CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

Milano, Best Western Hotel Madison

29 maggio 2026

Sindrome Emofagocitica nell'età Adulta

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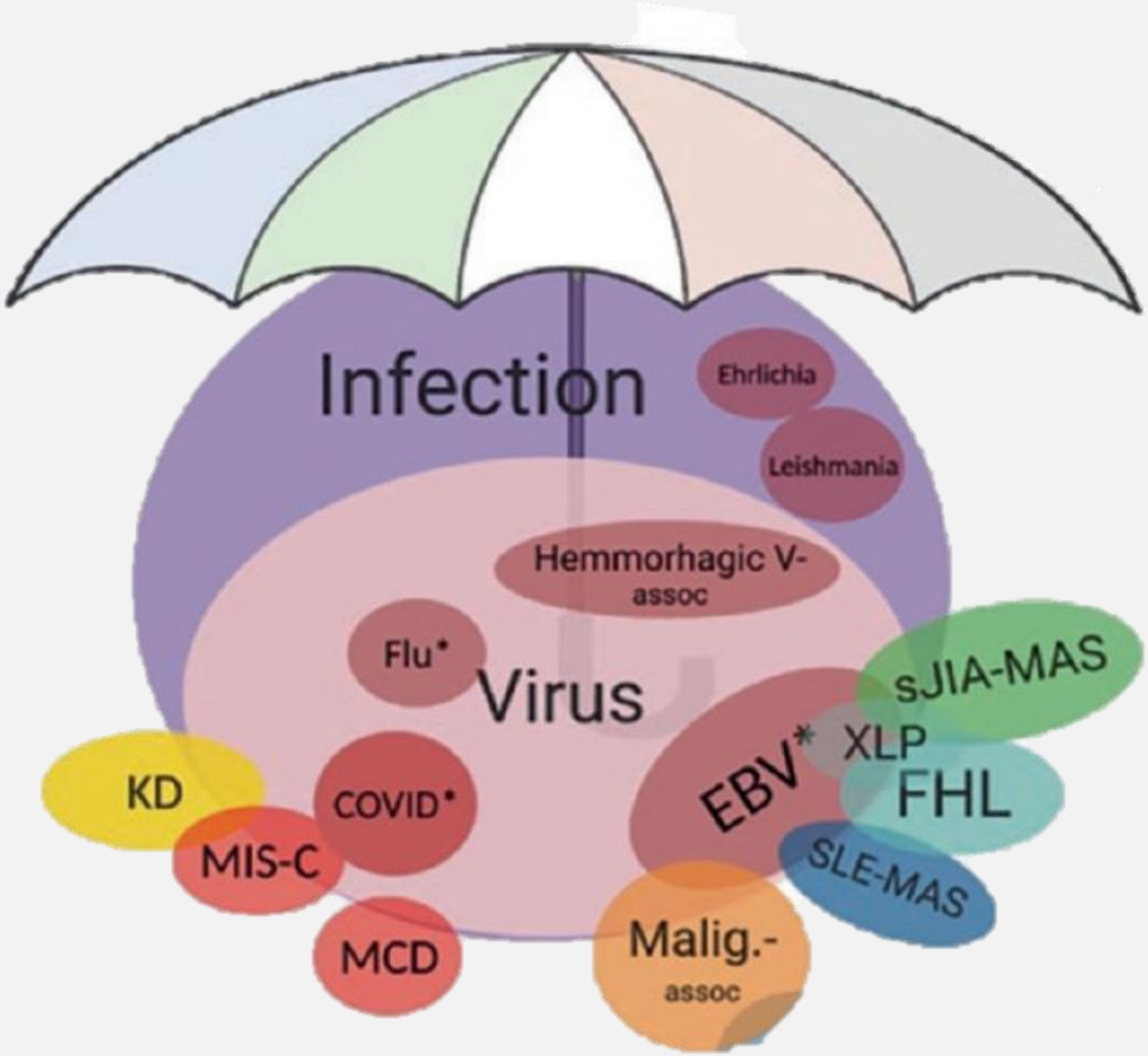
Fondazione IRCCS san Gerardo dei Tintori Monza

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
none							



CYTOKINE STORM SINDROMES

CYTOKINE STORM SINDROMES

Backbone: nomenclature

- first described in the medical literature in 1952
- only 3 publications on the topic in the 1950s, 1 in the 1960s, and <20 in the 1970s
- CSS, also referred to as **cytokine release syndrome**, is the systemic expression of a **vast array of inflammatory mediators that impact the body as a whole**

CSS

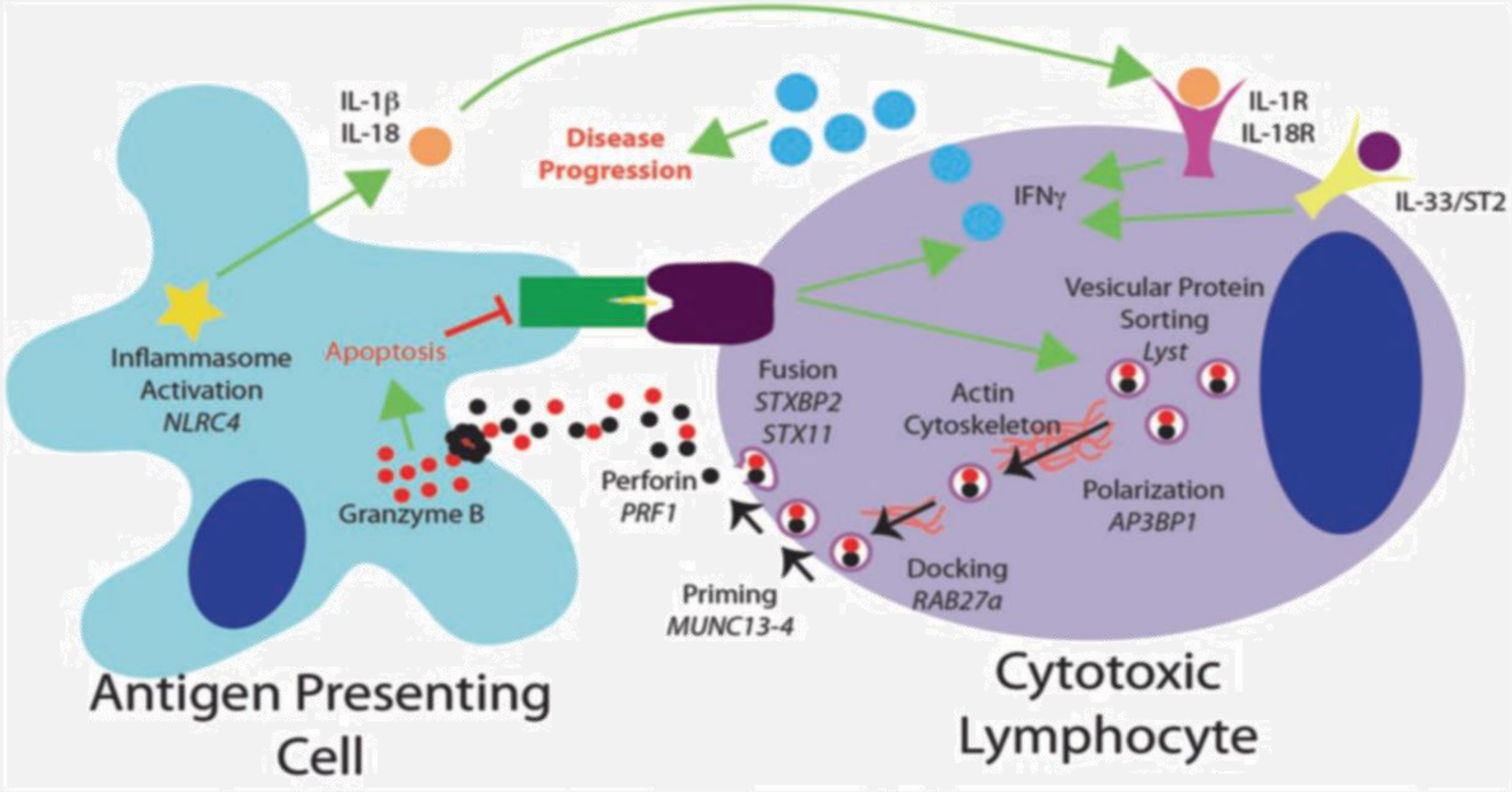
Hemophagocytic syndromes

hemophagocytic lymphohistiocytosis (HLH)

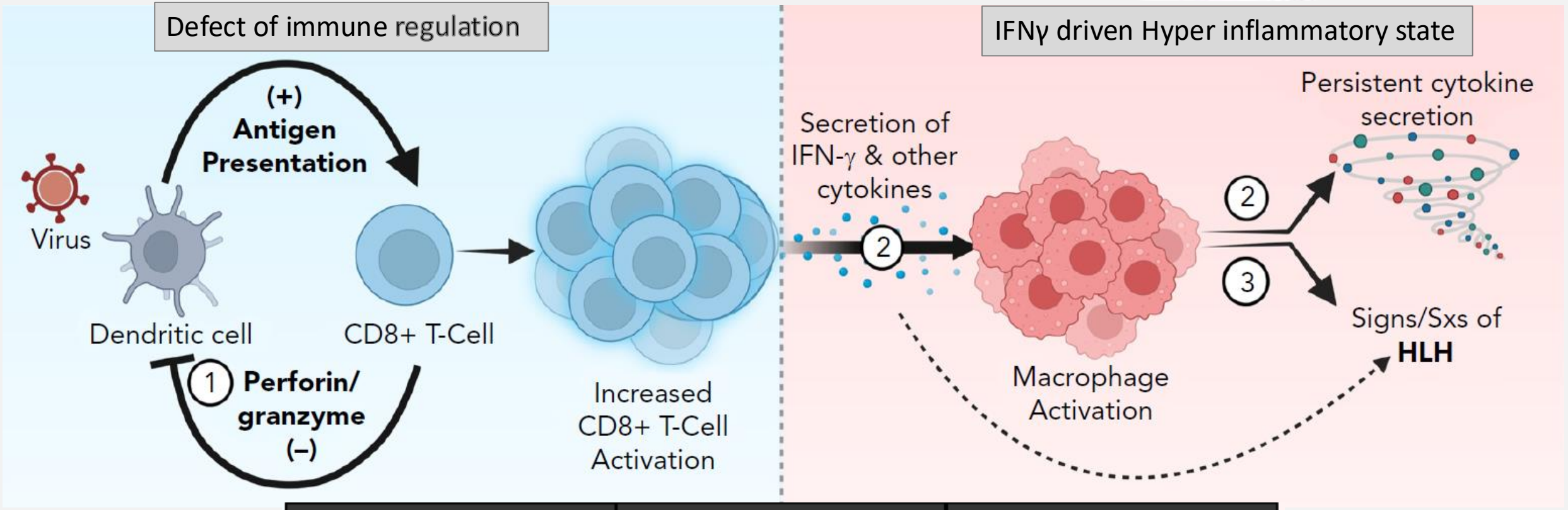
secondary (sHLH) (or acquired or reactive) forms

primary (or familial (fHLH))

fHLH: PATHOGENESIS



f or p HLH: PATHOGENESIS



1 Predisposing Immune Regulatory Defects	2 Significant/Unusual Immune Activation	3 Abnormal Immunopathology
• Genetic defect of cytotoxicity* • Family history of HLH • Other IEI • Impaired cytotoxicity* (CD107a, perforin, or SAP expression)	• Fever* • Splenomegaly* • Hepatomegaly • Elevated ferritin* • Elevated sIL-2Rα (sCD25)* • Elevated CXCL9 • $CD38^{hi}$/HLA-DR+ CD8+ T-cells	• Cytopenias* • Decreased fibrinogen* • Increased triglycerides* • Hemophagocytosis* • Hepatitis • CNS involvement • Evidence of TMA#

