



Saudi Arabia
Ministry of Health
National Newborn screening program

**MANAGEMENT GUIDELINES
FOR NEWBORN SCREENING
DISORDERS IN SAUDI
ARABIA**

Introduction:

Newborn screening has become an essential part of healthcare system in most of the developed countries. In Saudi Arabia, the NBSP officially started in August 2005 (Rajab 1426 H). Which aims to Maintain community health through promoting an early detection of selected genetic diseases to decrease resulting morbidity, mortality and disability, through early detection and identification of selected congenital endocrine and / or metabolic disorders in the newborns. And early treatment of those diseases and prevention of their complications like intellectual disability, physical handicap and possibly early death.

This dietary emergency protocols have been written to help you to manage the metabolic crises, It has been compiled previously 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 center (kfsh&rc)-Riyadh, in august 2011, this protocols updated recently in 2020, by the following genetic consultants: Dr. Mohammed Mahnashi, Dr. Omhani Malibari, and Dr. Maha Alotaibi.

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LIST OF METABOLIC DISEASES COVERED BY NEWBORN SCREENING:

1. Congenital Hypothyroidism (CH)
2. Congenital Adrenal Hyperplasia (CAH)
3. Maple Syrup Urine Disease (MSUD)
4. Phenylketonuria (PKU)
5. Propionic Acidemia (PPA)
6. Methylmalonic Acidemia (MMA)
7. Glutaric Acidemia type-1 (GA)
8. Isovaleric Acidemia (IVA)
9. HMG-Co Lyase Deficiency (HMG) 3-Hydroxymethylglutaryl
10. Argininosuccinic Acidemia (ASA)
11. Citrullinemia
12. Medium-chain Acyl CoA dehydrogenase deficiency
13. Very long-chain AcylCoA dehydrogenase deficiency (VLCAD)
14. Galactosemia (GALT)
15. Homocystinuria
16. Tyrosinemia
17. Beta-Ketothiolase Deficiency (BKT DEF.)
18. Biotinidase Deficiency (BTD)
19. 3-Methylmethcathinone (3MMC)
20. Primary Carnitine Deficiency

List of NBS Diseases, Summary of Common Presentation, Complications, Screening and Management

1.(Amino Acids Conditions)

العلاج***	المادة التي تفحص**	عمر المولود وقت ظهور الأمراض (فاليًا)	أعراض المرض ومضاعفاته عند عدم العلاج المبكر	المرض	
حمية غذائية، أدوية	Leucine	الأيام الخمسة الأولى	الإعاقة العقلية والحركية، ضعف النمو، التشنجات، الفيبوية، الوفاة	مرض داء البول القيقبي Maple Syrup Urine Disease (MSUD)	١
حمية غذائية أدوية	Tyrosine in DBS Confirmatory Succhenylacetone in blood or urine	٣ أشهر	-مشاكل فى الكبد -إضطراب عصبى -ضعف النمو	Tyrosinemia	٢
حمية غذائية أدوية	Methionine in DBS Then measurement of Homocystine level in plasma	بعد السنة الأولى أو أي مرحلة عمرية	-مشاكل فى العين -مشاكل فى الهيكل العظمى والجهاز العصبى -الجلطات الدموية	Homocystinuria	٣

2. (Organic Acids Conditions)

العلاج***	المادة التي تفحص**	عمر المولود وقت ظهور الأعراض (فألبًا)	أعراض المرض و مضاعفاته عند عصر العلاج المبكر	المرض	
حمية غذائية، أدوية	C3 C3/C2	الأيام الثلاثة الأولى	الإعاقة العقلية والحركية، التشنجات، الغيبوبة، الوفاة	حموضة البروبيونيك Propionic Acidemia (PPA)	٤
حمية غذائية، أدوية، فيتامين ب ١٢ (أحيانًا)	C3 C3/C2	الأيام الثلاثة الأولى	الإعاقة العقلية والحركية، ضعف النمو، التشنجات، الغيبوبة، الوفاة	حموضة ميثايلمالونيك Methylmalonic Acidemia (MMA)	٥
حمية غذائية Carnitine	C5OH C5OH +C4DC	الأيام الأولى من الولادة	ضعف بالنمو، تشنجات، غيبوبة، الوفاة	نقص إنزيم MCC-3 3-Methylcrotonyl Carboxylase Deficiency	٦
فيتامين بيوتين	Biotinidase	الأسابيع الأولى	الإعاقة العقلية والحركية، الصمم، العمى، تساقط الشعر، تحسس الجلد، التشنجات، الوفاة	نقص إنزيم بيوتينيداز Biotinidase Deficiency (BTD)	٧
حمية غذائية، أدوية	C5DC	الأشهر الأولى	الإعاقة الحركية، الغيبوبة، الوفاة	حموضة جلوتاريك - النوع الأول Glutaric Acidemia type-1 (GA)	٨
حمية غذائية، أدوية	C5	الأيام الأولى	الإعاقة العقلية والحركية، الغيبوبة، الوفاة	حموضة أيزوالريك Isovaleric Acidemia (IVA)	٩
حمية غذائية، أدوية	C5OH	الأيام الأولى	الإعاقة العقلية والحركية، الغيبوبة، الوفاة	نقص إنزيم HMG - كو أي البيز HMG-Co Lyase Deficiency (HMG)	١٠
حمية غذائية، أدوية	C5:1 C5OH	الأيام الأولى	الإعاقة العقلية والحركية، الغيبوبة، الوفاة	نقص إنزيم بيتا - كينوثايولاز Beta-Ketothiolase Deficiency (BKD)	١١

3. (Urea Cycle Conditions)

العلاج ***	المادة التي تفحص **	عمر المولود وقت ظهور الأعراض (فألياً)	أعراض المرض ومضاعفاته عند العلاج المبكر	المرض	
حمية غذائية، أدوية	Argininosuccinic Acid Citrulline	الأيام الثلاثة الأولى	الإعاقة العقلية والحركية، التشنجات، الغيبوبة، الوفاة	حموضة أرجينينوسكسنك Argininosuccinic Acidemia (ASA)	١٢
حمية غذائية، أدوية	Citrulline	الأيام الثلاثة الأولى	الإعاقة العقلية والحركية، التشنجات، الغيبوبة، الوفاة	ستروولينيميا Citrullinemia	١٣

4. (Fatty Acid Oxidation Conditions)

العلاج ***	المادة التي تفحص **	عمر المولود وقت ظهور الأعراض (فألياً)	أعراض المرض ومضاعفاته عند عدم العلاج المبكر	المرض	
وجبات غذائية متكررة	C6 C8 C10 C8/C10	الأيام الأولى	التشنجات، الغيبوبة، الوفاة	نقص إنزيم إم كاد Medium-chain Acyl CoA dehydrogenase deficiency	١٤
وجبات غذائية متكررة، حمية غذائية دواء (أحياناً)	C14 C14:1 C16 C16:1 C18 C18:1	الأيام الأولى	عف النمو، ضعف عضلات القلب، تضخم الكبد، الغيبوبة، الوفاة	نقص إنزيم في إل كاد Very long-chain AcylCoA dehydrogenase deficiency (VLCAD)	١٥
دواء Carnitine	C0	الشهور الأولى	فشل بالقلب، مشاكل بالكبد، غيبوبة، الوفاة	مرض عوز الكارنتين الأساسي Primary Carnitine deficiency	١٦

5. (Carbohydrate Conditions)

العلاج ***	المادة التي تفحص **	عمر المولود وقت ظهور الأعراض (فألياً)	أعراض المرض ومضاعفاته عند عدم العلاج المبكر	المرض	
حمية غذائية	Galactosemia enzyme (GALT)	الأسبوع الأول	ضعف النمو، ضعف القدرات العقلية، الماء الأبيض في العين، ضعف وظائف الكبد، الوفاة	مرض سكر اللبن في الدم Galactosemia (GALT)	١٧



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 BCAA (Leucine, Isoleucine, and Valine) as well as the organic acids.
- MSUD is disorder affecting the breakdown of BCAA.
- 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 hypoglycemia, 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 fontanelles occasionally seen.
- Maple syrup/burnt sugar like odor (from urine, bodily secretions and 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:

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.

Labs:

- Blood
- Plasma amino acids (Leucine, Isoleucine, and Valine)
- Newborn screening (via tandem mass spectrometry or 'Guthrie testing).
- Blood gas (Always calculate Anion Gap if metabolic acidosis).
- Electrolytes (Na, K, Cl, Hco₃, Po₄, Mg, and Ca)
- Glucose.
- CBC differential.
- Serum amylase, lipase (pancreatitis can accompany metabolic episodes).
- Ammonia if diagnosis not certain.
- Lactate 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 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 amino acid mixture.
 - If the peripheral circulation is compromised give intravenous fluids but may still be possible to give the amino acid mixture and some energy orally.
- 1. Discontinue natural protein.**
 - 2. Provide the large number of calories needed (120-140 kcal/kg/day).**

3. Provide fluids and sodium to treat dehydration, reestablish normal perfusion, 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 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 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 100 ml/kg for 1st 10kg then 50 ml/kg for next 10 kg then 20ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hrs.
- Give as D10N2 (half normal saline 0.45% /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.

2- Stat laboratory tests:

As described above

3- Branched chain amino acid-free formula

- There are a number of other medical product formulas.
- 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.

Product	Supplier	Designation	Nutrition prot Eg (g)	Energy (kCal)
Ketonex 1	Ross	Infant	15	480
MSUD 1	Milupa	Infant	41	280
MSUD Analog	SHS	Infant	31	475
Ketonex 2	Ross	Child/ Adult	30	410
BCAD-2	Mead Johnson	Child/ Adult	24	410
MSUD 2	Milupa	Child/ Adult	54	300
MSUD Maxamaid	SHS	Child	25	309
MSUD Maxamum	SHS	Adult	39	297
Complex MSUD Drink Mix	Applied Nutrition	Child/ Adult	25	410
Complex MSUD Amino Acid Blood	Applied Nutrition	Child/ Adult	77	323
Complex MSUD Amino Acid Blood	Applied Nutrition	Child/ Adult	21	575

- 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.
- Ondansetron can be used as 0.1 mg/kg IV to prevent vomiting.

