SÍNDROME HEMOFAGOCÍTICO SECUNDARIO: Causas y Manejo

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CASO CLÍNICO

-Lactante de 11 meses con proceso febril de 4 días de evolución, vómitos, decaimiento, distensión abdominal y edema.

-**Exploración física:**

- Pálidez cutánea, hematoma por venopunción.
- Faringe hiperémica, otoscopia normal.
- ACP normal.
- Abdomen: Hepatomegalia palpable de 2 traveses y esplenomegalia de 3 traveses.
- Neurológico normal para su edad.

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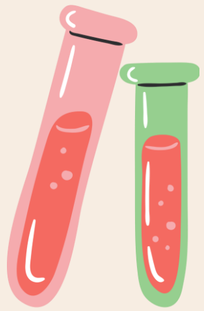

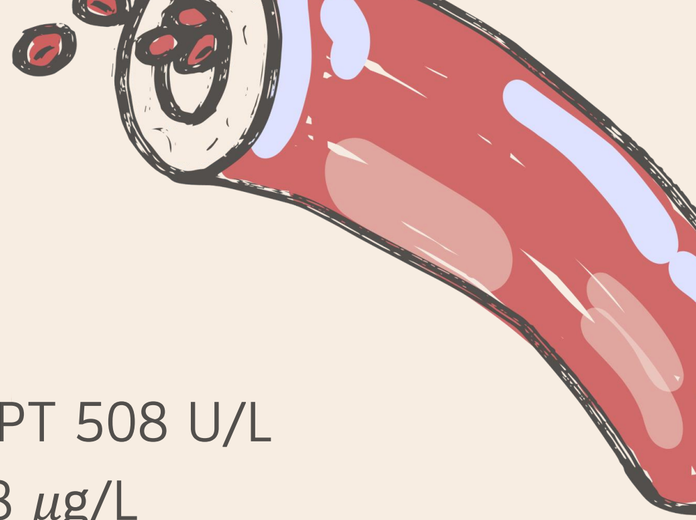

-**Bioquímica**: PCR 2,9 mg/dL PCT 2,93 ng/mL GOT 345 U/L GPT 508 U/L GGT 344 U/L // Iones normales. LDH 474 U/L Ferritina 1.138 μg/L Triglicéridos 868 mg/dL

-**Hemograma**: Leucocitos 13.600/μL Neutrofilos 350/μL Hb 7,7 g/dL Plaquetas 30.000/μL

-**Coagulación**: Fibrinógeno de Claus 47 mg/dL.

-**Sangre periférica**: Linfocitosis con abundantes linfocitos de aspecto activado. No células inmaduras de aspecto blástico. A descartar proceso infeccioso/vírico. Neutropenia grave. Anemia microcítica.

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Síndrome Hemofagocítico

- **Definición**: proceso de hiperinflamación grave y potencialmente letal, caracterizado por una disfunción inmunitaria profunda. Se manifiesta como una activación descontrolada del sistema inmune que conduce a una tormenta de citoquinas y daño tisular.
- **Fisiopatología**: el núcleo patogénico es el fallo de la vía citotóxica dependiente de perforina y granzima b.

