

Nutrition Management of Organic Acidemias

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Leucine

Isoleucine

Valine

α -ketoisocaproate

α -keto- β -methylvalerate

α -ketoisovalerate

MSUD

Isovaleryl-CoA

IVA

β -methylcrotonyl-CoA

3-MCC
DEFICIENCY

β -methylglutaconyl-CoA

Methyl-glutaconic
Aciduria

HMG-CoA

Acetyl-CoA

HL
DEFICIENCY

Acetoacetate

α -methylbutyryl-CoA

tiglyl-CoA

α -methyl- β -hydroxybutyryl-CoA

MHBD
DEFICIENCY

A-methylacetoacetyl-CoA

β KT
DEFICIENCY

Acetyl-CoA

Propionyl-CoA

PA

Succinyl-CoA

Isobutyryl-Co-A

methylacrylyl-CoA

β -hydroxybutyryl-CoA

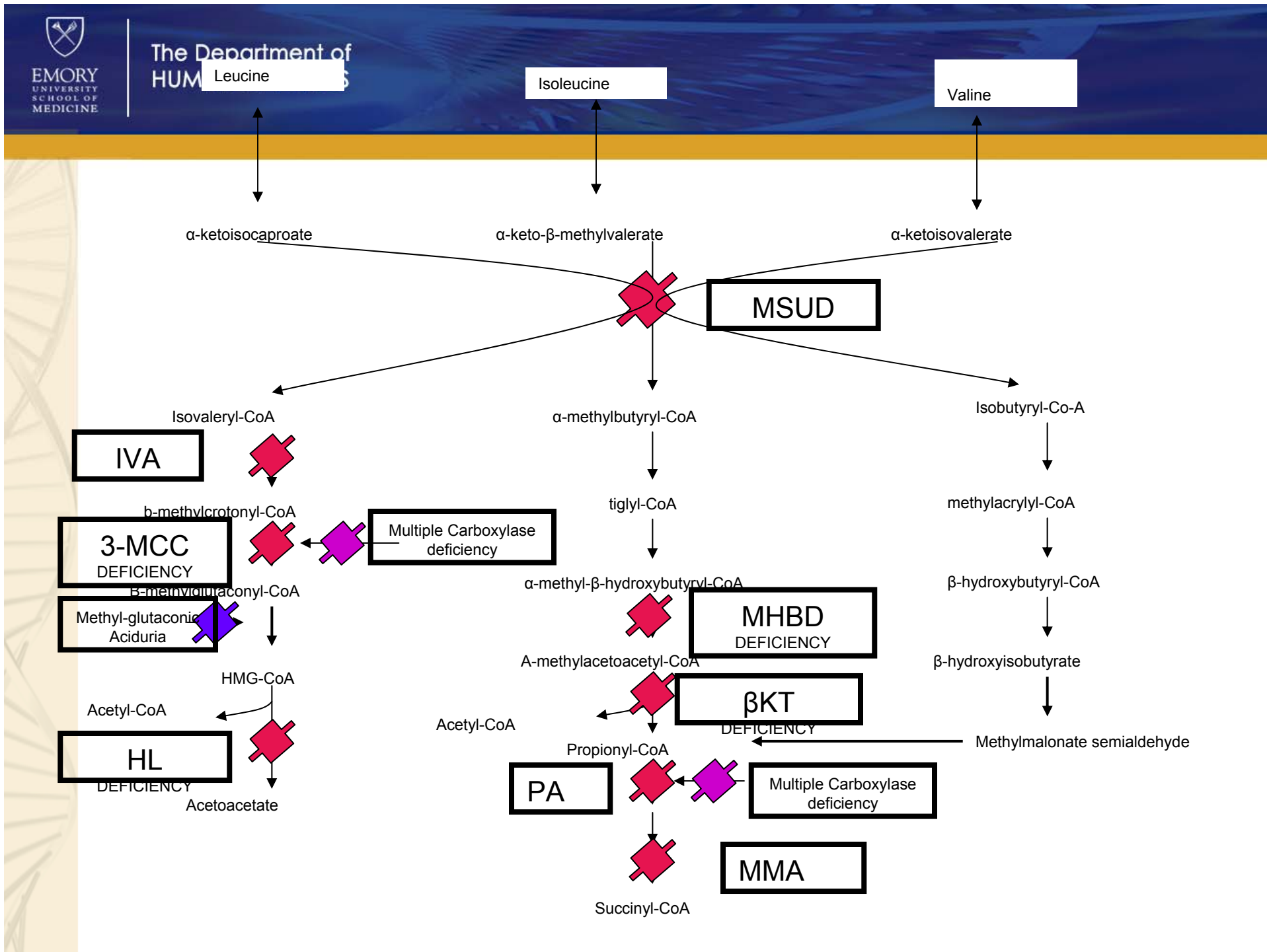
β -hydroxyisobutyrate

Methylmalonate semialdehyde

MMA

Multiple Carboxylase
deficiency

Multiple Carboxylase
deficiency





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Propionate and Methylmalonate Metabolism in Propionic and Methylmalonic Acidemias

Isoleucine


Methionine

Threonine

Valine

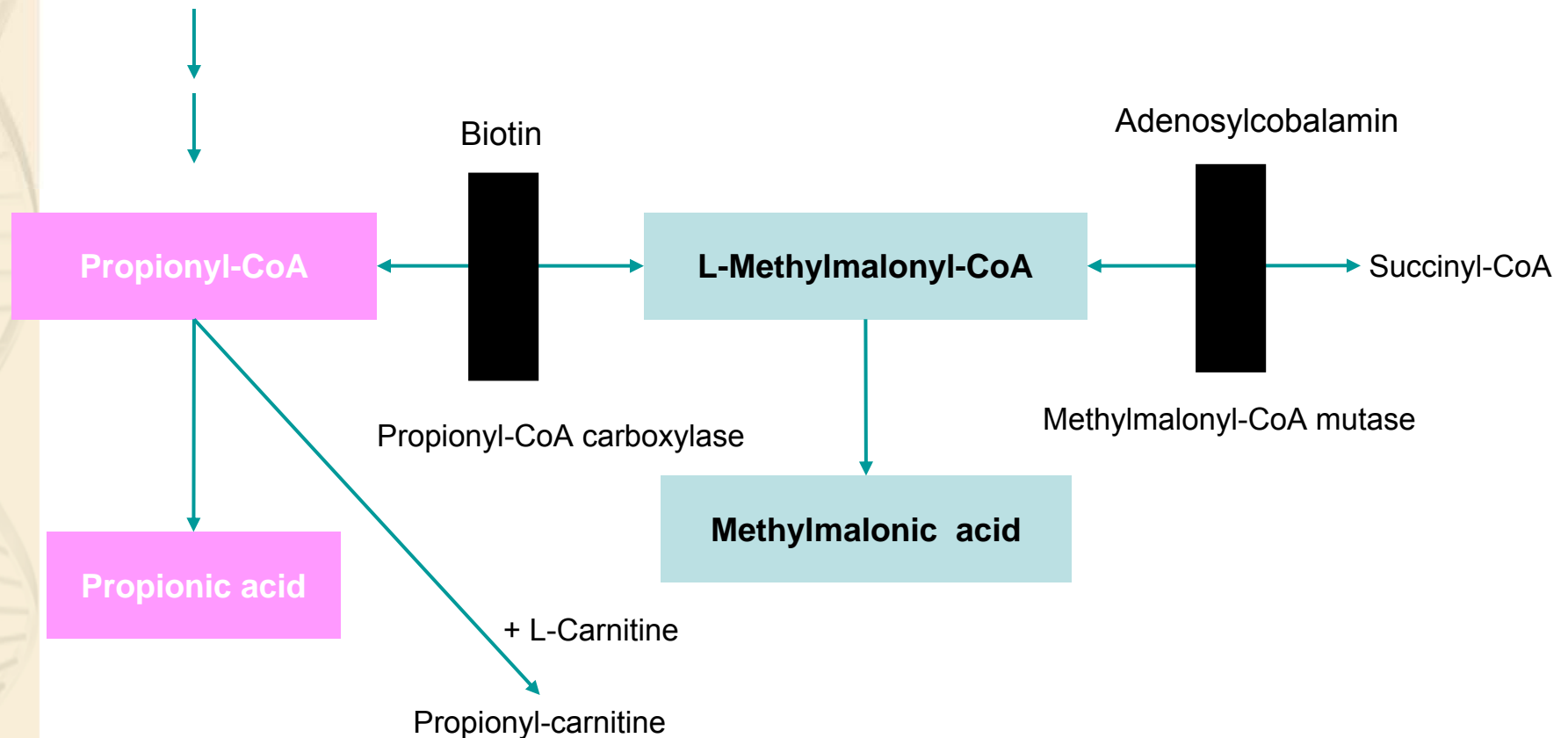
Odd-chain fatty acids (OCFA)

