



# GUÍAS PARA TRATAMIENTO EN MSUD

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# Guías Manejo Nutricional en MSUD

Nutrition management guideline for maple syrup urine disease: An evidence- and consensus-based approach



2014 → 2021

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## Acute Illness Protocol for Maple Syrup Urine Disease

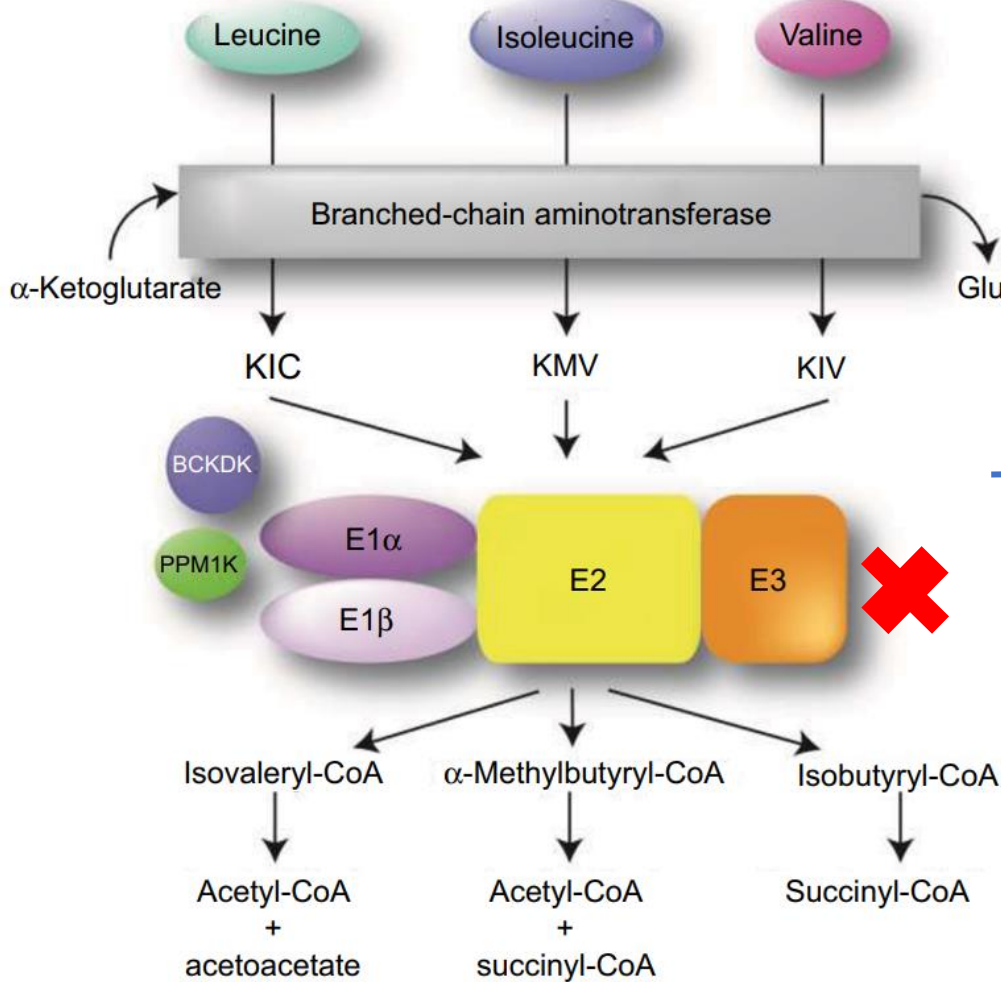
*Lance H. Rodan, MD,\* Saud H. Aldubayan, MD,\*† Gerard T. Berry, MD,\* and Harvey L. Levy, MD\**

2018

Branched-chain  $\alpha$ -ketoacid dehydrogenase deficiency (maple syrup urine disease): Treatment, biomarkers, and outcomes

