prove its value in the treatment of metabolic crises, theoretically it would appear to be a useful adjunct in reversing unwanted catabolism and facilitating the uptake of offending amino acid precursors.

4. ELIMINATION OF TOXIC METABOLITES
Correction of acute metabolic perturbations (acidosis, hypoglycemia) may help clear some of the factors contributing to the encephalopathy associated with acute metabolic crises. However, the presence of large quantities of toxic intermediate metabolites, believed to be toxic to the brain as well, are not cleared with glucose or bicarbonate, or rapidly with hydration. Consideration should be given to providing the means to help facilitate the excretion of these compounds:

a. L-CARNITINE
Free carnitine levels are low in the organic acidemias. L-Carnitine should be given intravenously - 200 mg/kg/24h given as a bolus of 100 mg/kg in 30 minutes and then 50 mg/kg every 6 hours intravenously. When oral fluids are tolerated, carnitine may be administered PO at a dose of 100 mg/kg/day.
b. L-GLYCINE
While glycine supplementation is controversial, it may prove helpful during acute crises for detoxifying toxic acyl-CoA accumulates. Glycine may be administered PO at a dose of 150-300 mg/kg/day. An intravenous preparation of glycine is not normally available. If possible therefore give glycine enterally by continuous infusion via a nasogastric tube. The dose is the same as that given orally 300 mg/kg/day.

c. DIALYSIS:
When a patient is comatose, dialysis is indicated to facilitate a more rapid clearance of metabolic toxins which would otherwise be dependent on renal excretion, a much slower process (see 6. DIALYSIS).

5. TREATMENT OF PRECIPITATING FACTORS
Infection should be treated vigorously when possible. Note that neutropenia (and thrombocytopenia) frequently accompany metabolic decompensation. Bone marrow recovery is expected once the levels of toxic metabolites diminish significantly

6. DIALYSIS
Dialysis (i.e., Peritoneal Dialysis, Hemodialysis, Continuous Renal Replacement Therapy) is indicated in cases with:
- Intractable metabolic acidosis
- Unresponsive hyperammonemia
- Coma
- Severe electrolyte disturbances (usually iatrogenic)
The Renal Service should be alerted early on in the hospital course.
MONITORING THE PATIENT

Reassess after 4-6 hours or earlier if there is any deterioration or no improvement. Clinical assessment should include:

- Mental status (Glasgow Coma Score)
- Vital signs specifically BP and temperature
- Fluid balance
- Symptoms of infection
- Evidence of bleeding (if thrombocytopenic)

Biochemical parameters:

- Electrolytes (including Na+, K+, Cl-, measured CO2, Ca++, PO4, Mg)
- Ammonia
- Urea, creatinine
- Blood glucose
- Blood gases
- CBC differential
- Urine for ketones and specific gravity

RECOVERY

- The patient should be kept NPO until his/her mental status is more stable.
- If the patient is not significantly neurologically compromised, enteral feeds (NG/GT) with the patient special formula containing all but the offending amino acids should be introduced as early as possible, as this allows a much higher energy intake and reduces the risk of malnutrition.
- If enteral feeds cannot be introduced within 48 hours start total parenteral nutrition (TPN) early to avoid malnutrition. (Note only moderate protein restriction when using TPN is necessary. Discuss with metabolic specialist team)
MONITORING THE PATIENT

→ ACT SHEET (2010), American College of Medical Genetics (ACMG), Medical Genetics Translating Genes Into Health, [on line], Accessed on 01 August 2011

→ EMERGENCY guidelines (2009), British Inherited Metabolic Disease Group (BIMDG) [on line], Accessed on 01 August 2011.

→ Emergency Treatment Protocol- New England Consortium on Metabolic Programs, [on line], Accessed in 01 August 2010
Dietary Emergency Protocol for Isovaleric Acidemia (IVA)

1. Discontinue regular diet/feeds

2. If your child is able to take fluids orally, start giving emergency solution every 2 hours during the day and every 3 hours during the night as follow:
   Add ................ Scoops Polycose/Prophree to ................. mls water

3. If your child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if your child is nauseated and/or vomiting

4. When using the available tube feeding, it is preferable to give the solution as:
   • Small boluses: Give ........ mls of emergency solution every ........ hour
   • Or continuously if a feeding pump is available

5. If a Rehydration Solution is to be given as in case of gastroenteritis:
   Add ........ Scoops Polycose/Prophree + Scoops .......... to .......... mls of Rehydration Solution

6. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen:
      If the child is doing well, go back to normal diet.
      If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
   b. Between 24 – 48 hours from starting the emergency regimen:
      If your child appears well, reintroduce all amount of amino acid mix excluding natural protein source.
      If no improvement is seen then continue giving the formula as instructed above if tolerated.
c. After 48 hours from starting the emergency regimen:
   → If the child is doing well and amino acid mix is well tolerated, start
     introducing natural protein in the diet gradually over few days starting
     with half amount especially if ammonia level is known to be elevated.
   → If no improvement is noticed or if the child is not taking above prescribed
     amounts of emergency solution, bring your child to the hospital with all
     medicines, special dietary products, and scoops.