Excess polyunsaturated fatty acids (PUFA)

 Accumulates in untreated MMA and PPA

 Accumulates in untreated MMA

 Indicates site of enzyme defect



Goals Of Nutrition Therapy

- **To decrease the accumulation of methylcitric acid, 3-hydroxypropionic acid & other toxic metabolites in the body fluids (TOXIC Products)**
- **Maintain anabolism & provide adequate Kcals**
- **Prevent ketoacidosis & Hyperammonemia**
- **Provide adequate protein for normal growth & intellectual development**
- **Prevent carnitine deficiency**
- **Prevent Nutrient deficiencies**
- **Improve Quality of Life**

Reported Sources of Propionate in Metabolic Disorders of Propionic Acid

Sources

- Amino acid catabolism¹
- Odd chain fatty acid oxidation²
- Anaerobic bacteria (gut)³

Percent

Contribution

- 50%
- 25%
- 25%

¹ Walters JG et al. Lancet. 1989; 1:1298

² Thompson GN, Chalmers RA. Pediatr Res. 1990; 27:413

³ Thompson GN et al. Metabolism. 1990; 39:1133

Nutritional Management

- **At Diagnosis**
- **Acute phase**
- **Chronic Management**

Management

- **CHRONIC TREATMENT:**
 - **Diet**
 - **Formulas**
 - **Cofactor Therapies**
 - **Other treatment options**
- **ACUTE MANAGEMENT**
 - **Monitoring**
 - **Sick Day Formula**
 - **Emergency Room**
 - **Resuming Regular Diet**

Dietary Management

- **Minimize intake of offending Amino acids (Protein)**
- **Reduce intake of odd chain fats**
- **Provide adequate calories**
- **Ensure sufficient Fluid Intake**
- **Provide nutritional support as needed**
- **Adjust diet to account for changes in nutrient needs**

Urine Organic Acids

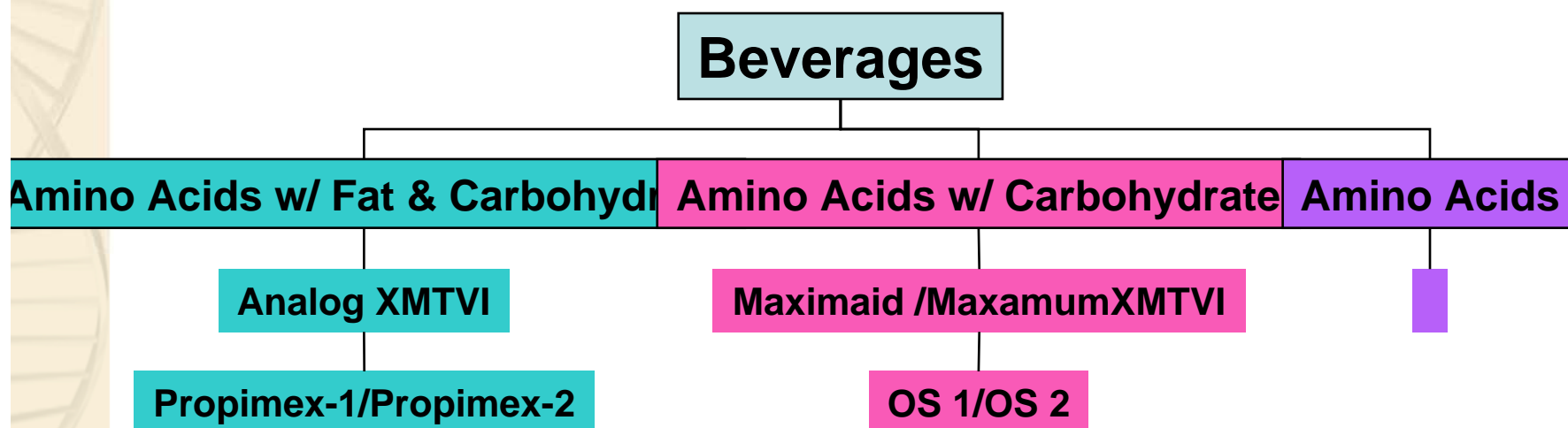
(mmol organic acid / mol creatinine)

DOB: 6-11-00

Wt: 3.2 kg

Age	Acetoacetic acid	3-OH - Butyric acid	Me - citrate /C24	3-OH - Propionate/ C24	Tigly glycine /C24	Propionyl glycine /C24
7 days	9352	1848	35	67	6	3.3
8 days	2141	152	40	72	ND	0.5
10 days	ND	46	6.6	0.9	Trace	ND
15 days	3	7	4.5	0.9	Trace	ND

MTVI Free Protein Supplements for Propionic Acidemia and Methylmalonic Acidemia



Meets nutritional needs

- Taste
- Method of administration
- GI tolerance
- State or Hospital Contract

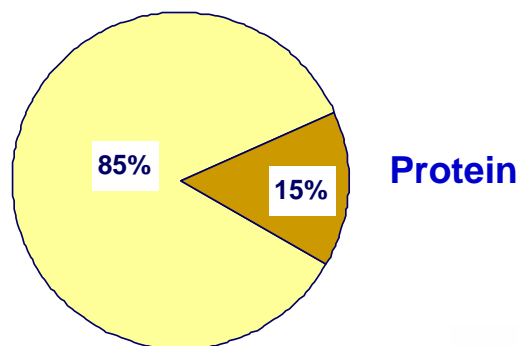
MTVI= XMET, THRE, VAL, ISOLEU

Percent of KCalories Coming from Dietary

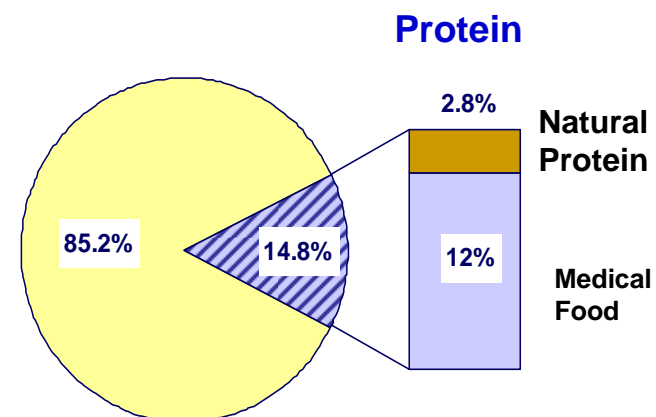
Protein

Average person with PKU (2004-2005)