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2020



Crecimiento y Desarrollo

Reducir metabolitos tóxicos

Dieta restringida en  
LEUCINA +  
suplementación de  
Iso y Val

Anabolismo

Catabolismo

# Guías

Agudo

Crónico

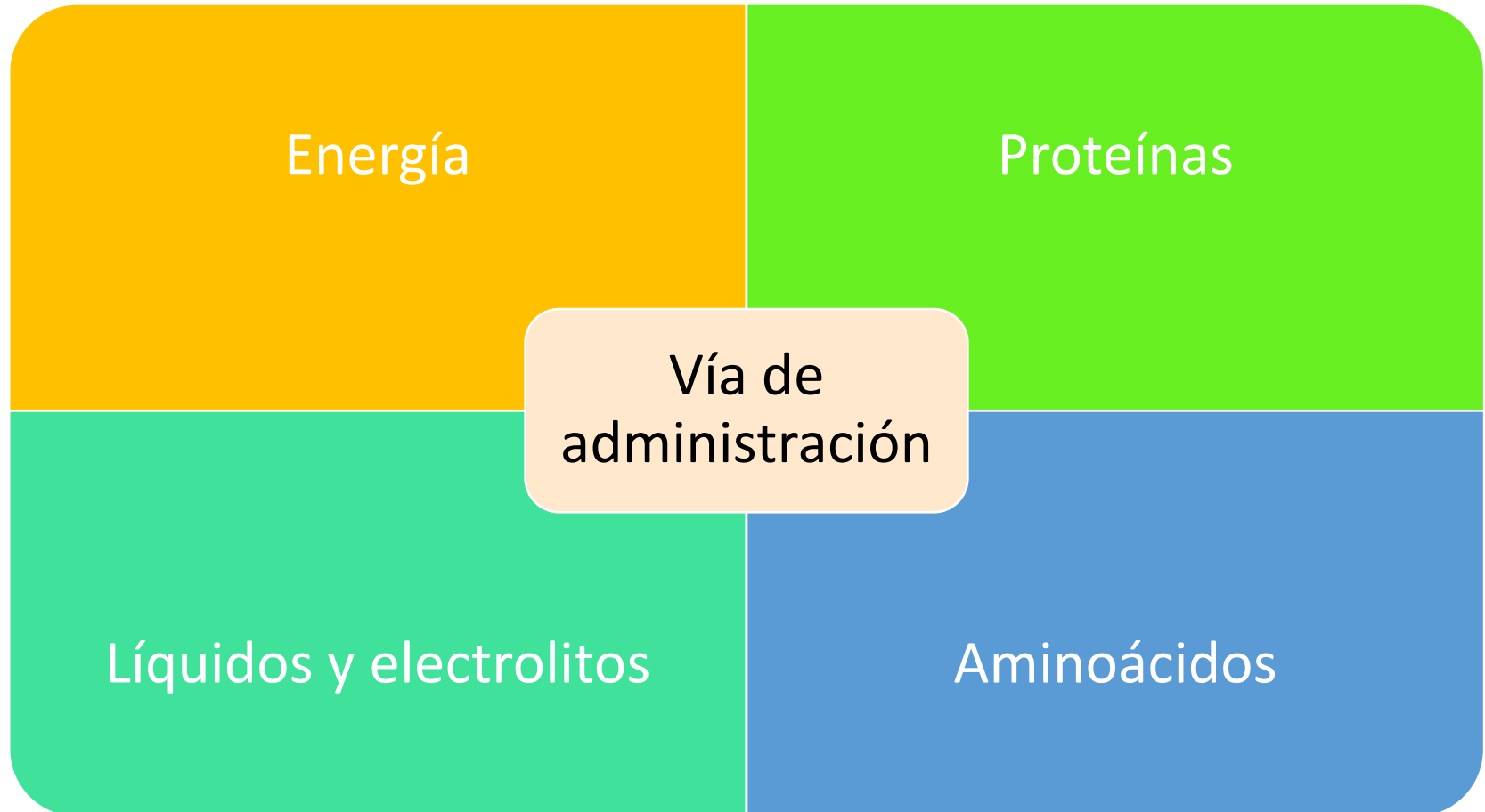
# OBJTIVOS GLOBALES DEL TRATAMIENTO

Los objetivos de la terapia de nutrición en MSUD son:

1. Reducir rápidamente los metabolitos tóxicos restringiendo los BCAA de la dieta a cantidades que permitan a los pacientes alcanzar y mantener concentraciones plasmáticas de aminoácidos de BCAA adecuadas (500–1000  $\mu\text{mol/L}$  por 24 horas).
2. Reducir el catabolismo
3. Promover el anabolismo
4. Supervisar el estado nutricional y modificar la ingesta para promover el crecimiento normal, el desarrollo y el mantenimiento de la salud
5. Evalúe la capacidad de respuesta a la tiamina si el paciente tiene actividad residual de BCKD; suplementar si responde.