Mechanism	Gene	Protein	Functional Assay; Biomarker	Disease Name
1: Granule Mediated Cytotoxicity	*PRF1*	Perforin	Perforin/granzyme expression	FHL2
	UNC13D	Munc13-4	CD107a degranulation	FHL3
	STX11	Syntaxin 11	CD107a degranulation	FHL4
	STXBP2	Munc18-2	CD107a degranulation	FHL5
	RAB27A	Rab27a	CD107a degranulation	Griscelli Syndrome type 2
	LYST	LYST	CD107a degranulation	Chediak-Higashi Syndrome
	AP3B1	AP-3 complex subunit β1	CD107a degranulation; platelet dense granule analysis	Hermansky-Pudlak syndrome type 2
	NBAS	NBAS	CD107a degranulation	NBAS deficiency
	RHOG	RhoG	CD107a degranulation	RhoG deficiency
2: T-Cell Signaling	*SH2D1A*	SAP	SAP expression	XLP1
	MAGT1	Mg transporter 1	NKG2D expression (REF)	XMEN disease
	CD70	CD70	CD70 expression (REF)	CD70 deficiency
	CD27	CD27	CD27 expression (REF)	CD27 deficiency
	ITK	IL-2-Inducible T-cell kinase	N/A	ITK deficiency
3: Macrophage Function/Signaling	*HMOX1*	Heme oxygenase 1	N/A	HMOX1 deficiency
	SLC7A7	Y+LAT1	Blood and urine amino acid analyses (REF)	Lysinuric protein intolerance
4: Inflammasome Function	*XIAP*	XIAP	XIAP expression/function; IL-18	XLP2
	NLRC4	NLRC4	IL-18	AIFEC
	CDC42	CDC42	IL-18	NOCARH

Verkamp et al, March 2026

f or p HLH: PATHOGENESIS

F-HLH

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	UNC13D	Munc13-4	CD107a degranulation	FHL3
	STX11	Syntaxin 11	CD107a degranulation	FHL4
	STXBP2	Munc18-2	CD107a degranulation	FHL5
	RAB27A	Rab27a	CD107a degranulation	Griscelli Syndrome type 2
	LYST	LYST	CD107a degranulation	Chediak-Higashi Syndrome
	AP3B1	AP-3 complex subunit β1	CD107a degranulation; platelet dense granule analysis	Hermansky-Pudlak syndrome type 2
	NBAS	NBAS	CD107a degranulation	NBAS deficiency
	RHOG	RhoG	CD107a degranulation	RhoG deficiency
2: T-Cell Signaling	*SH2D1A*	SAP	SAP expression	XLP1
	MAGT1	Mg transporter 1	NKG2D expression (REF)	XMEN disease
	CD70	CD70	CD70 expression (REF)	CD70 deficiency
	CD27	CD27	CD27 expression (REF)	CD27 deficiency
	ITK	IL-2-Inducible T-cell kinase	N/A	ITK deficiency
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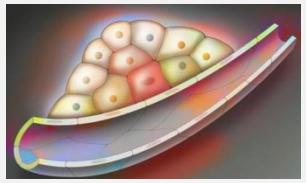
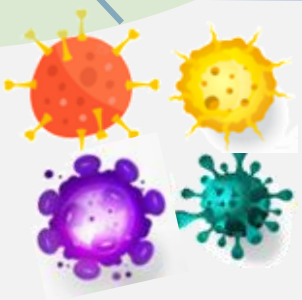
	NLRC4	NLRC4	IL-18	AIFEC
	CDC42	CDC42	IL-18	NOCARH

Pediatric Age directly to HLH

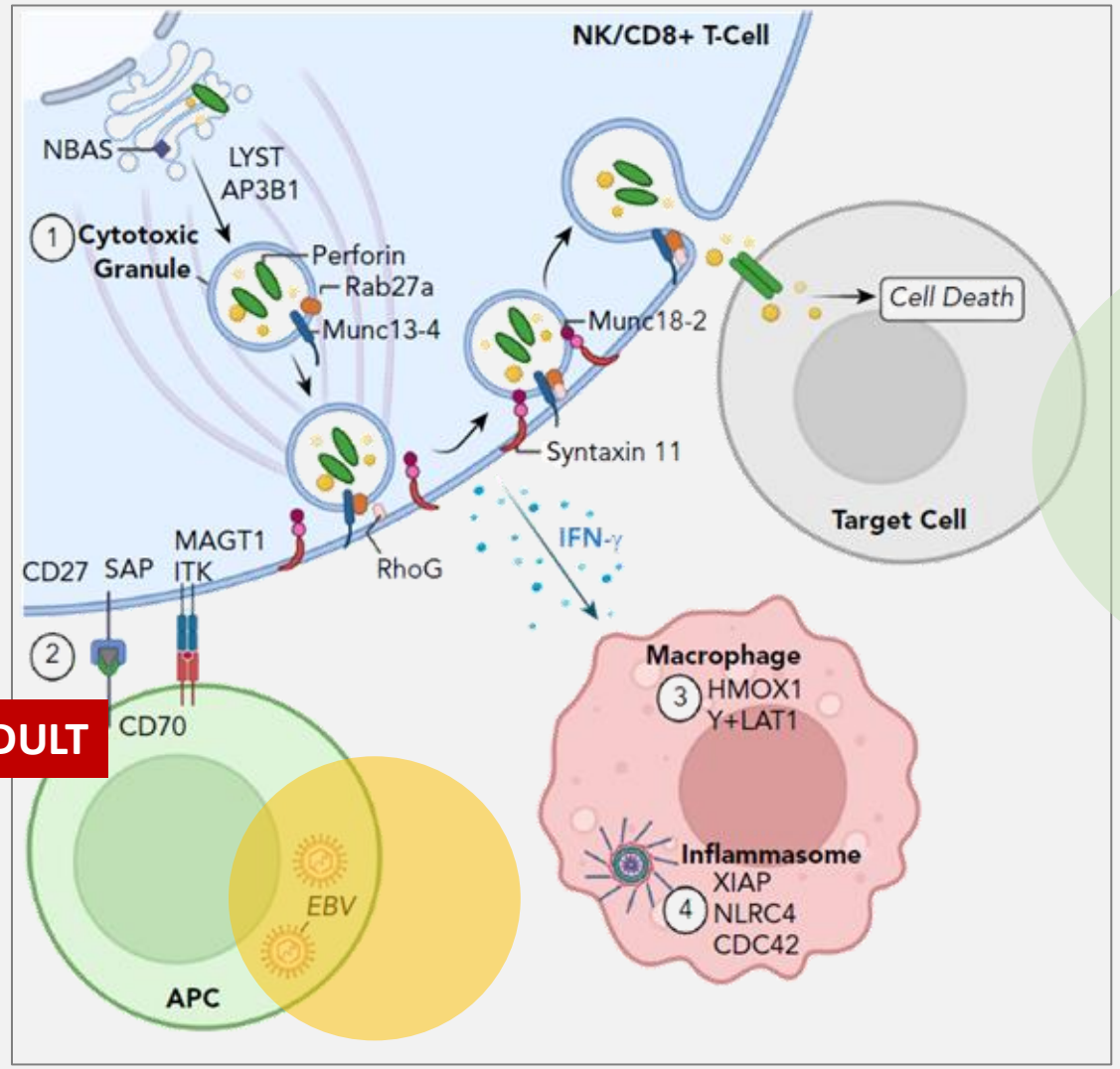
OR

Hypomoprhic mutations+
Strong immune trigger





ADULT

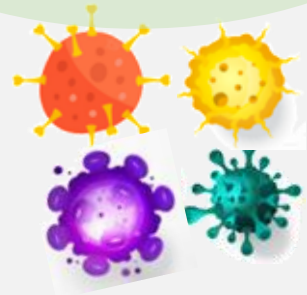


P-HLH

classic immunodeficiencies or inborn errors of immunity (IEIs), may develop an HLH-like process

+

Strong immune trigger



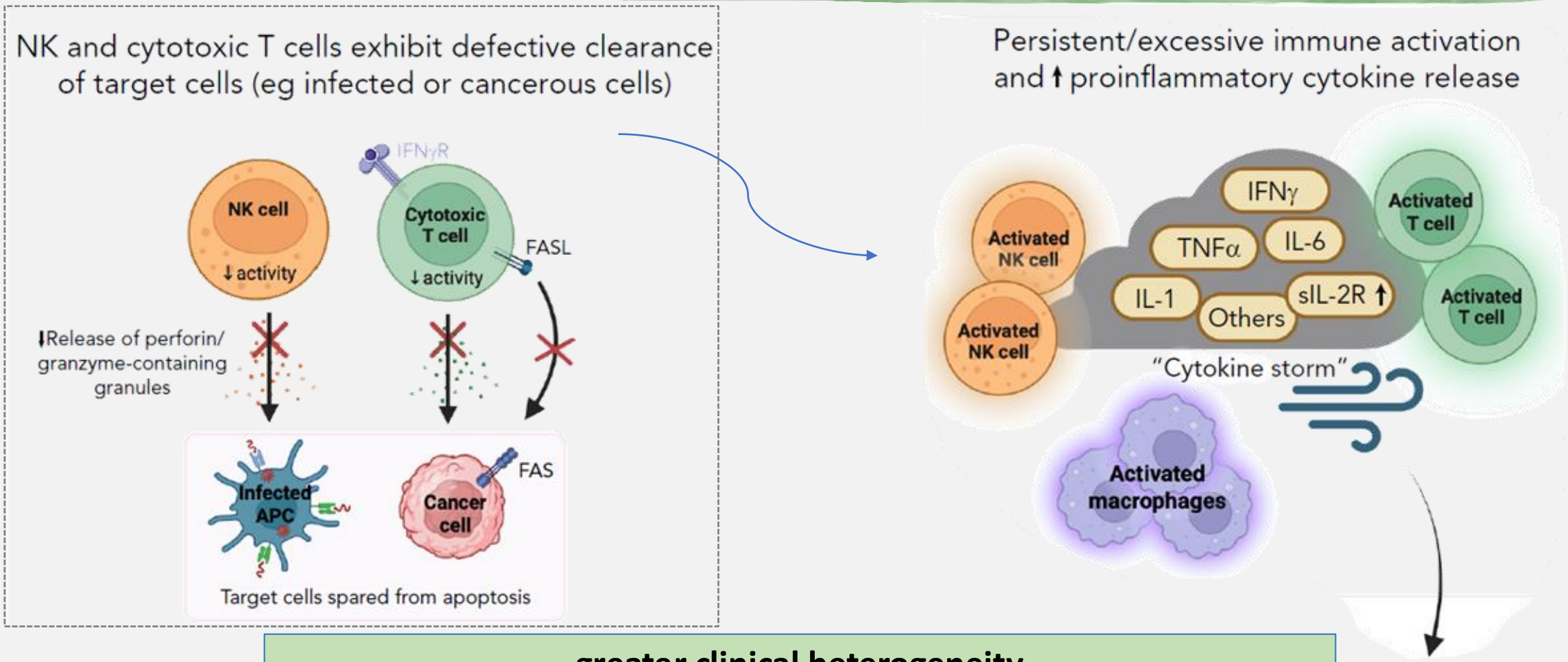
Verkamp et al, March 2026,modified

TAXONOMY

Common terms	Description
Primary HLH	HLH due to a genetic IEI with HLH as a common manifestation, lesions outside of the granule-mediated pathway (fHLH) may have a wider variability of recurrence risk
fHLH	HLH due to a genetic defect within the granule-mediated cytotoxic pathway (eg, PRF1, UNC13D, STX11, STXBP2), a form of primary HLH with very high recurrence risk
Secondary HLH	HLH predominantly driven by, or arising in the context of, another specific condition (eg, malignancies, rheumatologic diseases) without an identified genetic defect. Infection can trigger HLH in any category of HLH so are better thought of as "triggers" (see hereafter).
HLH trigger	An environmental factor, typically an infection, that activates the immune system, leading to abnormal immune hyperactivation recognized as HLH
MAS	A form of secondary HLH describing an HLH-like process in patients with a rheumatologic disease (most often Still disease; ie, sJIA)
Immune effector cell–associated HLH-like syndrome	An iatrogenic form of secondary HLH describing an HLH-like process after CAR T-cell infusions (similar to, but distinct from, CRS)