Average healthy American
(NHANES, 2003-2004)



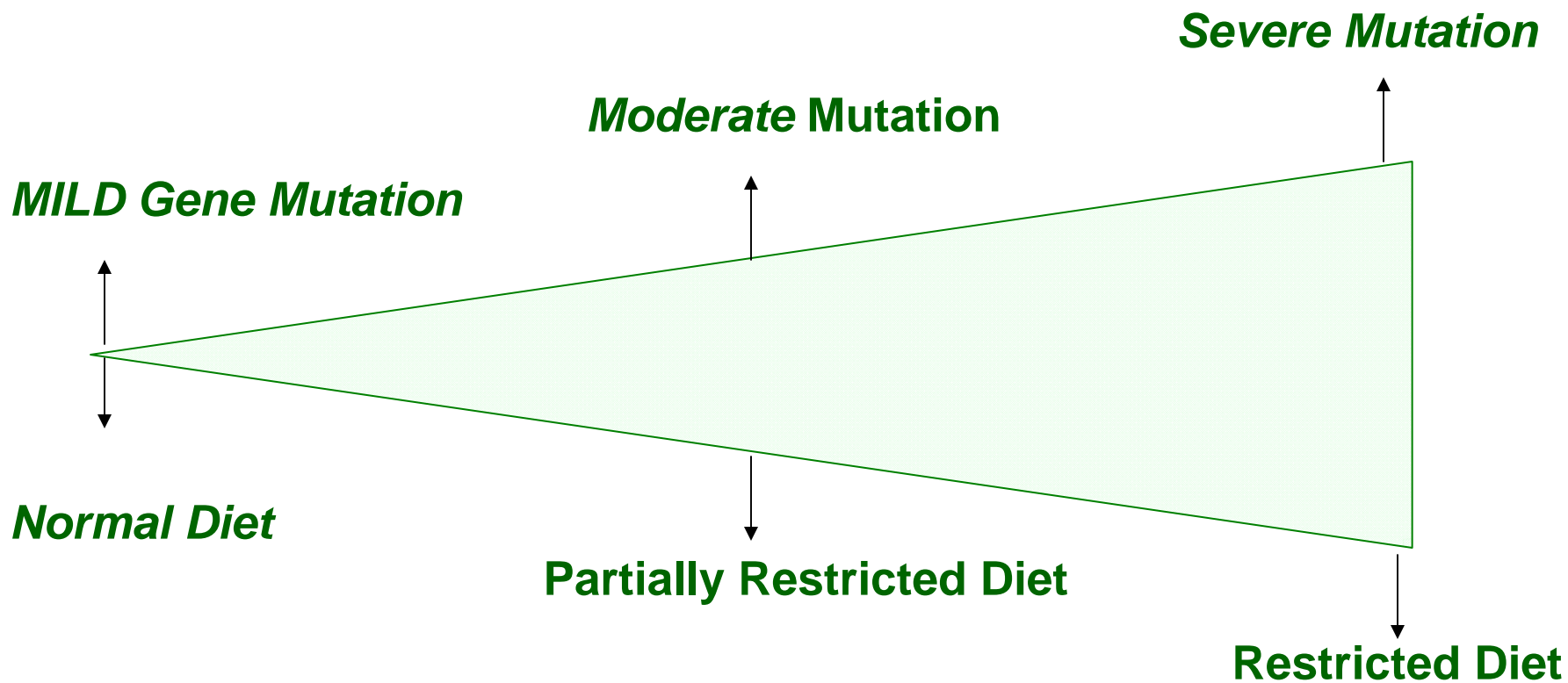
Fat 20-35%,
Carbohydrate 45-
65%, Alcohol



Fat, Carbohydrate,
Alcohol

**81% of protein in diet is from
Formula or Medical food**

Genotype/Phenotype Correlation





Oral-Motor
Difficulties

Metabolic
Decompensa
tion/ Infection

Anorexia

Failure-To-Thrive

Inadequate
Protein/Energy
Prescribed

Increased
Nutrient
Requirements

Excess
Nutrient
Loss

Pancreatitis

Adequate intake of Protein and Calories
All Essential Amino acids

all vitamins & minerals!

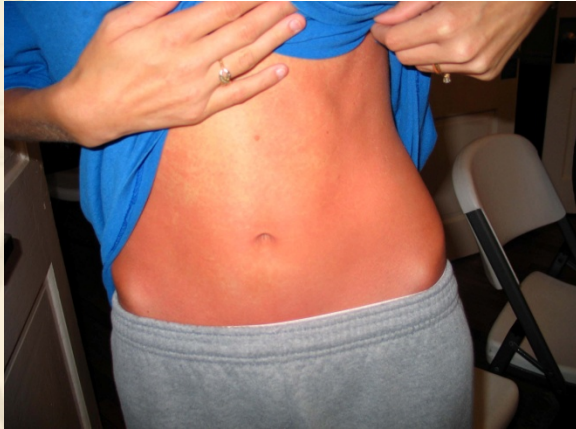
- Needs can increase due to medications &
- Medical foods
- Sufficient calcium intake to decrease risk of osteoporosis.
- Essential fatty acid intakes must be adequate



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Amino Acid Deficiencies in Patients



Isoleucine Deficiency

Protein Deficiency

Valine Deficiency

- **Poor Appetite**
- **Drowsiness**
- **Excess Irritability and Crying**
- **Weight Loss or Decreased Weight Gain**
- **Decreased Plasma Albumin**
- **Increased Plasma LEU**

Threonine Deficiency

- **Catabolism**
- **Little Weight Gain or Weight Loss**
- **Glossitis**
- **Reddening of Buccal Mucosa**
- **Decreased Plasma Globulin**
- **Decrease Plasma Threonine**