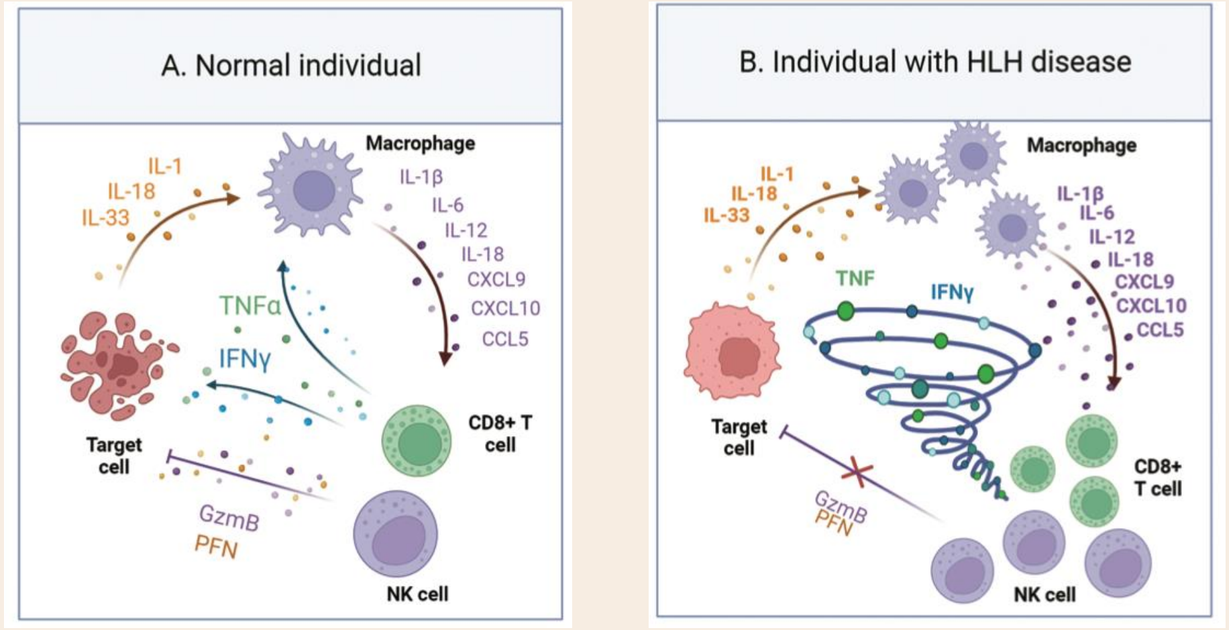

Figura 1. Adaptada de Deza Leon M, et al. Infectious diseases evaluation of the child with suspected hemophagocytic lymphohistiocytosis. J Pediatr Infect Dis Soc. 2024;13(3):página 223.

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CRITERIOS DIAGNÓSTICOS

- **El diagnóstico se establece con una mutación genética compatible o cumpliendo al menos 5 de los 8 criterios internacionales.**

1. Fiebre: ≥38,5ºC
2. Esplenomegalia: Detección clínica o por imagen
3. Citopenias (≥2 líneas): Hb < 90 g/L (neonatos < 100 g/L); Plaquetas < 100 x 109/L; Neutrófilos < 1 x 109/L
4. Hipertrigliceridemia y/o Hipofibrinogenemia: Triglicéridos ≥265 mg/dL y/o Fibrinógeno ≤150 mg/dL
5. Hemofagocitosis: En médula ósea, bazo o ganglios linfáticos
6. Actividad de células NK: Baja o ausente
7. Ferritina ≥500 ng/mL
8. CD25 soluble (sIL-2R) ≥2.400 U/mL

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CRITERIOS DIAGNÓSTICOS

TABLE 1.
Hemophagocytic Lymphohistiocytosis 2004 Criteria (3–6)

A) Molecular Diagnosis	Pathogenic Biallelic Mutation in Genes Associated With HLH: *PRF1*, *UNC13D*, *STX11*, *STXBP2*, *LYST*, *RAB27A*, *XIAP*, *SH2D1A*, and *NLCR4*		
B) Clinical and Laboratory Criteria	**For Clinical Diagnoses, Greater Than or Equal to Five of The Eight Criteria Below Must Be Met**		
Feature	**Cutoff**	**Assumed Mechanism**	**Comments**
HLH-2004 diagnostic criteria			
Fever		Elevated cytokines	May be altered by antipyretics & steroids
Splenomegaly		Infiltration by lymphocytes and histiocytes	
Cytopenia	≥ 2 cell lines	Suppression by cytokines and hemophagocytosis	Check for toxic marrow failure in patients after chemotherapy
Hemoglobin	< 90 g/L (neonates < 100 g/L)		
Platelets	$< 100 \times 10^9$/L		
Neutrophils	$< 1 \times 10^9$/L		
Hypertriglyceridemia or hypofibrinogenemia	≥ 265 mg/dL (≥ 3 mmol/L) ≤ 150 mg/dL (≤ 1.5 g/L)	Lipoprotein lipase suppression by cytokines; plasminogen activator produced by macrophages	Triglyceride levels may be altered by parenteral nutrition
Hemophagocytosis	Bone marrow, other tissues	Due to macrophage activation	
Hyperferritinemia	≥ 500 ng/mL (≥ 500 µg/L)	Released from activated macrophages	Test dilution may be required
Reduced or absent natural killer-cell cytotoxicity		Due to genetic defect or transient dysfunction	CD107a assays[a] may be more valuable
Elevated soluble CD25 (soluble IL-2 receptor)	≥ 2,400 U/mL	Released by activated T-cells	Test dilution may be required
Other features			
Elevated transaminases and bilirubin		Infiltration by lymphocytes and histiocytes; viral triggers	
Elevated lactate dehydrogenase		Cell death and proliferation	
Elevated D-dimers		Hyperfibrinolysis	
Elevated CSF cells or CSF protein		Cell infiltration into the CNS	
Elevated soluble CD25/ferritin ratio (> 2)			Can suggest underlying malignant neoplasm
Hypoalbuminemia		Hypercytokinemia	
Hepatomegaly		Infiltration by lymphocytes, macrophages, and histiocytes	

