Sd Hemafagocítico

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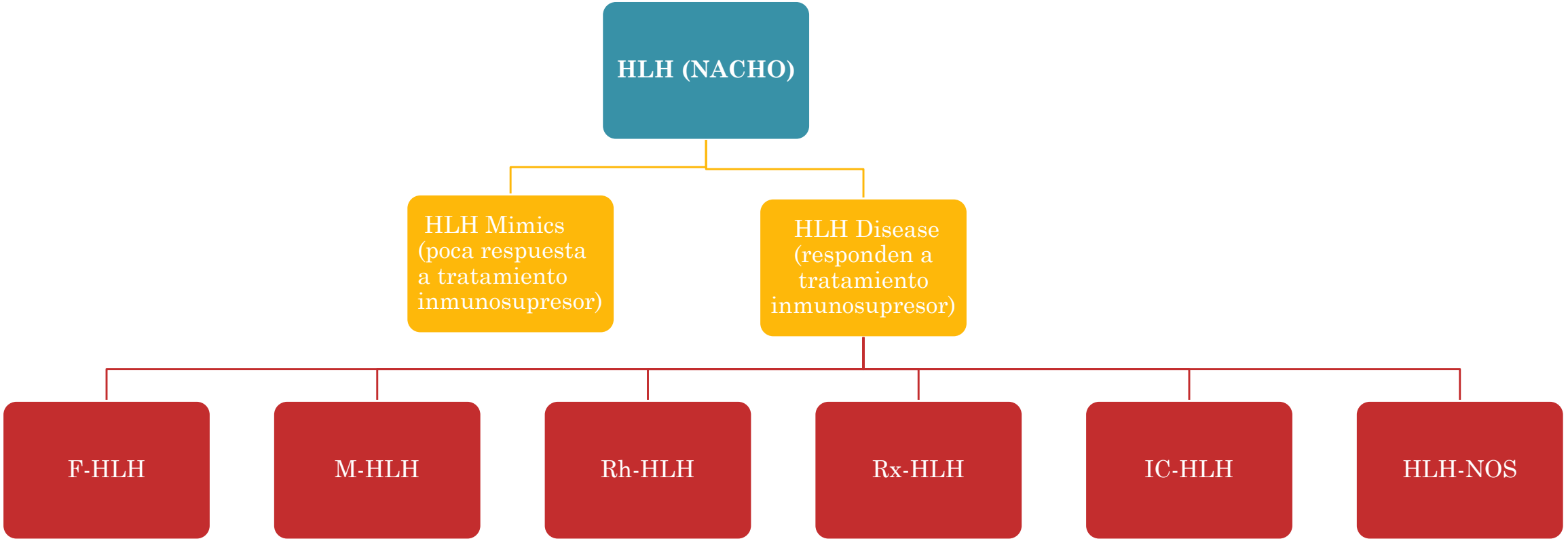
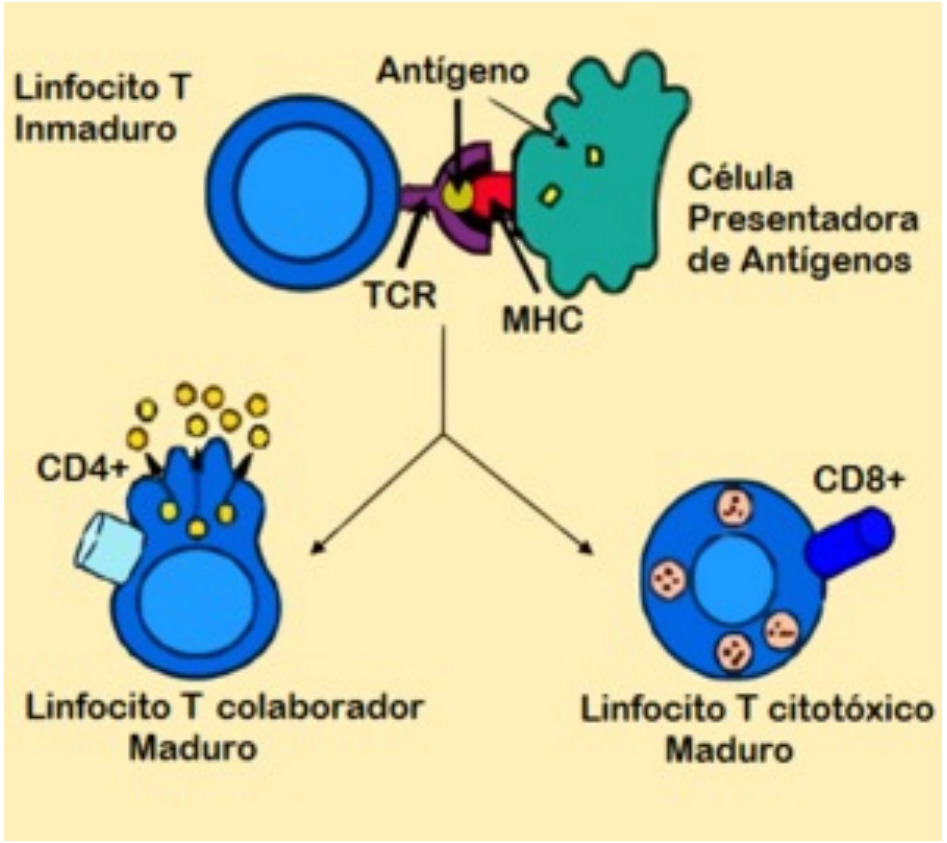
R1 Inmunología