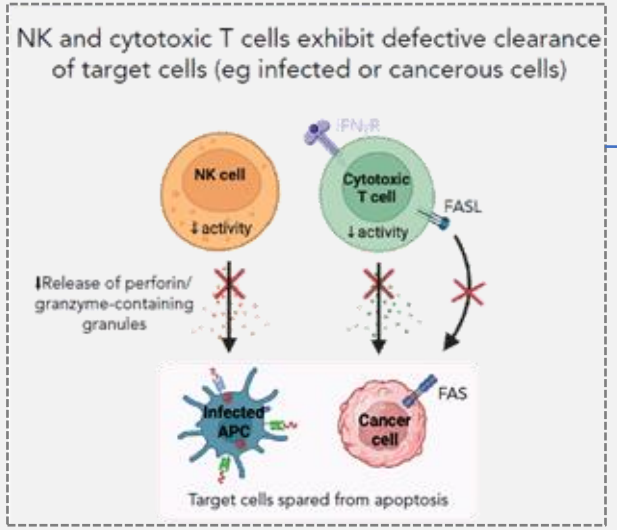
Verkamp et al, March 2026

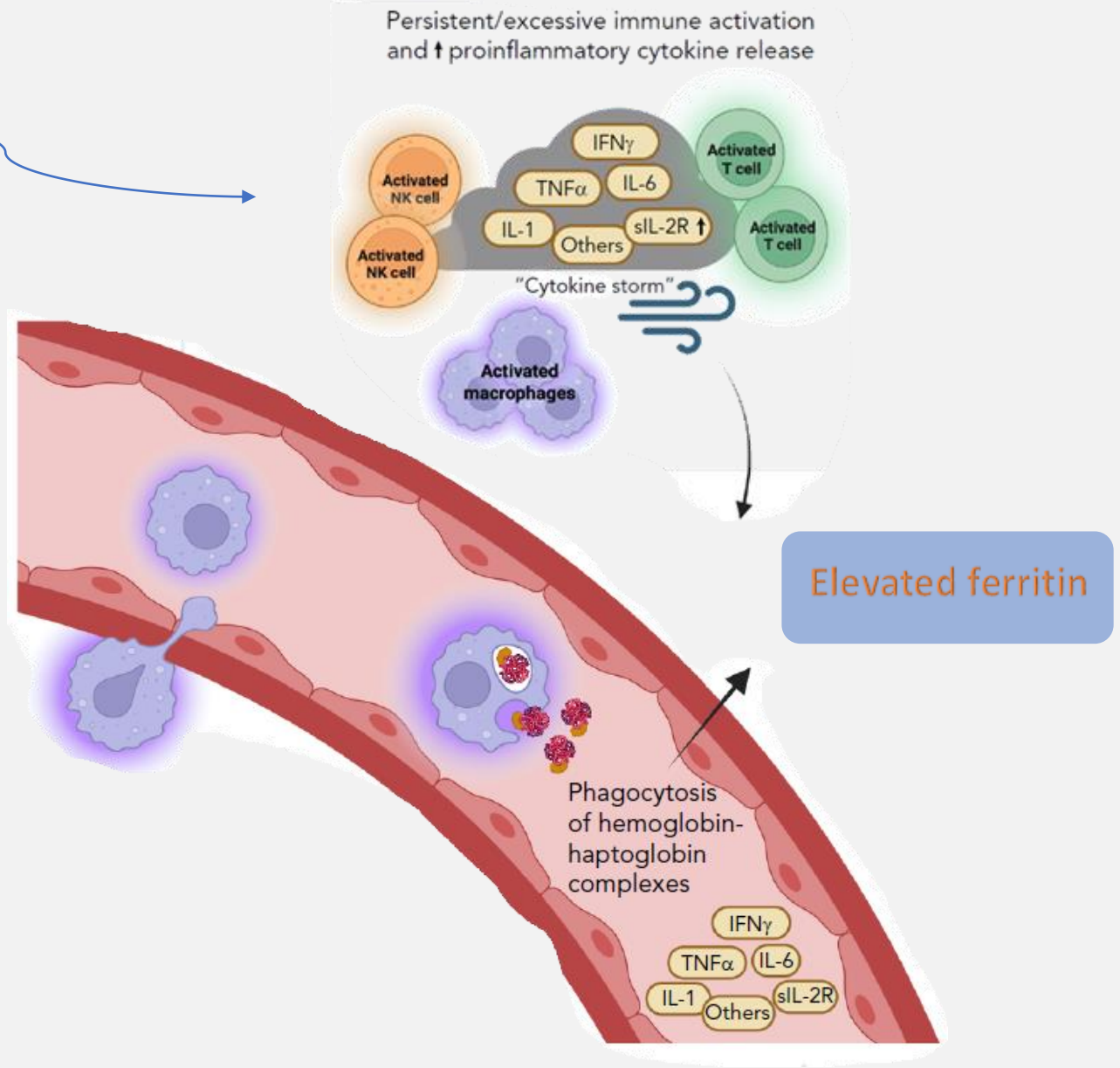
sHLH: PATHOGENESIS



greater clinical heterogeneity
its pathophysiology is still not completely understood
It originates from defects in the cytotoxic activity of NK cells o CD8+
triggered by specific clinical contexts.

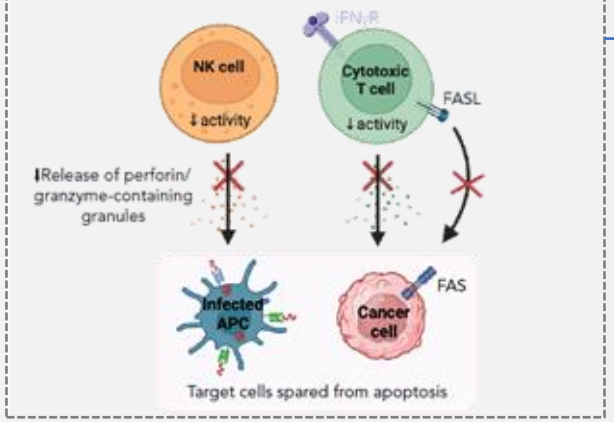
sHLH: PATHOGENESIS



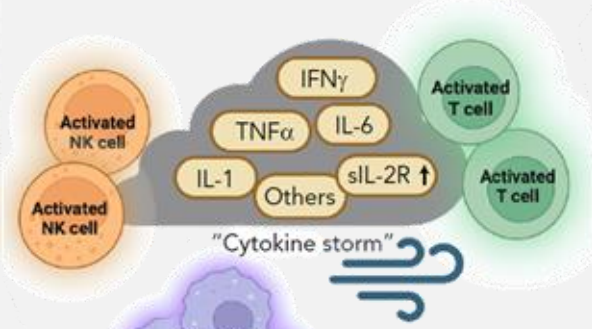


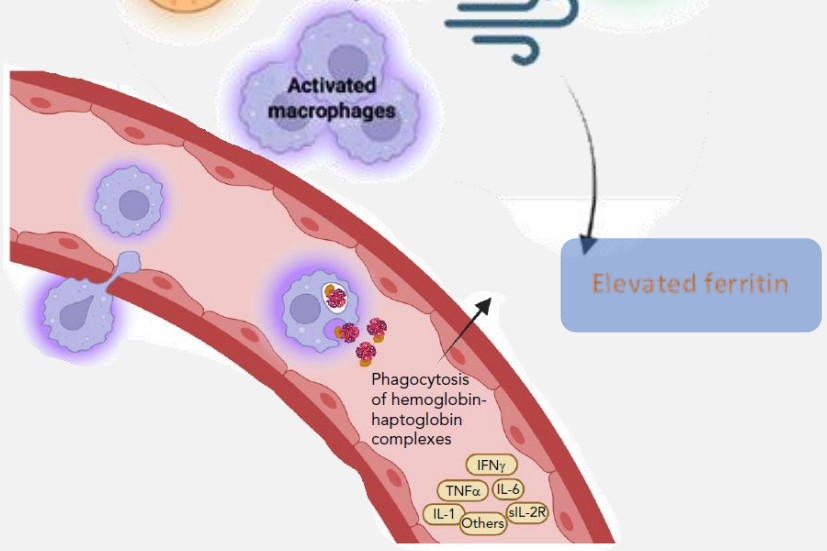
sHLH: PATHOGENESIS

NK and cytotoxic T cells exhibit defective clearance of target cells (eg infected or cancerous cells)



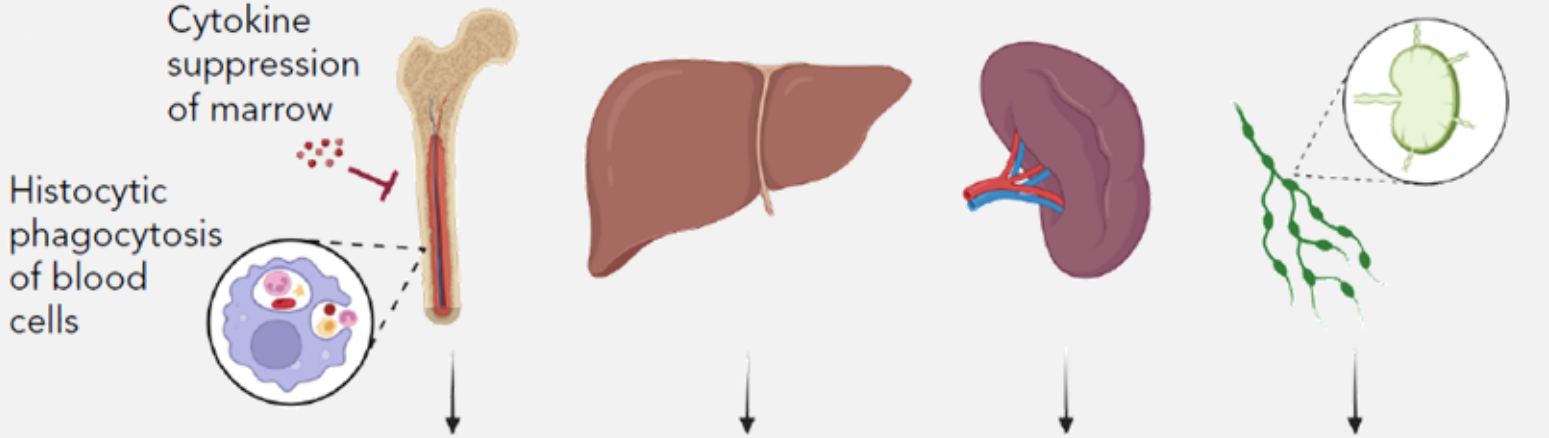
Persistent/excessive immune activation and ↑ proinflammatory cytokine release





Elevated ferritin

Tissue infiltration by activated macrophages



Fever

Lipoprotein lipase

High triglycerides

DIAGNOSTIC CRITERIA: HLH-2004 score

(1) A molecular diagnosis consistent with hemophagocytic lymphohistiocytosis (HLH)

(2) Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)

(A) Initial diagnostic criteria

Fever

Splenomegaly

Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood)

Hemoglobin < 9g/dL ; Platelets < 100x 10^9/L; Neutrophils < 1.0 x 10^9/L

Hypertriglyceridemia and/or hypofibrinogenemia:

Fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥ 2.65 g/L)

Fibrinogen ≤ 1.5 g/L

Hemophagocytosis in bone marrow or spleen or lymph nodes

(B) New diagnostic criteria

Low or absent NK-cell activity (according to local laboratory reference)

Ferritin ≥ 500 µg/L

Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2,400 U/ml

Developed in 2004 from pediatric trial databases (HLH-2004) and have since been adapted for diagnosing adult secondary HLH

HenterJI et al Pediatric Blood Cancer, 2007

DIAGNOSTIC CRITERIA: REVISED HLH-2004 CRITERIA

(1) A molecular diagnosis consistent with hemophagocytic lymphohistiocytosis (HLH)

Diagnostic criteria for HLH fulfilled (5 out 7 criteria below)

(A) Initial diagnostic criteria

Fever

Splenomegaly

Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood)

Hemoglobin < 9g/dL ; Platelets < 100x 10^9/L; Neutrophils < 1.0 x 10^9/L

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(B) New diagnostic criteria

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Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2,400 U/ml

Functional cellular findings (eg, perforin staining, T-cell degranulation, CD107a) consistent with fHLH in a patient with signs/symptoms of active HLH
Fever of ≥38.5°C
Splenomegaly (≥2 cm below the costal margin)

HenterJI et al Pediatric Blood Cancer, 2007

DIAGNOSTIC CRITERIA: H-SCORE

Hôpital Saint-Antoine AP-HP

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression*	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No. of cytopenias†	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (ng/ml)	0 (<2,000), 35 (2,000–6,000), or 50 (>6,000)
Triglyceride (mmoles/liter)	0 (<1.5), 44 (1.5–4), or 64 (>4)
Fibrinogen (gm/liter)	0 (>2.5) or 30 (≤2.5)
Serum glutamic oxaloacetic transaminase (IU/liter)	0 (<30) or 19 (≥30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)

Fardet L et al. Arthritis Rheumatol. 2014

DIAGNOSTIC CRITERIA: H-SCORE

Hôpital Saint-Antoine AP-HP

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No. of cytopenias†	0 (1 linea
Ferritin (ng/ml)	0 (<2,00
Triglyceride (mmoles/liter)	0 (<1.5),
Fibrinogen (gm/liter)	0 (>2.5)
Serum glutamic oxaloacetic transaminase (IU/liter)	0 (<30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or

HScore	Probability of hemophagocytic syndrome, %
90	<1
100	1
110	3
120	5
130	9
140	16
150	25
160	40
170	54
180	70
190	80
200	88
210	93
220	96
230	98
240	99
250	>99