HLH = hemophagocytic lymphohistiocytosis, CSF = cerebrospinal fluid.
[a]Also known as CD107a mobilization or degranulation assays.

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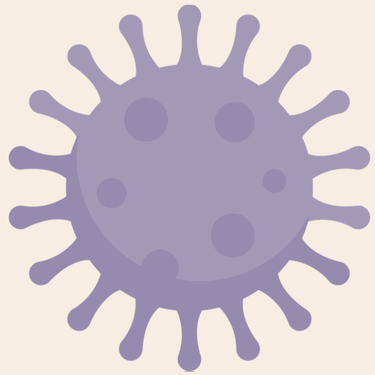
CASO CLÍNICO

PRUEBAS COMPLEMENTARIAS :

-Aspirado Nasofaríngeo (PCR): Positivo Rinovirus/Enterovirus y Parainfluenza.
-Hemocultivo negativo.
-PCR Leishmania no se detecta.
-Serología: Ac. heterófilos VEB Positivo.
-PCR VEB no se detecta.



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ETIOLOGÍA INFECCIOSA

Table 1. Infections that have been Associated with Development of HLH [5, 6]

Pathogen	Relevant Exposures	Testing
Virus		
Adenovirus	Contaminated swimming pools; childcare centers, military institutions, and healthcare settings	PCR on blood or nasopharyngeal sample
Cytomegalovirus	Childcare centers; healthcare settings	Serology
Dengue	Travel to or residence in endemic areas	RT-PCR, dengue virus NS-1 antigen by immunoassay, IgM serum antibodies
Enterovirus	Childcare centers; healthcare settings	RT-PCR of body fluid or stools
Epstein–Barr virus	Childcare centers, crowded housing, educational or military institutions	Serology
Hantavirus	Exposure to rodent droppings	Acute and convalescent serology
Hepatitis A virus	Foodborne outbreaks	Serology
Hepatitis B	Sharing or using nonsterilized needles; sexual contact with an infected person; perinatal exposure to an infected mother	Serology
Hepatitis C	Sharing or using nonsterilized needles; perinatal exposure to an infected mother	Serology; PCR on blood
Herpes simplex virus	Perinatal exposure to an infected mother	PCR on blood, CSF, or lesions
Human immunodeficiency virus	Sharing or using nonsterilized needles; sexual contact with an infected person; perinatal exposure to an infected mother	Antigen/antibody combination immunoassays
Human Herpesvirus-8	Travel to or residence in endemic areas; injection drug use	PCR on blood
Influenza A, B, and C	Contact with a symptomatic person during influenza season	Rapid molecular assays or RT-PCR of respiratory tract specimens
Measles	Childcare centers; unimmunized individuals	Acute and convalescent serology; RT-PCR of blood and NP sample
Parvovirus B19	Childcare centers	PCR of blood
Rotavirus	Childcare centers; unimmunized individuals	Stool antigen; multi-pathogen stool PCR
Rubella	Childcare centers; unimmunized individuals	Acute and convalescent serology
SARS-CoV-1	Travel to or residence in endemic areas	RT-PCR of respiratory tract specimens, stool, and blood; serum antibody testing