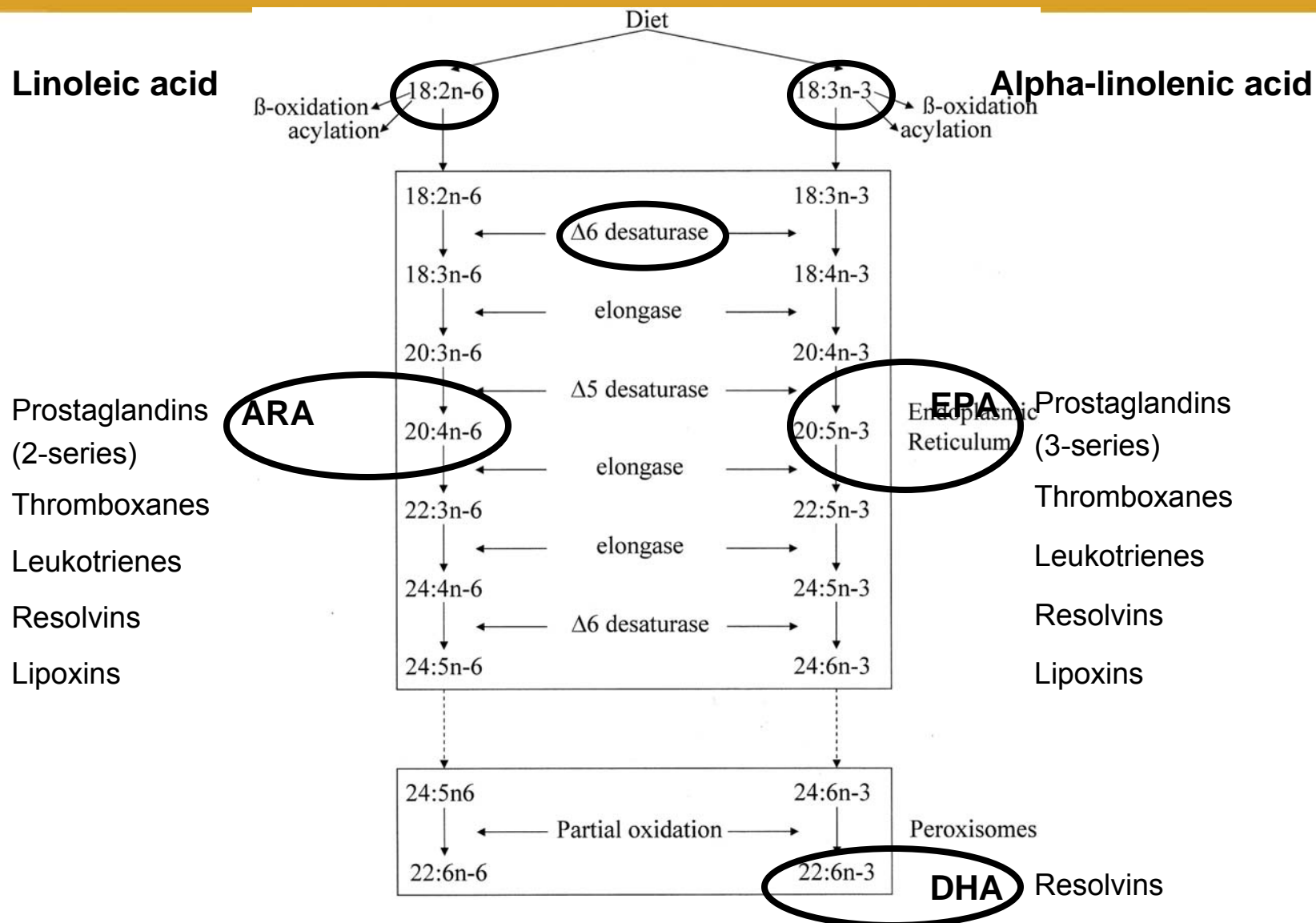
Isoleucine Deficiency

- **Weight Loss/Failure-to-Thrive**
- **Redness of Buccal Mucosa**
- **Fissures at Corners of Mouth**
- **Tremors**
- **Skin Desquamation**
- **Decreased Plasma Cholesterol**
- **Increased Plasma LEU**

Essential fatty acids: n-6s and n-3s

Linoleic acid

Alpha-linolenic acid



Schematic from: Innis SM, Dyer RA. Brain astrocyte synthesis of docosahexaenoic acid from n-3 fatty acids is limited at the elongation of docosapentaenoic acid. *J Lipid Res.* 2002 Sep;43(9):1529-36.

Chronic Treatment

Carnitine

Betaine

Bicarbonate

Hydroxy cobalamin vs. cyanocobalamin

Monitoring for Nutritional Management

- **Growth Parameters: Ht, Wt, HC.**
- **Plasma Amino acids**
- **Urine Organic acids**
- **Blood chemistries**
- **Labs for Nutritional status (Albumin, prealbumin, total protein)**
- **Diet analysis**
- **Ketonuria (Ketostix)**
- **Care coordination (Medical Home)**



Issues Related to Chronic Management

- **Reflux**
- **Feeding schedule**
 - Avoidance of recurrent catabolic periods inherent in regular feedings
- **G-Feeds (Home health company)**
 - NG feeds (Continuous feeds at night)
 - Gastrostomy
- **Constipation (Gut Motility)**
- **Blood in stools (Deficiency? Allergies?)**
- **GI distress**
- **Prevent Essential Amino acid deficiencies**



G-I

Sick Day Protocol

:

Monitor metabolic status

Switch to sick-day formula and diet

Adjust medications: carnitine, bicarb

Ensure adequate fluid intake

Adjust tube feedings

Additional meds may help: Zofran,

Kaepectate,

Imodium

Consult with your Health Care Team

Emergency Letter

Emergency Regimen

- **Frequent feeds clear liquid (PO)**
- **Antiemetic agent**
- **Use of G-feeds**
 - Frequent feeds
 - Continuous infusion
- **Psuedo-Hyperalimentation**
- **Psuedo-Hyperalimentation & Enteral feeding**
- **Total Parenteral Nutrition**
 - Peripheral Parenteral Nutrition
 - Central Hyperalimentation

Pseudo-Hyperalimentation & Enteral Feeding

If necessary

- May progress to PIC line (central) for extra dextrose kcals (maximum 35-40%) with sodium and potassium
- Continue IV intralipids 20% and NaHCO_3
- Continue IV L-carnitine @ 100 mg/kg/day
- Use antiemetic agents, if necessary
- Insulin for glucose > 180 mg/dl
- Resume enteral feeds with propimex as continuous feeds/slowrate via NG or G-tube (24 hrs)(Titrate with IV fluids)
- Gradually add natural protein back (0.5-1.0 g/kg/day)
- Vitamins are usually added to enteral feeds: biotin, thiamin, riboic acid, —?
- Gradually advance to bolus feeds & then to PO feeds.



Pregnancy and Propionic Acidemia

Reference:

Sandra C. Van Calcar, Cary O. Harding, Susan R. Davidson, Lewis A. Barness, and Jon A. Wolff

Case Reports of Successful Pregnancy in Women With Maple Syrup Urine Disease and Propionic Acidemia, *American Journal of Medical Genetics* 44:641-646 (1992)