# AGUDO

# TRATAMIENTO NUTRICIONAL AGUDO



# ENERGÍA

- Fraizer → 120-150% RDI
  - No especifica cantidades ni proporciones.
  - Vía parenteral (y enteral si es posible)
  - Insulina (0.05 to 0.3 U/hr → actualización GMDI)
- Rodan → 120-150% RDI
  - Glucosa 20% + lípidos 1-2 gr/kg/d
  - Vía Parenteral
  - Insulina (sin dosis)
- Strauss → 1.5 – 3 veces EER
  - Glucosa 50-70% + lípidos (30-50%)
  - Vía parenteral (y enteral si es posible)
  - Insulina: 0.02–0.15 units/kg/hr; para mantener glucosa 100–160 mg/dL





# PROTEÍNAS

- Suspendir leucina
- 3 guías indican aportar proteína sin BCAA:
  - Aminoácidos parenterales sin BCAA
  - Fórmulas especiales sin BCAA.
- Recomendado → 2-3.5 gr/kg/d
- En Chile: no contamos con NP sin BCAA
  - Sin tolerancia enteral → 24-48 hrs sin proteínas y luego reintroducir progresivamente.
- Solo Fraizer → indica reintroducir leucina con niveles 200 umol/L o 300 umol/L en mayores de 5 años.

# LÍQUIDOS Y ELECTROLITOS

- Fraizer → 150 ml/kg/d
  - Aporte de electrolitos de ser necesario (sin cantidad)
  - 1.5 – 2 veces mantención (actualización GMDI)
- Rodan → No establece aporte a entregar
- Strauss → No establece aporte a entregar
  - Mantener osmolalidad
  - Concentración plasmática de sodio 138-145 mEq/L (edema)

# AMINOÁCIDOS

- Isoleucina y Valina (Competencia BHE)
- Frazier → GMDI: 20-120 mg/kg/d
  - Niveles 200-400 umol/L
- Rodan → No indica aporte
  - Niveles 200-400 umol/L
- Strauss → 20-120 mg/kg/d
  - niveles 400-800 umol/L.



# MANEJO AGUDO

Fraizer y Strauss

Reintroducir  
leucina

<200  $\mu\text{mol/L}$   
< 300  $\mu\text{mol/L}$

Proteína  
natural = LM  
1 mg LEU/mL



LM extraída

# “Sick-Day”

- Solo Fraizer indica el “sick-day”
- Recomendaciones:
  1. Identificar y tratar el estresor catabólico
  2. Suspensión 50-100% leucina → clínica
  3. Aumentar fórmula especial
  4. Aumentar energía con aceite y MD
  5. Hidratación
  6. Monitoreo de niveles plasmáticos
- En Chile → carta de emergencia (centros de salud) y stock en casa.

# RESUMEN

Component	Goal	Source(s)
Energy	150% of recommended <sup>1,2</sup>	Enteral: BCAA-free medical food and, as needed, other BCAA/PRO free energy sources - e.g., Solcarb (Solace Nutrition), S.O.S. (VitaFlo USA), Pro-Phree (Abbott Nutrition), Duocal (Nutricia); PFD (Mead Johnson)
		Parenteral <sup>2</sup> : 10% glucose/dextrose <sup>3</sup> , 20% Intralipids @ 2 gm/kg/day.
BCAA-free AA	120-150% of recommended	Enteral: BCAA-free medical food <sup>4</sup>
		Parenteral: BCAA-free specialty TPN <sup>6</sup>
Fluids and electrolytes	Individualized <sup>3,5</sup>	Enteral: additional protein-free oral fluids, e.g., juices, sport drinks
		Parenteral <sup>5</sup> : Glucose/dextrose solutions and TPN
BCAA (ILE and VAL)	20-120 mg/kg/day <sup>6</sup> for each	Enteral: may be added to the medical food, as weighed powder, or in appropriate volume of 1% solutions
		Parenteral: from specialty pharmacies. Or, if no parenteral form is available, use small volumes given orally, or slow drip by NG or g-tube.
Insulin <sup>7</sup>	to prevent or reverse hyperglycemia	