Of 337 total possible points, **patients with a diagnosis of HLH had a median H-score of 230 and patients without HLH had a median H-score of 125.**

threshold of 169 points
→ sensitivity of 93%
→ specificity of 86%

Fardet L et al. Arthritis Rheumatol. 2014

DIAGNOSTIC CRITERIA: Optimized HLH Inflammatory INDEX -OHI-

HM/LA-HLH

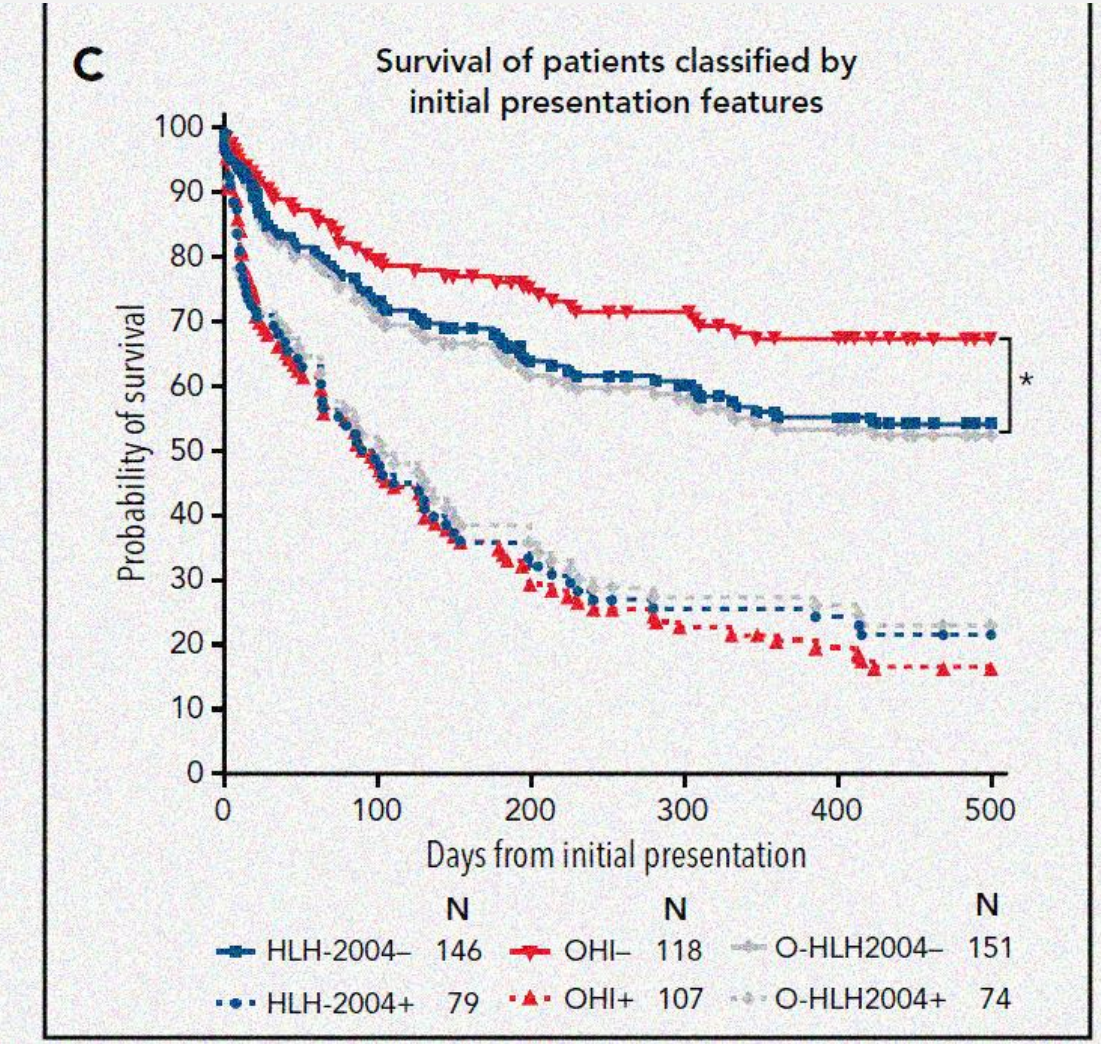
soluble CD25 >3900 U/mL

+

ferritin >1000 ng/mL

DIAGNOSTIC TOOL: Best identified HLH-2004–defining features (sensitivity 84%; specificity 81%)

PROGNOSTIC TOOL: highly predictive of mortality across diverse HMs



Adi Zoref-Lorenz Blood, 2022

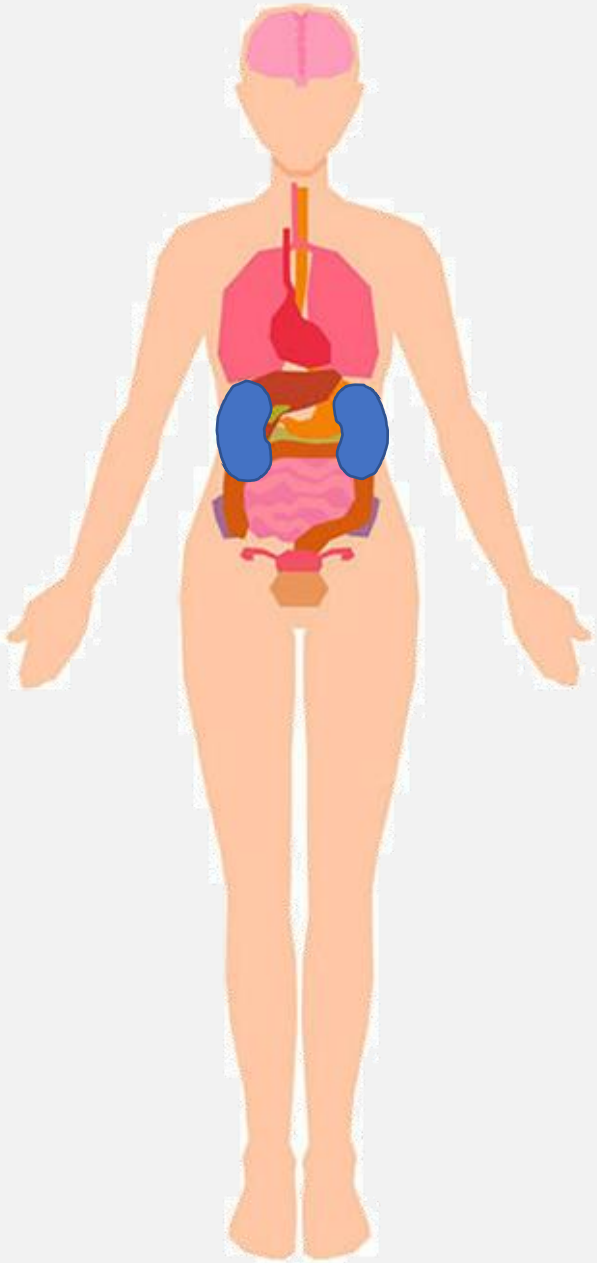
CLINICAL FEATURES

Symptoms may be due

- directly to cytokine induced tissue damage
- acute-phase physiological changes or
- may result from immune cell–mediated responses.

System	Clinical manifestations	Laboratory findings
General	Fever	Elevated C-reactive protein
		Fall in erythrocyte sedimentation rate
		Elevated soluble interleukin-2 receptor
Hematological	Petechiae	Leukopenia
	Purpura	Anemia
	Ecchymoses	Thrombocytopenia
	Epistaxis	Hemophagocytosis in bone marrow aspiration
	Lymphadenopathy	Hyperferritinemia
Skin	Rash	
	Erythroderma	
	Edema	
Respiratory	Acute respiratory distress	
	Pulmonary infiltrates	
Cardiac	Myocarditis	
Renal		Acute kidney injury
Gastrointestinal	Hematemesis	Transaminitis
	Rectal bleeding	Elevated bilirubin
	Hepatomegaly	Hypoalbuminemia
	Splenomegaly	Elevated ammonia
		Elevated triglycerides
Central nervous system	Altered mental state	Pleocytosis in cerebrospinal fluid
	Seizures	
	Encephalopathy	
	Coma	

CLINICAL FEATURES: ORGAN FAILURE



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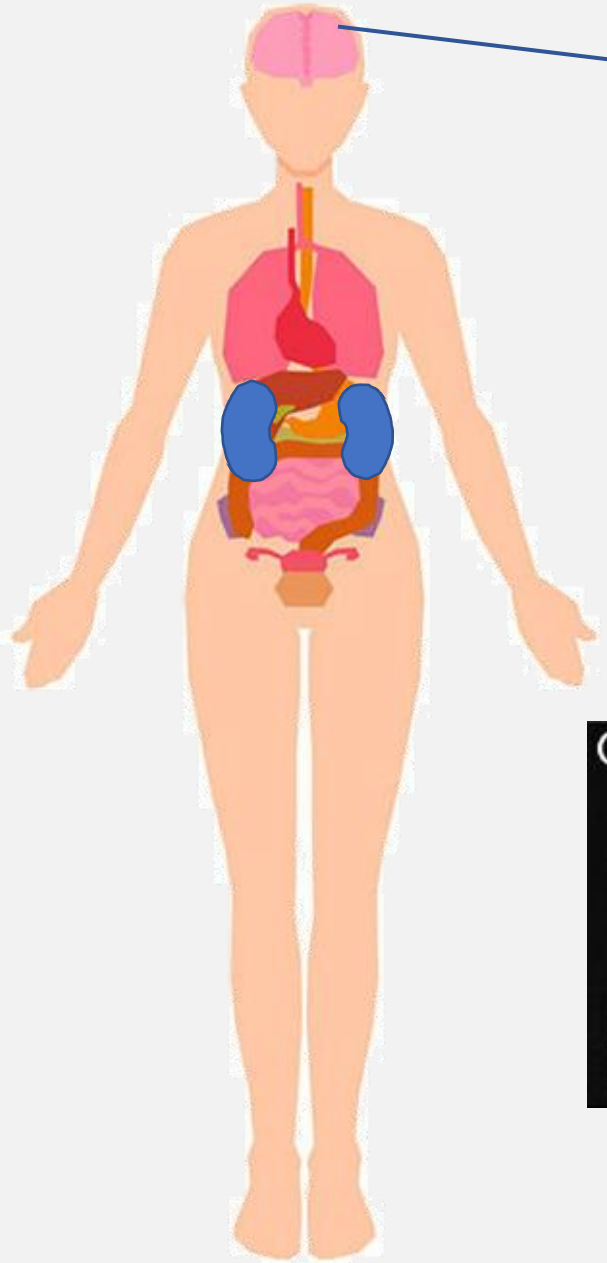
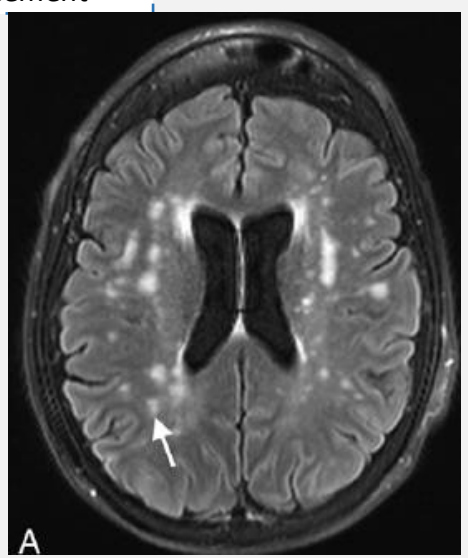
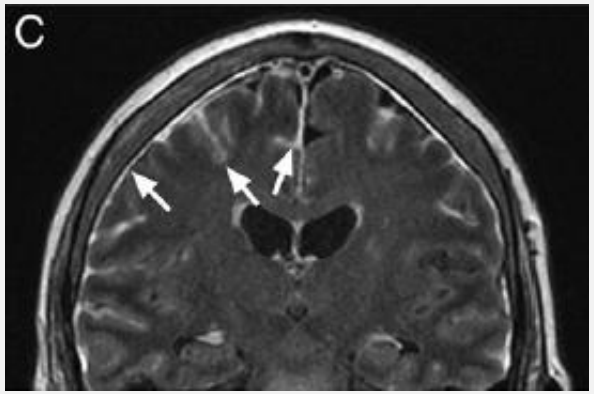


CEREBRAL (25%)

Mostly in children, abnormal CSF 58% cases
Very heterogeneous presentation ++
MRI = T2 hypersignal of the white matter, leptomeningeal contrast enhancement