GENERALIDADES

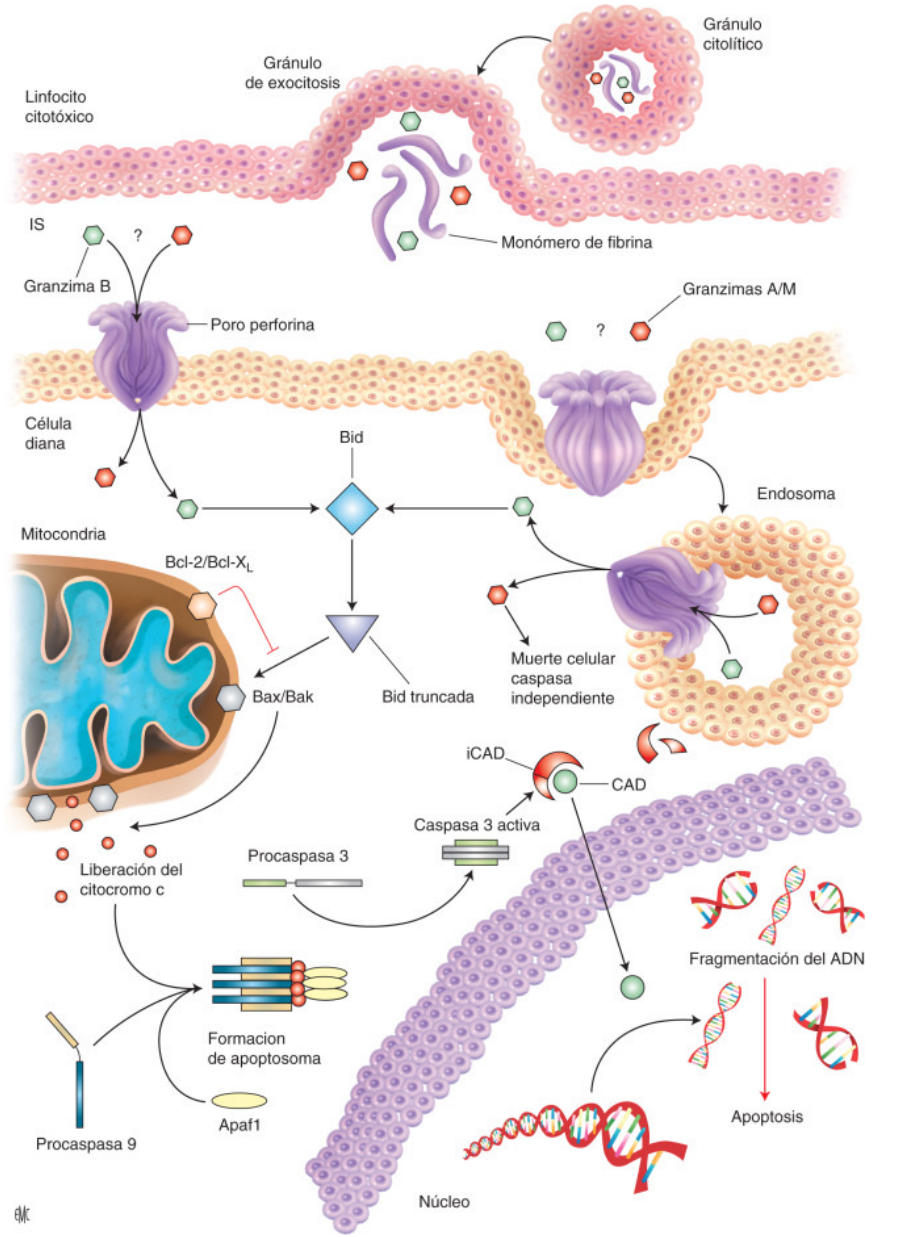
- HLH (Linfohistiocitosis hemofagocítica)
- Formas 1º y 2º (más frecuente HLH 2º)
- Niños: 1-225/300 000 RNV, 1.8 años, igual en niños y niñas
- Adultos: 50 años, varones (excepto MAS, mayor en mujeres).
- Alta tasa de mortalidad a pesar de tratamiento agresivo

PRIMARIA O FAMILIAR	SECUNDARIA O ADQUIRIDA
Genético Edad más temprana Mayor recurrencia	Desencadenante + Predisposición genética Más tardío Menos recurrencia y menos agresivo



