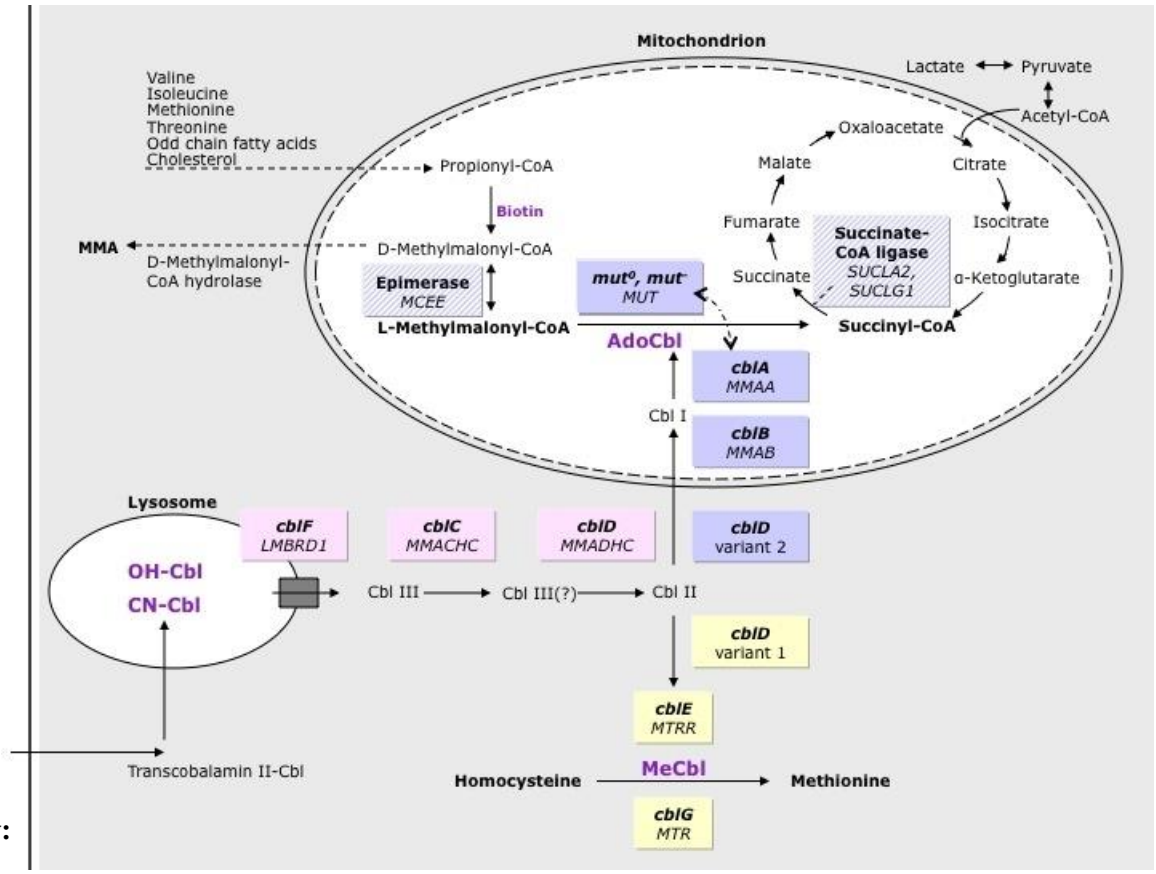
LONG TERM MANAGEMENT METHYLMALONIC ACIDEMIA (MMA)

OMIM# 251000

Definition:

- Autosomal recessive disorder, one of the most common organic acidemia.
- Isolated methylmalonic acidemia/aciduria is caused by complete or partial deficiency of;
    - The enzyme methylmalonyl-CoA mutase (mut^0 enzymatic subtype or mut^- enzymatic subtype, respectively).
    - Defect in the transport or synthesis of its cofactor, adenosyl-cobalamin (cblA, cblB, or cblD variant 2 type)
    - Deficiency of the enzyme methylmalonyl-CoA epimerase.(1, 2)
- All our diagnosed patients caused by methylmalonyl-CoA mutase deficiency, therefore, this protocol focused on this disorder only.