# CRÓNICO

# MANEJO CRÓNICO

- Mantener niveles plasmáticos BCAA dentro de rangos normalidad
- Favorecer crecimiento adecuado
- Evitar deficiencias



# MANEJO CRÓNICO

**Table 4**

Recommended daily nutrient intakes of BCAA, PRO, energy and fluids for individuals with MSUD when well.<sup>a</sup>

Age	Nutrient					
	LEU mg/kg	ILE mg/kg	VAL mg/kg	Protein g/kg	Energy kcal/kg	Fluid mL/kg
0 to 6 months	40–100	30–90	40–95	2.5–3.5	95–145	125–160
7 to 12 months	40–75	30–70	30–80	2.5–3.0	80–135	125–145
1–3 years	40–70	20–70	30–70	1.5–2.5	80–130	115–135
4–8 years	35–65	20–30	30–50	1.3–2.0	50–120	90–115
9–13 years	30–60	20–30	25–40	1.2–1.8	40–90	70–90
14–18 years	15–50	10–30	15–30	1.2–1.8	35–70	40–60
19 years + <sup>b</sup>	15–50	10–30	15–30	1.1–1.7	35–45	40–50

<sup>a</sup> Adapted from Marriage, B [21].

<sup>b</sup> Males and non-pregnant, non-lactating females.

Niveles plasmáticos → ingesta.

# INGESTA DE NUTRIENTES


Nutrient	Recommendation	Source
<b>LEU</b>	<p>Sufficient intake to allow adequate protein synthesis for growth, repair and health maintenance and to achieve LEU levels in recommended treatment range.</p> <p>LEU allowance is also dependent on residual BCKD activity, age, weight, sex, life stage and health of the individual with MSUD.</p> <p>In the newborn, the recommended intake is: 40-100 mg LEU/kg/day</p>	<ul style="list-style-type: none"> <li>• <b>Intact protein (PRO)</b></li> </ul> <p><i>In infants:</i> breast milk or infant formula with known LEU content</p> <p><i>In children and adults:</i> foods such as fruits/vegetables, some grains/cereals that are typically low in protein and for which there is known LEU content</p>
<b>PRO</b>	<p style="text-align: center;"><b>DRI</b><sup>1</sup></p> <p>Plus additional 20-40% if an amino acid-based medical food is used</p>	<ul style="list-style-type: none"> <li>• <b>Intact PRO</b> (as above)</li> <li>• <b>BCAA-free medical food</b></li> </ul>
<b>VAL, ILE</b>	<p>VAL and ILE are essential amino acids and may need to be supplemented when BCAA are restricted to achieve appropriate LEU blood levels. To promote anabolism of LEU, when LEU blood levels are high, additional supplementation of VAL and ILE is often required</p>	<ul style="list-style-type: none"> <li>• <b>Intact PRO</b></li> <li>• <b>Supplemental VAL, ILE</b><sup>2</sup></li> </ul>
<b>KCAL</b>	<p style="text-align: center;"><b>DRI</b><sup>1</sup></p>	<ul style="list-style-type: none"> <li>• <b>Intact PRO</b></li> <li>• <b>BCAA-free medical food</b></li> <li>• <b>Free foods</b><sup>3</sup></li> <li>• <b>Modified low PRO food</b><sup>4</sup></li> </ul>
<b>Other nutrients, minerals and vitamins</b> <sup>5</sup>	<p style="text-align: center;"><b>DRI</b><sup>1</sup></p>	<ul style="list-style-type: none"> <li>• <b>Intact PRO</b></li> <li>• <b>BCAA-free medical food</b></li> <li>• <b>Supplemental nutrients, vitamins and minerals</b><sup>6</sup></li> </ul>