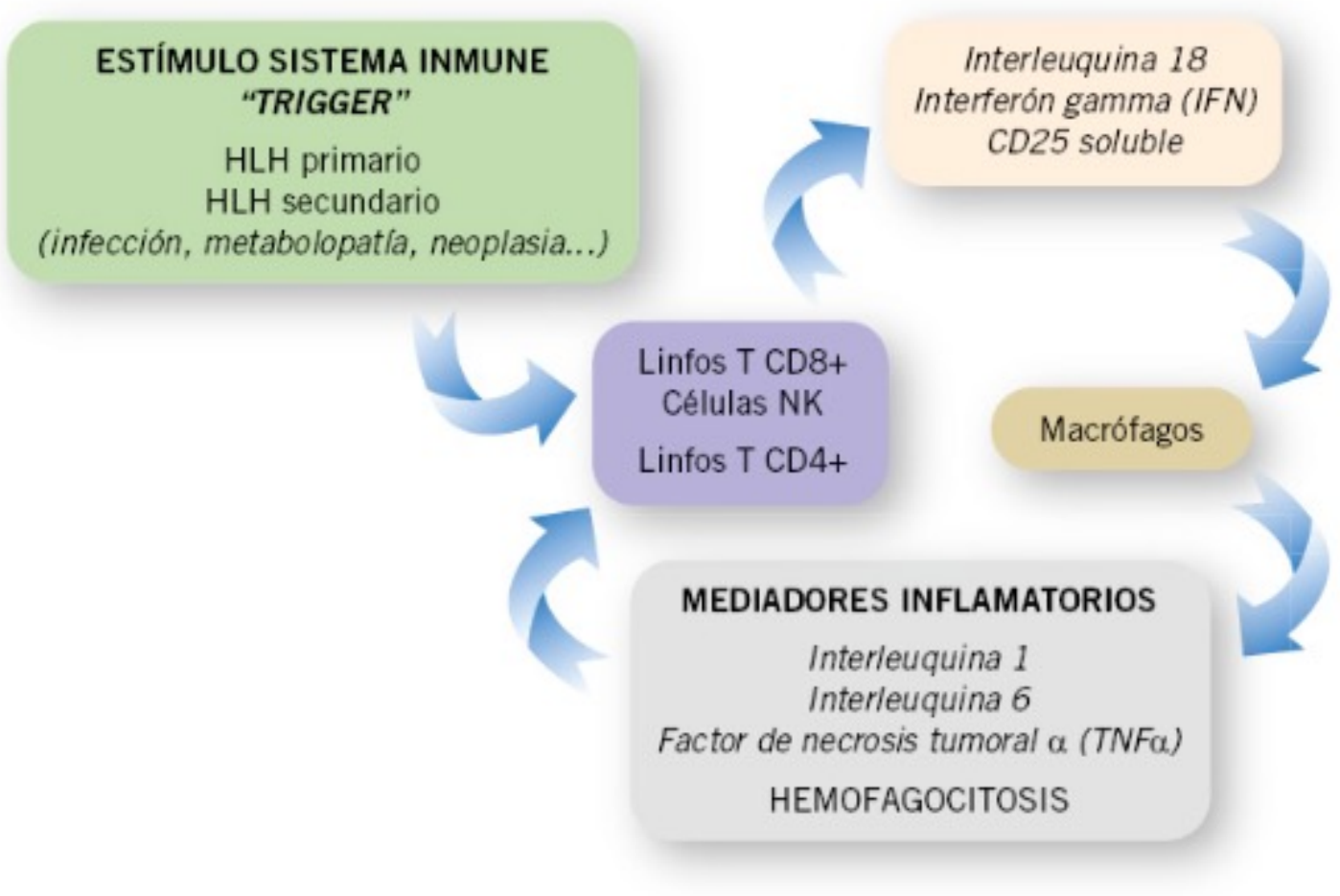


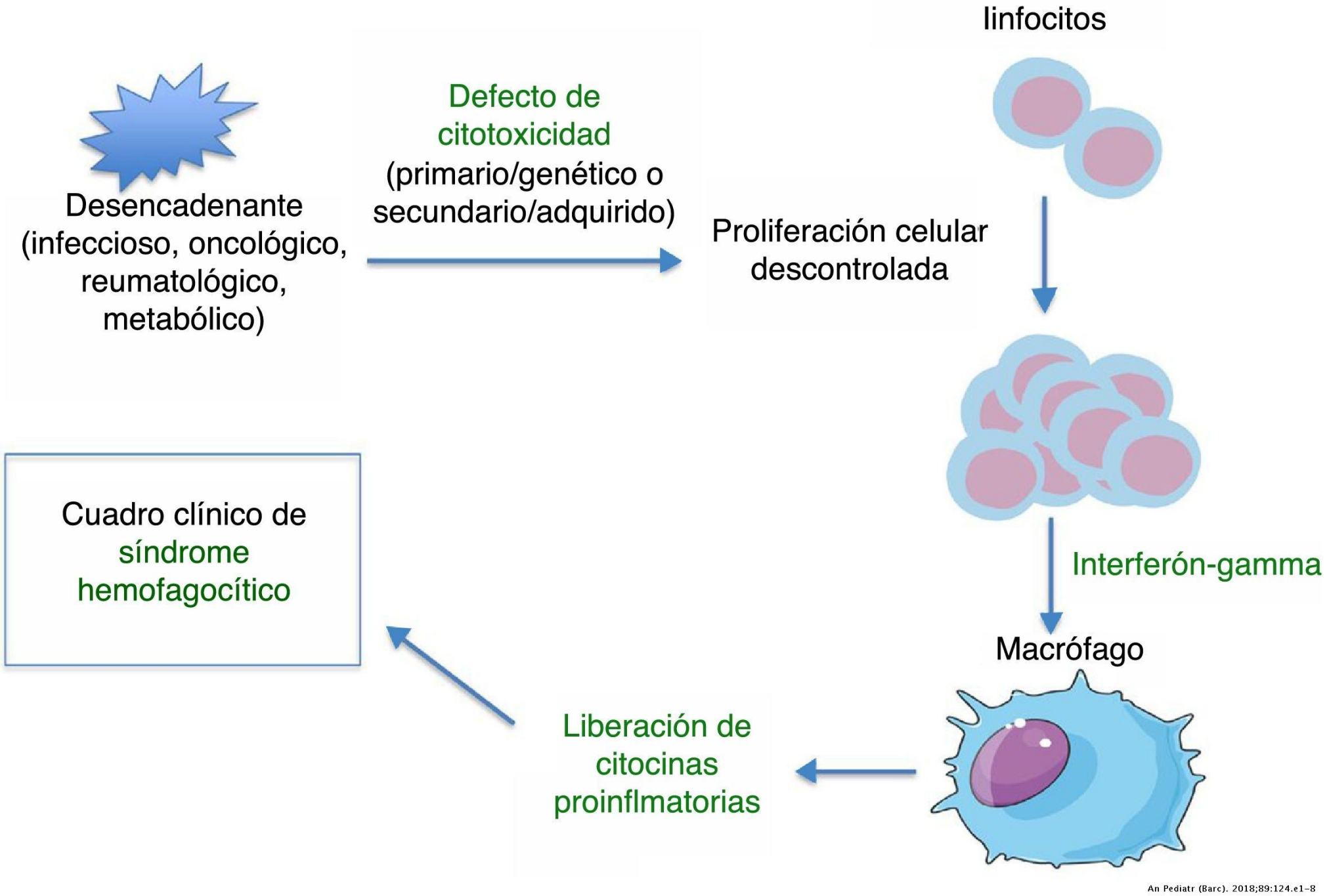
SINAPSIS



APOPTOSIS - Perforinas y Granzimas

Alt Citotoxicidad (NK y LTC) + Ausencia de apoptosis + Persistencia de estímulo inflamatorio + Hiperinflamación