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ETIOLOGÍA INFECCIOSA

Bacteria		
Bartonella henselae	Contact with kittens, shelter cats, and stray cats	Serology; PCR of tissue
Borrelia burgdorferi	Travel to or residence in endemic areas	Serology followed by confirmatory testing with western immunoblot
Brucella spp.	Ingestion of unpasteurized dairy products; direct contact with infected animals or their carcasses	Culture of blood, bone marrow, or tissue; serum agglutination test
Campylobacter jejuni	Ingestion of undercooked poultry and meat, unpasteurized dairy, or contaminated water; contact with infected animals	Stool culture and PCR
Coxiella burnetii	Exposure to birthing of sheep, cattle, and goats; ingestion of unpasteurized dairy products	Acute and convalescent serology
Ehrlichia chaffensis	Tick bites; travel to or residence in endemic areas	Whole blood PCR; acute and convalescent serology
Leptospira interrogans	Exposure to urine of infected animals; wading, swimming, or boating in contaminated water	Acute and convalescent serology
Listeria monocytogenes	Foodborne outbreaks	Culture of body fluid or tissue
Mycobacterium avium-intracellulare complex	Exposure to fresh and brackish waters in warm climates	AFB culture of body fluid or tissue
Mycobacterium bovis	Ingestion of unpasteurized dairy products	AFB culture of body fluid or tissue
Mycobacterium tuberculosis	Travel or residence in high-prevalence regions; healthcare settings; crowded housing; correctional facilities; long-term care facilities	Tuberculin skin test or IGRA; AFB culture of body fluid or tissue
Mycoplasma pneumoniae	Contact with a symptomatic person	NAAT on respiratory tract specimens
Rickettsia spp.	Travel to or residence in endemic areas	Acute and convalescent serology
Fungi		
Aspergillus fumigatus	Decaying vegetation and soil	Culture of body fluid or tissue; galactomannan in serum or BAL fluid
Cryptococcus neoformans	Soil contaminated with pigeon or other bird droppings	Culture of body fluid or tissue; antigen in blood, CSF, or urine
Histoplasma capsulatum	Travel to or residence in endemic areas; exposure to bat guano and bird droppings	Antigen in serum, urine, BAL fluid, or CSF; complement fixation; immunodiffusion
Parasites		
Babesia microtii	Travel to or residence in endemic areas; tick bites	Manual review of blood smears
Leishmania spp.	Travel to or residence in endemic areas; mosquito bites	PCR or microscopic examination of tissue

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Síndrome Hemofagocítico: Clasificación

- **Primario (Hereditaria):** debido a mutaciones genéticas que afectan la citotoxicidad de las células natural killer (NK) y linfocitos T.

- **Secundario (Adquirida)**: resultado de una respuesta inmunitaria masiva ante un trigger infeccioso, neoplásico o autoinmune. En pediatría, la etiología viral es la causa más frecuente de sHLH.

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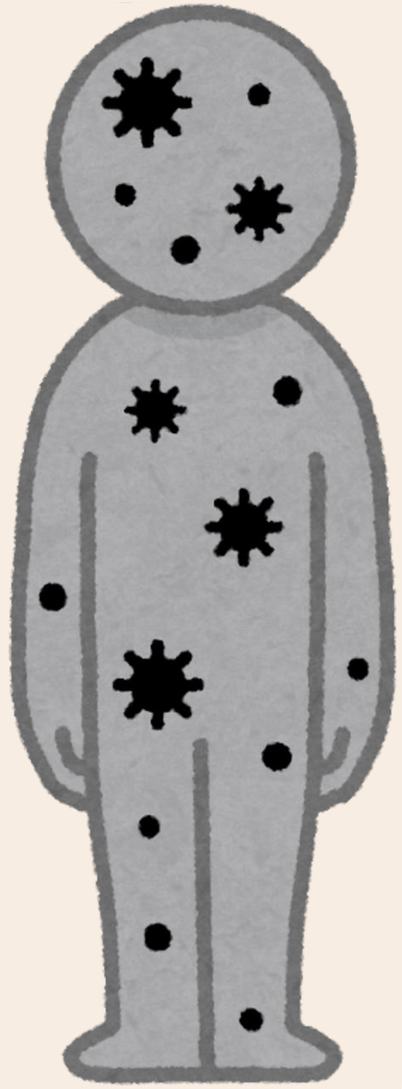
ETIOLOGÍA INFECCIOSA