Pathway:



Clinical Presentation:

- **Neonatal onset:** the disease can present with lethargy, vomiting, hypotonia, hypothermia, respiratory distress, severe ketoacidosis, hyperammonemia, neutropenia, and thrombocytopenia and can result in death.
- **Infantile/non-B_{12}-responsive phenotype:** the most common form, infants are normal at birth, but develop lethargy, vomiting, dehydration, hepatomegaly, hypotonia, and encephalopathy.
- **Intermediate B_{12}-responsive phenotype:** can occasionally present in neonates, but usually presents in the first months or years of life; affected children exhibit anorexia, failure to thrive, hypotonia, and developmental delay, and sometimes have protein aversion and/or vomiting and lethargy after protein intake.
- **Atypical and "benign"/adult methylmalonic academia:** are associated with increased, albeit mild, urinary excretion of methylmalonate; however,it is uncertain if some of these individuals will develop symptoms.(1, 2)

Diagnosis:

- By clinical presentation and lab finding: hyperammonemia, hyperlactacidemia, Metabolic acidosis, ketosis, hypoglycemia neutropenia+/- thrombocytopenia.
- Acylcarnitine profile (MS/MS): Increase propionyl carnitine in acylcarnitine profile measured by MS/MS (increase C3, C3/C2 ratio).
- Plasma aminoacids: increase glycine.
- Serum methylmalonic acid increase (200-2500).
- Urine organic acids: increase methylmalonate (20-1000), 3-hydroxypropionate and methylcitrate.
- Differentiate between subtypes by enzyme assay in fibroblast and confirmed by DNA molecular testing.(1, 2)
- Vitamin B12 loading test to determine vitamin B12 responsiveness should be tried in all patients.

Genetics:

- Autosomal recessive disorder.
- Parents of affected child are obligate carriers. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- MUT, MMAA, MMAB, MCEE, and MMADHC, the genes known to be associated with isolated methylmalonic acidemia, is available on a clinical basis.(1, 2)

Treatment:

1. **Acute episode treatment guidelines (Emergency):**

- ABC (or now CAB).
- Stop all source of protein central and parenteral nutrition.
- Check GlucoChecks.
- Insert an IV line and take blood for blood gases, chem 1, Ammonia (NH3), & CBC, liver enzymes, lactic acid and blood C/S (peripheral and central if patient has central line) as **STAT** order.. Other labs as needed.
- Ammonia blood sample should be taken with precaution because of high false positive rate (without tourniquet, in green-top tube, put on ice to the laboratory, separated within 20 minutes of collection and analyzed immediately).
- After taking the blood give Carbaglu® 100-250mg/kg by NGT or oral then continue on 100-250mg/kg/day q6.
- High caloric intake is the main stay of therapy. Therefore, Start 1 1/2 to double maintenance I.V.F as D10 1/2NS + Kcl 30meq/l. Re-adjust according to lab results (Keep GlucoChecks 5-8mmol/L). Consider start **insulin** if hyperglycemia develop at dose **of 0.01-0.05 unit/kg/hour** and titrate up until blood glucose controlled.
- If ammonia > 100 umol/l. Start intralipid 20% at 2-3 g/kg/day to provide additional calories.
- **DO NOT DECREASE DEXTROSE RATE** or amount and **DO NOT STOP** calorie delivery in the acute stage for any reason (e.g. medications, addition required fluid bolus, or hyperglycemia) as this can precipitate hypoglycemia and catabolism which will further worsen the patient's condition.
- If Ammonia elevated >100 umol/l and Carbaglu not available:
    1. If the patient has central line give ammonul® 250mg/kg IV over 90 minute as loading dose then maintenance dose 250mg/kg/day over 24 hours.
    2. If there is no central line give the patient sodium benzoate 250mg/kg PO/NGT as loading dose then maintenance dose 250mg/kg/day over 24 hours.
- Call pharmacy to expedite the intralipid20% and medications.
- Call metabolic genetics dietitian on-call.
- If ammonia < 100umol/l start 50% natural protein and propiomex formula.
- Give polycose or prophree PO/NGT as tolerated.
- According to clinical evaluation, empirical antibiotics may be started.