Anderson TL Clin Imaging. 2015
Schmid et al, EMBO 2009

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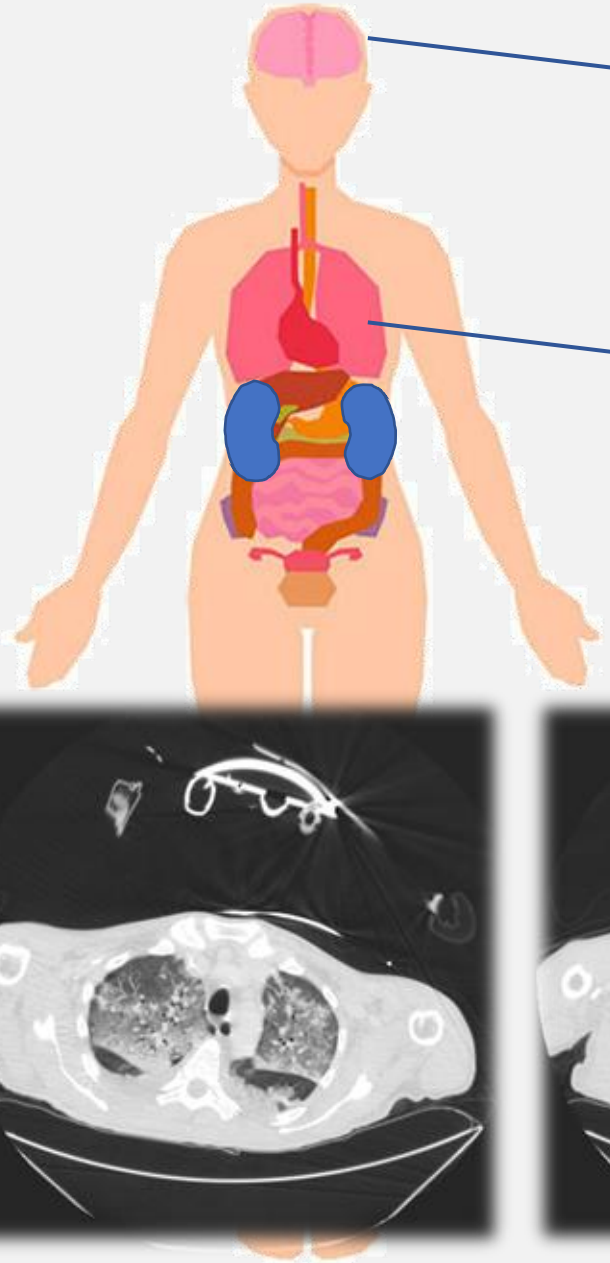

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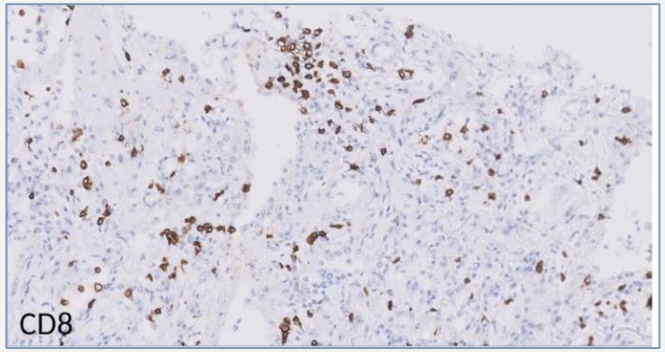
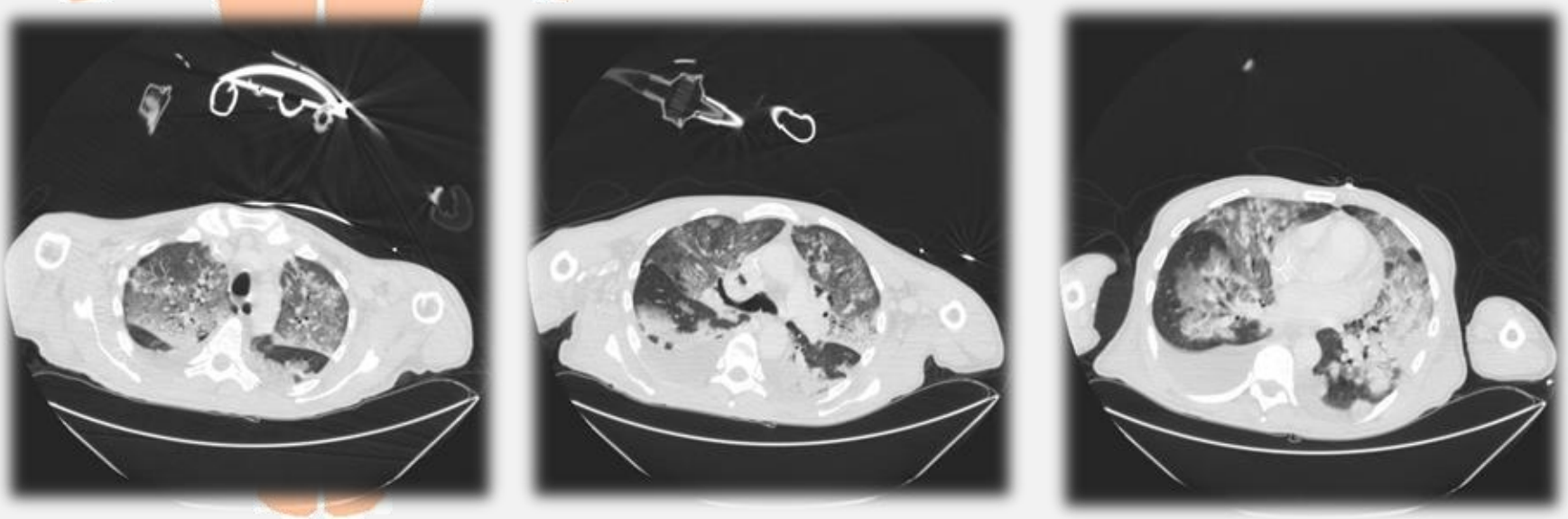
ICU: 45% of patients with abnormal GCS at ICU admission

PULMONARY (40%)

Aspecific: cough, dyspnea…
Acute respiratory failure = common reason for ICU admission
Mechanisms: **CD8 cells infiltration, pulmonary hemophagocytosis, capillary damage related to cytokine storm**
Chest X ray: non specific
Underlying etiology, multifactorial cause (20%)

ICU: 75% of patients with hypoxemia at ICU admission, MV 50%





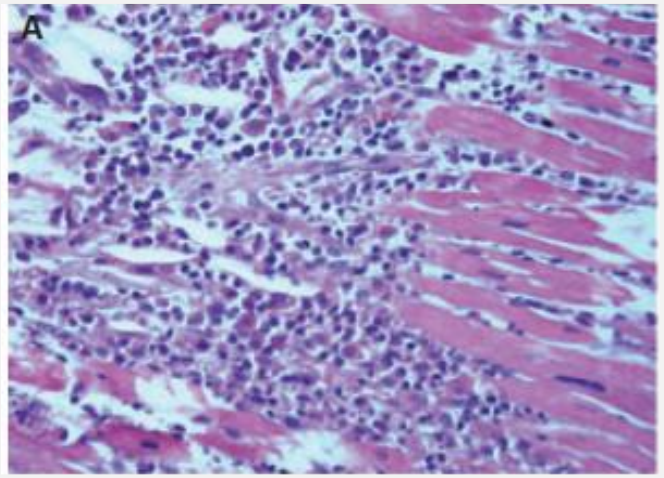
Prieto-Pérez L et al. Mod Pathol 2020
Ost et al. Histopathology. 1998
Seguin et al. Chest 2016

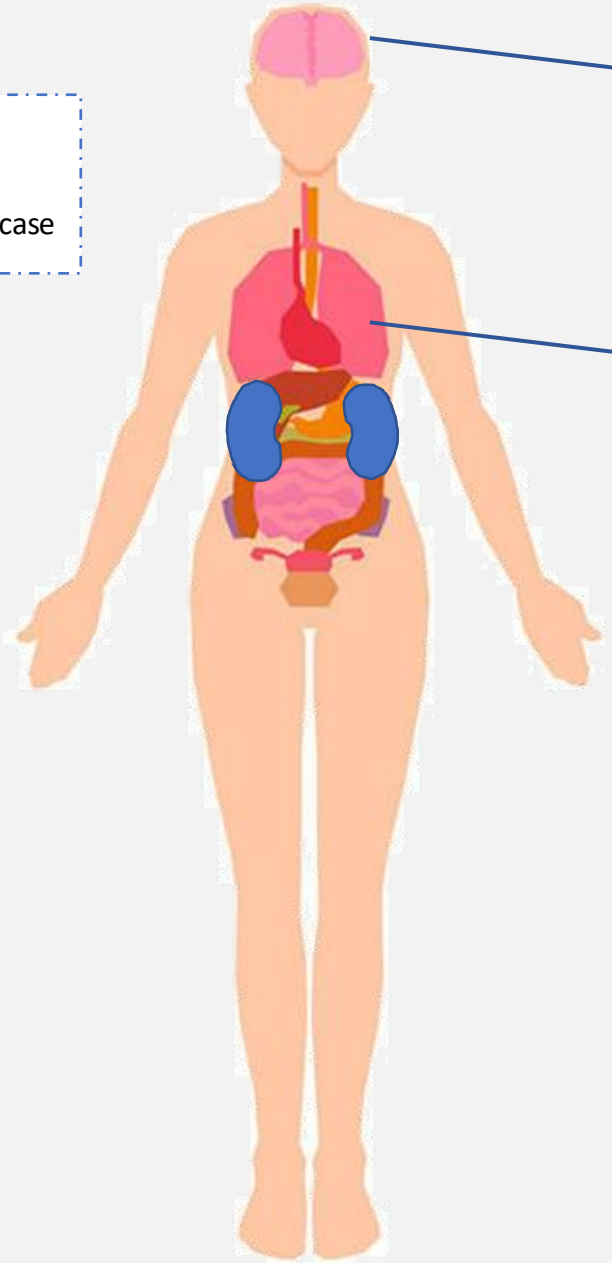
CLINICAL FEATURES: ORGAN FAILURE

ICU: 50% of patients with hemodynamic failure at ICU admission

CARDIAC (15%)

Specific myocarditis
Intra myocardial hemophagocytosis (case reports)





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Bal A et al. APMIS. 2009

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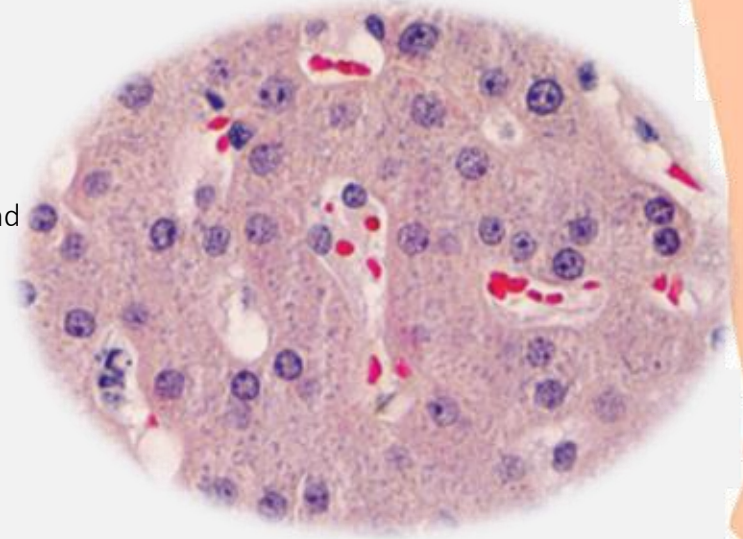
Intra myocardial hemophagocytosis (case reports)