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:

- Provide 120-140 kcal/kg/day and sufficient protein as amino acids free of the branched chain amino acids.
- Eliminate ketoacidosis as determined by:
 - Serum bicarbonate level of 24 meq/L.
 - Absence of ketones in urine.
 - Negative urine DNPH test.
- Maintain serum sodium at 140-145 meq/L. Monitor urine sodium output to establish loss and replacement requirement.
- 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.
- 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 1 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 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 emergency head CT.
 - If severe edema confirmed, infuse mannitol at 12 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.
 - Ondansetron 0.1 mg/kg 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.
- (Hemodialysis is superior to peritoneal dialysis).

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 Scale).
- Vital signs specifically BP and temperature.
- Fluid balance.
- Symptoms of infection.

Biochemical parameters:

- Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca⁺, PO₄, Mg).
- Amino acids (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. 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

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Dietary Emergency Protocol for Maple Syrup Urine Disease (MSUD)

1- Discontinue regular diet/feeds

2- If the child is able to take fluids orally, continue giving the 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 ofto ml water

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

4- When using the available tube feeding, it is preferable to give the prepared formula as:

- Small boluses: Givemls 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 the child every 4 hours: a. Within the first 24 hours from starting the emergency regimen:

a) 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 the child appears well, do the following.
- If a blood sample was NOT sent: Reintroduce gradually the natural protein at V4 normal intake for the first day, then / 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 the child is not taking adequate amounts of formula or not tolerating the formula, bring the child to the hospital with all the medications, special dietary products and scoops.

N.B:

If, at any time from starting this emergency regimen, the child is deteriorating and/or not tolerating the formula due to nausea and vomiting, bring the 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.

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.
- 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
- 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.
 - I. The neonatal form presents within the first days of life with a life-threatening picture of severe lethargy progressing to obtundation.
 - II. 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:

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.

LABS:

• **Blood**

- Blood gas (arterial or venous).
- Blood glucose.
- Ammonia.
- Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca⁺⁺, PO₄, Mg). Calculate anion gap if metabolic acidosis present.
- Urea, creatinine.
- Liver profile (including AST, ALT, ALP. PT. PTT. Albumin, and Bilirubin).
- CBC differential.
- Lipase, and 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.

Complications:

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

1. Pancreatitis:

- This is probably more common than recognized, 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 hypocalcemia.
- Plasma lipase and amylase activity may not be raised particularly at an early stage.
- Abdominal ultrasound maybe 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.

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.

- 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 acidemia) 120ml/kg for 1st 10 kg then 60 ml/kg for next 10 then 25 ml/kg thereafter using calculated rehydrated weight.

- Deduct the fluid already given from the total for the first 24 hours.

- **Note:** Many patients with methylmalonic 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%:

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 hypernatremia).
- Monitor the urea and electrolytes regularly 6 hourly particularly the plasma potassium concentration.
- Treat hypokalemia as necessary.
- **N.B:** Ringers lactate should NEVER be used for fluid/electrolyte therapy in a child with a known/suspected metabolic disorder.

2. CORRECTION OF BIOCHEMICAL ABNORMALITIES

Hypoglycemia

- 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.

Metabolic acidosis:

- Administer Sodium Bicarbonate (NaHCO_3) 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 NaHCO_3 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 [$0.15 \times \text{weight} \times \text{base deficit (mmol/l)}$] 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 hemofiltration (possibly peritoneal dialysis), assisted ventilation and inotropes. Such treatment should be under metabolic specialist supervision

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 hyperammonemia > 200 $\mu\text{mol/l}$ in first 24 hours or >250 $\mu\text{mol/l}$ thereafter) consider N-carbamylglutamate 100 - 250 mg/kg as a loading oral dose, then maintenance 100 – 200 mg/kg/d in 2 -4 divided doses.
- Alternatively give sodium benzoate 250 mg/kg/day enterally
- For extremely elevated ammonia or persistently elevated levels, dialysis should be considered.

3. REVERSAL OF CATABOLISM / PROMOTION OF ANABOLISM: 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.

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” , 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). Ondansetron 0.15 mg/kg IV can be used to prevent vomiting and can be given Q 6 - 8 hours as indicated.
- If enteral feeding is contra-indicated, consideration should be given to providing TPN.

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)

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.

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.

TREAT CONSTIPATION

- Constipation 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.
- 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.

1) L-CARNITINE:

- Carnitine levels are low in the organic acidemias,
- L-Carnitine be given intravenously 300 - 400 mg/kg/day.
- Give bolus of 100-150 mg/kg in 30 minutes and then 50 - 100 mg/kg every 6 hours intravenously.
- When oral fluids are tolerated, carnitine may be administered PO at a dose of 300 - 400 mg/kg/day accordingly.

2) ANTIBIOTICS:

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

3) DIALYSIS:

- When a patient is comatose, dialysis is indicated to facilitate a more rapid clearance of metabolic toxins.

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 (Glasgow Coma Scale).
- 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.
- 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

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EMERGENCY guidelines (2009). British Inherited Metabolic Disease Group (BIMDG) (online), Accessed on 01 August 2011

Emergency Treatment Protocol - New England Consortium on Metabolic Programs, (online]. Accessed in 01 August 2010

Dietary Emergency Protocol Propionic Acidemia (PPA)

1. Discontinue regular diet/feeds
2. If the 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..... mis of water
3. If the child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if the child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the solution as:
 Small boluses: Give mis 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 the 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 the 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 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 the child to the hospital with all medicines, special dietary products, and scoops.

N.B:

If, at any time from starting this emergency regimen, the child is deteriorating and /or not tolerating the emergency solution due to nausea and vomiting, bring the 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 ACIDEMIA (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 (High anion gap metabolic acidosis).
 - 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:

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.

LABS:

• Blood

- Blood gas (arterial or venous).
- Blood glucose.
- Ammonia.
- Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca⁺⁺, PO₄, Mg). Calculate anion gap if metabolic acidosis present.

- Urea, creatinine.
- Liver profile (including AST, ALT, ALP, PT, PTT, Albumin, and Bilirubin).
- CBC differential.
- Lipase, and 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.
- 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 (with 20% added because of the increased requirement in methylmalonic acidemia) 120 ml/kg for 1st 10kg then 60 ml/kg for next 10 then 25 ml/kg thereafter using calculated rehydrated weight.
 - Deduct the fluid already given from the total for the first 24 hours.
 - **Note:** Many patients with methylmalonic 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%

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 hypernatremia).

- Monitor the urea and electrolytes regularly 6 hourly particularly the plasma potassium concentration.
- Treat hypokalemia as necessary.
- N.B: Ringers lactate should NEVER be used for fluid/electrolyte therapy in a child with a known/suspected metabolic disorder.

CORRECTION OF BIOCHEMICAL ABNORMALITIES

- Hypoglycemia
 - 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.
- Metabolic acidosis:
 - Administer Sodium Bicarbonate (NaHCO_3) 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 NaHCO_3 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 hemofiltration (possibly peritoneal dialysis), assisted ventilation and inotropes. Such treatment should be under metabolic specialist supervision.

- **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 hyperammonemia > 200 pmol/l in first 24 hours or >250 umol/l thereafter) consider N-carbamylglutamate 100 - 250 mg/ kg as a loading oral dose, then maintenance 100 – 200 mg/kg/d in 2 -4 divided doses.
- Alternatively give sodium benzoate 250 mg/kg/day enterally
- For extremely elevated ammonia or persistently elevated levels, dialysis should be considered.

3. REVERSAL OF CATABOLISM / PROMOTION OF ANABOLISM:

- **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.

- **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” fi.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). Ondansetron 0.15 mg/kg IV can be used to prevent vomiting and can be given Q 6 - 8 hours as indicated.
 - If enteral feeding is contra-indicated, consideration should be given to providing TPN.
- **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)
- **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.
- **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.

- **TREAT CONSTIPATION:**

Constipation 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.

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.

[1]. L-CARNITINE:

Carnitine levels are low in the organic acidemias,

L-Carnitine should be given intravenously 300 - 400 mg/kg/day.

Give bolus of 100-150 mg/kg in 30 minutes and then 50 - 100 mg/kg every 6 hours intravenously.

When oral fluids are tolerated, carnitine may be administered PO at a dose of 300 - 400 mg/kg/day accordingly.

[2]. ANTIBIOTICS:

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

[3]. DIALYSIS:

When a patient is comatose, dialysis is indicated to facilitate a more rapid clearance of metabolic toxins.

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 Scale).
- 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.
- 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).

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Dietary Emergency Protocol Methylmalonic Acidemia (MMA)

1. Discontinue regular diet/feeds
2. If the 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 ml water

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

4. When using the available tube feeding, it is preferable to give the solution as:

- Small boluses: Give ml 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 ml of Rehydration Solution

6. Reassess the 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 the 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 the child to the hospital with all medicines, special dietary products, and scoops.**

N.B:

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

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GLUTARIC ACIDURIA TYPE I

GAI

GLUTARIC ACIDURIA TYPE 1

- **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:

- 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 appearance philopatric
- 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.
- 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 a 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 as loading 100 mg/kg/dose over 2 hours then maintenance 300 – 400 mg/kg/day Q 6 – 8 hours.

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.
 - 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 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 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**
 - Carnitine levels are low in the organic acidemias.
 - L-Carnitine should be given intravenously 300 - 400 mg/kg/day.
 - Give bolus of 100-150 mg/kg in 30 minutes and then 50 - 100 mg/kg every 6 hours intravenously.
 - When oral fluids are tolerated, carnitine may be administered PO at a dose of 300 - 400 mg/kg/day accordingly.
- Potassium 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, creatinine, and 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:

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

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EMERGENCY guidelines (2009), British Inherited Metabolic Disease Group (BIMDG) (online), Accessed on 01 August 2011.