An Pediatr (Barc). 2018;89:124.e1-8

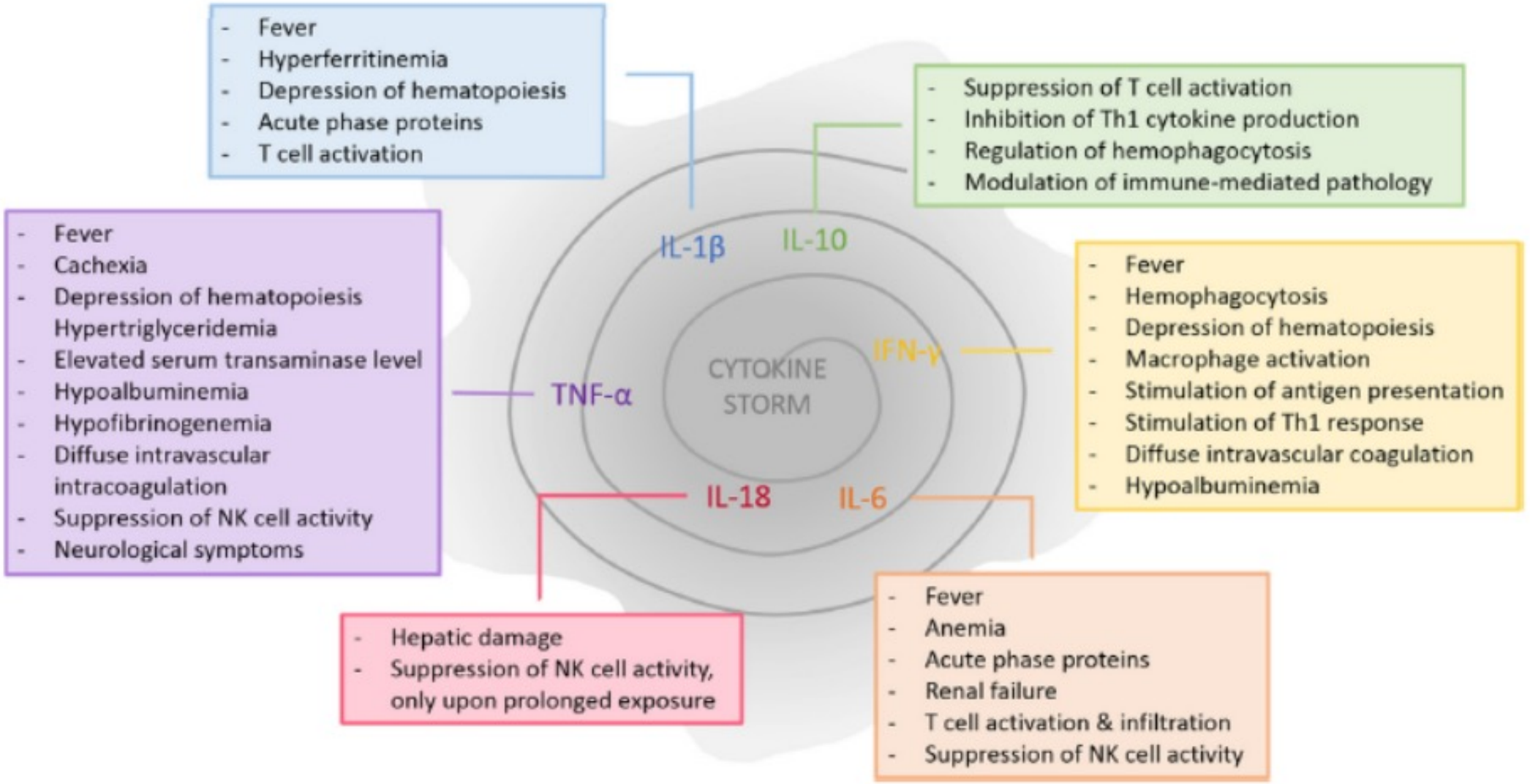
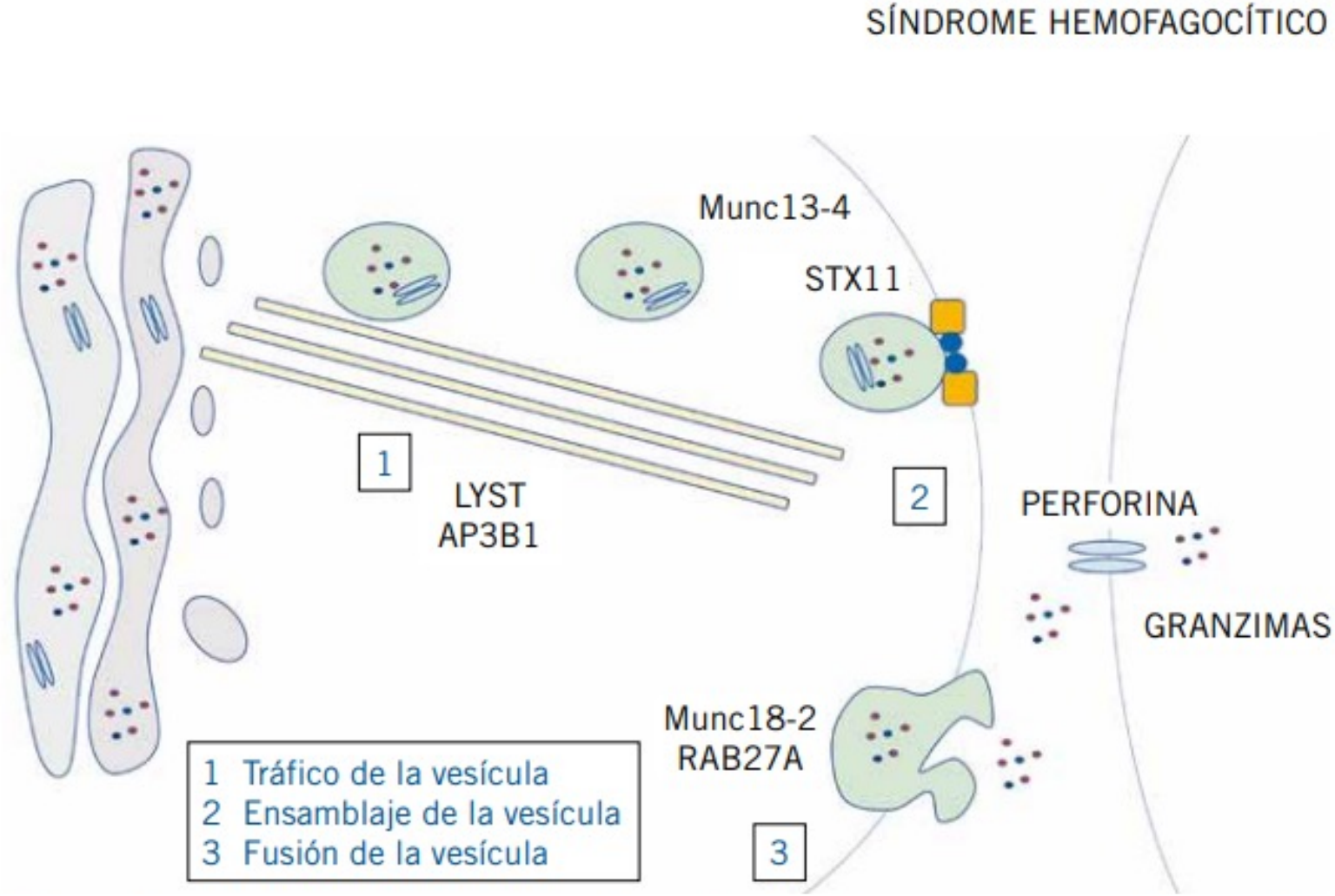


Fig. 4. Relationship between key cytokines detected in HLH patients and characteristic features of HLH they can mediate. Serum levels of IL-10 are reported to be elevated in patients, but its anti-inflammatory effects seem insufficient in tempering the observed hyperinflammation [7,125–131].

F-HLH



En 1/3 de los pacientes no se ha logrado identificar una mutación

Galán Gómez V, Pérez Martínez A. Sindrome Hemofagocítico. Pediatría Integral 2021; XXV (6): 326.e1–326.e9

Table 4 Diseases of immune dysregulation

1. Familial Hemophagocytic Lymphohistiocytosis (FHL syndromes)							
Disease	**Genetic defect**	**Inheritance**	**OMIM**	**Circulating T Cells**	**Circulating B cells**	**Functional defect**	**Associated Features**
Perforin deficiency (FHL2)	*PRF1*	AR	170280	Increased activated T cells	Normal	Decreased to absent NK and CTL activities cytotoxicity	Fever, HSM, hemophagocytic lymphohistiocytosis (HLH), cytopenias
UNC13D / Munc13-4 deficiency (FHL3)	*UNC13D*	AR	608897	Increased activated T cells	Normal	Decreased to absent NK and CTL activities (cytotoxicity and/or degranulation)	Fever, HSM, HLH, cytopenias,
Syntaxin 11 deficiency (FHL4)	*STX11*	AR	605014				
STXBP2 / Munc18-2 deficiency (FHL5)	*STXBP2*	AR or AD	601717				
FAAP24 deficiency	*FAAP24*	AR	610884	Increased activated T cells	Normal	Failure to kill autologous EBV transformed B cells. Normal NK cell function	EBV-driven lymphoproliferative disease
SLC7A7 deficiency	*SLC7A7*	AR	222700	Normal	Normal	Hyper-inflammatory response of macrophages Normal NK cell function	Lysinuric protein intolerance, bleeding tendency, alveolar proteinosis
RHOG deficiency (1 patient)	***RHOG***	**AR**	NA	**Normal**	**Slightly reduced**	**Impaired CTL and NK cell cytotoxicity**	**HLH (hemophagocytosis, hepatosplenomegaly, fever, cytopenias, low hemoglobin, hyper-triglyceridemia, elevated ferritin, sCD25)**