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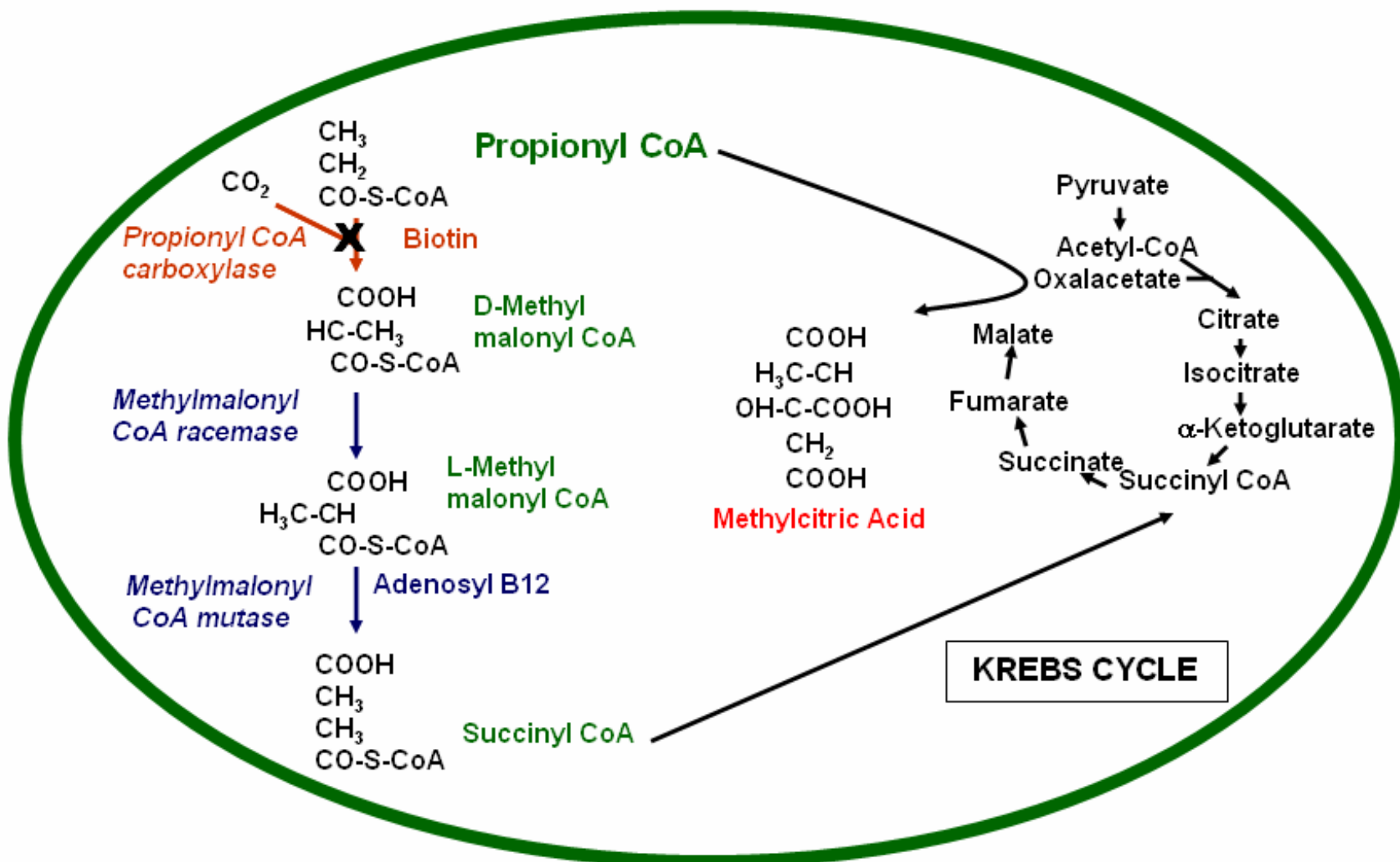


Patients
with
Organic Acidemia



Thank you

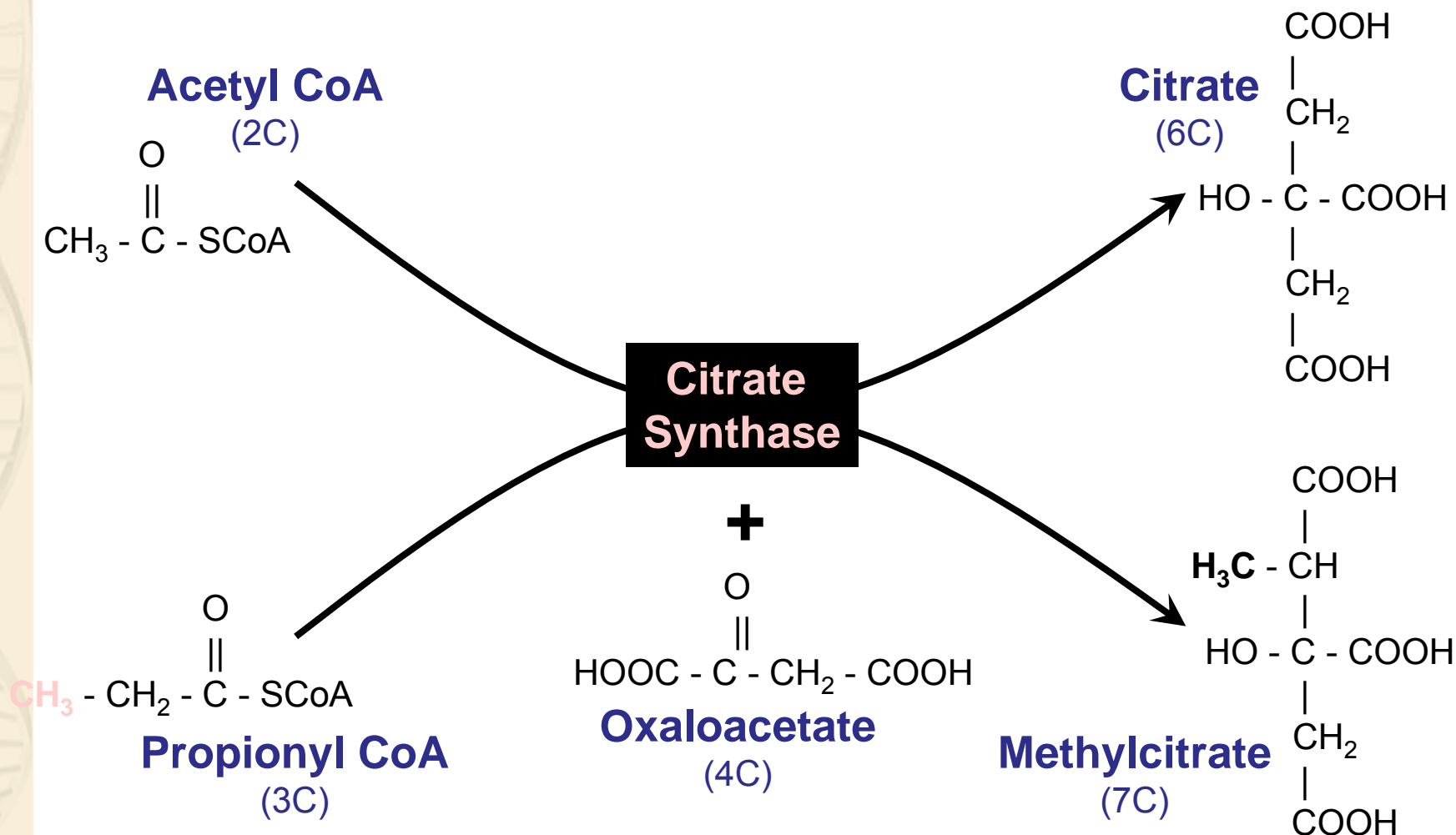
Propionyl CoA Metabolism in Propionic Acidemia



Results

- **In PPA hyperammonemia is triggered by catabolism with the accumulation of propionic acid derivatives.**
- **Decreased levels of glutamine/glutamate with hyperammonemia in pts with PPA indicate that the mechanism producing hyperammonemia is different from that in urea cycle defects.**
- **The increase in methylcitric acid and decline in of citric acid urinary excretion suggest that hyperammonemia in PPA might be related to the inability to maintain adequate levels of glutamine precursors via a dysfunctional Krebs cycle.**

Production of Methylcitrate



Clinical Features

- **Vomiting → GER**
- **Lethargy → Hypotonia → Coma**
- **Ketoacidosis → Shock**
- **Periodic Neutropenia, thrombocytopenia, anemia, hypogammaglobulinemia**
- **Hyperammonemia**
- **Hyperglycinemia (Ketotic)**
- **Organic acidemia**
 - 3-OH propionate
 - propionylglycine
 - *methylcitrate*
- **Carnitine deficiency**
- **Failure to thrive**