- In case of refractory acidosis, give bolus of NaHCO3 and start NaHCO3 infusion as 0.5-2 meq/kg/h.(5)
- Continue on metronidazole at 10–20 mg/kg per day divided Q8.
- Increase Carnitine dose to 300-400 mg/kg/day divided Q8 hours IV, orally or NGT.
- For Nausea and vomiting give serotonin receptor-blocking agent Granisetron 10 to 40 microgram / kg, infused over 3 to 5 minutes.
- Continue on same hydroxocobalamin dose (if patient still on it)
- For constipation give glycerin suppositories, Dulcolax or Docusate by NGT.
- **Consider hemodialysis:**
    1. Hyperammonemic coma.
    2. Dilated pupils.
    3. Failure to improve or deterioration within 4 hours of initial treatment
    4. Ammonia more than 500micromol/l.
    5. Extreme acidosis or electrolytes imbalances.
- Ammonia, electrolyte and blood gases need to be followed at regular intervals during this acceleration of management stage. The frequency is dictated by the patient's condition and the speed at which results can be obtained.
- **DO NOT STOP** other oral chronic medications.
- Proteins should be reintroduce within 24 hours-36 hours of initiation of therapy even if the patients on dialysis.

1. Transition to long term management (Wards protocol):

- Continue on above measures including high caloric intake, aminoacids mixture eg. Propimex® formula with close monitoring of ammonia level, blood gas and electrolytes until normalization of their levels.
- Ensure appropriate caloric intake and medication dosages by calculating calories and medication dosages/ kg daily and document it in the chart.
- Provide remaining prescribed energy with Polycose® or Pro-Phree ®.
- Discontinue IV lipid when target calori intake can be achieved through other sources because long administration of lipid may cause fatty liver.
- Patient need daily evaluation from metabolic dietitian with gradually introduction of natural protein 50% of normal intake at home then upgrade to 100% if patient improve clinically and normalization of ammonia level, blood gas and electrolytes.
- Titrate IVF according to PO intake until discontinue. Measure electrolytes and urine analysis for ketones, blood gas and CBC once before discharge.
- Discharge the patient if the following parameters achieved:
    1. Normal clinical status as home before crises.
    2. Normal plasma level ammonia achieved.
    3. Normal eletrolytes and no ketones in the urine.
    4. For new diagnosed case: parents educated about the disease natural history, formula, medications and sick day protocol.
    5. For new diagnosed case: Emergency card provided to the parents
    6. Family are comfortable with preparation of formula and sick day protocol
    7. Calculate the dosage of medications and ensure that had appropriate dosages / kg.
- Give appointment with General Metabolic Genetics Clinic 2 week after discharge with plasma aminoacids and electrolytes, prealbumin prior to appointment.

3. Long term management (home and outpatient visits)

a. Nutritional management:

The aim of dietary management includes:

- Normal weight gain, linear growth, and head growth.
- Normal psychomotor development, as assessed by serial examinations and valid developmental screening tools (e.g., Denver Developmental Screening Test II).
- Protein is restricted in the diet to provide limited amounts of isoleucine, methionine, threonine, valine and odd chain fatty acids and the further

supplemented with aminoacids mixture to provide additional amino acids without the offending amino acids (see table 1 and 2).

- Avoidance of essential amino acid, fatty acid, and micronutrient deficiencies.

Metabolic dietitian should ensure the following:

- Home formula supplies include aminoacids mixture eg: Propimex-1® (for infant and toddler), Propimex-2® (for children; adolescents, and adults) see appendix 1.
- For infant: Breast milk or regular formula as a natural protein source. For older children: the source of natural protein from regular diet.
- Compliance of the mother with weighing skills, appropriate preparation of formula and 3-days diet records prior to clinic visit.
- Monitoring of amino acid concentrations. The frequency of amino acid monitoring varies by age, metabolic stability, compliance, and regional clinical practice. For rapidly growing infants, monitoring weekly is recommended (see monitoring section).

Table 1: Treatment Ranges for Target Amino Acids in PA:

Amino Acid	(2-4 hr postprandial)			
	Newborn	1-3 m	3m-6y	6-18y
GLY	106-254	105-222	125-318	158-302
ILE	27-80	32-87	13-81	38-95
MET	6-36	4-39	5-34	16-37
THR	65-147	64-225	40-139	74-202
VAL	78-264	96-291	85-334	156-288

Note: the optimal levels should be near the lower limit of normal ranges.
These levels based on BC Children Hospital reference ranges.