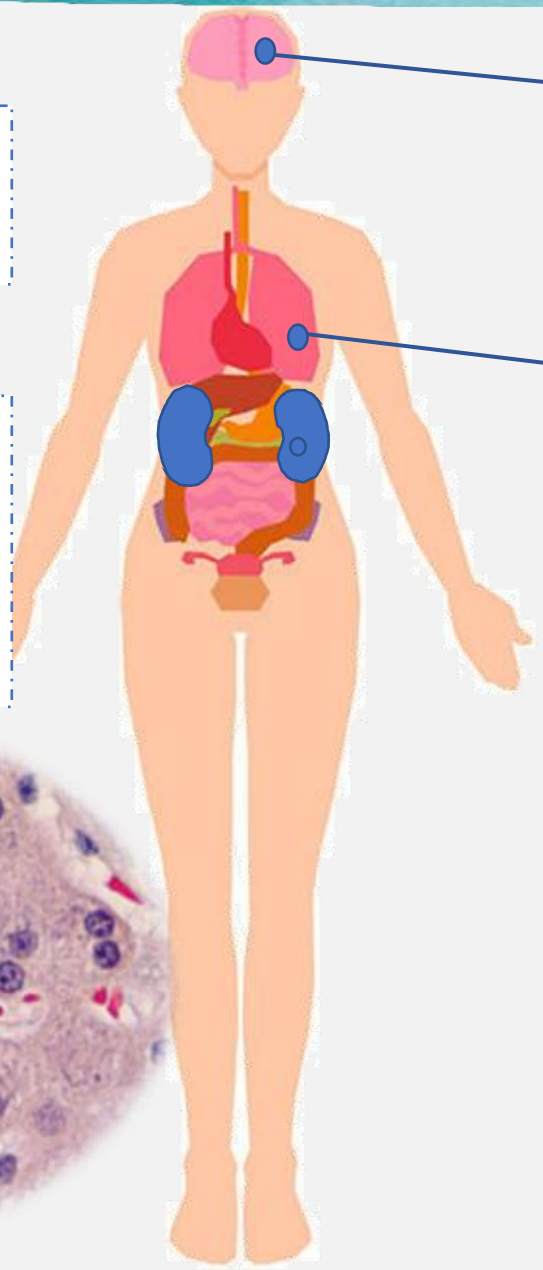
ICU: 70% of patients with elevated bilirubin level at ICU admission

HEPATIC (66%)

No correlation between ferritin levels and hepatic necrosis
Cholestasis > moderate cytolysis (if very high, think HSV++)
Histology: hemophagocytosis, necrosis, sinusoidal dilatation



Liver: there is typically Kupffer cell hyperplasia and scattered macrophages infiltrating the sinusoids



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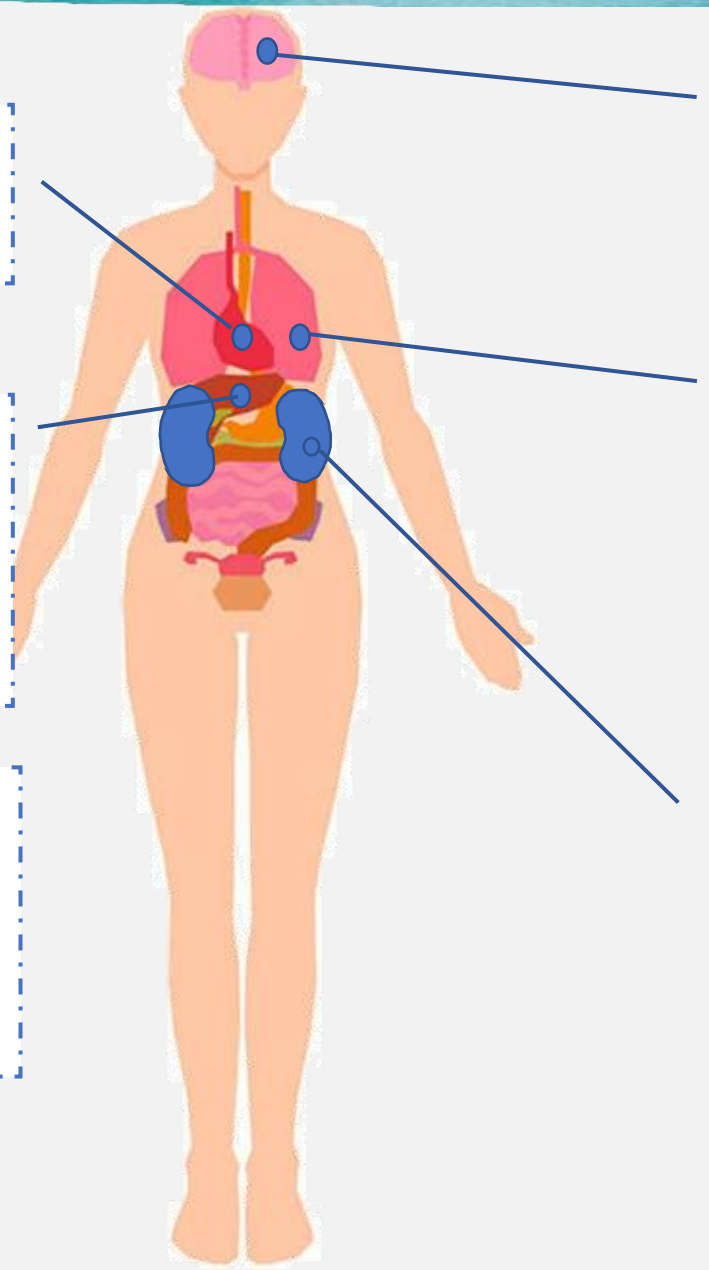
60% of pts present BM hemophagocytosis

CYTOPENIA (gradually development)

Infiltration of the bone marrow by macrophages with phagocytose of both mature and precursor hematopoietic cells +
Suppression of hematopoiesis by cytokines



CEREBRAL (25%)

Mostly in children, abnormal CSF 58% cases
Very heterogeneous presentation ++
MRI = T2 hypersignal of the white matter, leptomeningeal contrast enhancement

ICU: 45% of patients with abnormal GCS at ICU admission

PULMONARY (40%)

Aspecific: cough, dyspnea…
Acute respiratory failure = common reason for ICU admission
Mechanisms: **CD8 cells infiltration, pulmonary hemophagocytosis, capillary damage related to cytokine storm**
Chest X ray: non specific
Underlying etiology, multifactorial cause (20%)

ICU: 75% of patients with hypoxemia at ICU admission, MV 50%

RENAL (25%)

Acute renal failure (88%), nephrotic syndrome (38%)
Kidney biopsy: ischemic or inflammatory lesions, tubular necrosis +++, interstitial nephropathy, collapsing glomerulopathy…

ICU: 70% of patients with AKI at ICU admission, dialysis in 50%

SKIN (25%)

Erythematous, maculopapular skin rash, (frequently morbilliform) , no pruritus, sometimes generalized, transient
Sweet syndrome and pyoderma gangrenosum have been linked.
It can also be related to thombosytopenia

CLINICAL FEATURES: ORGAN FAILURE

ICU: 50% of patients with hemodynamic failure at ICU admission

CARDIAC (15%)

Specific myocarditis
Intra myocardial hemophagocytosis (case reports)

ICU: 70% of patients with elevated bilirubin level at ICU admission

HEPATIC (66%)

No correlation between ferritin levels and hepatic necrosis
Cholestasis > moderate cytolysis (if very high, think HSV++)
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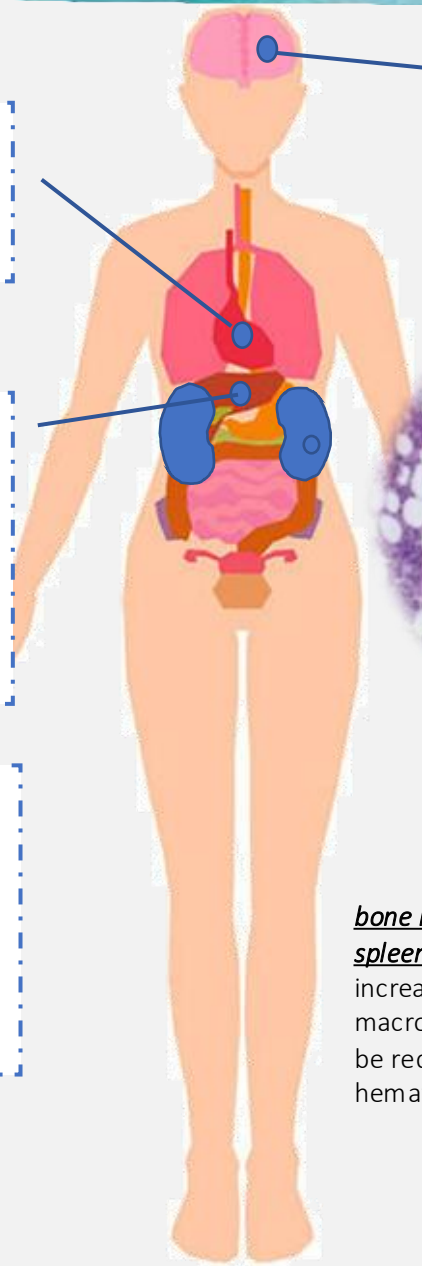

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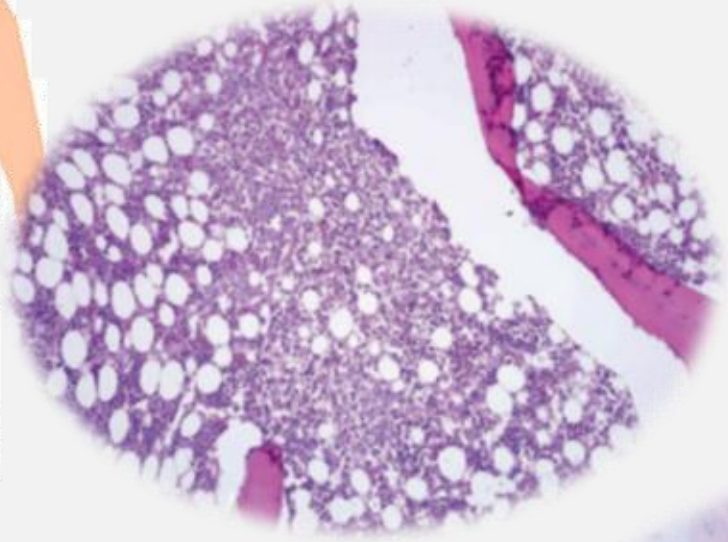
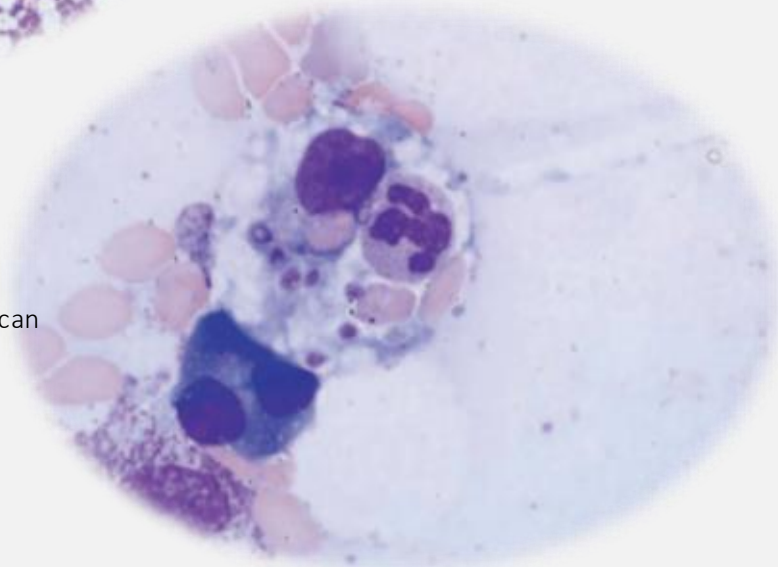


In the bone marrow, macrophages are accompanied by **small reactive lymphocytes, predominantly T cells**



bone marrow (but also inlymph nodes, spleen,skin, lungs,meninges, CSF:
increase in the number of phagocytizing macrophages containing intact cells, which can be red cells, white cells, platelets, or hematopoietic precursors