# NIVELES PLASMÁTICOS NORMALES

Consenso en 3 guías:

- LEUCINA:
  - 75-200  $\mu\text{mol/L}$  para < 5 años.
  - 75-300  $\mu\text{mol/L}$  para >5 años.
- VALINA E ISOLEUCINA:
  - 200-400  $\mu\text{mol/L}$
  - Identificar síntomas de deficiencia
- Mantener de por vida

# EMBARAZO Y LACTANCIA

- Fraizer:
- Sin efectos teratogénicos
- > aporte proteico y energético.
- Leucina 75-300 umol/L, Isoleucina y valina 200-400 umol/L.
- Prevenir catabolismo:
  - Primer trimestre
  - Parto y  parto

Manejo agudo

**TABLE #21: Recommended Nutrient Intake for Pregnant Woman with MSUD**

Age/Stage	PREGNANCY and POSTPARTUM (classical MSUD)					
	NUTRIENT					
	LEU mg/kg	Approx Intact PRO g/day	ILE mg/day	VAL mg/day	Total PRO g/day	ENERGY kcal/day
1st trimester	300 - 500	5.0 - 8.0	250-450	325-500	120% DRI plus 0.5g/d	DRI plus 85 kcal/d
2nd trimester	600 -1000	10 - 16	400-800	600-1000	120% DRI plus 7.7g/d	DRI plus 285 kcal/d
3rd trimester	800 - 2000	13 - 33	650-1200	800-1800	120% DRI plus 25g/d	DRI plus 375 kcal /d
Postpartum	If not breast feeding, return to pre-pregnancy intake					
Lactation	Intake while breastfeeding should be approximately the same as in the 3rd trimester					

# TIAMINA

- Fraizer → prueba con dosis 10-1000 mg/d
  - Respuesta: aumento tolerancia BCAA (subunidad E2)
  - Dosis crónicas: 50-200 mg/D
- Rodan → 50-200 mg/d
- Strauss → No hace referencia

En Chile se da 50 mg/d a todos los pacientes = sin estudio molecular

# SEGUIMIENTO

**TABLE #6: Recommendations for the Nutritional Monitoring of Individuals with MSUD**

Domain Measures	Infants (0- <1 yr)	Children (1- <8 yrs)	Children (8-18 yrs)	Adults	Planning Pregnancy or Pregnant	Postpartum and Lactation
<b>Assessment of Clinical Status <sup>2</sup></b> Physical findings, growth, and laboratory results should be within normal for age, sex, and life stage, except for blood levels of BCAA <sup>5</sup>						
Nutrition assessment and counseling  (dietary intake <sup>3</sup> and nutrient analysis, nutrition-related physical findings, nutrition counseling, diet education)	Weekly to monthly	Monthly to every 6 months	Every 6 to 12 months	Every 6 to 12 months	Monthly to per trimester	At 6 weeks postpartum, then every 6 months
Interim nutrition contact  (diet adjustment based on blood BCAA levels, or counseling at clinic or by phone/electronic communication)	Twice weekly to weekly	Weekly to monthly	Weekly to monthly	Monthly	Once to twice weekly	Weekly to monthly
Anthropometrics  (weight, length or height, weight for length or BMI, head circumference through 36 months and as indicated)	At every clinic visit; include head circumference	At every clinic visit; include head circumference until age 4 years	At every clinic visit	At every clinic visit	At every clinic visit; include growth of the fetus	At every clinic visit; assess growth of the offspring during lactation