Table 2: proposed nutrient intake when prescribing nutrition support in patients with MMA:(6)

Nutrients	0-5m	5m-1y	1<4y	4<7y	7<11y	11<19y
ISL	110-60/kg	90-40/kg	485–735/day	630–960/day	715–1090/day	956–1470/day
MET	50-20/kg	40–15/kg	275–390/day	360–510/day	410–580/day	550–780/day
THR	125-50/kg	75–20/kg	415–600/day	540–780/day	610–885/day	830–1200/day
VAL	105/60/kg	80–40/kg	550–830/day	720–1080/day	815–1225/day	1105–1655/day
Protein	2.5/kg	2.5/kg	≥30/day	≥35/day	40/day	50/day
Energy	100-125% of RDA for age					

Chronic medications for life(1, 2):

Medication	Dose	Route	Comments
Carnitine	200-300mg/kg/day divided 2-3 times /day	PO	
Hydroxocobalamin	1 mg daily or every other day IM or 10 mg daily orally(7)	PO	Discontinue if not responsive phenotype
Metronidazole	10-20 mg/kg/day, one week on drug with three weeks off	PO	
Laxative agents	Daily use of laxatives at age/weight-appropriate doses	PO	

Other supportive measures:

- **Sodium benzoate:** There is no evidence that would support a role for benzoate in chronic treatment.

- **Growth hormone:** only considered if there is low level of growth hormone/IGF1 and normal nutritional parameters.
- **Gastrostomy tube insertion:** recommend consideration be given to the placement of GT tube particularly in infants and young children with PA at the time of diagnosis.
- **Placement of a port-a-cath** (totally implantable central venous access device): may be considered when unreliable peripheral venous access is significantly compromising patient care but should be balanced by the increased risk of destabilizing infection.
- **Carbaglu®:** There is no current published evidence for its use in chronic management, although ongoing studies suggest a utility for PA associated chronic hyperammonemia.
- **Antiepileptic drugs:** as needed.
- **Therapy for arrhythmia** as needed.
- **Anti-emetics** such as ondansetron may be used on individual bases. Dose:(body weight 8 to 15 kg) 2 mg, (body weight 15 to 30 kg) 4 mg, and (body weight over 30 kg) 8 mg (0.13 to 0.26 mg/kg), dissolved ORALLY on the tongue usually as a single dose.
- **Alkali therapy:** There are no published evidence for the use of alkali therapy like polycitra or sodium bicarbonate on chronic bases.

Look for complications of MMA which includes(1, 2, 8):

1. **Iatrogenic essential amino acid deficiency**:
    a. **ILE deficiency: Weight loss or no weight gain; redness of buccal mucosa; fissures at corners of mouth; tremors of extremities; decreased plasma cholesterol and ILE; increased concentrations of plasma lysine, phenylalanine (PHE), serine (SER), tyrosine (TYR), and VAL; skindesquamation, and corneal de-epithelialization.**
    b. **MET deficiency: Decreased plasma MET and cholesterol and increased plasma PHE, proline, SER, THR, and TYR concentrations.**
    c. **THR deficiency: Arrested weight gain; glossitis and redness of buccal mucosa; and decreased plasma THR and globulin concentrations.**
    d. **VAL deficiency: Poor appetite, drowsiness; excessive irritability and crying in infants; weight loss or decrease in weight gain; and decreased plasma albumin concentration.**
2. **Intellectual and developmental delay:** to maximize patients intellectual-developmental outcome patients need the following:
    a. Early initiation of physical, occupational and speech therapy services, to continue throughout childhood
    b. Optimize nutrition.
    c. Avoid acute metabolic decompensation.
    d. Treat episodes of metabolic decompensation swiftly and aggressively.
3. **Tubulointerstitial nephritis with progressive impairment of renal function:(9, 10)**
4. **Neurologic findings:** Some individuals develop a "metabolic stroke" or infarction of the basal ganglia, characteristically the globus pallidus, during acute metabolic decompensation, which can produce an incapacitating movement disorder.(11)
5. **Pancreatitis:(12)**
6. **Growth failure:(13)**
7. **Functional immune impairment:** This results in an increased susceptibility to severe infections, particularly by fungal and gram-negative organisms.
    a. CBC with differential at diagnosis annually, and as needed to follow abnormalities.
    b. If neutropenia present, institute infection control precautions isolation, gown and glove, etc.), as indicated by hospital policy.
    c. Expectant management with judicious use of colony stimulating factors only in cases where neutropenia is not resolving or there is evidence of bacterial infection with neutropenia.