N.B:
If, at any time from starting this emergency regimen, your child is deteriorating
and/or not tolerating the emergency solution due to nausea and vomiting,
bring your child immediately to the hospital with all medicines, special dietary
products, and scoops.

ACKNOWLEDGMENT

Dietary Emergency Protocols have been compiled by Metabolic Nutritionist-Medical
Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the British
Inherited Metabolic Disease Group (BIMDG), and have been revised by Medical
Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital
& Research Centre (KFSH&RC)-Riyadh, in August 2011.
PROPIONIC ACIDEMIA (PPA)
PROPIONIC ACIDEMIA (PPA)

Please read carefully

- Meticulous and prompt treatment is important as there is a high risk of serious complications.
- Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children. Listening to them is important when prioritizing the plan of care of their children.

INTRODUCTION

Propionic acidemia, an autosomal recessive disease, is caused by a deficiency of a specific enzyme on the catabolic pathway of amino acids (isoleucine, valine, threonine and methionine) as well as cholesterol side chains, odd chain fatty acids and free propionate from the gut.
Decomposition is often triggered by metabolic stress such as fasting and/or febrile illness particularly gastro-enteritis and flu; but an obvious cause is not always apparent.
The central emergency features of PPA are profound metabolic ketoacidosis and hypoglycemia.
Treatment is aimed at reducing the sources of the precursors so the patients are treated with a low protein diet and medicines (i.e., carnitine).

PRESENTATION

The early signs of decompensation include:
   → Lethargy
   → Poor appetite
Vomiting: is common and should always be taken seriously
However, some signs may be difficult to assess such as irritability or just ‘not right’. Always listen to parents carefully as their knowledge might exceed your expectations.

Later signs and symptoms of decompensation may include:

- Change/Altered level of consciousness
- Rapid and deep breathing (Kussmaul breathing)
- Seizures
- Hepatomegaly

The constellation of laboratory findings in these organic acid disorders:

- Ketoacidosis
- Hypoglycemia
- Neutropenia
- Hyperammonemia
- Hypocalcemia/hypokalemia

The ketoacidosis, hyperammonemia and hypoglycemia can explain the lethargy and obtundation. The ketoacidosis also produces vomiting. Mobilization of free fatty acids from stores to the liver produces a fatty liver. The increased organic acids may also be toxic to hepatocytes.

There are two types of presentation, depending on the severity of the metabolic defect. The neonatal form presents within the first days of life with a life threatening picture of severe lethargy progressing to obtundation. The infantile or late-onset form has a more insidious presentation with failure to thrive, developmental delay, and perhaps other neurologic features such as seizures and spasticity. These children can decompensate acutely during catabolic stress, usually brought on by infection.

**ASSESSMENT**

**a. Clinical assessment**

- Vital signs, cardiovascular stability
- STAT glucocheck (blood sugar) to check for hypoglycemia
Neurologic status (including Glasgow coma score); evidence of
increased intracranial pressure
Hydration status
Presence of fever; signs of infection
Hepatomegaly

b. LABS:

Blood
- Blood gas (arterial or venous)
- Blood glucose
- Ammonia
- Electrolytes (including Na+, K+, Cl-, measured CO2, Ca++, PO4, Mg)
- Urea, creatinine
- Liver profile (including AST, ALT, AlkPO4)
- CBC differential
- Lipase
- Plasma amino acids
- Serum carnitine

Urine
- Urine dipstick for ketones
- Urinalysis for specific gravity

Culture
If patient is febrile, cultures of blood, urine, and/or throat are needed depending on
the patient’s clinical presentation.

Initial plan and management in hospital

- Almost all patients who present to hospital will require admission.
- If there is any doubt at all, the child must be admitted, even if only
  necessary for a short period of observation.
- If the child is shocked or clearly very ill, arrange for admission to High
dependency unit or Intensive Care Unit.
- If admitted to metabolic / general ward make a careful clinical assessment
  including blood pressure and Glasgow Coma Score (even if the patient
does not appear encephalopathic).
Complications

There are many complications of the disorders but some are particularly problematic.

1. Pancreatitis. This is probably more common than recognised, partly because it is not easy to diagnose with confidence. It should be suspected if there is abdominal pain, shock out of proportion to other symptoms or hypocalcaemia. Plasma lipase and amylase activity may not be raised particularly at an early stage. Abdominal ultrasound may be helpful.

2. Cardiomyopathy. This may develop at any time but for reasons not well understood may occur during recovery phase. Arrange Echocardiography if there are signs of cardio-respiratory problems

3. Stroke-like episodes. These may occur at any time, frequently of sudden onset and when appearing to recover. They often involve the basal ganglia and present as a movement disorder.