Emergency Treatment Protocol- New England Consortium on Metabolic Programs, (online], Accessed in 01 August 2010

Dietary Emergency Protocol for Glutaric Aciduria Type 1 (GA1)

1. Discontinue regular diet/feeds

2. If the 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 Polycose/Prophree + Scoops.
to..... mls water

3. If the child has an enteral tube feeding (NGT/GT), use this tube for formula administration for better tolerance, especially if the 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 Polycose/ Prophree + Scoops..... to.....
mls of Rehydration Solution**

6. Reassess the 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 the 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 the child to the hospital with all medicines, special dietary products, and scoops.**

N.B:

If, at any time from starting this emergency regimen, the child is deteriorating and /or not tolerating the emergency solution due to nausea and vomiting, bring the 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
IVA**

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.
- 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.
- 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.
 - [1]. The neonatal form presents within the first days of life with a life-threatening picture of severe lethargy progressing to obtundation.
 - [2]. 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:

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.

LABS:

- **Blood**
- Blood gas (arterial or venous).
- Blood glucose.
- Ammonia.
- Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca⁺⁺, PO₄, Mg). Calculate anion gap if metabolic acidosis present.
- Urea, creatinine.
- Liver profile (including AST, ALT, ALP. PT. PTT. Albumin, and Bilirubin).

- CBC differential.
- Lipase, and lipase.
- **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.
- 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 10 kg then 60 ml/kg for next 10 then 25 ml/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 hypernatremia).
 - 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

- Hypoglycemia
 - 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.
- Metabolic acidosis
 - administer Sodium Bicarbonate (NaHCO_3) 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 NaHCO_3 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 [$0.15 \times \text{weight} \times \text{base deficit (mmol/l)}$] 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 hemofiltration (possibly peritoneal dialysis), assisted ventilation and inotropes. Such treatment should be under metabolic specialist supervision
- **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 hyperammonemia > 200 pmol/l in first 24 hours or >250 umol/l thereafter) consider N-carbamylglutamate 100 - 250 mg/ kg as a loading oral dose, then maintenance 100 – 200 mg/kg/d in 2 -4 divided doses.
- Alternatively give sodium benzoate 250 mg/kg/day enterally
- For extremely elevated ammonia or persistently elevated levels, dialysis should be considered.

3. REVERSAL OF CATABOLISM / PROMOTION OF ANABOLISM:

• 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.

• 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.
- 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.

- **LIPID**

- Intralipid may be given to supply extra calories.

- **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.

- **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.

- 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:

[1]. L-CARNITINE:

- Carnitine levels are low in the organic acidemias.
- L-Carnitine should be given intravenously 300 - 400 mg/kg/day.
- Give bolus of 100-150 mg/kg in 30 minutes and then 50 - 100 mg/kg every 6 hours intravenously.
- When oral fluids are tolerated, carnitine may be administered PO at a dose of 300 - 400 mg/kg/day accordingly.

[2]. 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.

[3]. ANTIBIOTICS:

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

[4]. DIALYSIS:

- When a patient is comatose, dialysis is indicated to facilitate

2. TREATMENT OF PRECIPITATING FACTORS:

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

5. 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 Scale).
- 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.

- 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).

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Emergency Treatment Protocol - New England Consortium on Metabolic Programs, (online]. Accessed in 01 August 2010

Dietary Emergency Protocol for Isovaleric Acidemia (IVA)

1. Discontinue regular diet/feeds
2. If the 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 the child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if the 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 ml of Rehydration Solution
6. Reassess the 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 the 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 the child to the hospital with all medicines, special dietary products, and scoops**

ACKNOWLEDGMENT

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**3-HYDROXYMETHYLGLUTARYL
-COA LYASE DEFICIENCY
(3 - HMG COA LYASE DEF.)**

3-HYDROXYMETHYLGLUTARYL-COA LYASE DEFICIENCY (HMG COA LYASE DEF):

• 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 (Nonketotic or Hypoketotic), 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-hydroxymethylglutaryl-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- like syndrome.
- Developmental delay.
- Seizures.
- Sudden death.

ASSESSMENT:

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

Clinical assessment:

- Vital signs.
- STAT glucocheck blood sugar.
- Neurologic status (including Glasgow coma scale).
- Hydration status.
- Presence of fever, signs of infection.

LABS:

- Blood
- Blood gas (arterial or venous).
- Blood glucose.
- Ammonia. (to be kept in ice and tested within 20 minutes, delay testing may result in factitious hyperammonemia).
- Electrolytes (including Na⁺, K⁺, Ch, measured CO₂, Ca⁺⁺, PO₄. Mg), calculate Anion gap.

- Urea, creatinine.
 - Liver profile (including AST, ALT, ALP, PT, PTT, Bilirubin, Albumin).
 - CBC differential.
 - Lipase, and amylase. (pancreatitis is a known presentation in HMG COA lyase def.).
- **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 IVF (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 - double maintenance to provide 7-8 mg/kg/min glucose infusion rate

2. DO NOT ADMINISTER LIPIDS IN ANY FORM.

3. HYPOGLYCEMIA

- Push 25% dextrose 2 ml/kg and follow with a continuous 10% dextrose infusion at 1.5 - double maintenance to provide 8– 10 mg/kg/min glucose infusion rate.

4. METABOLIC ACIDOSIS (Bicarbonate level <10)

- Must be treated aggressively with IV Sodium bicarbonate 1 mEq/kg bolus).
- Start infusion of Sodium bicarbonate at rate of 1.5 – 3 meq/kg/hr and tailored according to blood gas result.
- 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:

- Start as IV 100 mg/kg/dose loading over 120 minutes then maintenance of total 300 – 400 mg/kg/day in divided doses every 6 - 8 hours.

6. PRECIPITATING FACTORS:

- Should be treated aggressively to help minimize further catabolism (Infection with proper antibiotics).

7- VOMETING AND EMESIS:

- Give Ondansetron 0.15 mg/kg over 30 minutes and can be given Q 6 -8 hours if indicated.

MONITORING THE PATIENT:

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

Blood tests:

- Blood gases.
- Glucose check.
- Urea, creatinine, and 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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- ACT SHEET (2010), American College of Medical Genetics (ACMG), Medical Genetics Translating Genes Into Health, [online]. Accessed on 01 August 2011
- EMERGENCY guidelines (2009), British Inherited Metabolic Disease Group (BIMDG) (online), Accessed on 01 August 2011
- Emergency Treatment Protocol- New England Consortium on Metabolic Programs, [online], Accessed on 01 August 2010

Dietary Emergency Protocol for 3-HYDROXYMETHYLGUTARYL-COA (3-HMG COA) LYASE DEFICIENCY

1. Discontinue regular diet/feeds
2. If the 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 tomls water
3. If the child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if the child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the solution as:
 - Small boluses: Givemls 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 the 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 the 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 the child to the hospital with all medicines, special dietary products, and scoops**

N.B:

If, at any time from starting this emergency regimen, the child is deteriorating and for not tolerating the emergency solution due to nausea and vomiting, bring the 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.



UREA CYCLE DEFECTS

UCDs

UREA CYCLE DEFECTS (UCDs):

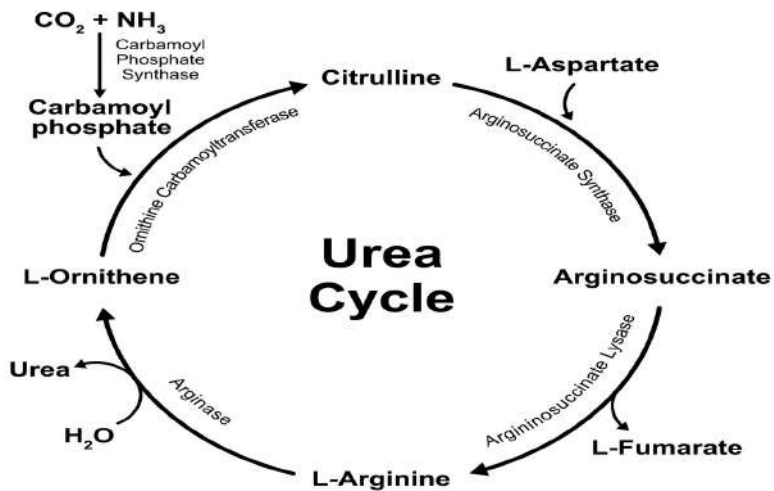
- **Please read carefully**

- 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 except Arginase deficiency.
- 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.
- 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 seven biochemical reactions within the urea cycle is associated with a known enzyme deficiency and a related clinical disorder as shown in the diagram below.
- 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.



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 hyperammonemic 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.
- 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 (Na, Cl, K, Hco₃, Mg, Po₄, and Ca).
- Blood gas (calculate the anion gap).
- Ammonia.
- Plasma amino acids (include Glutamine, Glycine, Citruline, Arginosuccinate, Arginine). And urine for orotic acid if indicated.
- LFTS (AST, ALT, Alkaline phosphatase, bilirubin, PT, PTT, and albumin).
- Plasma amino acids should be drawn first thing in the morning.
- 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. Initially keep patient NPO.
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.
- Ondansetron 0.1 mg/kg may be indicated to prevent vomiting.

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 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 up to 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.

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 100 ml/kg for 1st 10 kg then 50 ml/kg for next 10 kg then 20ml/kg thereafter, using calculated rehydrated weight.

- Deduct the fluid already given from the total for the first 24 hours.
- **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 concomitant 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.

1. PROMOTE WASTE NITROGEN EXCRETION:

- To help facilitate the excretion of waste nitrogen, the following medications are employed:
 - Sodium benzoate - conjugates with glycine to form hippuric acid which bypasses the urea cycle and is excreted in urine.
 - Sodium phenylacetate - conjugates with glutamine to form phenyl acetyl-glutamine which bypasses the urea cycle and is excreted in the urine.
 - 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.
- In an emergency the doses given should always be an increase from those used routinely.
- 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.
- In an emergency the loading dose should be given initially followed by the maintenance.
- 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 infants are often low in carnitine, it is known to conjugate with sodium benzoate.
- 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:

- First line is Arginine 200-400 mg/kg/dose loading over 90 minutes then immediately start maintenance of the same dose either continuous infusion over 24 hours or divided Q 6 hours.
- Second line Ammonul 250 mg/kg or 5.5 g/m² loading over 90 minutes then the same dose maintenance over 24 hours (can be used diluted in peripheral line with recent studies).