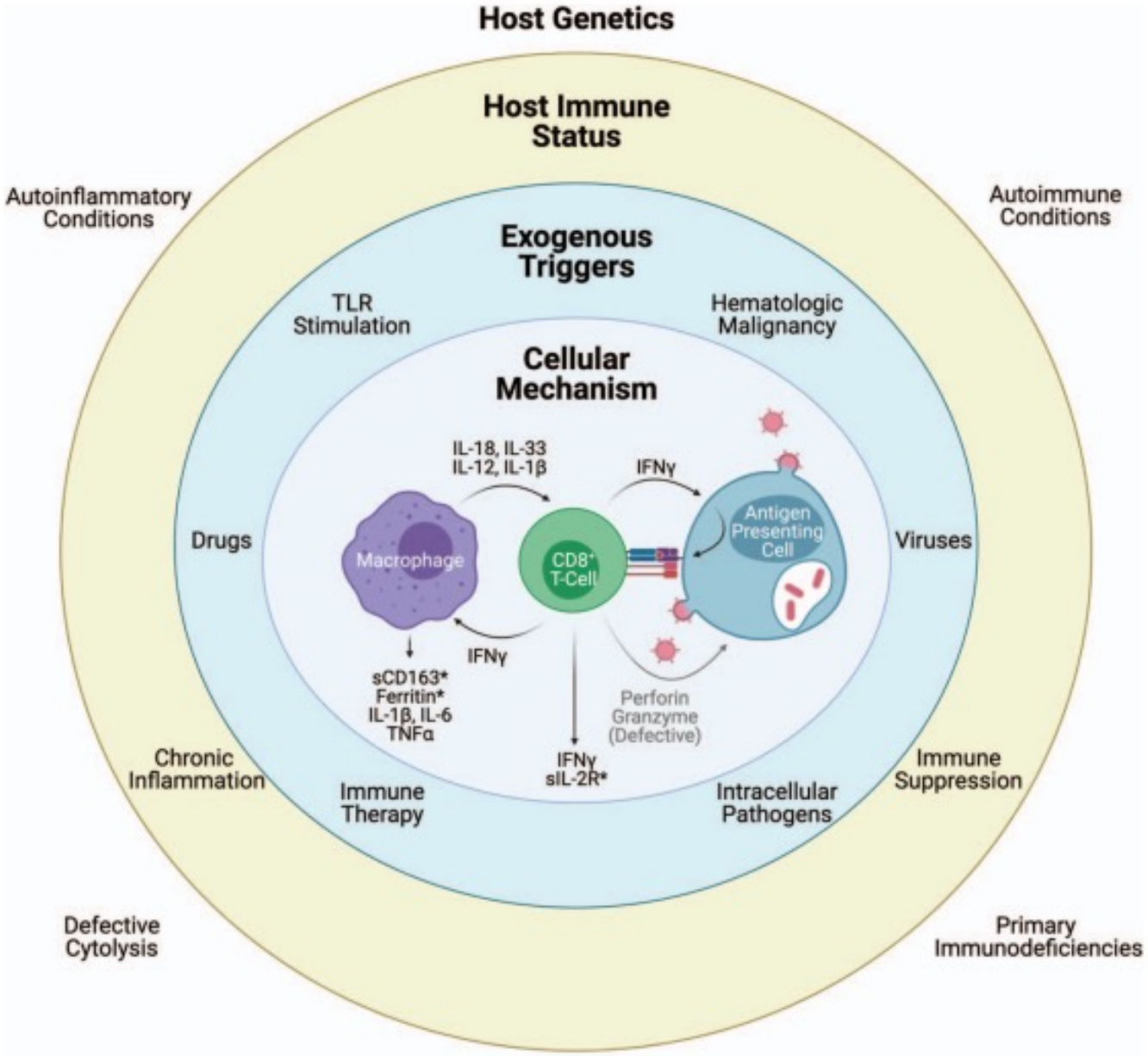
Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, Klein C, Morio T, Oksenhendler E, Picard C, Puel A, Puck J, Seppänen MRJ, Somech R, Su HC, Sullivan KE, Torgerson TR, Meyts I. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022 Oct;42(7):1473-1507.

2. FHL Syndromes with Hypopigmentation

Disease	Genetic defect	Inheritance	OMIM	Circulating T Cells	Circulating B cells	Functional defect	Associated Features
Chediak-Higashi syndrome	*LYST*	AR	606897	Increased activated T cells	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Partial albinism, recurrent infections, fever, HSM, HLH, giant lysosomes, neutropenia, cytopenias, bleeding tendency, progressive neurological dysfunction
Griscelli syndrome, type 2	*RAB27A*	AR	603868	Normal	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Partial albinism, fever, HSM, HLH, cytopenias
Hermansky-Pudlak syndrome, type 2	*AP3B1*	AR	603401	Normal	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Partial albinism, recurrent infections, pulmonary fibrosis, increased bleeding, neutropenia, HLH
Hermansky-Pudlak syndrome, type 10	*AP3D1*	AR	617050	Normal	Normal	Decreased NK and CTL activities (cytotoxicity and/or degranulation)	Oculocutaneous albinism, severe neutropenia, recurrent infections, seizures, hearing loss and neurodevelopmental delay
CEBPE neofunction (3 patients)	***CEBPE***	**AR GOF**	245480	**Mild reduction**	**Not done**	**Autoinflammasome activation/ ↑ IFN gene expression, altered chromatin occupancy of mutant CEBPE, and transcriptional changes**	**Recurrent abdominal pain, aseptic fever, systemic inflammation; abscesses, ulceration, infections; mild bleeding diathesis**

Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, Klein C, Morio T, Oksenhendler E, Picard C, Puel A, Puck J, Seppänen MRJ, Somech R, Su HC, Sullivan KE, Torgerson TR, Meyts I. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022 Oct;42(7):1473-1507.