VIRAL:

- **Herpesviridae**: Virus de Epstein-Barr (EBV) , Citomegalovirus (CMV), Virus del Herpes Simple (HSV) y Virus Varicela-Zóster (VZV).
- **Enterovirus:** Riesgo crítico y fulminante en etapa neonatal.
- **Virus Respiratorios:** Adenovirus, Influenza, Parainfluenza y SARS-CoV-2.
- **Otros**: Virus de Inmunodeficiencia Humana (HIV), Parvovirus B19 y Parechovirus 3.



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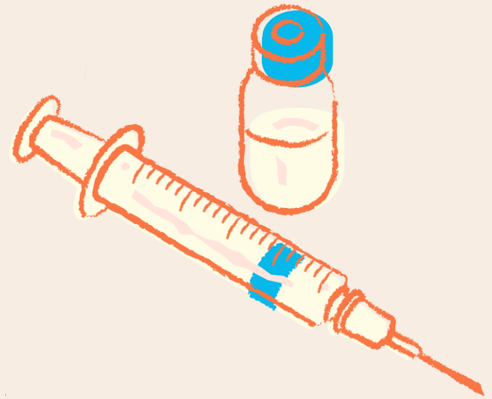
CASO CLÍNICO

-**Inicio Dexametasona a 10mg/m2/día** en dos dosis el segundo día de ingreso.



-A los dos días de tratamiento:

- Mejoría de criterios analíticos (Ferritina 264 μg/L, Neutrófilos 2.630/μL, Plaquetas 176.000/μL, Fibrinógeno 103 mg/dL) pese a persistencia de Hemoglobina de 8 g/dL.
- Hepatomegalia y esplenomegalia no palpables a exploración física.
- Mejoría estado general, manteniéndose afebril.

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MANEJO Y TRATAMIENTO

TABLE 4.

Organ Dysfunction in Secondary Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome-Hemophagocytic Lymphohistiocytosis Stratified by Severity and Response Criteria in ICUs According to Expert Consensus (19, 60, 61)

Proposed Severity of Secondary HLH in ICU-Admitted Patients		Therapy See Statement 9 Text and Supplementary Material (http://links.lww.com/CCM/G882) for Recommendations
Mild	No evidence of organ dysfunction except coagulation/hematologic system	Treat underlying trigger; consider glucocorticoid therapy in case of rapid deterioration
Moderate	Evidence of moderate organ dysfunction (SOFA or pSOFA score 2 or less per organ system excluding coagulation/hematologic system) Possible need for supplemental oxygen	Treat underlying trigger; strongly consider glucocorticoid therapy
Severe	Evidence of severe organ dysfunction (SOFA or pSOFA Score 3 or more of at least one organ system excluding coagulation/hematologic system) and/or any need for organ replacement therapy due to organ failure, including positive-pressure ventilation, renal replacement therapy, vasopressors, and extracorporeal life support	Treat underlying trigger; glucocorticoid therapy; add etoposide or additional immunomodulatory therapy based on underlying disease
Proposed Response to Therapy		**Therapy** **See Statement 9 Text and Supplementary Material (http://links.lww.com/CCM/G882) for Recommendations**
Response	Improvement in ferritin, normalization of temperature, and clinical stabilization (i.e., no worsening organ dysfunction) within 48–72 hr after start of therapy	Continue full treatment of trigger; reassess disease daily, and wean therapy as tolerated
Nonresponse	Lack of improvement in ferritin, persistent fever, and/or lack of clinical improvement > 48–72 hr after start of therapy	Reevaluate triggers to ensure they are treated; consider adding additional HLH-directed therapy
Progression	Increasing ferritin and/or persistent fever > 48–72 hr after start of therapy. Increasing need for support of organ dysfunction (i.e., positive-pressure ventilation, renal replacement therapy, increasing blood product replacement, and/or need for vasopressors and extracorporeal life support) at any point	Aggressively reevaluate triggers to ensure they are treated; highly consider the addition of other or additional HLH-directed therapies

HLH = hemophagocytic lymphohistiocytosis, pSOFA = pediatric sequential organ failure assessment, SOFA = sequential or assessment.