For Arginosuccinic acidemia:

- First line is Arginine 400 – 600 mg/kg/dose loading over 90 minutes then immediately start maintenance of the same dose either continuous infusion over 24 hours or divided Q 6 hours.

- Second line Ammonul 250 mg/kg or 5.5 g/m² loading over 90 minutes then the same dose maintenance over 24 hours (can be used diluted in peripheral line with recent studies).

For OTC, CPS deficiencies:

- First line Ammonul 250 mg/kg or 5.5 g/m² loading over 90 minutes then the same dose maintenance over 24 hours (can be used diluted in peripheral line with recent studies).
- Second line is Arginine 120 - 200 mg/kg/dose loading over 90 minutes then immediately start maintenance of the same dose either continuous infusion over 24 hours or divided Q 6 hours.

For NAGS:

- First line is Caulomic acid (Carbaglu) Synthetic NAGS with loading of 100 – 250 mg/kg po or through NGT then adjust according to ammonia level with maintenance of 100 – 200 mg/kg/day in two to four divided doses.
- Second line Ammonul 250 mg/kg or 5.5 g/m² loading over 90 minutes then the same dose maintenance over 24 hours (can be used diluted in peripheral line with recent studies).
- Always, reload with medication if ammonia level still rising.
- 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 contro- versial) 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/phenylacetateregime 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, Arginine according to the deficiency (see up) to slightly retard ammortise 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 behavior, etc) start neurological observations - at least hourly- and 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 (Always keep in ice and test within 20 minutes of drawn to avoid factitious rise).
- 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 described in “treatment” section.

- The use of oral sodium benzoate and sodium phenylbutyrate 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.
- There may be a rebound hyperammonemia initially with the efflux of intracellular ammonia into the 'relatively' ammonia depleted blood.
- It is important to continue closely monitoring ammonia levels until they remain stable in the normal range.

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.

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Dietary Emergency Protocol for Urea Cycle Disorders (UCD)

1. Discontinue regular diet/feeds
2. If the 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 the child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if the 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 the 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 the 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 the child to the hospital with all medicines, special dietary products, and scoops.**

N.B:

If, at any time from starting this emergency regimen, the child is deteriorating and for not tolerating the emergency solution due to nausea and vomiting, bring the 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.



**MEDIUM CHAIN ACYL-COA
DEHYDROGENASE DEFICIENCY
MCAD**

MEDIUM CHAIN Acyl-CoA DEHYDROGENASE

• 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.

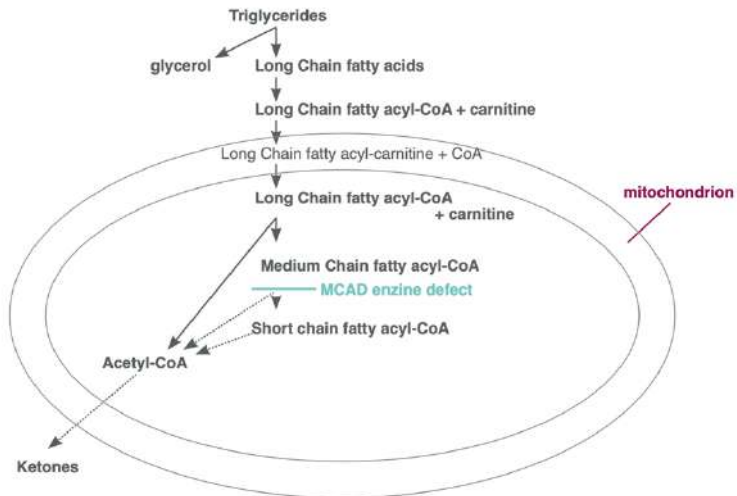
INTRODUCTION:

- Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) is the most frequent of the fatty acid oxidation disorders (FAOD) and one of the most frequently identified inborn errors of metabolism.\
- The incidence of MCADD may be as high as 1/10,000 with mortality rates of 13-43% at initial crises.
- it is caused by an intramitochondrial defect in the boxidation of fatty acids and is a major cause of hypoketotic hypoglycemia.
- MCADD is also a cause for lethargy, liver dysfunction with hepatomegaly, metabolic acidosis, hyperammonemia and sudden death.

PATHOPHYSIOLOGY:

- Below is the fatty acid b-oxidation metabolic pathway indicating the MCADD block.

Medium chain ceryl Co-A dehydrogenase deficiency (MCADD)



- 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.
- The resulting hypoglycemia leads to mobilization of free fatty acids (FFAs) from adipose tissue which enters the mitochondria via the carnitine cycle.
- In the mitochondria, as shown in the diagram above, the fatty acids in the acyl-CoA form are normally oxidized to acetyl-CoA which is used to produce the ketones that can supply the energy needs to compensate for the lack of adequate glucose.
- The block at MCAD prevents oxidation of medium chain CoA to short chain CoA, thereby markedly reducing the production of ketones.

- This block also results in the accumulation of fatty acid intermediates that inhibit gluconeogenesis (thus preventing endogenous glucose production), have a toxic effect on the liver and produce metabolic acidosis.
- 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.
- 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.

CLINICAL PRESENTATION:

- Lethargy.
- Nausea or vomiting.
- Hypoglycemia with lack or only 'trace' of urinary ketones.
- Hepatomegaly.
- Reye' like syndrome.
- Seizures.
- Coma.
- Near/rescued SIDS.
- Affected infants and children usually present between 3 and 24 months of age particularly when being weaned from nighttime feeds but neonatal cases have been described and adults have become ill after severe exertion (e.g. jogging).
- The presentation is characterized by marked lethargy, often in association with vomiting after a period of fasting.

- This block also results in the accumulation of fatty acid intermediates that inhibit gluconeogenesis (thus preventing endogenous glucose production), have a toxic effect on the liver and produce metabolic acidosis.
- 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.
- Metabolic stress such as fasting and/or febrile illness particularly gastroenteritis and flu can lead to serious illness, with encephalopathy and even sudden death.
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- The presentation is characterized by marked lethargy, often in association with vomiting after a period of fasting.

- This can progress to hypoglycemic seizures or coma within 1-2 hours of ONSET of symptoms.
- On occasion seizures or coma may be the presenting sign.
- Hepatomegaly is usually present.
- There may, or may not, be a history of a recent viral infection associated with diminished oral intake, or of a similar episode in the past.
- A history of “recurrent Reye syndrome” should alert you to the possibility of FAODs, as affected children have often been misdiagnosed as having Reye syndrome or ‘episodic hypoglycemic coma.
- FAODs are responsible for 5-10% of sudden infant death syndrome.
- Immediate attention and therapy is the key to preventing sudden death.
- NOTE that in the acute crisis’s 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.
- Parents of children with diagnosed metabolic disorders know the early signs of decompensation in THEIR children. Listen to them.

ASSESSMENT:

- Hydration status.
- Fever.
- Infection or any other physical stressor e.g., surgery, as a potential precipitant for metabolic decompensation.
- As a rule, decompensation occurs more quickly in infants but children and adults, though more resistant, are still at risk of sudden death.
- Blood glucose.

- Electrolytes.
- Blood gas.
- Ammonia (1.5 ml blood in sodium-heparin tube sent STAT to lab on ice).
- LFTs (AST, ALT, ALP, PT, PTT, bilirubin)
- ALL siblings of known cases should be tested for MCADD whether or not they have a history of symptoms.

TREATMENT:

1. INDICATION FOR IV (NEVER less than 10% dextrose IV infusion)
(One or more indication is sufficient for IV):

Vomiting,
Hypoglycemia,
Poor PO 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.

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.

3. 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 (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.

4. PRECIPITATING FACTORS

- Should be treated aggressively to help minimize further catabolism

5. CARNITINE

- The use of care 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 1.5x 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:

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

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Dietary Emergency Protocol for Medium Chain CO A Acyl Dehydrogenase Deficiency (MCADD)

1. Discontinue regular diet/feeds
2. If the 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 the child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if the 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.....
tomls of Rehydration Solution**

7. Reassess the 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 the 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.

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 the child to the hospital with all medicines, special dietary products, and scoops

N.B:

If, at any time from starting this emergency regimen, the child is deteriorating and /or not tolerating the emergency solution due to nausea and vomiting, **bring the 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



**VERY LONG CHAIN ACYL
COA DEHYDROGENASE
DEFICIENCY (VLCADD)**

VERY LONG CHAIN ACYL COA DEHYDROGENASE DEFICIENCY (VLCADD)

• 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:

- 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 B- 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.
- 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 screened 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 (Nonketotic) or only 'trace' of urinary ketones (Hypoketotic).
 - 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.

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.

Labs:

• Blood:

- Blood gas (arterial or venous).
- Blood glucose.
- CBC differential
- Ammonia.
- Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca⁺⁺, PO₄, Mg), Urea, and creatinine.
- Creatine kinase (CK).
- Liver profile (including AST, ALT, Alkaline phosphatase, PT, PTT, bilirubin).

• Urine:

- Urine dipstick for ketones.

• Cultures:

- 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 or double maintenance, to provide 8- 10 mg/kg/min glucose infusion rate (GIR).

$$\text{GIR} = \frac{(\text{Concentration, g/100 mL}) \times (\text{Infusion rate, mL/hr}) \times (1000 \text{ mg/g})}{(\text{Weight, kg}) \times (60 \text{ min/hr})}$$

- 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 (9% NaCl 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.
 - 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 Quickly calculate the deficit and maintenance and prepare the intravenous fluids. (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 1.5 - double maintenance, to provide 8 - 10 mg/kg/min glucose infusion rate.
- 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 < 10 mEq/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.
- (last studies showed that IV carnitine during acute illness may increase long chain acylcarnitine which have negative impact on heart, oral carnitine outside crises may increase free carnitine level).