HLH Secundario



Ponnatt TS, Lilley CM, Mirza KM. Hemophagocytic Lymphohistiocytosis. Arch Pathol Lab Med. 2022 Apr 1;146(4):507-519.

COVID

Table 2. Important Causes of Acquired Hemophagocytic Lymphohistiocytosis (HLH)[a]

Secondary HLH	Inducer
Infection-associated (50%)	Virus: Epstein-Barr virus, cytomegalovirus, and other viruses from the Herpesviridae family, adenovirus, human immunodeficiency virus, parvovirus, measles virus
	Bacteria: *Brucella, Rickettsia, Leptospira, Mycobacterium, Borrelia, Bartonella, Listeria, Mycoplasma, Ehrlichia*
	Parasites: *Leishmania, Malaria, Toxoplasma, Babesia*
	Fungi: *Candida, Cryptococcus, Penicillium, Pneumocystis, Histoplasma*
Malignancy-associated (45% adultos 8% niños)	Hematologic malignancies
	T-cell lymphomas: peripheral T-cell lymphoma, primary cutaneous γδ-T-cell lymphoma, anaplastic large cell lymphoma, lymphoblastic lymphoma, angioimmunoblastic T-cell lymphoma
	B-cell lymphomas: commonly diffuse large B-cell lymphoma
	B- and T-cell leukemias
	NK-cell lymphoma/leukemias
	Hodgkin lymphoma
	Myeloid neoplasia
	Others: Langerhans cell histiocytosis, histiocytic sarcoma, multicentric Castleman disease
	Solid tumors
Autoimmune disease-associated	Systemic-onset juvenile idiopathic arthritis, adult-onset Still disease, systemic lupus erythematosus, vasculitis
Transplant-associated	Immunological reaction at engraftment, graft-versus-host disease
Drug-associated	Carbamazepine, phenobarbital, sulfamethoxazole, cancer immunotherapy drugs

Ponnatt TS, Lilley CM, Mirza KM. Hemophagocytic Lymphohistiocytosis. Arch Pathol Lab Med. 2022 Apr 1;146(4):507-519.

CLÍNICA

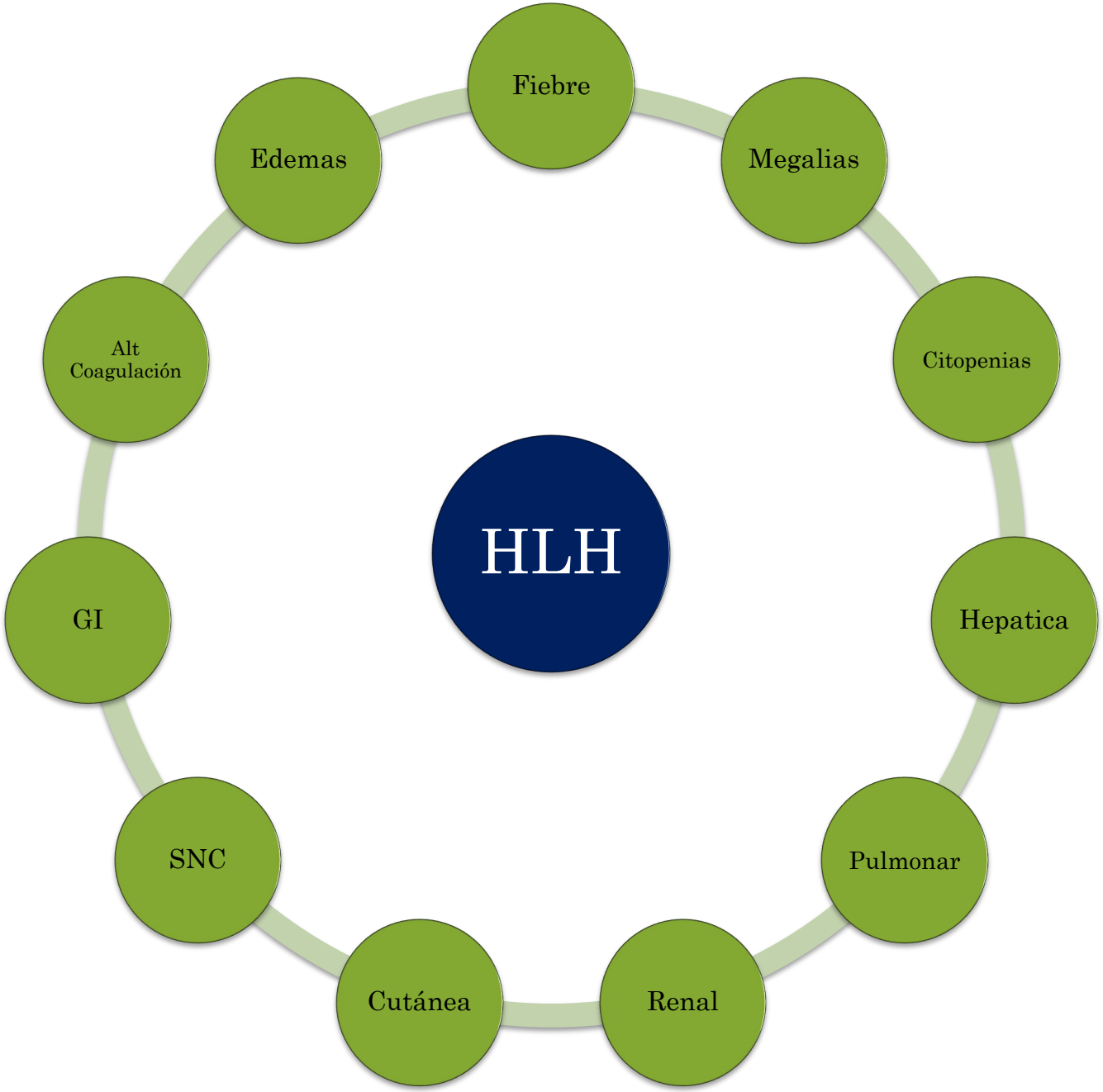
- Síntomas inespecíficos, sepsis-like, que progresan rápidamente.
- No nos permiten diferenciar entre 1º y 2º
- Más frecuentes: fiebre, hepatoesplenomegalia y citopenias.