MANAGEMENT

The treatment for acute metabolic decompensation in these disorders includes:

1. Hydration
2. Correction of the biochemical abnormalities (metabolic acidosis, hyperammonemia, hypoglycemia)
3. Reversal of catabolism/promotion of anabolism
4. Elimination of toxic metabolites
5. Treatment of the precipitating factor when possible (e.g. infection, excess protein ingestion)
6. Cofactor supplementation
7. Consider hemodialysis

1. HYDRATION

→ Give 20 ml/kg normal saline as a bolus immediately. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.

→ Continue with normal saline 10 ml/kg/hour until next solution ready. – see below
→ Quickly calculate the deficit and maintenance and prepare the intravenous fluids

- Deficit: estimate from clinical signs if no recent weight available
- Maintenance: The formula for calculating maintenance fluid (This is the BNF recommendation for children with 20% added because of the increased requirement in propionic acidemia) 120ml/kg for 1st 10kg then 60 ml/kg for next 10 then 25ml/kg thereafter using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.
- Note: Many patients with propionic acidemia have a renal tubular defect so that they cannot concentrate or acidify their urine normally. The recommended volumes have been adjusted to take account of this. Additional water, sodium and sometimes bicarbonate may be necessary but beware of oliguria in those with very poor renal function.
- Give 10% dextrose with normal saline 0.45%:
  o Intravenous fluids should be administered with enough glucose to prevent further catabolism and sufficient alkali to treat the acidosis
  o Consider running 10% dextrose with a piggybacked bicarbonate infusion of 1.25-1.5 X times the maintenance rate. Piggybacking allows individual Adjustment/titration of the IV solutions. Add KCl if renal function is not compromised.

Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.
After the initial 24 hours, continue with glucose 10% with saline 0.45% (unless evidence of continuing sodium depletion or hypernatremia). Monitor the urea and electrolytes regularly 6 hourly particularly the plasma potassium concentration. Treat hypokalemia as necessary.

Ringer’s lactate should NEVER be used for fluid/electrolyte therapy in a child with a known/suspected metabolic disorder.
2. CORRECTION OF BIOCHEMICAL ABNORMALITIES

a. Hypoglycemia: if hypoglycemic, Give Glucose 200 mg/kg at once (2 ml/kg of 10% glucose or 1 ml/kg of 20% glucose) over a few minutes; follow with (at least) a 10% glucose solution.

b. Metabolic acidosis: administer Sodium Bicarbonate (NaHCO₃) as a bolus (1 mEq/kg) if acutely acidic with pH < 7.22 or bicarb level < 14, followed by a continuous infusion. If hypernatremia becomes a problem, reduce the rate of the NaHCO₃ drip; replace with K acetate.
   - WARNING severe acidosis (pH < 7.2 or base deficit > 10 mmol/l) is potentially very dangerous. Patients who have a respiratory (or cardiac) arrest are usually difficult to resuscitate. Always consider elective assisted ventilation.
   - Sodium bicarbonate is not given routinely but if acidosis persists after correction of perfusion, sodium bicarbonate may be needed if the pH < 7.2 or the pH is deteriorating rapidly or the base deficit is greater than 10 mmol/l.
   - Initially give a half correction [0.15 x weight x base deficit (mmol/l)] mmol sodium bicarbonate over at least 30 minutes. 1 ml of sodium bicarbonate 8.4% contains 1 mmol of sodium and bicarbonate and must be diluted at least 1 ml to 5 ml of 5% glucose. Then review and check plasma urea and blood gases. Repeat as clinically needed.

c. Hyperammonemia: the elevated ammonia reflects a secondary inhibition of the urea cycle. As treatment for the organic acidemia proceeds, the ammonia level should diminish.
   - If hyperammonemic (> 200 μmol/l in first 24 hours or >250 μmol/l thereafter) consider N-carbamylglutamate 250 mg/kg as a single oral dose if available. Alternatively give sodium benzoate 250 mg/kg/day enterally.
   - For extremely elevated ammonia or persistently elevated levels, dialysis should be considered (see Dialysis, Part 7).
If further doses of sodium bicarbonate appear to be needed, ask why? Is perfusion normal? What is the blood pressure, capillary refill time and urine flow? Could the patient have pancreatitis or cardiomyopathy? The treatment that will need to be considered is haemofiltration (possibly peritoneal dialysis), assisted ventilation and inotropes. Such treatment should be under metabolic specialist supervision.

3. REVERSAL OF CATABOLISM / PROMOTION OF ANABOLISM

a. GLUCOSE: Catabolism can be diminished by providing large amounts of glucose (10% dextrose at maintenance or above), thereby surpassing hepatic glucose production. This therapy should be started as soon as possible after the patient presents to the emergency room.

b. PROTEIN: Amino acid therapy may be very beneficial in facilitating clinical improvement but should be implemented only under the supervision of a metabolic nutritionist or physician with expertise in metabolic management.