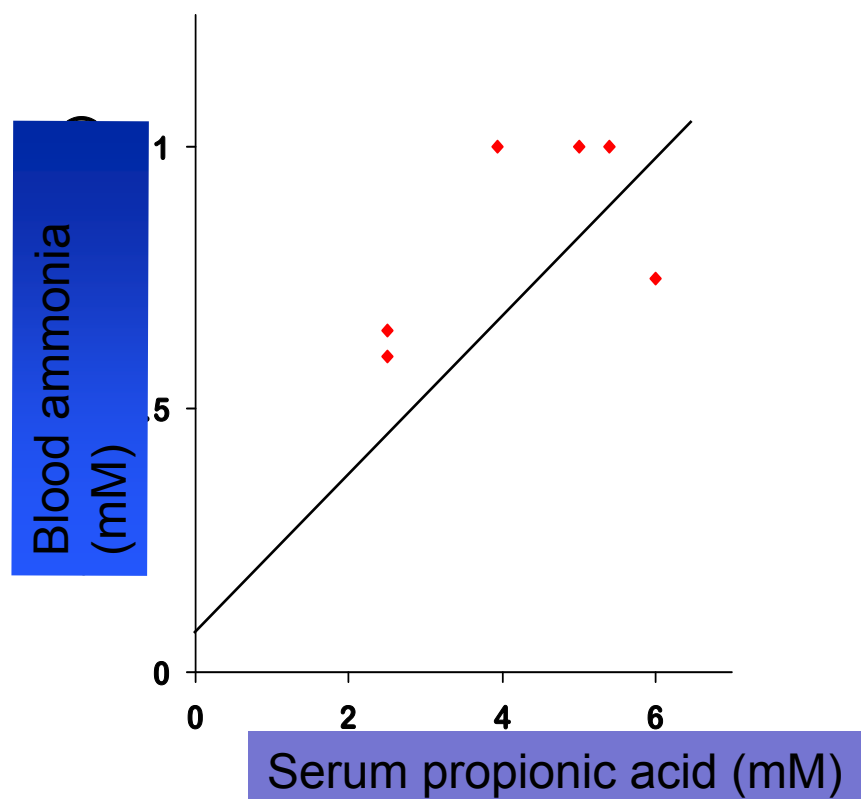
Clinical Problems Associated with Inadequate Protein

- **Malnutrition (Protein/Energy)**
- **Vitamin/Mineral Deficiencies**
- **Growth Retardation**
- **Amino Acid Deficiencies**
- **Hair Loss**
- **Osteopenia**

Carnitine Deficiency

- **Fatty Myopathy**
- **Cardiomyopathy**
- **Depressed Liver Function**
- **Neurologic Dysfunction**
- **Defective Fatty Acid Oxidation**
- **Hypoglycemia**

Relationship Between Blood Ammonia Concentrations and Serum Propionic Acid



$r = .893, n = 20, P < .001$

Pediatrics Vol. 69, No. 1 January 1982



Propionic Acidemia, Case Presentation

A 6 day white female was admitted to a local ER after she had denied her formula (similac) all day & acted sleepy. She was sent to ECC for GI problems.

She had lethargy at 6 days of age -found to have elevated ammonia ($660\mu\text{m/L}$) and acidosis. Urine was positive for Ketones. On day 7 She was diagnosed with propionic acidemia by Genetics. Diagnosis was based on urine Organic & plasma Amino Acid results. During hospitalization had hypoglycemia induced seizure secondary to newborn insulin responsiveness.

Had GI bleed, likely secondary to Isoleucine deficiency.

Carnitine Profile

	Plasma μM			Urine nmol/mg creatinine				
	Total	Free	Acyl /Free	Total	Free	Acyl	Acyl /Free	
	38±11	29±9	0.4±0.1	187-313	35-93	153-226	<4.4	
	26-58	18-48	0.2-0.5					
7 day	14	0	0	7 day	806	20	786	39.9
10 day	624	573	0.1	10 day	28265	5988	22276	3.7
15 day	206	116	0.8	15 day	5809	1637	4172	2.5

Hemoglobin & Hematocrit

	HGB (10.5-13.5) GM/DL	HCT (33.0-39.0) %
Day 15	32.9	11.2
Day 19	29.8	10.0
1 m	29.7	10.2
1 m 14 days	22.7	7.9
2 m 4 days	21.6	7.3

Chronic Management

- Adequate Kcal : (Maintain Anabolism)
- Normal Protein (2-3.0 gm/kg/day) BUT
 - Low Threonine odd chain FA
 - Ileu cholesterol
 - Val
 - Met
- Correct anemia, thrombocytopenia, neutropenia
- Correct carnitine losses (100-150 mg/kg/day)
- Continue, Biotin, thiamin
- PT/OT

Recommended Daily Nutrient Intakes(Range) for infants, Children, and Adults With Propionic or Methylmalonic Acidemia

Age	Nutrient						
	ILE (mg/kg)	MET (mg/kg)	THR (mg/kg)	VAL (mg/kg)	Protein (g/kg)	Energy (kcal/kg)	Fluid (mL/kg)
Infants							
0 to < 3 mo	70-120	20-50	50-135	65-105	3.50-3.00	(130) 95-145	125-200
3 to < 6 mo	60-100	15-45	50-100	60-90	3.50-3.00	(125) 95-145	130-160
6 to < 9 mo	50-90	10-40	40-75	35-75	3.00-2.50	(120) 80-135	125-145
9 to < 12 mo	40-80	10-30	20-40	30-60	3.00-2.50	(115) 80-135	120-135
Girls and Boys	(mg/day)	(mg/day)	(mg/day)	(mg/day)	(g/day)	(kcal/day)	(mL/day)
1 to < 4 yr	485-735	180-390	415-600	550-830	≥30.0	(1300) 900-1800	900-1800
4 to < 7 yr	630-960	255-510	540-780	720-1080	≥35.0	(1700) 1300-2300	1300-2300
7 to < 11 yr	715-1090	290-580	610-885	815-1225	≥40.0	(2400) 1650-3300	1650-3300
Women							
11 to < 15 yr	965-1470	390-780	830-1195	1105-1655	≥55.0	(2200) 1500-3000	1500-3000
15 to < 19 yr	965-1470	275-780	830-1195	1105-1655	≥55.0	(2100) 1200-3000	1200-3000
≥19 yr	925-1410	265-750	790-1145	790-1585	≥50.0	(2100) 1400-2500	1400-2500
Men							
11 to < 15 yr	540-765	290-765	810-1170	1080-1515	≥50.0	(2700) 2000-3700	2000-3700
15 to < 19 yr	670-950	475-950	1010-1455	1345-2015	≥65.0	(2800) 2100-3900	2100-3900
≥19 yr	1175-1190	475-950	1010-1455	1345-2015	≥65.0	(2900) 2000-3300	2000-3300

Measured & Predicted Resting Energy Expenditure (Median)

	No.	REE (kcal/d)	Predicted (kcal/d)	% *
All patients	14	690 (186-1687)	1112 (141-1689)	80 ±18
Male	6	805 (186-1687)	1118 (141-1689)	88 ±18
Female	8	646 (290-1244)	1099 (360-1331)	75 ± 16
Neonatal	5	576 (186-1136)	555 (141-1480)	90 ± 29
Late onset	9	761 (557-1687)	1128 (582-1689)	78 ± 15

* % represents measured REE as percentage of the predicted value. *P<.01.