TABLE 1. Symptoms of Hemophagocytic Lymphohistiocytosis and Relation with Hypercytokinemia

• Fever	IL-1, IL-6, and TNF
• Profound cytopenias	TNF, IFN-γ, hemophagocytosis, hyperferritinemia, increased sIL-2 receptor
• Hypertriglyceridemia	TNF-α, suppressed lipoprotein lipase by cytokines
• Hyperfibrinolysis	Activated macrophages and increased plasminogen activator
• Hyperferritinemia	GDF15 upregulation of ferroportin
• Elevated LDH	Cell death
• Elevated D-dimer	Hyperfibrinolysis
• Elevated CSF cells/protein	Central nervous system infiltration

IL, interleukin; LDH, lactate dehydrogenase; IFN, interferon, TNF: Tumor necrosis factor, CSF: Cerebrospinal fluid

Kaçar AG, Celkan TT. Hemophagocytic Lymphohistiocytosis. Balkan Med J. 2022 Sep 9;39(5):309-317


HLH
Fiebre
Megalias
Citopenias
Hepatica
Pulmonar
Renal
Cutánea
SNC
GI
Alt Coagulación
Edemas

DIAGNOSTICO

Tabla III. Criterios diagnósticos del síndrome hemofagocítico (HLH-2004)

Criterios genéticos	*Criterios clínico-analíticos*
Presencia de alteración genética conocida	- Fiebre - Esplenomegalia - Citopenias (al menos, 2 líneas): • Hemoglobina < 9 g/dL (< 12 g/dL primeras 4 semanas de vida) • Trombopenia < 100.000/mm3 • Neutropenia < 1.000/mm3 - Hipertrigliceridemia y/o hipofibrinogenemia: • Triglicéridos > 300 mg/dL • Fibrinógeno < 150 mg/dL - Hiperferritinemia > 500 ng/mL (valores > 10.000 ng/mL son muy sugerentes de HLH) - Valores CD25 soluble ≥ 2.400 U/mL - Disminución/ausencia actividad citotóxica NK - Evidencia de hemofagocitosis en tejido

Sostienen el diagnóstico: pleocitosis e hiperproteinorraquia en el LCR, disfunción hepatobiliar (hipertransaminasemia, hiperbilirrubinemia, coagulopatía con elevación de D-dímero), hipoalbuminemia, elevación de LDH sérica o hiponatremia

El diagnóstico se establece a partir de un criterio genético o con la presencia, al menos, de 5 criterios clínico-analíticos

SCD25
CD163
CD107a
IL-1, IL-6, IL-18, TNF-α,

Known underlying immunosuppression HIV positive or receiving long-term immunosuppressive therapy (i.e., glucocorticoids, cycloSPORINE, azaTHIOprine)	**No 0**	Yes +18
Temperature, °F (°C)	**<101.1 (<38.4) 0**	
	101.1–102.9 (38.4-39.4)	+33
	>102.9 (>39.4)	+49
Organomegaly	**No 0**	
	Hepatomegaly or splenomegaly	+23
	Hepatomegaly and splenomegaly	+38
Number of cytopenias Defined as hemoglobin ≤9.2 g/dL (≤5.71 mmol/L) and/or WBC ≤5,000/mm³ and/or platelets ≤110,000/mm³	**1 lineage 0**	
	2 lineages	+24
	3 lineages	+34
Ferritin, ng/mL (or µg/L)	**<2,000 0**	
	2,000–6,000	+35
	>6,000	+50
Triglyceride, mg/dL (mmol/L)	**<132.7 (<1.5) 0**	
	132.7-354 (1.5–4)	+44
	>354 (>4)	+64
Fibrinogen, mg/dL (g/L)	**>250 (>2.5) 0**	
	≤250 (≤2.5)	+30
AST, U/L	**<30 0**	≥30 +19
Hemophagocytosis features on bone marrow aspirate	**No 0**	Yes +35

0 points
HScore

<1 %
Probability of hemophagocytic syndrome

Copy Results | Next Steps

HScore

- 0 a 337 puntos
- A mayor puntaje, mayor probabilidad
- 162 puntos : 40-50%
- 192 puntos : 80-85%
- 227 puntos : 96-98%

Table 5. Laboratory Findings in Pediatric Hemophagocytic Lymphohistiocytosis (HLH) Versus HLH in Adults

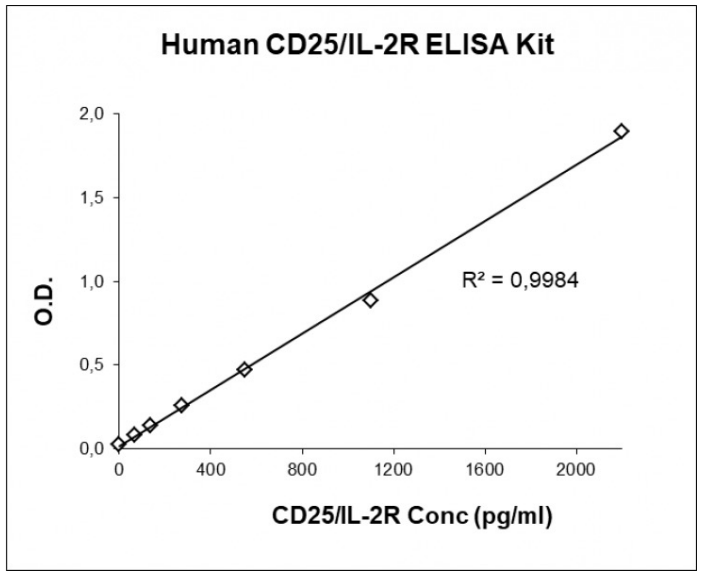
Laboratory Finding	Pediatric HLH[a]	Adult HLH[b]	Comments
Cytopenias of >2 lines	~100%	>85%	Anemia and thrombocytopenia are more common. Leukopenia is less common
Hypertriglyceridemia (fasting >265 mg/dL)	40%–85%	22.1%–88.6%	Caused by elevated TNF-α which inhibits lipoprotein lipase
Hypofibrinogenemia (<150 mg/dL)	53%–79%	24%–93.3%	Associated with poor prognosis
Ferritin >500 ng/mL	~100%	77.2%–100%	High negative predictive value in both children and adults
Elevated soluble CD-25 (>2400 U/mL)	~100%	100%–76.2%	Level >10,000 U/mL or slow rate of decline is associated with poor prognosis in children
Hypoalbuminemia	69%	86.3%–97%	Associated with poor prognosis in adults
Abnormal renal function	9%	16%–61%	Associated with poor prognosis. Acute kidney injury is the most common renal manifestation of HLH
Elevated transaminases	76%	63%–98.1%	Elevated AST is one of the diagnostic criteria of the HScore but not the HLH-2004 criterion
Hemophagocytosis	92%	53.3%–100%	Not sensitive nor specific to the diagnosis of HLH in children and adults
Low or absent NK cell activity	22%–100%	28.6%–86%	Predictive value is better for HLH in children than in adults

Situaciones fisiológicas (transfusiones, infecciones, enf autoinmunes, etc)

Ponnatt TS, Lilley CM, Mirza KM. Hemophagocytic Lymphohistiocytosis. Arch Pathol Lab Med. 2022 Apr 1;146(4):507-519.

sCD25 (IL-2Rα)