- All natural protein (containing all amino acids) should be withheld for 48-72 hours while the patient is acutely ill.
- Providing specialized diet which includes only "non-offending amino acids" (i.e., avoiding isoleucine, valine, threonine, and methionine) during the initial crisis period may not only stimulate anabolism but help prevent significant weight loss.
- If the patient is not significantly neurologically compromised, these formulas can be provided enterally (NG or GT).
- If enteral feeding is contra-indicated, consideration should be given to providing TPN

c. LIPID: If TPN considered, intralipid may be given to supply extra calories; intralipid is composed of even chain fatty acids, so it should not increase concentrations of propionate (a 3- carbon organic acid), a precursor of methylmalonate, or methylmalonate. Intra-lipid of 20% solution may be added at 2g/kg/day (0.4ml/kg/hour)

d. CALORIES: A goal for calories during a period of decompensation, in order to support anabolism, would be about 20% greater than ordinary maintenance needs. One must remember that withholding natural protein from the diet also eliminates this source of calories and should be replaced by other dietary or nutritional sources.
e. INSULIN: Insulin is a potent anabolic hormone, promoting protein and lipid synthesis. Hyperglycemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using the local diabetic protocol for treatment of DKA rather than reducing the glucose intake. Strict supervision is essential.

f. TREAT CONSTIPATION: which increases propionate absorption from the gut. Do not use lactulose as this can be fermented to propionate by gut bacteria

Medicines to be avoided: Sodium Valproate, Lactulose

4. ELIMINATION OF TOXIC METABOLITES
Correction of acute metabolic perturbations (acidosis, hypoglycemia) may help clear some of the factors contributing to the encephalopathy associated with acute metabolic crises. However, the presence of large quantities of toxic metabolites, believed to be toxic to the brain as well, is not cleared with glucose or bicarbonate, or rapidly with hydration. Consideration should be given to providing the means to help facilitate the excretion of these compounds:

a. L-CARNITINE: Free carnitine levels are low in the organic acidemias. L-Carnitine should be given intravenously - 200 mg/kg/24h given as a bolus of 100 mg/kg in 30 minutes and then 50 mg/kg every 6 hours intravenously. When oral fluids are tolerated, carnitine may be administered PO at a dose of 100 mg/kg/day.

b. ANTIBIOTICS: Administering broad-spectrum antibiotic may speed recovery in a patient in acute crisis.

c. DIALYSIS: When a patient is comatose, dialysis is indicated to facilitate a more rapid clearance of metabolic toxins (see 7. DIALYSIS)
5. TREATMENT OF PRECIPITATING FACTORS

Infection should be treated vigorously when possible. Note that neutropenia (and thrombocytopenia) frequently accompany metabolic decompensation. Bone marrow recovery is expected once the levels of toxic metabolites diminish significantly.

6. COFACTOR SUPPLEMENTATION FOR METHYLMALONIC ACIDEMIA

Biotin 10 mg/day might be useful in cases of vitamin-responsive enzyme deficiencies. In children with established diagnoses, parents will often know whether or not their child is a responder.

7. DIALYSIS

Dialysis (i.e., Peritoneal Dialysis, Hemodialysis, Continuous Renal Replacement Therapy) is indicated in cases with:

- Intractable metabolic acidosis
- Unresponsive hyperammonemia
- Coma
- Severe electrolyte disturbances (usually iatrogenic)

The Renal Service should be alerted early on in the hospital course.

MONITORING THE PATIENT

Clinical parameters:
- Mental status including Glasgow Coma Score
- Vital signs specifically
- BP and temperature
- Fluid balance
- Evidence of bleeding (if thrombocytopenic)
- Symptoms of infection (if neutropenic)

Biochemical parameters:
- Electrolytes (including Na+, K+, Cl-, measured CO2, Ca++, PO4, Mg)
- Urea, creatinine, glucose
- Ammonia
- Amylase/Lipase
- Blood gases
- CBC differential
- Urine for ketones and specific gravity
RECOVERY

- The patient should be kept NPO until his/her mental status is more stable.
- If the patient is not significantly neurologically compromised, enteral feeds (NG/GT) with the patient special formula containing all but the offending amino acids should be introduced as early as possible, as this allows a much higher energy intake and reduces the risk of malnutrition.
- If enteral feeds cannot be introduced within 48 hours start total parenteral nutrition (TPN) early to avoid malnutrition.