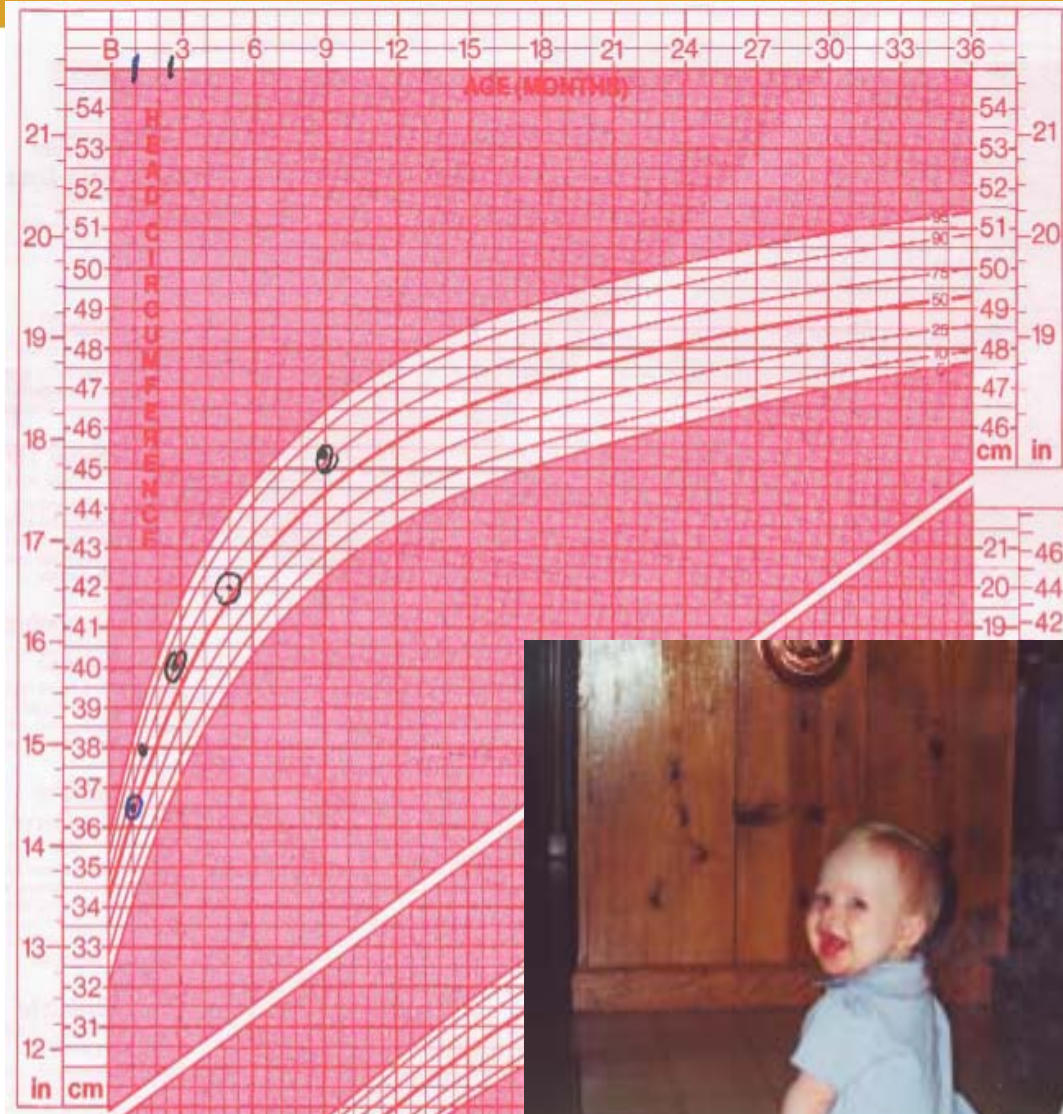
Ref: Feillet F et. Al: J Pediatr. 2000 May;136(5):659-63



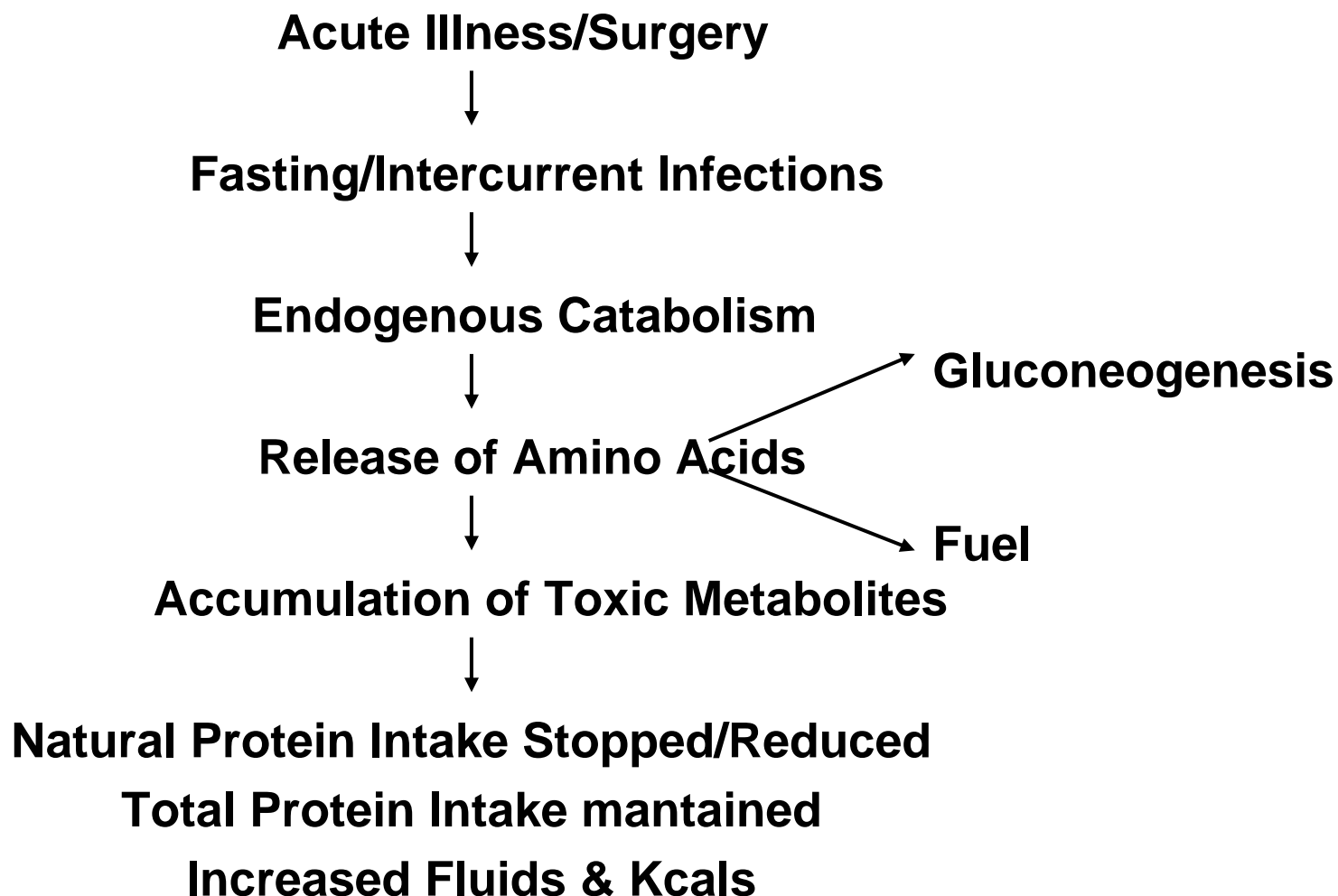
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Head Circumference for SB