# SEGUIMIENTO

Domain Measures	Infants (0- <1 yr)	Children (1- <8 yrs)	Children (8-18 yrs)	Adults	Planning Pregnancy or Pregnant	Postpartum and Lactation
Leucine (plasma, serum, or whole blood) <sup>5</sup>	Daily, until stabilized. Once to twice weekly until 6 months, then weekly	<b>SEMANAL</b> Weekly until 24 months, then monthly	Monthly	Monthly	Weekly	Weekly until 6 weeks postpartum then monthly
Valine, isoleucine, alloisoleucine (plasma, serum, or whole blood) <sup>5</sup>	Daily, until stabilized. Once to twice weekly until 6 months, then weekly	<b>Quincenal</b> Weekly until 24 months, then monthly	Monthly	Monthly	Weekly	Weekly until 6 weeks postpartum then monthly
a-keto acids (or ketones) <sup>6</sup>	Daily, until stabilized. Once to twice weekly until 6 months, then weekly	Weekly until 24 months, then monthly	Monthly	Monthly	Weekly	Weekly until 6 weeks postpartum then monthly
Amino acids, plasma (full panel)	Monthly	Monthly until 24 months, then every 6 months	With every clinic visit/assessment	With every clinic visit/assessment	With every clinic visit/assessment	With every clinic visit/assessment
Transthyretin (prealbumin)	Every 6 months	Every 6 months	With every clinic visit/assessment	With every clinic visit/assessment	With every clinic visit/assessment	With every clinic visit/assessment
Albumin	Every 6 months	Every 6 months	With every clinic visit/assessment	With every clinic visit/assessment	With every clinic visit/assessment	With every clinic visit/assessment
Complete Blood Count (CBC)	Every 6 months	Every 6 months	With every clinic visit/assessment	With every clinic visit/assessment	With every clinic visit/assessment	With every clinic visit/assessment
Ferritin	Every 6 months	Every 6 months	With every clinic visit/assessment	With every clinic visit/assessment	With every clinic visit/assessment	With every clinic visit/assessment

# SEGUIMIENTO

Domain Measures	Infants (0- <1 yr)	Children (1- <8 yrs)	Children (8-18 yrs)	Adults	Planning Pregnancy or Pregnant	Postpartum and Lactation	
25-OH vitamin D	> 5 años				In addition, preconceptually or as soon as pregnancy is confirmed	In addition, once in the postpartum period	
Vitamin B <sub>12</sub>					In addition, preconceptually or as soon as pregnancy is confirmed	In addition, once in the postpartum period	
RBC essential fatty acids					In addition, preconceptually or as soon as pregnancy is confirmed	In addition, once in the postpartum period	
Trace minerals (Zn, Cu, Se)		Ante alguna sospecha				In addition, preconceptually or as soon as pregnancy is confirmed	In addition, once in the postpartum period
Vitamin A						In addition, preconceptually or as soon as pregnancy is confirmed	In addition, once in the postpartum period
Comprehensive metabolic panel						In addition, preconceptually or as soon as pregnancy is confirmed	In addition, once in the postpartum period
Folic acid <sup>8</sup>						In addition, preconceptually or as soon as pregnancy is confirmed	In addition, once in the postpartum period
L-carnitine (free, esterified and total) <sup>8</sup>						In addition, preconceptually or as soon as pregnancy is confirmed	In addition, once in the postpartum period



# SEGUIMIENTO

Domain Measures	Infants (0- <1 yr)	Children (1- <8 yrs)	Children (8-18 yrs)	Adults	Planning Pregnancy or Pregnant	Postpartum and Lactation
<b>Radiologic</b>						
DEXA scan (Dual-energy X-ray absorptiometry)	n/a	> 5 años n/a	Every 3 to 5 years beginning at age 8 years if low vitamin D or frequent fractures	If low vitamin D or frequent fractures	n/a	n/a
Ultrasound	n/a	n/a	n/a	n/a	First trimester, 18 to 20 weeks then every 4 weeks until delivery	n/a
Echocardiogram (fetal)	n/a	n/a	n/a	n/a	18 to 20 weeks	n/a