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.
- 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 (Stressors):

- Should be treated aggressively to help minimize further catabolism (treat infection with antibiotics. etc.)

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 Scale).
- Vital signs.
- Fluid balance.
- Symptoms of infection.

Biochemical parameters:

- Electrolytes (including Na⁺, K⁺, Cl⁻, measured CO₂, Ca⁺, PO₄, Mg).

Ammonia. (secondary hyperammonemia due to deficiency of NAGS enzyme is the cause in VLCADD and the treatment of choice is synthetic NAGS Carglumic acid (Carbaglu) with dose of 200 mg/kg oral loading then adjust according to Ammonia level with maintenance dose 100 – 200 mg/kg/day divided 2 -4 doses).

- 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 formulould 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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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, A Delphi clinical practice protocol for the management of very long chain acyl-CoA dehydrogenase deficiency *Mol Genet Metab.* 2009 March; 96(3): 85–90. doi:10.1016/j.ymgme.2008.09.008

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- EMERGENCY guidelines (2009), British Inherited Metabolic Disease Group (BIMDG) (online], Accessed on 01 August 2011
- Emergency Treatment Protocol- New England Consortium on Metabolic Programs, (online], 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 the 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 mis water

3. If the child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if the 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..... mis of Rehydration Solution

6. Reassess the 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 the 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 the child to the hospital with all medicines, special dietary products, and scoops.**

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

N.B:

If, at any time from starting this emergency regimen, the child is deteriorating and for not tolerating the emergency solution due to nausea and vomiting, bring the 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.



CLASSICAL GALACTOSEMIA (GALT)

CLASSICAL GALACTOSEMIA (GALT)

- **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.
- Galactosemia is a preventable disease, a close follow up with an expert metabolic specialist and use of treatment can prevent the serious complications.

INTRODUCTION:

- Classic galactosemia, which can result in life-threatening complications including feeding problems, failure to thrive, hepatocellular damage, bleeding, and E. coli sepsis in untreated infants
- If a lactose-restricted diet is provided during the first ten days of life, the neonatal signs usually quickly resolve and the complications of liver failure, sepsis, and neonatal death are prevented.

Diagnosis:

The diagnosis of classic galactosemia is established by:

1. Reduced erythrocyte galactose-1-phosphate uridylyltransferase (GALT) enzyme activity.
2. Detection of elevated erythrocyte galactose-1-phosphate concentration.
3. Biallelic pathogenic variants in GALT gene.

- In classic galactosemia, erythrocyte galactose-1-phosphate is usually higher than 10 mg/dL and erythrocyte GALT enzyme activity is absent or barely detectable.
- Classic galactosemia should be suspected in individuals with the following Newborn screening results, clinical features, family history, and supportive laboratory findings:

Newborn screening

- Positive newborn screen for galactosemia (Low GALT level).
- Newborn screening utilizes a small amount of blood obtained from a heel prick to quantify Erythrocyte GALT enzyme activity.

Clinical features

• **Untreated infant:**

- Feeding problems
- Failure to thrive
- Liver failure
- Bleeding
- E. coli sepsis

• **Untreated older person:**

- Developmental delay
- Speech problems
- Abnormalities of motor function, including extrapyramidal findings with ataxia
- Cataracts
- Liver failure/cirrhosis
- Premature ovarian failure in females
- **Family history** of an affected sibling. Note: Lack of a family history of galactosemia does not preclude the diagnosis.

Supportive laboratory findings:

- In **classic galactosemia**:
- Erythrocyte galactose-1-phosphate may be as high as 120 mg/dL, but usually is >10 mg/dL in the newborn period. When the individual is on a lactose-free diet, the level is ≥ 1.0 mg/dL.
- Plasma free galactose is usually >10 mg/dL but may be as high as 90-360 mg/dL (5-20 mmol/L).
- Galactose-1-phosphate uridylyltransferase (GALT) enzyme activity that is absent or barely detectable.

Management:

Evaluations Following Initial Diagnosis in the Newborn Period

To establish the extent of disease and needs in a newborn diagnosed with classic galactosemia, the following evaluations are recommended:

1. Consultation with a specialist in biochemical genetic disorders
2. Measurement of erythrocyte galactose-1-phosphate concentration and urinary galactitol as a baseline for monitoring the effect of treatment.
3. Neurologic examination and brain MRI as needed
4. Ophthalmologic examination, including slit lamp examination for cataracts
5. If applicable, evaluation for hepatocellular disease, especially in affected individuals with late-treated disease who may be at risk for cirrhosis.

Treatment of primary manifestations:

- Because 90% of the newborn's carbohydrate source is lactose and human milk contains 6%-8% lactose, cow's milk 3%-4% lactose, and most proprietary infant formulas 7% lactose, all of these milk products must be replaced immediately by a formula that is free of lactose (e.g., Isomil® or Prosobee®). Such soy formulas contain sucrose, fructose, and galactose-containing oligosaccharides that cannot be hydrolyzed in the small intestine.
- Elemental formulas that contain small amounts of galactose such as Alimentum®, Nutramigen®, and Pregestimil® made with casein hydrolysates have been employed in the past without obvious side effects. A formula (Neocate®) that contains neither free nor bound galactose has been used without any side effects.
- Dietary restrictions on all lactose-containing foods including cow's milk and other dairy products should continue throughout life; however, managing the diet becomes less important after infancy and early childhood, when milk and dairy products are no longer the primary source of energy.

- refer to Expert Metabolic for further treatment.

N.B:

1. GALT level affected by Packed RBCs transfusion, prematurity, storage, humidity, and delay testing.
2. If GALT is low start Restriction till confirmation.
3. There is no Emergency decompensation in Classic Galactosemia.
4. Late presentation is liver cirrhosis, cataract, Fanconi syndrome, and developmental delay.

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1. National Newborn Screening and Genetics Resource Center. National newborn screening status report. Available online. 2014. Accessed 8-13-19.
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Revised 9 March 2017 (ma) Comprehensive update posted.



HOMOCYSTINURIA

HOMOCYSTINURIA

• 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.

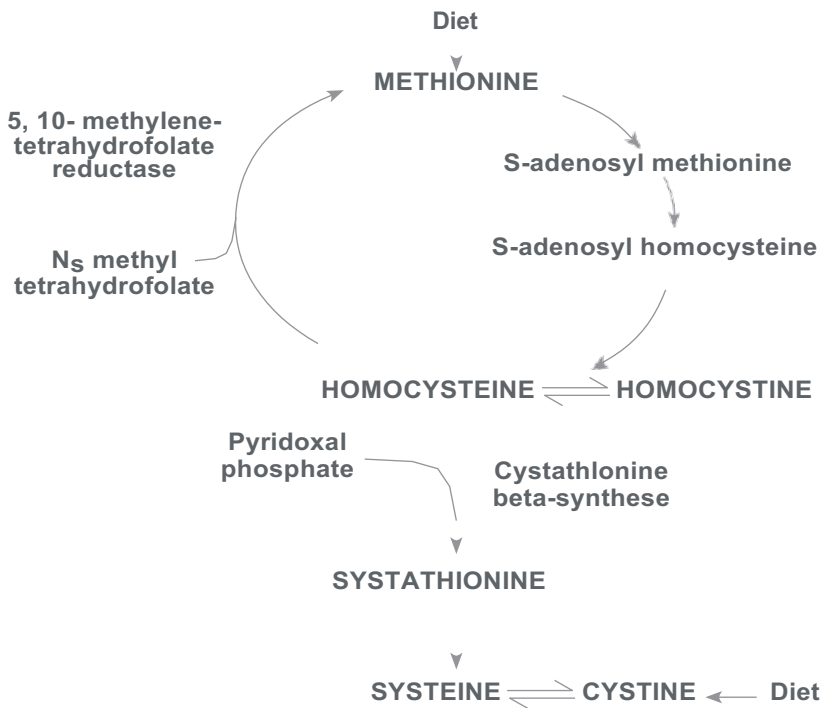
Introduction:

- Cystathionine beta-synthase (CBS) deficiency is a rare inherited disorder, also known as classical homocystinuria.
- Homocysteine (Hcy) is a non-structural amino acid (AA) that is formed in the catabolic pathway for the essential AA methionine (Met).
- CBS deficiency impairs the conversion of Hcy to cystathionine and leads to its accumulation.
- Patients with CBS deficiency show a wide spectrum of severity and age at presentation.
- Some patients have a severe childhood-onset multisystem disease, whilst others are asymptomatic into adulthood.
- The main clinical features are dislocation of the optic lenses, osteoporosis and a 'marfanoid' habitus, learning difficulties and a predisposition to thromboembolism.
- Other causes of hyperhomocysteinemia include in born errors of Hcy remethylation, vitamin deficiencies (especially B12), renal insufficiency and medication.

Pathway:

- Classic homocystinuria is caused by deficiency of cystathionine -synthase (CBS), a pyridoxine (vitamin B6)-dependent enzyme.
- Because homocysteine is at the branch point between transculturation and methionine remethylation in the methionine metabolic cycle,

a block at CBS limits transsulfuration and results in both increased homocysteine and increased methionine, the latter caused by enhanced remethylation (Figure 1)



Clinical Findings:

- There is a wide spectrum of severity, from individuals who are currently asymptomatic to those with severe multisystem disease, with a wide range of ages at presentation.
- The phenotype broadly relates to pyridoxine-responsiveness. Four main organs/systems can be involved:

1. Ectopia lentis

- dislocation of the ocular lens) and/or severe myopia.

2. Skeletal abnormalities

- Excessive height, long narrow limbs [dolichostenomelia], scoliosis, pectus excavatum) that may give the clinical impression of Marfan syndrome, but without joint hypermobility.

3. Vascular abnormalities

- characterized by thromboembolism.

4. Developmental delay/intellectual disability.

Patients with CBS deficiency vary markedly in their symptoms, age of onset and rate of progression of clinical signs.

Pyridoxine-responsive patients generally have a milder phenotype and a later onset than the pyridoxine-unresponsive one.