Approaches to Treatment During Acute Illness



Nutritional Therapy

Acute Phase/Surgery

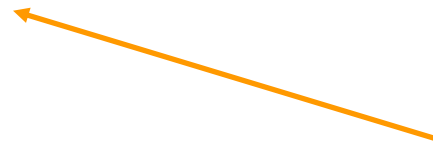
- **Create Anabolic State:**
- **Maintain hydration status**
- **Correct Acidosis**
- **Correct Hyperammonemia**
 - Adjust protein
 - Buphenyl or Sodium Benzoate (PO) or Ucephan (IV)
- **Correct Carnitine Deficiency (150-200 mg/kg/day)**
- **Augment PCC (Biotin 5 mg/day)**
- **Enhance Pyruvate Utilization (Thiamine 5 mg/kg/day)**
- **Correct Anemia/Thrombocytopenia**
- **Maintain Normoglycemia**



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G-Button



G-Button

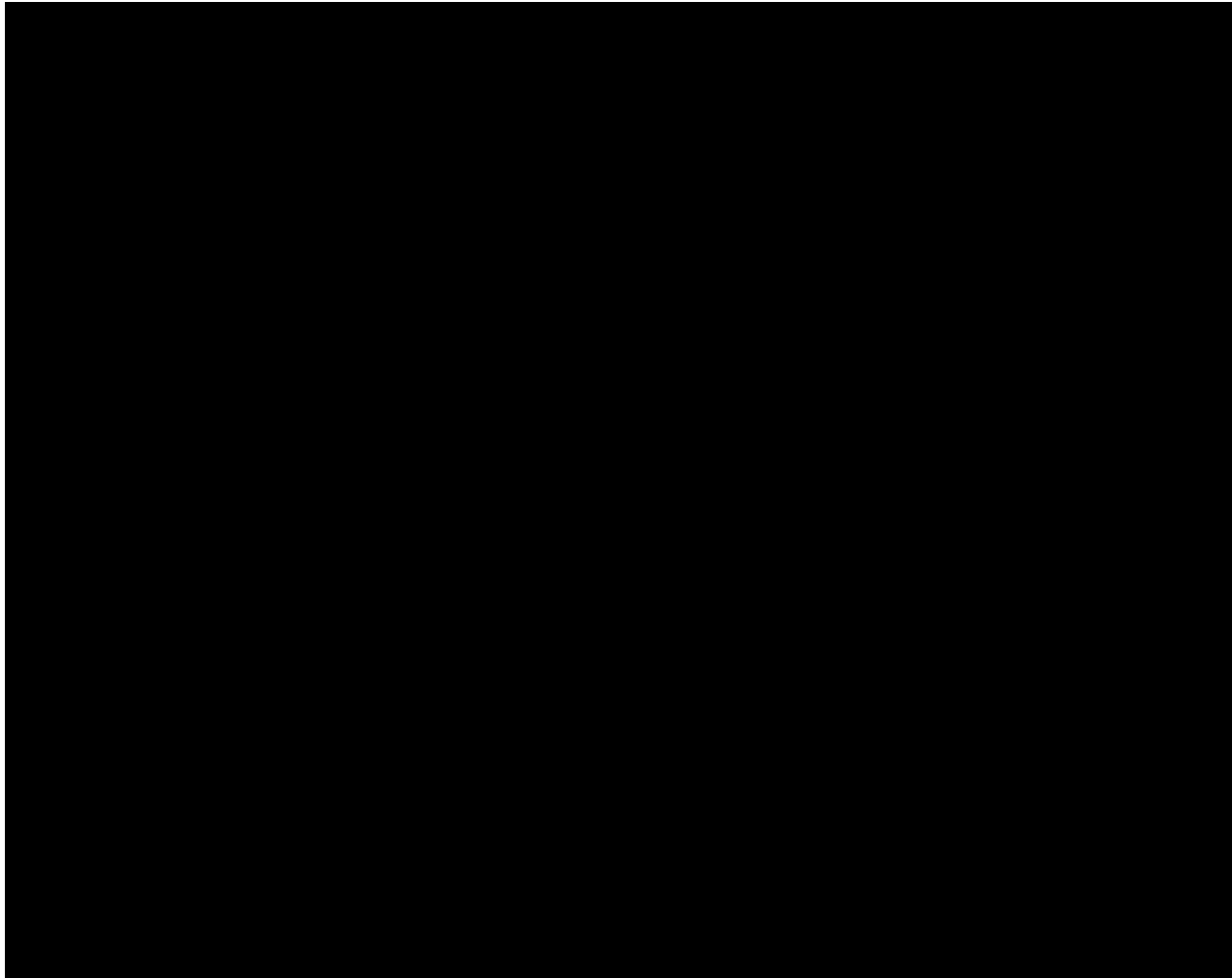
Recommended Daily Allowance for Components of Maintenance Parenteral Nutrition in Infants and Children

Requirements	Preterm Infants	Infants 0-1 Years	1-3 Years	4-10 Years	11-18 Years
Fluid mL/kg	100-150	100-150	*	*	*
Total calories kcal/kg	90-120	108-90	90-75	75-55	55-40
Dextrose mg/kg/min (3.4 kcal/gm)	12-15				
Protein g/kg (1 g protein – 0.16 g Nitrogen)	2.5-3	3-1.6	2.5-1.2	2.5-1.2	2.0-0.8
Fat g/kg	3.0	0.5-4	0.5-3.0	0.5-3.0	0.5-3.0



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Use of peripheral line

- **IV Glucose D₁₀ @ 1½ to 2 maintenance fluids with sodium and potassium**
- **IV Intralipids 20% @ a rate to provide 1.5-2 gm/kg/day for 20 hrs**
- **Buffering if metabolic acidosis, 50-75 meq/L Na Bicarbonate (if acidotic)**
- **IV L-carnitine 50 mg/kg for 1 h, then 100-200 mg/kg/d**
- **Antiemetic agents (if necessary)**

Factors Considered in Choosing a Medical Food

- **Age**
- **Nutrient Needs**
- **Taste**
- **Amount Required**
- **Cost/Availability**
- **Clinical Experience**
- **Product Support**
- **Convenience/Ease of Preparation**

Patient Profile

Patient	1	2	3	4	5	6
Gender	F	F	F	F	F	F
Ethnic origin	H	W	W	W	W	W
Age	3y 11m	5m	5y 6m	9m	2y 10m	1y 4m
HC percentile	90%	50-75%	50-98%	>95%	90-95%	>95%
WT percentile	70%	50-75%	>95%	>95%	95%	>95%
HT percentile	50%	10%	25%	25-50%	90%	75%
G-Tube	N	N	Y	Y	Y	Y
Medical Food	Propimex-1	Propimex-1	Propimex-1	Propimex-1	Propimex-2	Propimex-1
Kcal/kg/day	78	85	89	98	61	81
%RDA	89%	74%	131%	89%	98%	80%
natural pro/kg/day	1.2	0.9	0.8	0.7	0.9	1.2
total pro/kg/day	2.2	2.18	1.6	2.02	1.86	2.09

Patient Profile (cont.)

Patient	1	2	3	4	5	6
Gender	F	F	F	F	F	F
Ethnic origin	H	W	W	W	W	W
Age	3y 11m	5m	5y 6m	9m	2y 10m	1y 4m
HC percentile	90%	50-75%	50-98%	>95%	90-95%	>95%
WT percentile	70%	50-75%	>95%	>95%	95%	>95%
HT percentile	50%	10%	25%	25-50%	90%	75%
G-Tube	N	N	Y	Y	Y	Y
Medical Food	Propimex-1	Propimex-1	Propimex-1	Propimex-1	Propimex-2	Propimex-1
Carnitine/kg/day	178	150	157	209	152	193
Carnitine/kg/day- medical food	60	38	49	82	56	53
Carnitine/kg/day- supplement	117	112	108	127	96	141
Valine supplementation	N	Y	Y	Y	N	Y



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