- Proteína transmembrana en CT activadas (cadena α del receptor de IL-2)
- Marcador de LT activados
- PRONOSTICO: Supervivencia a los 5 años con ≤10 000 U/mL al diagnostic es del 78%, y con ≥10 000 U/mL del 36%
- Niveles bajan muy rápido al recibir tratamiento adecuado



CD163

- Proteínas transmembrana de monocitos y macrófagos
- Elevadas en estados inflamatorios (niveles extremos en HLH)
- Marcador de activación de macrófagos

CD107a

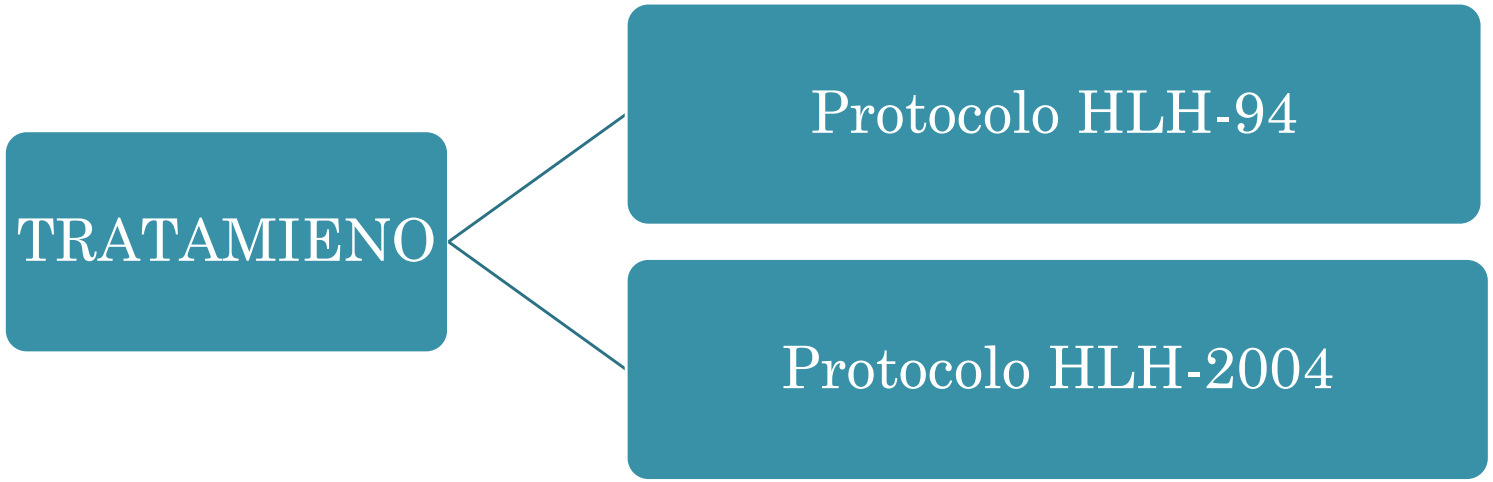
- ✓ Glicoproteína de membrana asociada a lisosomas (bicapa lipídica d los granulos citotóxicos de CD8+ y NK)
- ✓ Marcador de degranulación
- ✓ Mutaciones de UNC130 y STX11
- ✓ Correlación con la producción de citoquinas y de actividad citolítica

MONITORIZAR

Dx Diferencial

Tabla V. Diagnóstico diferencial de la linfohistiocitosis hemogafocítica (HLH)

- Origen infeccioso:
  - Fiebre de origen desconocido
  - Sepsis grave
  - Infecciones víricas: VEB, CMV, SARS-CoV-2 y VHS
  - Parasitosis: leishmania
- Hepatopatías que cursen con fallo hepático agudo
  - Hepatitis aloinmune gestacional (GALD): presentación en periodo neonatal
- Coagulopatías
- Hemopatías:
  - Histiocitosis de células de Langerhans
  - Síndrome de Castleman
  - Leucemia aguda
  - Linfoma
- Tumores sólidos
- Reacciones alérgicas
- Cuadros con afectación neurológica:
  - Meningitis/Meningoencefalitis vírica/bacteriana
  - Encefalomielitis diseminada autoimmune (ADEM)
  - Vasculitis
  - Encefalitis de Rasmunssen's
  - FIRES *(febril infection-related epilepsy)*
  - Encefalopatía necrotizante aguda
- Enfermedades autoinmunes:
  - Esclerosis múltiple
  - Síndrome linfoproliferativo autoinmune (ALPS)
  - Enfermedad de Kawasaki
- Errores innatos del metabolismo:
  - Osteopetrosis
  - Enfermedad de Wolman
  - Enfermedad de Gaucher
- Otros: interferonopatías



TPH es el único tratamiento curativo

Epipodofilotoxinas (Etoposido, Temiposido)

Corticoides (1º dexametasona en HLH SNC)

± Inmunosupresores + Tto etiológico específico

± Tto Soporte: Profilaxis con Contrimoxazol + Antifungicos + Antivirales
Inmunoglobulina IV 0.5mg/kg c/4ss

F-HLH, Recaída o Refractario

- Continuar después de 8ss
- Biológicos (Alemtuzumab, Ruxolitinib, Siltuximab, Emapalumab)
- Luego: TPH
- Si Recaída SNC: MTX intratecal

M-HLH

- ✓ QT lo antes posible
- ✓ Si se alcanza remisión, se puede continuar solo QT.
- ✓ Vigilar sobreinfección y complicaciones de QT.

MAS

- ❑ Complicación en Enf. Reumatogógicas (debut o desencadenado por tto inmunosupresor)
- ❑ No cumple criterios de HLH
- ❑ Corticoides (altas dosis)
- ❑ Si no responde: Ciclosporina
- ❑ Si refractario: Biológicos

TPH

- ➢ Único tratamiento curativo
- ➢ En F-HLH y Forma 2º refractario
- ➢ Alogénico, compatibilidad HLA
- ➢ Supervivencia a los 5 años del 81% en niños.
- ➢ Supervivencia a los 5 años de HLH 2º del 86 % si causa infecciosa y 15% si tumoral.

EMAPALUMAB

- ❖ Anti INF-γ
- ❖ F-HLH, Refractario o Recaída
- ❖ Antes de inicarlo: D/C TB
- ❖ En combinación: Emapalumab+Etoposido+Dexametasona

PRONOSTICO

- Principal factor pronóstico: Remisión tras 8 semanas de tratamiento
- Otros:
  - M-HLH (peor pronóstico)
  - Controlar desencadenante cuanto antes
  - FRA y FMO
  - Carga viral
  - Hiperferritinemia, Hipofibrinogenemia, Hipoalbuminemia

PREVENCIÓN → Consejo Genético

GRACIAS

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