Diagnosis:

- The diagnosis of classic homocystinuria is established in a proband by measurement of plasma total homocysteine (tHcy) and amino acids in plasma and/or by identification of biallelic pathogenic variants in CBS through molecular genetic testing.
- Enzyme analysis of cystathionine -synthase (CBS) activity may be performed if pathogenic variants are not identified

1. Plasma Homocysteine and Amino Acids

- Plasma total homocysteine(tHcy)should be the frontline test for diagnosis of CBS deficiency.
- Plasma free homocysteine(fHcy)only becomes detectable at tHcy concentrations above approximately 50-60µmol/L, in untreated patients with CBS deficiency,

- tHcy concentrations are usually above 100 μ mol/L. when accompanied by high or borderline high methionine, makes the diagnosis very likely.

2. Newborn screening:

- Newborn screening for CBS deficiency can be performed by detecting elevated Methionine (Met), Methionine -to-phenylalanine ratio and/or hyperhomocysteinemia in DBS although Total homocysteine(tHcy) has only exceptionally been used as a primary marker.
- Sensitivity of Methionine as a primary marker for pyridoxine non-responsive CBS deficiency is limited and inversely related to the chosen cut-off concentrations of Methionine.
- For the pyridoxine-responsive form of the disease, sensitivity is largely unknown and probably very low.
- Specificity of Met as a primary marker may be substantially increased by analysing tHcy as a second-tier marker and calculating the Met/tHcy ratio

Treatment:

The aim of treatment:

- Early diagnosed patients to prevent all the complications of CBS deficiency, to lower the plasma total homocysteine concentration to a safe level whilst maintaining normal nutrition, including normal concentrations of methionine and other essential AA.
- To establish the extent of disease and needs in all individuals diagnosed with homocystinuria caused by cystathionine -synthase deficiency,

The Following are recommended:

1-Consultation with a clinical geneticist/medical biochemical geneticist for additional testing and treatment plan.

2-Pyridoxine (vitamin B6) challenge prior to initiation of treatment.

Pyridoxine-responsive homocystinuria (Pyridoxine (B6) challenge test)

- To assess pyridoxine responsiveness after infancy, recommended to giving 10 mg/kg/day pyridoxine up to a maximum of 500 mg/day for 6 weeks.
- The plasma tHcy concentration should be measured at least twice before treatment and twice on treatment.
- The test should not be done if the patient is catabolic.
- The protein intake should be normal, folate supplements should be given and vitamin B12 deficiency should be corrected prior to testing.
- Patients who achieve plasma tHcy levels below 50 μmol/l on pyridoxine are clearly responsive and do not need any other treatment.
- If the tHcy falls >20% but remains above 50 μmol/l Additional treatment should be reconsidered (i.e., diet and/or betaine).
- If tHcy falls by <20% on pyridoxine, the patient is likely to be unresponsive.

Adverse effects of pyridoxine:

- Peripheral neuropathy is the most important adverse effect of pyridoxine. It has been reported in a number of patients treated with long-term high doses of pyridoxine >900 mg/day

Dietary management:

- Dietary treatment should be considered for all patient's with homocystinuria unless target Hcy levels are achieved entirely by pyridoxine supplementation.
- Diet may be used either as a sole treatment or adjunctive therapy along with pyridoxine and/or betaine.
- Most pyridoxine-unresponsive patient's require a diet that is very low in natural protein, with supplements of a Met-free L-AA mixture.
- Lifelong treatment is required.

- Dietary treatment reduces methionine intake by restricting natural protein intake. However, to prevent protein malnutrition, a methionine-free amino acid formula supplying the other amino acids (as well as cysteine, which may be an essential amino acid in CBS deficiency) is provided.

Folate and vitamin B12 supplementation:

- All patients should receive adequate folate supplementation. Vitamin B12 should be monitored and supplemented if deficient.
- Folate and vitamin B12 optimize the conversion of homocysteine to methionine-by-methionine synthase, thus helping to decrease the plasma homocysteine concentration.
- When the red blood cell folate concentration and serum B12 concentration are reduced.

Dose:

- Folic acid is given orally at 5 mg per day.
- Vitamin B12 is given as hydroxycobalamin at 1 mg IM per month

Betaine treatment:

- Betaine should be considered as adjunctive treatment in patients who cannot achieve target levels of Hcy by other means.
- Treatment with betaine provides an alternate remethylation pathway to convert excess homocysteine to methionine and may help to prevent complications, particularly thrombosis.

Dose:

- Children: initial betaine dose is 50 mg/kg twice daily.
- Adults: the starting dose is 3 grams twice a day.
- The dose and frequency are adjusted according to biochemical response.
- There is unlikely to be any benefit in exceeding a dose of 150-200 mg/kg/day.

- Betaine may be added to the treatment regimen in individuals poorly compliant with dietary treatment or may become the major treatment modality in those intolerant of the diet.
- Individuals who are pyridoxine non-responsive who were unable to attain metabolic control with diet substantially reduced their plasma homocysteine concentrations when betaine was supplemented

Side effects of betaine:

- Betaine is well tolerated and safe.
- Higher doses have been associated with a fishy odor. Cerebral edema is a very rare side effect.

Monitoring:

- Monitoring of plasma tHcy, AA, folate and vitamin B12 is recommended in all patients.
- The frequency depends on the severity of homocystinuria, treatment, age and clinical condition of the patient.
- These factors also determine the need for additional monitoring; for example, patients on dietary treatment require regular nutritional assessment.
- In adult patients who are fully pyridoxine-responsive it may be adequate to monitor tHcy levels every six months. In contrast
- In children on dietary treatment for pyridoxine-unresponsive CBS deficiency, tHcy and Met will need to be monitored much more frequently.
- The serum vitamin B12 and folate levels should be measured annually; if the vitamin B12 is low, an intramuscular supplement is generally given, and levels repeated every 3-6 months thereafter.

Test	Frequency
Height& Weight	Every clinic visit
Dietary intake analysis	Every clinic visit if on dietary treatment
Hcy, Met	Three to six months
vitamin B12, folate	At least annually
Blood count, albumin, plasma AA, ferritin, zinc, 25-hydroxyvitamin D	At least annually if on dietary treatment
Eye examination	At least annually
Bone density. DEXA	Every 3-5 years from adolescence unless clinically indicated earlier
Lipid profile, cardiovascular risk factor review	Once in childhood, annually in adulthood

TYROSINEMIA

TYROSINEMIA

• 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:

- Tyrosinaemia type 1 (HT1) is a rare autosomal recessive genetic metabolic disorder, caused by a defect in the final enzyme of the pathway of the degradation of tyrosine, namely fumarylacetoacetase (FAH) (Figure 1).
- As a result of the metabolic block toxic metabolites are formed including succinylacetone, maleylacetoacetate and fumarylacetoacetate.
- These are responsible for severe disruption of intracellular metabolism of the liver and kidney

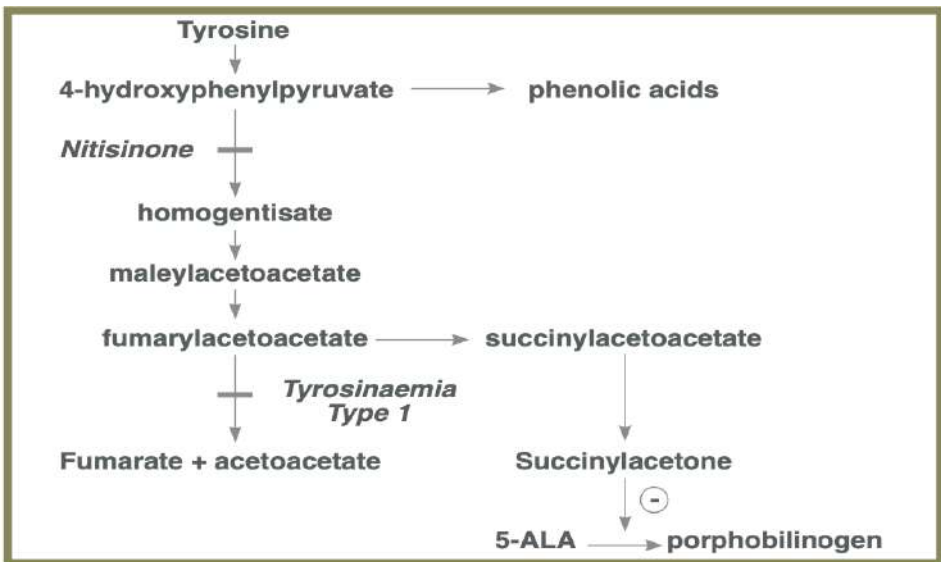


Figure 1 Tyrosine degradation pathway: HT1 is caused by a defect in the fumarylacetoacetase.

presentation:

- For children who were not detected by newborn screening, tyrosinemia type I HT1 usually presents either in young infants with:
 - severe liver involvement.
 - liver dysfunction.
 - Significant renal involvement.
 - Growth failure.
 - Rickets.
 - Chronic renal disease.
 - Death in the undetected or untreated child usually.

Clinical illness:

1. Severe acute liver failure in young infants

- Acute liver failure with onset in the first weeks or months of life is common with clotting abnormalities, ascites and edema secondary to hypoalbuminaemia. Hemorrhage is frequent but jaundice is usually mild and the plasma aminotransferases may be only slightly or moderately elevated.
- Patients go on to develop cirrhosis, liver nodules and hepatocellular carcinoma.
- On clinical examination the liver is firm or even hard.
- Hypoglycemia may be caused by liver failure and hyperinsulinism.

2. Signs of renal disease, and/or neurologic crises in children older than age six months

A. Renal disease

- The characteristic renal disease is a tubular disorder with Fanconi syndrome.
- The severity of which is variable.
- The typical features include aminoaciduria, glycosuria, phosphaturia and renal tubular acidosis.

- Patients may develop hypophosphataemic rickets, which can be severe.
- The renal disease may progress with nephrocalcinosis, glomerulosclerosis and chronic renal failure.