8. **Optic nerve atrophy:**
    a. Annual examination by an ophthalmologist to include visual acuity as well as visual examination of the anterior chamber and dilated evaluation of the fundus.
    b. Treatment of decreased visual acuity, as indicated.

9. **Dermatologic manifestations :** resembling acrodermatitis enteropathica are frequently associated with deficiency of essential amino acids, particularly isoleucine, which is excessively restricted in the diet of persons with MMA.
10. **Osteoporosis and osteopenia and failure to thrive.**
11. **Cardiomyopathy(14)**

Monitoring:

Age	**Plasma aminoacids, ammonia, urine dipsticks for ketones, acylcarnitine profile, serum and urine methylmalonic acids**	**Clinic visit and dietitian visit**
0-3 months	**weekly**	**Monthly**
3-18months	**Every 2 weeks**	**Every 3 months**
18months-10years	**monthly**	**Every 3 months**
10-18years	**Every 3 months**	**Every 6 months**

Test/action	**Time**
CBC, albumin, prealbumin, Se, Zn, ferritine, Ca, Mg, 25-hydroxy vitamin D, Growth parameters, chem1, bone profile, liver ezymes, thiamine,lactic acid and cholesterol	Prior to each clinic visit
ECG, Echocardiogram, 24-hour Holter monitoring	At diagnosis and then Yearly
EEG	At diagnosis and then yearly
Ophthalmology exam	At diagnosis and then yearly
Referral to physical, occupational and speech therapy services	At 18 months and continue throughout child hood
Detailed developmental assessment	At diagnosis, 6 months, 1 year then yearly
MRI brain and MRS	At diagnosis and then if there is neurological deterioration
Hearing test	At diagnosis
Bone age	At 3 years and then every 2 years
X-ray of long bones	When osteoporosis suspected

Management of feeding problems:

1. General recommendations:
    - Monitor growth and intake of essential nutrients with every 200 gram change in weight.
    - Consider overnight tube feeding or limited nocturnal fasting times
2. Children with mild to moderate feeding problems
    - Use a combination of pureed foods and commercial enteral feeds to meet the nutritional prescription in addition to the medical protein and other energy modules.
    - increase the frequency of meals and reduce quantity per feed
3. Children with severe feeding problems
    - G-tube feeding consisting of an enteral product to the natural protein in addition to the medical protein and other energy modules
    - if severe vomiting: use pharmacotherapy, consider fundoplication or J-tube feeding.

Sick day management:

- At the first sign of illness start sick day formula.
- Sick-day diet to provide 120-130 kcal/kg/day for neonates or 110 to 120% of normal energy needs in older individuals.
- Minor illness like URTI can normally be managed with a sick day formula providing 50% of normal protein intake and high in calories and meeting or exceeding CHO requirements.
- Give prophree or polycose as tolerated.
- Give ibuprofen (10 mg/kg/dose q 6 h) when fever >38 C.
- Give ondansetron (0.15 mg/kg/dose q 8 h) to manage vomiting.

Management with immunizations:

Give sick day formula 50% for 24 hours

- Manage fever >38 C with ibuprofen
- Give double dose of carnitine (200 mg/kg/day)
- If not improved within 24 hours bring to ER

Management with surgical procedure:

- Ensure that the patient on his usual state of health prior to procedure
- Ensure stability of metabolic parameters including ammonia, plasma aminoacids, chem1, urine for ketones prior to procedure.
- High caloric intake with IVF D10 and lipid which provide 110 to 120% of normal energy needs starting 12-24 hours prior to procedure.
- After surgery follow the guidelines mentioned in Transition to long term management (Wards protocol).