# NUEVAS TERAPIAS

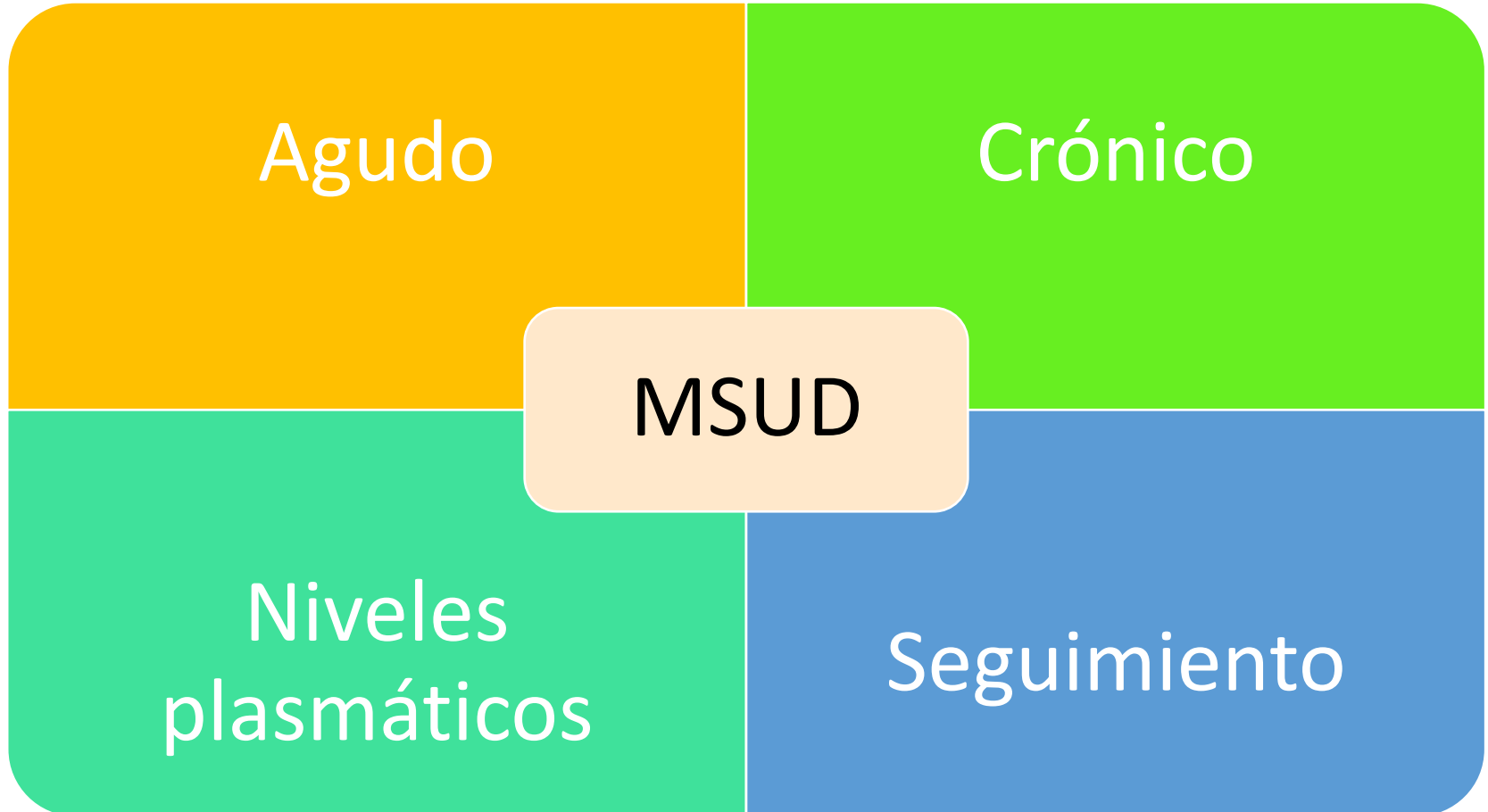
# L-CARNITINA

- Fraizer → refiere como terapias nuevas, sin evidencia aun.
  - Rodan → No hace referencia
  - Strauss → No hace referencia
  - Diversos artículos de Wajner, M → recomiendan L-CARNITINA como antioxidante. En Chile = 50 mg/kg/d
- 

# FENILBUTIRATO DE SODIO

- Ninguna guía hace referencia.
- Literatura muestra casos: 250 mg/kg/d ↓ niveles BCAA
  - Favorece acción de BCKD y disminuye pool de glutamina → reduce BCAA

# RESUMEN





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