B. Neurological disease

- The most characteristic neurological problem is aporphyria-like syndrome usually precipitated by intercurrent infection.
- The crises, which may be severe, are characterised initially by pain (including abdominal pain mimicking an acute surgical emergency), weakness and autonomic changes such as hypertension.
- Patients may develop an acute progressive ascending motor neuropathy, often with respiratory distress requiring assisted ventilation.

Investigations:

Diagnostic tests:

- The most useful test is for succinyl acetone (SA) that may be measured in plasma, dried blood spot as used in new-born screening (DBS) or urine.
- SA may not be detected in routine organic acids analyses in urine, particularly if the concentration of SA very low or the urine very dilute so specific assays may be needed.
- Testing is urgent if tyrosinemia type 1 is suspected.
- Babies with tyrosinemia are rarely symptomatic in the first days of life.
- Newborn screening enables treatment of children who are not yet clinically ill.
- Newborn babies diagnosed by screening have markedly raised AFP levels.

Baseline tests Initial tests for HT1 should include the following:

• Blood/ plasma

- Blood gases.
- Liver function tests: bilirubin, aspartate and alanine aminotransferase (AST, ALT), alkaline phosphatase, glutamyl transpeptidase (GT) albumin.
- Coagulation: Prothrombin time, partial thromboplastin time, fibrinogen,
- Urea and electrolytes, creatinine.
- Calcium, phosphate.
- Glucose and ammonia (in acute liver failure).
- Full blood count.
- Aminoacids (quantitative).
- -fetoprotein (AFP).
- Succinylacetone SA (if available).

• **Note:** plasma SA is protein bound and is a better test with which to monitor metabolic control than urine SA, although urine SA is more widely available at present.

• Urine

- Glucose.
- Aminoacids.
- Tubular re-absorption of phosphate (TRP).
- Calcium/creatinine ratio.
- Albumin, protein, 2-microglobulin.

• **Note:** Organic acids and succinyl acetone (Note: Routine organic acid analysis may not be sufficiently sensitive)

• Interpretation: Initial tests may show evidence of liver disease, usually with a striking disorder of clotting.

- Plasma amino acids may show raised tyrosine as well as raised methionine, abnormalities that are consistent with any severe liver disease.
- AFP is usually markedly raised but it is not specific.
- Imaging:
 - All patients should have an ultrasound examination of the liver and kidneys.
 - If nodules are present in the liver further imaging, preferably by MRI, should be done.
 - Bone X-ray (for those with a definite tubulopathy): wrist or chest

Treatment:

Management guidelines have been published.

US recommendations include European recommendations include:

- **Acute management of liver failure.:**
 - Initial efforts should be directed at managing these life-threatening symptoms and may involve ventilator and pressor support.
 - Treatment of underlying infections.
 - Intravenous 10% dextrose/normal saline solutions initially infused at 1.5–2.0 times the normal IV fluid maintenance rate for age, \
 - Administration of fresh frozen plasma and vitamin k (to correct coagulopathy) should be similarly considered.
 - Treatment of metabolic acidosis caused by RTA may be required.
- **Nitisinone (NTBC) drug therapy for tyrosinemia:**
 - NTBC should be started as soon as the diagnosis of HT-1 is suspected either from NBS results or clinical presentation.
 - The recommended starting dose is 1 mg/kg/day.

- Doses as low as 0.55 mg/kg per day have been used with success.
- Dosage should be adjusted to maintain blood nitisinone levels between 40 and 60 $\mu\text{mol/L}$.

- **Side effects:**

- Transient low platelet counts.

- Transient low neutrophil count that resolved without intervention.

- Photophobia that resolved with stricter dietary control and subsequent lowering of blood tyrosine concentrations.

Diet:

- Nitisinone increases blood concentration of tyrosine, necessitating a low-tyrosine diet to prevent tyrosine crystals from forming in the cornea.
- Dietary management should be started immediately upon diagnosis and should provide a nutritionally complete diet with controlled intakes of phenylalanine and tyrosine using a vegetarian diet with low-protein foods and a medical formula such as Tyrex® (Ross) or Tyros-1® (Mead Johnson).
- Phenylalanine and tyrosine requirements are interdependent and vary from individual to individual and within the same individual depending on growth rate, adequacy of energy and protein intakes, and state of health.
- With appropriate dietary management, plasma tyrosine concentration should be 300-600 $\mu\text{mol/L}$.
- Regardless of age; plasma phenylalanine concentration should be 20-80 $\mu\text{mol/L}$ (0.3-1.3 mg/dL).
- If the blood concentration of phenylalanine is too low (<20 $\mu\text{mol/L}$), additional protein should be added to the diet from milk or foods.

liver transplantation:

- Liver transplantation should be reserved for those children who:
 - Have severe liver failure at clinical presentation and fail to respond to nitisinone therapy.
 - Have documented evidence of malignant changes in hepatic tissue.

Monitoring:

Test	Frequency
Blood Succinylacetonea (plasma/ blood on filter paper)	Every 6 months
Blood NTBC concentration	Every 6 months
Plasma amino acids (plasma/ blood on filter paper)	Every 6 months
CBC: hemoglobin, hematocrit, WBC, platelet count and coagu- lations profile	Yearly
Serum AFP concentration	Every 6 months
Imaging: CT or MRI (with con- trast) or ultrasound	Yearly

Test	Frequency
Blood chemistries: bicarbonate, BUN, creatinine. Blood calcium and phosphate	Yearly
Neuropsychology assessment	Before school age
Ophthalmology: slit lamp examination	Initially, when symptomatic or at increased risk



**BETA-KETOTHIOLASE
DEFICIENCY
(BKT DEF.)**

Beta-ketothiolase deficiency (BKT DEF.)

• 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:

- BKT deficiency is one of several defects in the degradation pathway of Isoleucine (a major branched-chain amino acid).
- Most of the defects produce metabolic ketoacidosis. Thus, this is a cause of hyperketotic 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 Isoleucine and fatty acid degradation is an attempt by the body to produce the needed energy in the form of ketones.
- When Betaketothiolase enzyme is deficient, the increased fluxes in both Isoleucine degradation and fatty acid oxidation result in an accumulation of 2-methylacetoacetyl- 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- like syndrome.
- Developmental delay.
- Seizures.
- Sudden death.

ASSESSMENT:

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

Clinical assessment:

- Vital signs.
- STAT glucocheck blood sugar.
- Neurologic status (including Glasgow coma scale).
- Hydration status.
- Presence of fever, signs of infection.

LABS:

- Blood
- Blood gas (arterial or venous).
- Blood glucose.
- Ammonia. (to be kept in ice and tested within 20 minutes, delay testing may result in factitious hyperammonemia).
- Electrolytes (including Na⁺, K⁺, Ch, measured CO₂, Ca⁺⁺, PO₄. Mg), calculate Anion gap.
- Urea, creatinine.
- Liver profile (including AST, ALT, ALP, PT, PTT, Bilirubin, Albumin).
- CBC differential.
- Lipase, and amylase. (pancreatitis is a known presentation in HMG COA lyase def.).

- **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.**

- **N.B: BKT deficiency may mimic Diabetic ketoacidosis and the measurement of Glycosylated Hemoglobin (HbA1C) may differentiate between the two disorder; consider BKT deficiency in bizarre DKA presentation.**

TREATMENT:

1. **INDICATION FOR IVF** (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 - double maintenance to provide 7-8 mg/kg/min glucose infusion rate

2. **DO NOT ADMINISTER LIPIDS IN ANY FORM.**

3. **HYPOGLYCEMIA**

- Push 25% dextrose 2 ml/kg and follow with a continuous 10% dextrose infusion at 1.5 - double maintenance to provide 8 – 10 mg/kg/min glucose infusion rate. .

4. **METABOLIC ACIDOSIS (Bicarbonate level <10)**

- Must be treated aggressively with IV Sodium bicarbonate 1 mEq/kg bolus).
- Start infusion of Sodium bicarbonate at rate of 1.5 – 3 meq/kg/hr and tailored according to blood gas result.

- 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:

- Start as IV 100 mg/kg/dose loading over 120 minutes then maintenance of total 300 – 400 mg/kg/day in divided doses every 6 - 8 hours.

6. PRECIPITATING FACTORS:

- Should be treated aggressively to help minimize further catabolism (Infection with proper antibiotics).

7- VOMETING AND EMESIS:

- Give Ondansetron 0.15 mg/kg over 30 minutes and can be given Q 6 -8 hours if indicated.

MONITORING THE PATIENT:

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

Blood tests:

- Blood gases.
- Glucose check.
- Urea, creatinine, and 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

REFERENCES

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

Dietary Emergency Protocol for Beta-Ketothiolase deficiency

1. Discontinue regular diet/feeds
2. If the 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 the child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if the child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the solution as:
 - Small boluses: Givemls 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 the 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 the 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 the child to the hospital with all medicines, special dietary products, and scoops**

N.B:

If, at any time from starting this emergency regimen, the child is deteriorating and for not tolerating the emergency solution due to nausea and vomiting, bring the 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.



BIOTINIDASE DEFICIENCY (BTD)

BIOTINIDASE DEFICIENCY (BTD)

- **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.
- Biotinides deficiency is a preventable disease, a close follow up with an expert metabolic specialist and use of treatment can prevent the serious complications.

INTRODUCTION:

- Biotinides deficiency is a biotin-responsive, inherited neurocutaneous disorder.
 - Biotin, a water-soluble B-complex vitamin, is the coenzyme for four carboxylases in humans that are essential for glucogenesis, fatty acid synthesis, and the catabolism of several branch-chain amino acids.
 - Two subtypes of the disease:
 1. Profound biotinides deficiency: <10% mean normal serum biotinides activity
 2. Partial biotinides deficiency: 10%-30% of mean normal serum biotinides activity.
- Profound biotinides deficiency:

Children or adults with untreated profound biotinides deficiency

usually exhibit one or more of the following nonspecific features (which are also observed in many other inherited metabolic disorders):

- Seizures
- Hypotonia
- Respiratory problems including hyperventilation, laryngeal stridor, and apnea
- Developmental delay
- Hearing loss
- Vision problems, such as optic atrophy

Features more specific to profound biotinidase deficiency include the following:

- Eczematous skin rash
- Alopecia
- Conjunctivitis
- Candidiasis
- Ataxia

Children or adults with untreated partial biotinides deficiency may exhibit any of the above signs and symptoms, but the manifestations are mild and occur only when the person is stressed, such as with a prolonged infection.