Liver transplantation:

The overall experience reported does not clearly demonstrate
the effectiveness of this therapy to either prevent further deterioration or to improve survival and quality of life.(5)

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Appendix 1:

Table 3: Propiomex formula composition

Nutrient	Propimex-1		Propimex-2	
	(per 100 g pwd)	(per g protein equiv)	(per 100 g pwd)	(per g protein equiv)
Energy, kcal	480	32	410	13.7
Nitrogen, g	2.40	0.160	4.80	0.160
Protein equiv, g	15.00	1.000	30.00	1.000
Amino acids[5], g	16.17	1.078	32.34	1.078
Cystine, g	0.45	0.030	0.90	0.030
Histidine, g	0.42	0.028	0.84	0.028
Isoleucine, g	0.12	0.008	0.24	0.008
Leucine, g	1.38	0.092	2.76	0.092
Lysine, g	1.00	0.067	2.00	0.067
Methionine, g	trace	0	trace	0
Phenylalanine, g	0.88	0.059	1.76	0.059
Threonine, g	0.10	0.007	0.20	0.007
Tryptophan, g	0.17	0.011	0.34	0.011
Tyrosine, g	0.89	0.059	1.78	0.059
Valine, g	trace	0	trace	0
Other Nitrogen-Containing Compounds				
Carnitine, mg	900	60	1,800	60
Taurine, mg	40	2.66	50	1.67
Carbohydrate, g	53.0	3.53	35.0	1.17
Fat, g	21.7	1.45	13.0	0.43
Linoleic acid, g	2.00 [4]	0.133	2.00 [5]	0.07
α-Linolenic acid, g	0.36 [6]	0.024	0.17 [7]	0.006
Minerals				
Calcium, mg	575	38	880	29
Chloride, mg/mEq	410/11.56	27/0.77	1,160/32.72	38.7/1.09
Chromium, µg	11	0.73	27	0.90
Copper, mg	1.10	0.073	1.00	0.033
Iodine, µg	65	4.33	100	3.33
Iron, mg	9.0	0.6	13.0	0.43
Magnesium, mg	50	3.33	225	7.5
Manganese, mg	0.50	0.033	0.80	0.027
Molybdenum, µg	12	0.80	30	1.00
Phosphorus, mg	400	27	760	25
Potassium, mg/mEq	675/17.26	45/1.15	1370/35.04	45.7/1.17
Selenium, µg	20	1.33	35	1.17
Sodium, mg/mEq	190/8.26	12.7/0.55	880/38.28	29.3/1.28
Zinc, mg	8.0	0.53	13	0.43
Vitamins				
A, µg RE	420	28	660	22
D, µg	7.50	0.50	7.50	0.25
E, mg α-TE	10.10	0.67	12.10	0.40
K, µg	50	3.33	60	2.00
Ascorbic acid, mg	50	3.33	60	2.00
Biotin, µg	65	4.3	100	3.33
B_6, mg	0.75	0.05	1.30	0.043
B_{12}, µg	4.90	0.33	5.00	0.167
Choline, mg	80	5.3	100	3.33
Folate, µg	230	15	430	14.33
Inositol, mg	40	2.7	70	2.33
Niacin equiv, mg	12.8	0.85	21.7	0.72
Pantothenic acid, mg	6.90	0.46	8.00	0.267
Riboflavin, mg	0.90	0.06	1.80	0.060
Thiamin, mg	1.90	0.127	3.25	0.108

[1] Designed for infants and toddlers. [2] Designed for children, adolescents, and adults.

[3] Approximate **packed** weight of Propimex-1 and Propimex-2 in level, dry US standard household measures:

Propimex-1		Propimex-2	
1 Tbsp	=	7 g	8 g
1/4 cup	=	26 g	32 g
1/3 cup	=	35 g	41 g
1/2 cup	=	53 g	61 g
1 cup =	105 g	117 g	

[4] Analytical data at manufacture = 4.32 g/100 g powder. [5] Analytical data at manufacture = 2.66 g/100 g powder.

[6] Analytical data at manufacture = 0.40 g/100 g powder. [7] Analytical data at manufacture = 0.28 g/100 g powder.