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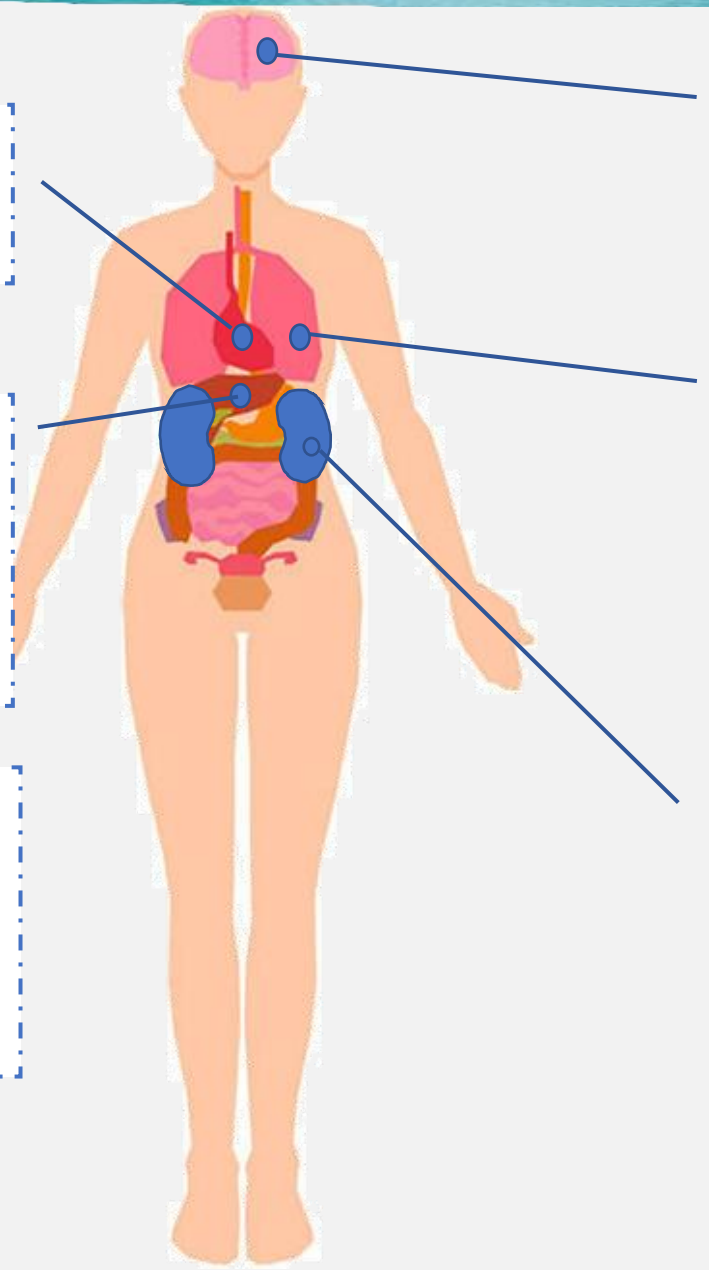

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HEMATOLOGISTS AND INFLAMMATION

SYSTEMIC BUT CLINICALLY INAPPARENT

- inflammaging

CHRONIC SYMPTOMATIC INFLAMMATION

- HM with inflammation or systemic autoimmune/inflammatory disorders

HEMATOLOGISTS AND INFLAMMATION: DD

SYSTEMIC BUT CLINICALLY INAPPARENT

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CHRONIC SYMPTOMATIC INFLAMMATION

- HM with inflammation or systemic autoimmune/inflammatory disorders

TOO MUCH INFLAMMATION

- Sepsis
- Macrophage activation like syndrome (MALS)
- Cytokine release syndrome (CRS)
- MAS-HLH
- Immune effector cell-associated HLH-like syndrome
- HLH

HEMATOLOGISTS AND INFLAMMATION: DD

Macrophage activation like syndrome (MALS)

sepsis → an inadequate host response to infection

High mortality rates in sepsis complicated by MALS (79%)

MALS:
Sepsis+
hyperinflammatory phenotype

excessive release of proinflammatory cytokines, IL-6,TNF-a, IFN-g, hyperferritinemia

MALS definition:

- ferritin cut-off of 4420 mg/ L in sepsis patients
- Dynamic rise of ferritin to 8000ng/ml
- hepatobiliary dysfunction and DIC

MAS-HLH

Macrophage activation syndrome (MAS), a serious complication of systemic rheumatoid arthritis and other childhood systemic inflammatory disorders, is thought to be caused by **excessive activation and proliferation of T lymphocytes and macrophages**.

It is also a **complication of autoimmune diseases in adults**.

The recognition that MAS belongs to the **secondary or reactive hemophagocytic syndromes** has led to a proposal to rename it according to the contemporary classification of histiocytic disorders

Sepsis may mimic part or all features of HS in ICU patients!

HLH	Sepsis
Molecular diagnosis: present	Molecular diagnosis: absent
Fever	Fever
Splenomegaly	Organomegaly
Cytopenia of 2 of 3 lineages	Cytopenia of 2 of 3 lineages
Hypertryglyceridemia ≥ 3mmol/L or hypofibrinogenemia ≤ 1.5 g/L	Hypertryglyceridemia ≥ 3mmol/L or hypofibrinogenemia ≤ 1.5 g/L
Hemophagocytosis in bone marrow, spleen or lymph nodes	Hemophagocytosis in bone marrow, spleen or lymph nodes
Ferritin ≥ 500 g/L	Ferritin ≥ 500 g/L
Low or absent NK cell activity	Low or absent NK cell activity
Soluble CD25 (soluble IL-2 receptor) > 2400 U/mL	Soluble CD25 (soluble IL-2 receptor) > 2400 U/mL

Castillo et al, Pediatr Crit Care 2009

HEMATOLOGISTS AND INFLAMMATION: DD

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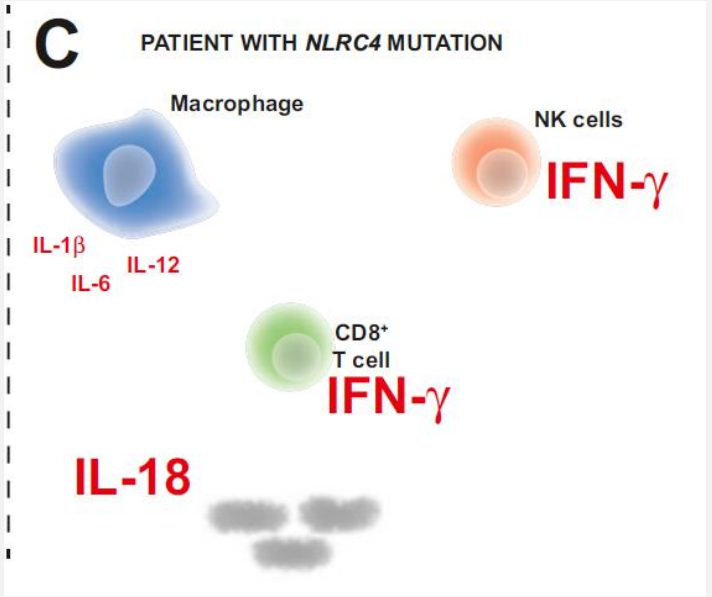
Completely unclear whether both are independent syndromes or constitute a continuum of hyperinflammation

MAS-HLH



The CSSs associated with sJIA and AOSD are essentially identical, consistent with the increasing recognition of these disorders as a single entity extending across age groups.
Hyperinflammation is driven primarily by a dysregulated IL-1 inflammasome, resulting in excess release of both IL-1 and IL-18; gain-of-function inflammasome mutations are becoming more widely recognized in affected patients with sJIA or AOSD

TRIGGERS OF HLH

Infections

MALS-HLH?

Viruses — EBV-HLH

- Epstein-Barr virus
- Herpes simplex virus
- Cytomegalovirus
- HIV
- COVID-19
- Influenza
- HHV-6, HHV-8
- Enterovirus, adenovirus, parvovirus
- Dengue virus

Bacteria

- *Mycobacterium tuberculosis*
- *Brucella* spp
- Tick-borne bacteria *(Ehrlichia, Rickettsia, Anaplasma)*
- *Salmonella*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*

Fungi/Parasites

- *Histoplasma* spp
- *Candida* spp
- *Plasmodium* spp
- *Aspergillus* spp
- *Cryptococcus neoformans*
- *Toxoplasma gondii*
- *Babesia* spp

Malignancy

Hematologic Cancers

Lymphomas

- T-cell lymphoma (eg anaplastic large cell, lymphoblastic, peripheral)
- B cell lymphoma (eg DLBCL)
- Hodgkin lymphoma
- NK cell lymphoma

Leukemias

- Acute myeloid leukemia
- Acute lymphoid leukemia
- NK cell leukemia

Multicentric Castleman Disease

(Solid cancers - rare)

Autoimmune disease

MAS-HLH

Systemic lupus erythematosis

Rheumatoid arthritis

Inflammatory bowel disease

Adult-onset Still disease

Others

- Vasculitis
- Dermatomyositis
- Systemic sclerosis

Drugs and Therapies

Antiepileptics:

- Lamotrigine,
- Carbamazepine
- Phenytoin

Antibiotics:

- Sulfamethoxazole
- Sulfasalazine

Immune checkpoint inhibitors:

- Nivolumab
- Pembrolizumab
- Ipilimumab

Targeted therapies

- Dabrafenib
- Trametinib

IEC-associated HLH-like syndrome

CAR T-cell therapy

Others

Immunodeficiency (congenital or acquired)

Hematopoietic stem cell or solid organ transplantation

Pregnancy

Idiopathic

J.I. Hsu, Blood 2026

TRIGGERS OF HLH

Infections — 40%

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Others

Immunodeficiency (congenital or acquired)

Hematopoietic stem cell or solid organ transplantation

Pregnancy

8%

Idiopathic

J.I. Hsu, Blood 2026

TRIGGERS OF HLH: MALIGNANCY

Poor outcome → 5ys OS 10-30%

1. HLH arises around the malignancy <u>diagnosis, transformation, or recurrence</u> (MA-HLH)
   - the hyperinflammatory nature of HLH is presumably driven by the neoplasm
   - pathogenesis unknown
   - the overlap of HLH features and neoplastic disease, especially hematologic malignancies, is substantial

Invasion of the bone marrow to induce cytopenias or secretion of inflammatory cytokines by themselves

2. Triggered by deep-seated infections (IC-HLH)
   - HLH occurs after months of immune- and marrow-suppressive anticancer therapy

viral triggers (e.g., EBV, cytomegalovirus (CMV), BK virus, HHV6, HSHV/HHV8 , IFI, bacteria

3. HLH occurs following immune-activating therapies
   → cytokine release syndrome (CRS) or Rx-HLH

BITES,
CAR T-cell therapies, or ICI,
CHEMO, post ALLOHSCT

TRIGGERS OF HLH:HM

Type of malignancy	Sub entities with particular risk of HLH	Prevalence in adults with M-associated HLH
T and NK cell Lymphoma		35%
	Subcutaneous panniculitis like T cell lymphoma	
	Hepatosplenic T cell lymphoma	
	Nodal/extranodal T and NK cell lymphoma	
	Anaplastic large cell lymphoma	
	Angioimmunoblastic T cell lymhpoma	
B cell lymphoma		32%
	DLBCL	
	Intravascular large B cell lymhpoma	
	Indolent B cell Lymphoma	
Hodgkin Lymphoma		6%
Leukemia		
	B/ T cell ALL	6%
	AML	

TRIGGERS OF HLH:HM

Type of malignancy	Sub entities with particular risk of HLH	Prevalence in adults with M-associated HLH
Others and related disorders		
	EBV+ T and NK cell lymphoprliferative disorders	
MCD		
	iMCD	
	HHV8/KSHV MCD	

Pay attention to **iMCD!**

Pay attention to **viruses** in the context of M-HLH!!

The OHI index predicts early mortality from organ dysfunction and survival benefit from etoposide in patients with lymphoma

Retrospective study, 135pts

AIM: 1. whether mortality OHI+ and OHI- pts differed from that predicted by standard prognostic indexes and
2. whether this mortality was associated with conditions related to abnormal inflammation

Characteristic	OHI^- (n = 70)	OHI^+ (n = 65)	All (N = 135)
Age at diagnosis, median (25%-75%), y	66 (54-77)	64 (55-69)	64 (55-72)
Sex, n (%)			
Female	31 (44.2)	27 (41.5)	58 (43)
Male	39 (55.7)	38 (58.5)	77 (57)
Diagnosis, n (%)			
B-NHL	41 (58.6)	39 (67.7)	80 (59.2)
DLBCL	23 (33.0)	20 (31.0)	43 (32)
IVLBCL	6 (8.6)	8 (12.3)	14 (10.4)
FL	5 (7.1)	3 (4.6)	8 (6)
MZL	1 (1.4)	2 (3.1)	3 (2.2)
THRLBCL	1 (1.4)	2 (3.1)	3 (2.2)
Other B-NHL	5 (7.1)	4 (7.7)	9 (6.6)
Mature T-cell lymphoma	20 (28.6)	21 (32.3)	41 (30)
PTCL, NOS	4 (6)	7 (10.7)	11 (8.1)
AITL	3 (4.2)	2 (3.1)	5 (3.7)
ALCL	0 (0)	4 (6.1)	4 (3)
Extranodal T/NK	4 (6)	1 (1.5)	5 (3.7)
PCγδTCL	3 (4.2)	0 (0)	3 (2.2)
Other T-cell lymphoma	6 (8.6)	7 (10.7)	13 (9.6)
HL	5 (7.7)	5 (7.7)	10 (7.4)
EBV^{+*}	14 (20)†	6 (9)‡	20 (15)