ACKNOWLEDGMENT

These recommendations have been compiled by Advanced Clinical Specialist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the American College of Medical Genetics (ACMG), the British Inherited Metabolic Disease Group (BIMDG), and the New England Consortium on Metabolic Programs; and have been revised by Medical Genetics Consultants in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011

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- Emergency Treatment Protocol- New England Consortium on Metabolic Programs, [on line]. Accessed on 01 August 2010
Dietary Emergency Protocol
Propionic Acidemia (PPA)

1. Discontinue regular diet/feeds
2. If your child is able to take fluids orally, start giving emergency solution every 2 hours during the day and every 3 hours during the night as follow:
   Add .................. Scoops of Polycose/Prophree to ................. mls of water
3. If your child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if your child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the solution as:
   - Small boluses: Give ........ mls of emergency solution every .......... hour
   - Or continuously if a feeding pump is available
5. If a Rehydration Solution is to be given as in case of gastroenteritis:
   Add ..................... Scoops of Polycose/Prophree to .................. mls of Rehydration Solution
6. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen:
      - If the child is doing well, go back to normal diet.
      - If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
   b. Between 24 – 48 hours from starting the emergency regimen
      - If your child appears well, reintroduce amino acid mix excluding natural protein source.
      - If no improvement is seen then continue giving the emergency solution as instructed above if tolerated
c. After 48 hours from starting the emergency regimen:
   ➔ If the child is doing well and amino acid mix is well tolerated, start introducing
   natural protein in the diet gradually over few days starting with half amount espe-
   cially if ammonia level is known to be elevated.
   ➔ If no improvement is noticed or if the child is not taking above prescribed
   amounts of emergency solution, bring your child to the hospital with all medicines,
   special dietary products, and scoops.

N.B:
If, at any time from starting this emergency regimen, your child is deterio-
rating and /or not tolerating the emergency solution due to nausea and
vomiting, bring your child immediately to the hospital with all medicines,
special dietary products, and scoops.

ACKNOWLEDGMENT

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cal Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the British
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Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital
& Research Centre (KFSH&RC)-Riyadh, in August 2011
GLUTARIC ACIDURIA TYPE 1
GLUTARIC ACIDURIA TYPE 1

Please read carefully

- Meticulous and prompt treatment is important as there is a high risk of serious complications.
- TREATMENT IS URGENT. DO NOT DELAY.
- Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children.

INTRODUCTION

Glutaric aciduria is an inherited disorder of the breakdown of certain amino acids, notably lysine. Any metabolic stress can lead to serious illness, with encephalopathy - a reduced level of consciousness and other neurological abnormalities. Following these episodes, patients often have severe permanent neurological disability, particularly a movement disorder. The damage results from the accumulation of glutaric acid and other toxic metabolites. Patients under 6 years of age are at most risk of neurological damage so treatment of the children must be very careful.

Decompensation is often triggered by metabolic stress such as fasting and/or febrile illness particularly gastro-enteritis and flu, but an obvious cause is not always apparent.

Treatment aims to minimize the accumulation of toxic metabolites by preventing protein breakdown and to promote their excretion by the use of carnitine.

PRESENTATION

The early signs of decompensation may be subtle, such as:
- Minor changes in tone
- Vomiting is common and should always be taken seriously
- However, the signs may be difficult to assess such as irritability or just 'not right'. Always listen to parents carefully; their knowledge might exceed your expectations
**ASSESSMENT**

If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation.

- If the child is shocked or clearly very ill arrange for admission to intensive care unit.
- If admitted to metabolic/general ward make a careful clinical assessment including blood pressure and Glasgow Coma Score even if the patient does not appear encephalopathic.
- The following tests should be done:

  **BLOOD:**
  * Blood gases
  * Urea and electrolytes
  * Glucose (laboratory and bedside strip test)
  * Full blood count
  * Blood culture

  **URINE:**
  * ketones

**TREATMENT**

Treatment is urgent. Do not delay. Unless you are very confident and certain, treat with intravenous fluids.

**A. ENTERAL:**

Enteral treatment should only be used occasionally and with caution. If tolerated, the dietary emergency regimen should be used. See attached “GAI dietary Emergency Regimen”.

**Electrolytes** should be added to the drinks if vomiting and/or diarrhea is a problem using standard rehydration mixtures following manufacturer’s instructions, but substituting glucose polymer solution for water
**Aminoacids**: As soon as available, the lysine free aminoacid mixture should be added to the glucose polymer drinks and initially given at the rate of 1g/kg/d. If this is not tolerated, the quantity can be reduced to 0.5 g/kg/d but for as short a period as possible. Do not delay giving drinks if the aminoacid mixture is not immediately available.

**Fever**: If the temperature is > 38.5 °C (101 F), ibuprofen should be given. (10-15 mg/kg per dose, 3-4 doses daily). Paracetamol is not recommended because of the potential for glutathione depletion.

**Medicines**: Carnitine should be given 200 mg/kg/24h in 4 divided doses.

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**B. INTRAVENOUS**:
This route should be used in most circumstances.