Laboratory Findings

The following findings are suggestive of biotinides deficiency:

- Metabolic ketolactic acidosis
- Organic aciduria (usually with the metabolites commonly seen in multiple carboxylase deficiency; however, 3-hydroxyisovalerate may be the only metabolite present). Note: Urinary organic acids can be normal even in individuals with biotinides deficiency who are symptomatic.
- Hyperammonemia

TREATMENT:

Biotin 5 – 20 mg / day for life in profound deficiency; and 1 – 10 mg /day in partial deficiency.

N.B:

1. A protein-restricted diet is not necessary.
2. Prematurity is a cause of false positive result of BDT in DBS, any positive result for premature repeat.
3. Packed RBCs transfusion is not a cause of false- negative result as no BTD enzyme on erythrocytes; but Whole blood is a cause of false-negative.

4. Raw egg white contains the protein avidin, which binds biotin tightly, rendering it unavailable for absorption; avoid as possible in BTB patients.
5. No emergency decompensation in biotinides deficiency patients.

References:

1. National Research Council. Food and Nutrition Board, Institute of Medicine. National Academy Press; Washington, DC, USA: 1998. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline.
2. Camporeale G, Zempleni J. Biotin. In: Bowman BA, Russell RM, editors. Present Knowledge in Nutrition. International Life Sciences Institute; Washington, DC, USA: 2006. pp. 314–326.
3. **Biotinides Deficiency: A Booklet for Families and Professionals** by DL Thibodeau, MS, and B Wolf, MD, PhD; revised 9 June 2016 (bp) Comprehensive update posted live.



**3-METHYLCROTONYL-COA
CARBOXYLASE DEFICIENCY
(3MCC deficiency)**

3-METHYLCROTONYL-COA CARBOXYLASE DEFICIENCY (3MCC deficiency).

> 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-MCC deficiency is one of several defects in the degradation pathway of leucine (a major branched-chain amino acid).
- The clinical picture of 3-MCC deficiency is heterogeneous and often highly variable even within the same family.
- It ranges from neonatal onset with severe neurological involvement and even lethal cases to asymptomatic adults.
- Patients may develop an acute metabolic crisis usually triggered by intercurrent infections or introduction of a protein-rich diet.
- Symptoms include vomiting, opisthotonos, involuntary movements, seizures, coma and apnea typically associated with metabolic acidosis, hypoglycemia and in some cases mild hyperammonemia.
- Presentation maybe different in undiagnosed patients, with neurological abnormalities such as seizures, muscular hypotonia or developmental delay.

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- like syndrome.
- Developmental delay.
- Seizures.
- Sudden death.

ASSESSMENT:

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

Clinical assessment:

- Vital signs.
- STAT glucocheck blood sugar.
- Neurologic status (including Glasgow coma scale).
- Hydration status.
- Presence of fever, signs of infection.

LABS:

- > Blood
- Blood gas (arterial or venous).
- Blood glucose.
- Ammonia. (to be kept in ice and tested within 20 minutes, delay testing may result in factitious hyperammonemia).
- Electrolytes (including Na⁺, K⁺, Ch, measured CO₂, Ca⁺⁺, PO₄. Mg), calculate Anion gap.
- Urea, creatinine.
- Liver profile (including AST, ALT, ALP, PT, PTT, Bilirubin, Albumin).
- CBC differential.
- Lipase, and amylase. (pancreatitis is a known presentation in 3 – MCC def.).

➤ **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 IVF (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 - double maintenance to provide 7-8 mg/kg/min glucose infusion rate.

2. HYPOGLYCEMIA

- Push 25% dextrose 2 ml/kg and follow with a continuous 10% dextrose infusion at 1.5 - double maintenance to provide 8 – 10 mg/kg/min glucose infusion rate.

3. METABOLIC ACIDOSIS) Bicarbonate level <10(

- Must be treated aggressively with IV Sodium bicarbonate 1 mEq/kg bolus).
- Start infusion of Sodium bicarbonate at rate of 1.5 – 3 meq/kg/hr and tailored according to blood gas result.
- 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. CARNITINE:

- Start as IV 100 mg/kg/dose loading over 120 minutes then maintenance of total 300 – 400 mg/kg/day in divided doses every 6 - 8 hours.

5. PRECIPITATING FACTORS:

➤ Should be treated aggressively to help minimize further catabolism (Infection with proper antibiotics).

6- VOMETING AND EMESIS:

➤ Give Ondansetron 0.15 mg/kg over 30 minutes and can be given Q 6 -8 hours if indicated.

MONITORING THE PATIENT:

➤ Reassess after 4-6 hours or earlier if there is any deterioration or no improvement.

➤ **Clinical assessment** should include Glasgow coma scale and blood pressure.

Blood tests:

- Blood gases.
- Glucose check.
- Urea, creatinine, and 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.

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- Emergency Treatment Protocol- New England Consortium on Metabolic Programs, [online], Accessed on 01 August 2010

Dietary Emergency Protocol for 3-Methylcrotonyl Coenzyme A deficiency

1. Discontinue regular diet/feeds
2. If the 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 the child has an enteral tube feeding (NGT/GT), use this tube for emergency solution administration for better tolerance, especially if the child is nauseated and/or vomiting
4. When using the available tube feeding, it is preferable to give the solution as:
 - Small boluses: Givemls 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 the 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 the 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 the child to the hospital with all medicines, special dietary products, and scoops**

N.B:

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

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Primary Carnitine Deficiency

Primary Carnitine Deficiency

➤ **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:

- Systemic primary carnitine deficiency is a disorder of the carnitine cycle that results in defective fatty acid oxidation.
- It encompasses a broad clinical spectrum including the following:
 - Metabolic decompensation in infancy typically presenting between age three months and two years with episodes of hypoketotic hypoglycemia, poor feeding, irritability, lethargy, hepatomegaly, elevated liver transaminases, and hyperammonemia triggered by fasting or common illnesses such as upper respiratory tract infection or gastroenteritis.
 - Childhood myopathy involving heart and skeletal muscle with onset between age two and four years.
 - Pregnancy-related decreased stamina or exacerbation of cardiac arrhythmia.
 - Fatigability in adulthood.
 - Absence of symptoms.

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.
- Cardiomyopathy.
- Arrythemia.
- Developmental delay.
- Seizures.
- Sudden death.

ASSESSMENT:

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

Clinical assessment:

- Vital signs.
- STAT glucocheck blood sugar.
- Neurologic status (including Glasgow coma scale).
- Hydration status.
- Presence of fever, signs of infection.

LABS:

> Blood

- Blood gas (arterial or venous).
- Blood glucose.
- Ammonia. (to be kept in ice and tested within 20 minutes, delay testing may result in factitious hyperammonemia).
- Electrolytes (including Na⁺, K⁺, Ch, measured CO₂, Ca⁺⁺, PO₄. Mg), calculate Anion gap.
- Urea, creatinine.
- Liver profile (including AST, ALT, ALP, PT, PTT, Bilirubin, Albumin).
- CBC differential.
- CK level.

> **Urine:**

➤ **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 IVF (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 - double maintenance to provide 7-8 mg/kg/min glucose infusion rate.

2. HYPOGLYCEMIA

➤ Push 25% dextrose 2 ml/kg and follow with a continuous 10% dextrose infusion at 1.5 - double maintenance to provide 8 – 10 mg/kg/min glucose infusion rate.

3. METABOLIC ACIDOSIS) Bicarbonate level <10

- Must be treated aggressively with IV Sodium bicarbonate 1 mEq/kg bolus).
- Start infusion of Sodium bicarbonate at rate of 1.5 – 3 meq/kg/hr and tailored according to blood gas result.
- 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. CARNITINE:

➤ Start as IV 100 mg/kg/dose loading over 120 minutes then maintenance of total 300 – 400 mg/kg/day in divided doses every 6 - 8 hours.

5. PRECIPITATING FACTORS:

➤ Should be treated aggressively to help minimize further catabolism (Infection with proper antibiotics).

6- VOMETING AND EMESIS:

- Give Ondansetron 0.15 mg/kg over 30 minutes and can be given Q 6-8 hours if indicated.

MONITORING THE PATIENT:

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

Blood tests:

- Blood gases.
- Glucose check.
- Urea, creatinine, and 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.

MANAGEMENT PEARLS:

1. Treatment of manifestations:

- Metabolic decompensation and skeletal and cardiac muscle function improve with 100-400 mg/kg/day oral levocarnitine (L-carnitine) if it is started before irreversible organ damage occurs.
- Hypoglycemic episodes are treated with intravenous dextrose infusion.
- Cardiomyopathy requires management by specialists in cardiology.

2. Prevention of primary manifestations:

- Maintain appropriate plasma carnitine concentrations with oral L-carnitine supplementation.
- Prevent hypoglycemia with frequent feeding and avoiding fasting.
- Hospitalization for intravenous glucose administration for individuals who are required to fast for a procedure or who cannot tolerate oral intake due to illness such as gastroenteritis.

3. Prevention of secondary complications:

- Oral metronidazole and/or decreasing the carnitine dose usually results in the resolution of the fishy odor due to Lcarnitine supplementation.

4. Surveillance:

- Echocardiogram and electrocardiogram: annually during childhood and less frequently in adulthood.
- monitor plasma carnitine concentration frequently until levels reach the normal range, then, measure three times a year during infancy and early childhood, twice a year in older children, and annually in adults.
- Evaluate serum creatine kinase concentration and liver transaminases during acute illnesses.

5. Agents/circumstances to avoid:

- Fasting longer than age-appropriate periods.

ACKNOWLEDGMENT:

These recommendations have been compiled by Medical geneticist at King Fahad Central hospital KFCH based on the November, 2016 updated GENERVIEWS of the American College of Medical Genetics (ACMG).

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