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MANEJO Y TRATAMIENTO

TABLE 5.
Recommended Therapies for Hemophagocytic Lymphohistiocytosis

HLH Type	Severity	Therapy
Primary and familial HLH	All	Per Ehl et al (58) based on HLH-94 therapy (17, 68)
Secondary HLH	Mild	Consider addition of corticosteroid therapy (58)
	Moderate	Dexamethasone 10 mg/m² daily divided every 12 hr (17, 58, 68) or equivalent methylprednisolone dosing (2 mg/kg/d) (58); consider addition of anakinra 2–10 mg/kg/d, divided in two to four daily doses (subcutaneous or IV) (22, 56, 62, 64, 65)
	Severe, progressive, or refractory	Addition of etoposide with dose reduction as follows (35, 66, 67) 100 mg/m² once weekly in older teens 75 mg/m² once weekly in adults 50 mg/m² once weekly in the elderly Renal dose reduction is recommended, per Ehl et al (58); dose reduction for hypoalbuminemia, hyperbilirubinemia alone, other evidence of liver dysfunction, and/or cytopenias is not recommended (58)
Macrophage activation syndrome-HLH	Mild	Steroids (such as methylprednisolone 30 mg/kg/d with max 1 g/d, for 3–5 d) with or without IVIG (69)
	Moderate	Consider addition of anakinra (dosing as above) and/or cautiously dosed cyclosporine (2 mg/kg/d in two divided doses aiming for serum levels of 100–150 ng/mL) and/or consideration of tocilizumab (35, 62, 70)
	Severe, progressive, or refractory	Consider addition of etoposide or cyclophosphamide (63, 69)
Malignancy-associated HLH	HLH-triggered organ damage (e.g., cytopenias, cholestatic icterus, pulmonary infiltrates, encephalopathy, or renal failure)	Two-step approach (11, 67) Etoposide (75–100 mg/m²), corticosteroids, and IVIG Once stabilized, start cancer-directed therapy
Additional Therapies	**Agent**	**Indication**
Adjunctive therapies	IVIG (18, 35, 56)	General anti-inflammatory and antiviral effects
	Plasmapheresis (71)	Anti-inflammatory effects; use with caution if giving a monoclonal antibody
	Cytokine adsorption columns (72)	Anti-inflammatory effects
Salvage therapies and agents under investigation	Alemtuzumab (73) Tocilizumab (74) Emapalumab (75) Ruxolitinib (76–79)	These agents have some evidence for specific use in HLH. Please see Supplementary Material (http://links.lww.com/CCM/G882) for list of current clinical trials

HLH = hemophagocytic lymphohistiocytosis, IVIG = IV immunoglobulin.

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GUÍA CONSENSO 2022
PUNTOS CLAVE

- **No retrasar la terapia**. El inicio de la terapia dirigida al SHF no debe posponerse mientras se espera a resultados de pruebas si existe una alta sospecha del mismo

- **Diagnóstico**. Los criterios diagnósticos del HLH-2004 sirven de guía práctica para el diagnóstico en pacientes pediátricos, 4 o más criterios han demostrado tener una sensibilidad del 95% y especificidad del 93%, siendo suficiente para iniciar tratamiento.

- **Soporte vital.** El manejo agresivo en la UCIP (ventilación, vasopresores, reemplazo renal) es crucial; el SHF no es una contraindicación para el soporte de vida extracorpóreo como puente al tratamiento específico

- **Alta mortalidad.** A pesar de los avances, el HLH pediátrico mantiene tasas de mortalidad elevadas (36–40%), a menudo debido a diagnósticos tardíos.