- Give Glucose 200 mg/kg at once (2 ml/kg of 10% glucose or 1ml/kg of 20% glucose) over a few minutes.
- Give normal saline 10 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give 20 ml/kg normal saline instead of the 10 ml/kg.. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
- Continue with glucose 10% at 5 ml/kg/h until next solution ready. – see below
- Quickly calculate the deficit and maintenance and prepare the intravenous fluids
  - Deficit: estimate from clinical signs if no recent weight available
  - Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children) 100ml/kg for 1st 10kg then 50 ml/kg for next 10kg then 20ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.
  - Give 0.45% saline/10% glucose

- Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.
- Recheck the electrolytes every 24 hours if still on IV fluids.
**Aminoacids** : A lysine free aminoacid mixture for intravenous use is rarely available. If at all possible therefore give the lysine free aminoacid mixture orally, either as drinks or an a continuous infusion. Initially it can be given at the rate of 1g/kg/d. If this is not tolerated, the quantity can be reduced to 0.5 g/kg/d but for as short a period as possible. Do not delay giving other treatment if the mixture is not immediately available.

* **L- CARNITINE** : Free carnitine levels are low in the organic acidemias. L-Carnitine should be given intravenously - 200 mg/kg/24h given as a bolus of 100 mg/kg in 30 minutes and then 50 mg/kg every 6 hours intravenously. When oral fluids are tolerated, carnitine may be administered PO at a dose of 100 mg/kg/day.

* **Potassium** can be added, if appropriate, once urine flow is normal and the plasma potassium concentration is known.

* **Hyperglycemia** can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using the local diabetic protocol rather than reducing the glucose intake. Strict supervision is essential.

**Fever** : If the temperature is > 38.5°C (101 F), ibuprofen should be given (10-15 mg/kg per dose, 3-4 doses daily). Paracetamol is not recommended because of the potential for glutathione depletion.

- Treat any infection

**MONITORING THE PATIENT**

Reassess after 4-6 hours or earlier if there is any deterioration or no improvement. Clinical assessment should include Glasgow coma score and blood pressure. Blood tests:

- Blood gases
- Glucose (laboratory): high values can occur due to insulin resistance
- Urea & electrolytes

For intravenous fluids after 24 hours please refer to the previous section.
RECOVERY

Re-introduction of enteral feeds:
As many more calories can be given enterally safely, feeds should be introduced as early as possible. It is usual to give soluble glucose polymer initially 10% and increase this both volume and concentration as tolerated. It is also customary to delay the introduction of any protein or aminoacids but this will only prolong the period of catabolism so early re-introduction is recommended. Aminoacids should be given and increased to 2g/kg/d.

Going Home:
Only allow the child home if you and the family are entirely happy. The family must have a clear management plan upon discharge.

ACKNOWLEDGMENT

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→ EMERGENCY guidelines (2009), British Inherited Metabolic Disease Group (BIMDG) [on line], Accessed on 01 August 2011.
Dietary Emergency Protocol for Glutaric Aciduria Type 1 (GA 1)

1. Discontinue regular diet/feeds

2. If your child is able to take fluids orally, start giving emergency solution + amino acid mix (half usual amount) every 2 hours during the day and every 3 hours during the night as follow:
   Add ................ Scoops Polyose/Prophree + ............ Scoops ...........
to ................... mls water

3. If your child has an enteral tube feeding (NGT/GT), use this tube for formula administration for better tolerance, especially if your child is nauseated and/or vomiting

4. When using the available tube feeding, it is preferable to give the solution as:
   • Small boluses: Give ........ mls of formula every ........ hour
   • Or continuously if a feeding pump is available

5. If a Rehydration Solution is to be given as in case of gastroenteritis:
   Add ........... Scoops Polyose/Prophree + Scoops ............ to ............. mls
   of Rehydration Solution

6. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen:
      ➔ If the child is doing well, go back to normal diet.
      ➔ If no improvement is seen then continue giving the formula as instructed above if tolerated
   b. Between 24 – 48 hours from starting the emergency regimen:
      ➔ If your child appears well, reintroduce all amount of amino acid mix excluding natural protein source.
      ➔ If no improvement is seen then continue giving the formula as instructed above if tolerated.
c. After 48 hours from starting the emergency regimen:
   → If the child is doing well and amino acid mix is well tolerated, start introducing natural protein in the diet gradually over few days starting with half amount especially if ammonia level is known to be elevated.
   → If no improvement is noticed or if the child is not taking above prescribed amounts of formula bring your child to the hospital with all medicines, special dietary products, and scoops.

N.B:
If, at any time from starting this emergency regimen, your child is deteriorating and/or not tolerating the emergency solution due to nausea and vomiting, bring your child immediately to the hospital with all medicines, special dietary products, and scoops.

ACKNOWLEDGMENT

Dietary Emergency Protocols have been compiled by Metabolic Nutritionist-Medical Genetics, KFSH&RC-Riyadh based on protocols and guidelines of the British Inherited Metabolic Disease Group (BIMDG), and have been revised by Medical Genetics team in Department of Medical Genetics at King Faisal Specialist Hospital & Research Centre (KFSH&RC)-Riyadh, in August 2011
MEDIUM CHAIN Acyl-CoA DEHYDROGENASE
MEDIUM CHAIN Acyl-CoA DEHYDROGENASE

Please read carefully

- Meticulous treatment is important as there is a high risk of serious complications.
- Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children.
- Intervention should occur whilst the blood glucose is still normal.

INTRODUCTION

Very long Chain Acyl CoA Dehydrogenase Deficiency (VLCADD), an autosomal recessive disease, is a common disorder of fat breakdown. It is caused by an intramitochondrial defect in the β- oxidation of fatty acids and is a major cause of severe hypoketotic hypoglycemia. It can also cause encephalopathy, lethargy, liver dysfunction with hepatomegaly, cardiomyopathy, metabolic acidosis, hyperammonemia and sudden death.

The pathophysiological process begins with reduced glucose intake as a result of a fasting state or increased energy needs from a catabolic state (infection, stress, fever, etc…) not sufficiently provided for by caloric intake

For most of the time patients are healthy and do not require a special diet. However metabolic stress such as fasting and/or febrile illness particularly gastroenteritis and flu can lead to serious illness, with encephalopathy and even sudden death. This results from the accumulation of toxic fatty acids that inhibit gluconeogenesis (thus preventing endogenous glucose production), have a toxic effect on the liver and produce metabolic acidosis. Muscle, particularly myocardium, requires a lot of energy and, therefore, becomes functionally impaired resulting in lethargy, hypotonia and hypertrophic cardiomyopathy.

Note ALL siblings of known cases should be tested for VLCADD whether or not they have a history of symptoms.
Marked Lethargy
Poor appetite
Nausea
Vomiting: is common and should always be taken seriously
However, some signs may be difficult to assess such as irritability or just ‘not right’. Always listen to parents carefully; their knowledge might exceed your expectations

Later signs and symptoms of decompensation may include:
Change/Altered level of consciousness
Hypoglycemia with lack or only ‘trace’ of urinary ketones: Hypoglycemia only occurs at a relatively late stage (or very late) so that blood glucose should not be relied on. Do not delay treatment just because the blood glucose is not low. The aim should always be to intervene whilst the blood glucose is normal. Treatment aims to prevent mobilization of fat by providing ample glucose enterally or intravenously
Metabolic acidosis
Hyperammonemia
‘Reye’ like syndrome
Seizures
Near/rescued SIDS
Hepatomegaly

NOTE that in the acute crises patients can be seriously ill WITHOUT hypoglycemia although typically FAOD crises are associated with hypoglycemia. At these times the urine typically tests ‘absent’ or ‘small’ for the presence of ketones. Liver function tests may be mildly elevated; hyperammonemia and hyperuricemia are often present during acute episodes.
INITIAL MANAGEMENT IN HOSPITAL

If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation. Management decisions should be based primarily on the clinical status. The first decision about therapy is whether the child can be treated orally or will need intravenous therapy.

- If the child is relatively well, may be treated orally but assess very carefully
- If the child is obviously unwell, must be treated with intravenous fluids.
- If there is any doubt at all, put up an intravenous line
- If the child is shocked or clearly very ill, arrange for admission to Intensive Care Unit

ASSESSMENT

As a rule, decompensation occurs more quickly in infants but children and adults, though more resistant, are still at risk of sudden death.

a. Clinical assessment:
   - Vital signs, cardiovascular stability
   - STAT glucocheck (blood sugar) to check for hypoglycemia
   - Neurologic status (including Glasgow coma score);
   - Hydration status
   - Presence of fever; signs of infection
   - Hepatomegaly

b. Labs Blood
   - Blood gas (arterial or venous)
   - Blood glucose
   - Ammonia
   - Electrolytes (including Na+, K+, Cl-, measured CO2, Ca++, PO4, Mg)
   - Urea, creatinine
ASSESSMENT

→ Liver profile (including AST, ALT, AlkPO4, PT, PTT, bilirubin)
→ CBC differential

Urine
→ Urine dipstick for ketones

Culture
If patient is febrile, cultures of blood, urine, and/or throat are needed depending on the patient clinical presentation.

TREATMENT

1. INDICATION FOR IV (NEVER less than 10% dextrose IV infusion). One or more indication is sufficient for IV:
   • Vomiting
   • Hypoglycemia
   • Poor oral intake
   • Dehydration. Do not rely on urinary ketones as indicating dehydration!
   • Decreased alertness
   • Metabolic Acidosis
     Start 10% glucose continuous infusion at 1.5x maintenance, to provide 7-8mg/kg/min.

   • Give Glucose 200 mg/kg at once (2 ml/kg of 10% glucose or 1ml/kg of 20% glucose) over a few minutes.
   • Give normal saline 10 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give 20 ml/kg normal saline instead of the 10 ml/kg. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient.
   • Continue with glucose 10% at 5 ml/kg/h until next solution ready. – see below
   • Quickly calculate the deficit and maintenance and prepare the intravenous fluids
Deficit: estimate from clinical signs if no recent weight available

Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children) 100ml/kg for 1st 10kg then 50 ml/kg for next 10kg then 20ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.