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GUÍA CONSENSO 2022

PUNTOS CLAVE

- **No retrasar la te** no debe posponerse mientras se espe lta sospecha del mismo
- **Diagnóstico**: Los de guía práctica para el diagnóstico en p demostrado tener una sensibilidad del 9 nte para iniciar tratamiento.
- **Soporte vital:** El sopresores, reemplazo renal) es crucial; soporte de vida extracorpóreo c
- **Alta mortalidad:** mantiene tasas de mortalidad eleva icos tardíos.

REVIEW ARTICLE

Consensus-Based Guidelines for the Recognition, Diagnosis, and Management of Hemophagocytic Lymphohistiocytosis in Critically Ill Children and Adults

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OBJECTIVE: Hemophagocytic lymphohistiocytosis is a hyperinflammatory syndrome that often requires critical care support and remains difficult to diagnose. These guidelines are meant to aid in the early recognition, diagnosis, supportive care, and treatment of patients with hemophagocytic lymphohistiocytosis in ICUs.

DATA SOURCES: The literature searches were performed with PubMed (MEDLINE).

STUDY SELECTION: Keywords and medical subject headings terms for literature search included "macrophage activation syndrome," hemophagocytic lymphohistiocytosis," and "hemophagocytic syndrome."

DATA EXTRACTION: The Histiocyte Society developed these consensus recommendations on the basis of published reports and expert opinions with level of evidence provided for each recommendation. They were endorsed by the Society of Critical Care Medicine.

DATA SYNTHESIS: Testing for hemophagocytic lymphohistiocytosis should be initiated promptly in all patients admitted to ICUs with an unexplained or disproportionate inflammatory response, especially those with rapid clinical deterioration. Meeting five or more of eight hemophagocytic lymphohistiocytosis 2004 diagnostic criteria serves as a valuable diagnostic tool for hemophagocytic lymphohistiocytosis. Early aggressive critical care interventions are often required to manage the multisystem organ failure associated with hemophagocytic lymphohistiocytosis. Thorough investigation of the underlying triggers of hemophagocytic lymphohistiocytosis, including infections, malignancies, and autoimmune/autoinflammatory diseases, is essential. Early steroid treatment is indicated for patients with familial hemophagocytic lymphohistiocytosis and is often valuable in patients with acquired hemophagocytic lymphohistiocytosis (i.e., secondary hemophagocytic lymphohistiocytosis) without previous therapy, including macrophage activation syndrome (hemophagocytic lymphohistiocytosis secondary to autoimmune/autoinflammatory disease) without persistent or relapsing disease. Steroid treatment should not be delayed, particularly if organ dysfunction is present. In patients with macrophage activation syndrome, whose disease does not sufficiently respond, interleukin-1 inhibition and/or cyclosporine A is recommended. In familial hemophagocytic lymphohistiocytosis and severe, persistent, or relapsing secondary macrophage activation syndrome, the addition of prompt individualized, age-adjusted etoposide treatment is recommended.

CONCLUSIONS: Further studies are needed to determine optimal treatment for patients with hemophagocytic lymphohistiocytosis in ICUs, including the use of novel and adjunct therapies.

KEY WORDS: extracorporeal life support; hemophagocytic lymphohistiocytosis; hyperferritinemia; macrophage activation syndrome; multiple organ failure

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CONCLUSIONES

- El Síndrome Hemofagocítico debe sospecharse en todo paciente con una **respuesta inflamatoria inexplicada o desproporcionada**, que no responde al tratamiento estándar.
- Sigue siendo un **desafío diagnóstico** por el solapamiento clinico con otros procesos hiperinflamatorios como la sepsis.
- La **causa más frecuente de SHF secundario** en edad pediátrica es viral. Sin embargo, incluso ante un desencadenante viral claro, es altamente recomendable realizar pruebas genéticas, ya que las formas primarias suelen debutar tras una infección común.
- El diagnóstico y **tratamiento precoz** siguen siendo determinantes en el pronóstico de este proceso hiperinflamatorio por su elevada mortalidad en el paciente pediátrico.

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