Give 0.45% saline/10% glucose

- Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.
- Recheck the electrolytes every 24 hours if still on intravenous fluids.

2. HYPOGLYCEMIA
Push 25% dextrose 2ml/kg and follow with a continuous 10% dextrose infusion at 1.5x maintenance, to provide 7-8 mg/kg/min glucose.

Hyperglycemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using the local diabetic protocol for treatment of DKA rather than reducing the glucose intake. Strict supervision is essential.

3. METABOLIC ACIDOSIS (Bicarbonate level <16mEq/L)
Must be treated aggressively with IV sodium bicarbonate (1mEq/kg). Treating conservatively in the expectation of a re-equilibration of acid/base balance as other biochemical/clinical parameters are normalized can lead to tragic consequences.

4. PRECIPITATING FACTORS
Should be treated aggressively to help minimize further catabolism

5. CARNITINE
The use of carnitine in FAODs is controversial and there are concerns that excessive long chain acyl carnitines which may be produced may induce arrhythmias. Consult with the primary metabolic physician for guidance regarding this in each individual case.

6. DO NOT ADMINISTER LIPIDS IN ANY FORM

7. Other medications
Epinephrine may stimulate lipolysis, therefore if indicated in these children should be covered with 10% dextrose infusion. It is wise to check drug interaction and side effects such as hypoglycemia whenever prescribing for these children.
MONITORING THE PATIENT

Reassess after 4-6 hours or earlier if there is any deterioration or no improvement. If child is unable to take/maintain PO intake, start, or continue, 10% glucose continuous infusion at 1.5 x maintenance.

Clinical assessment should include:
→ Mental status (Glasgow Coma Score)
→ Vital signs specifically BP and temperature
→ Fluid balance
→ Symptoms of infection

Biochemical parameters:
→ Electrolytes (including Na+, K+, Cl-, measured CO2, Ca++, PO4, Mg)
→ Ammonia
→ Urea, creatinine
→ Blood glucose
→ Blood gases

RECOVERY

• The patient should be kept NPO, while on IV infusion, until his/her mental status is more stable.
• If the patient is not significantly neurologically compromised, enteral feeds (NG/GT) with the patient special formula should be introduced as early as possible, as this allows a much higher energy intake and reduces the risk of malnutrition.
• If drinking oral fluids well, and none of the above factors present, there is no need for emergent IV infusion. But history of earlier vomiting, pyrexia, or other stressor should be taken seriously and a period of observation undertaken to ensure that PO fluids are taken frequently and well tolerated, with glucose status monitored periodically.
• Avoidance of fasting when stop IV infusion: This may include complex carbohydrate in the form of cornstarch supplementation to get through the night as the child gets older and a high carbohydrate/low fat diet is to be followed.
ACKNOWLEDGMENT

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> Emergency Treatment Protocol- New England Consortium on Metabolic Programs, [on line], Accessed in 01 August 2010
Dietary Emergency Protocol for Medium Chain Co A Acyl Dehydrogenase Deficiency (MCADD)

1. Discontinue regular diet/feeds
2. If your child is able to take fluids orally, start giving emergency solution every 2 hours during the day and every 3 hours during the night as follow:
   Add ................ Scoops Poly cose/Prophree to ................... mls water
3. If your child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if your child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the solution as:
   - Small boluses: Give ........ mls of emergency solution every ........ hour
   - Or continuously if a feeding pump is available
5. If a Rehydration Solution is to be given as in case of gastroenteritis:
   Add.......... Scoops Poly cose/Prophree + Scoops.............. to......... mls of Rehydration Solution
6. Reassess your child every 4 hours:
   a. Within the first 24 hours from starting the emergency regimen:
      If the child is doing well, go back to normal diet.
      If no improvement is seen then continue giving the emergency solution as instructed above if tolerated.
   b. Between 24 – 48 hours from starting the emergency regimen:
      If your child appears well, reintroduce all amount of amino acid mix excluding natural protein source.
      If no improvement is seen then continue giving the formula as instructed above if tolerated.
c. After 48 hours from starting the emergency regimen:
   → if the child is doing well and amino acid mix is well tolerated, start introducing natural protein in the diet gradually over few days starting with half amount especially if ammonia level is known to be elevated.
   → If no improvement is noticed or if the child is not taking above prescribed amounts of emergency solution, bring your child to the hospital with all medicines, special dietary products, and scoops.

N.B:
If, at any time from starting this emergency regimen, your child is deteriorating and/or not tolerating the emergency solution due to nausea and vomiting, bring your child immediately to the hospital with all medicines, special dietary products, and scoops.

ACKNOWLEDGMENT

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