Adi Zoref-Lorenz Blood, 2025

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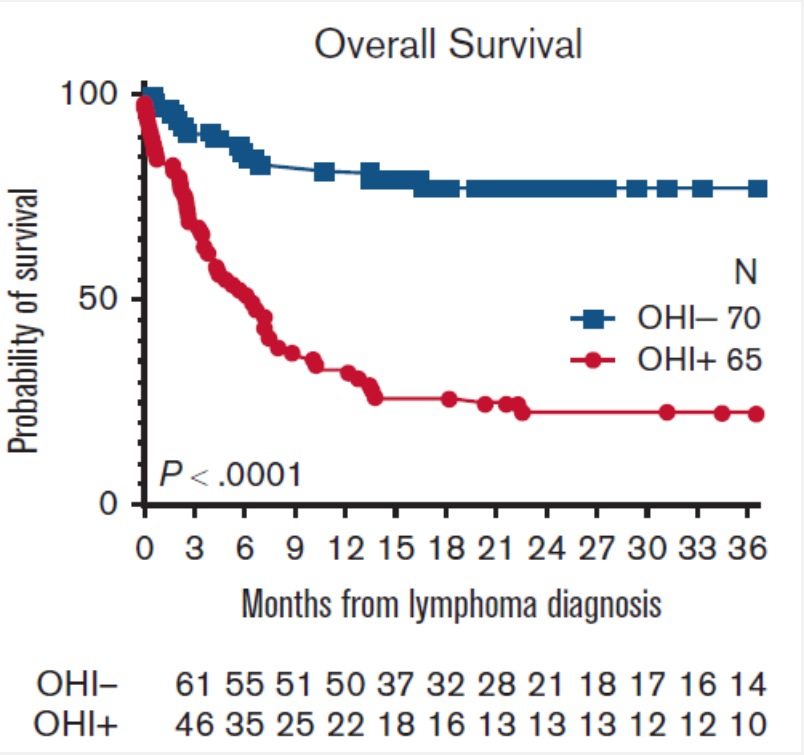

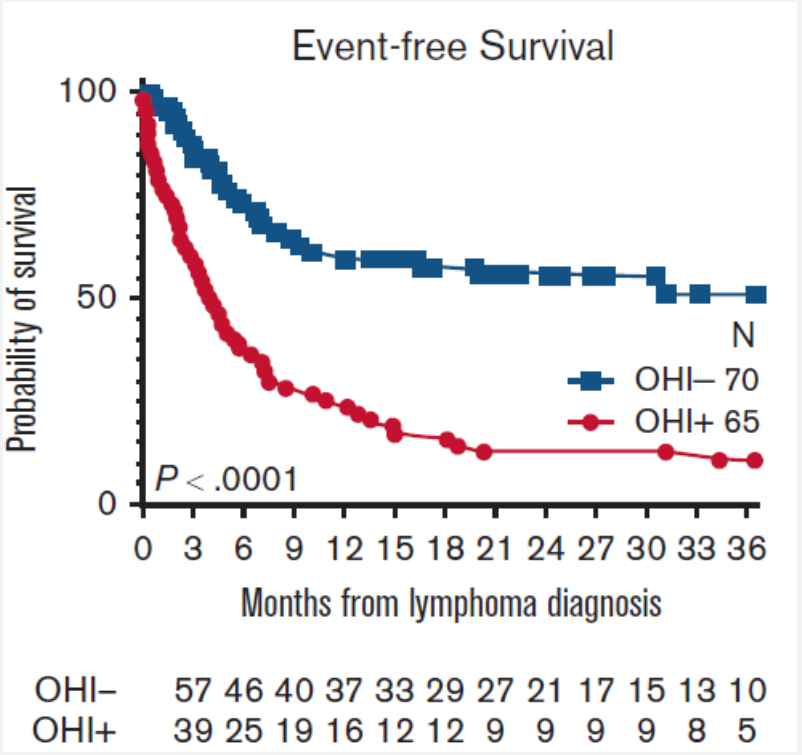

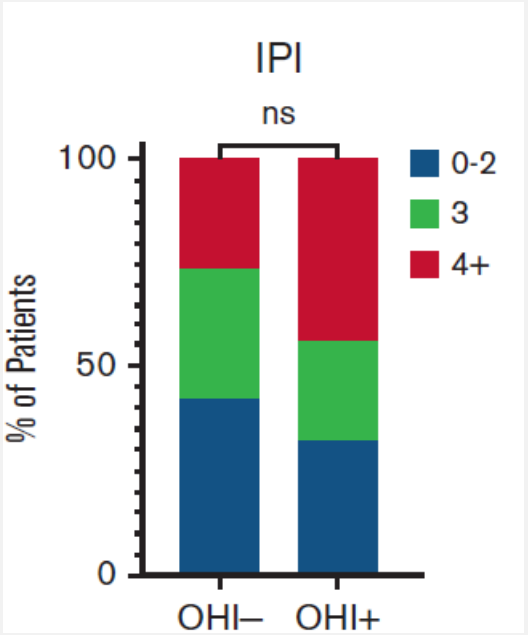

An event was defined as death, refractoriness, progression, or relapse of lymphoma

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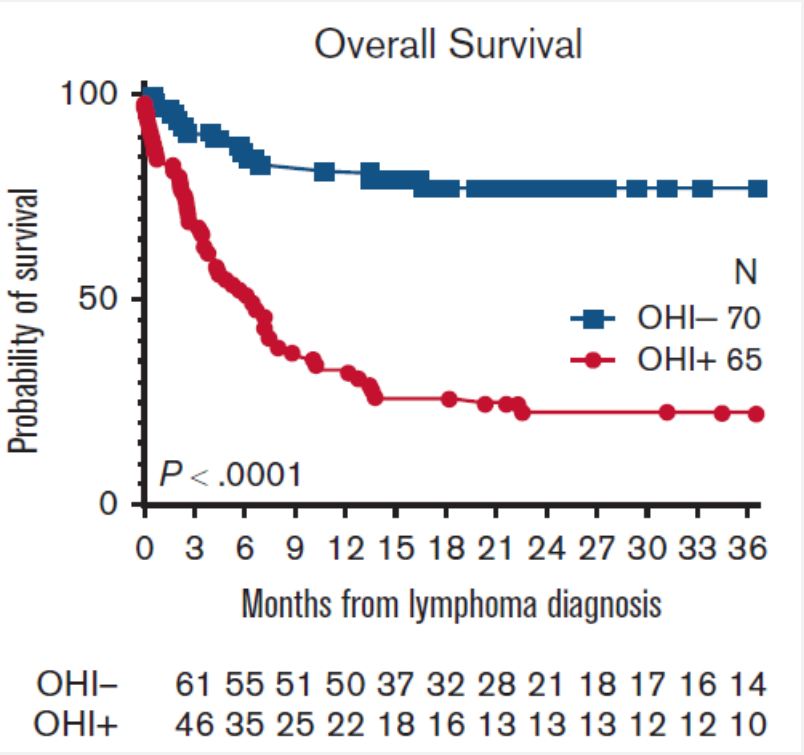

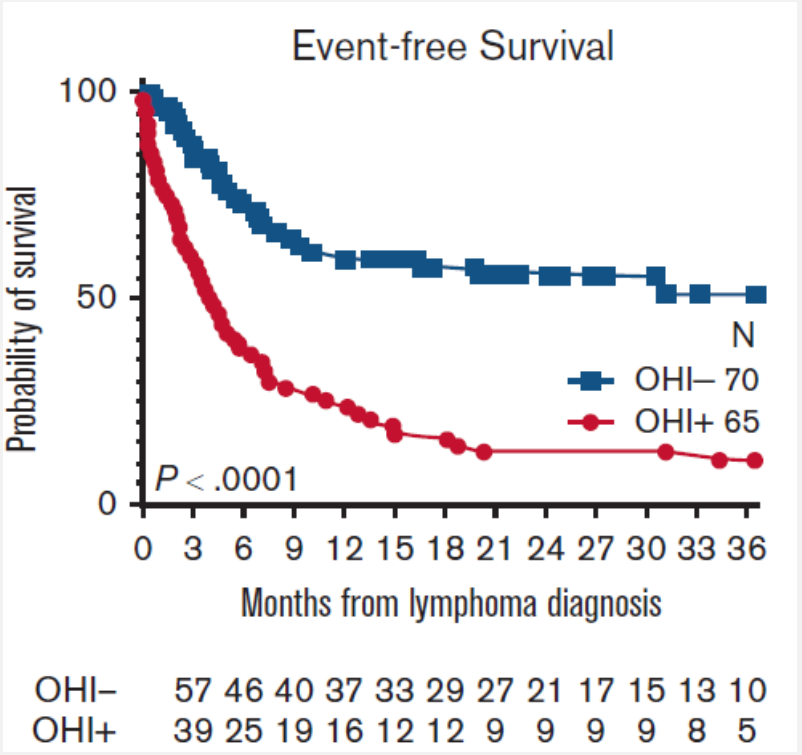

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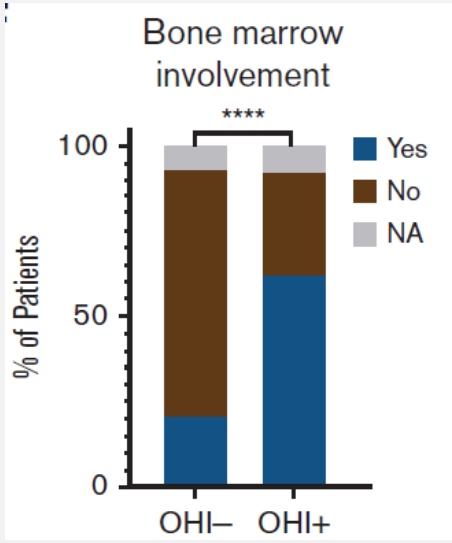

OHI identified a novel, high-risk subgroup of patients with lymphoma who were not captured by the traditional prognostic indexes

Adi Zoref-Lorenz Blood, 2025

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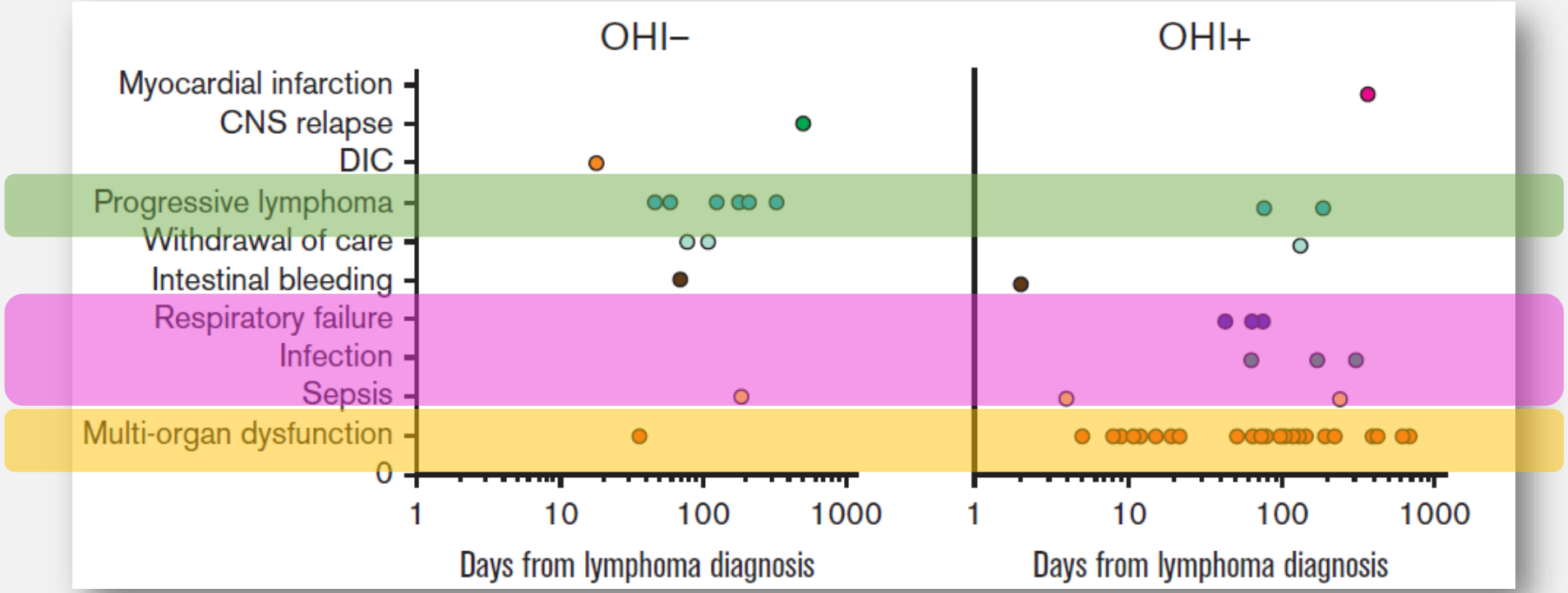
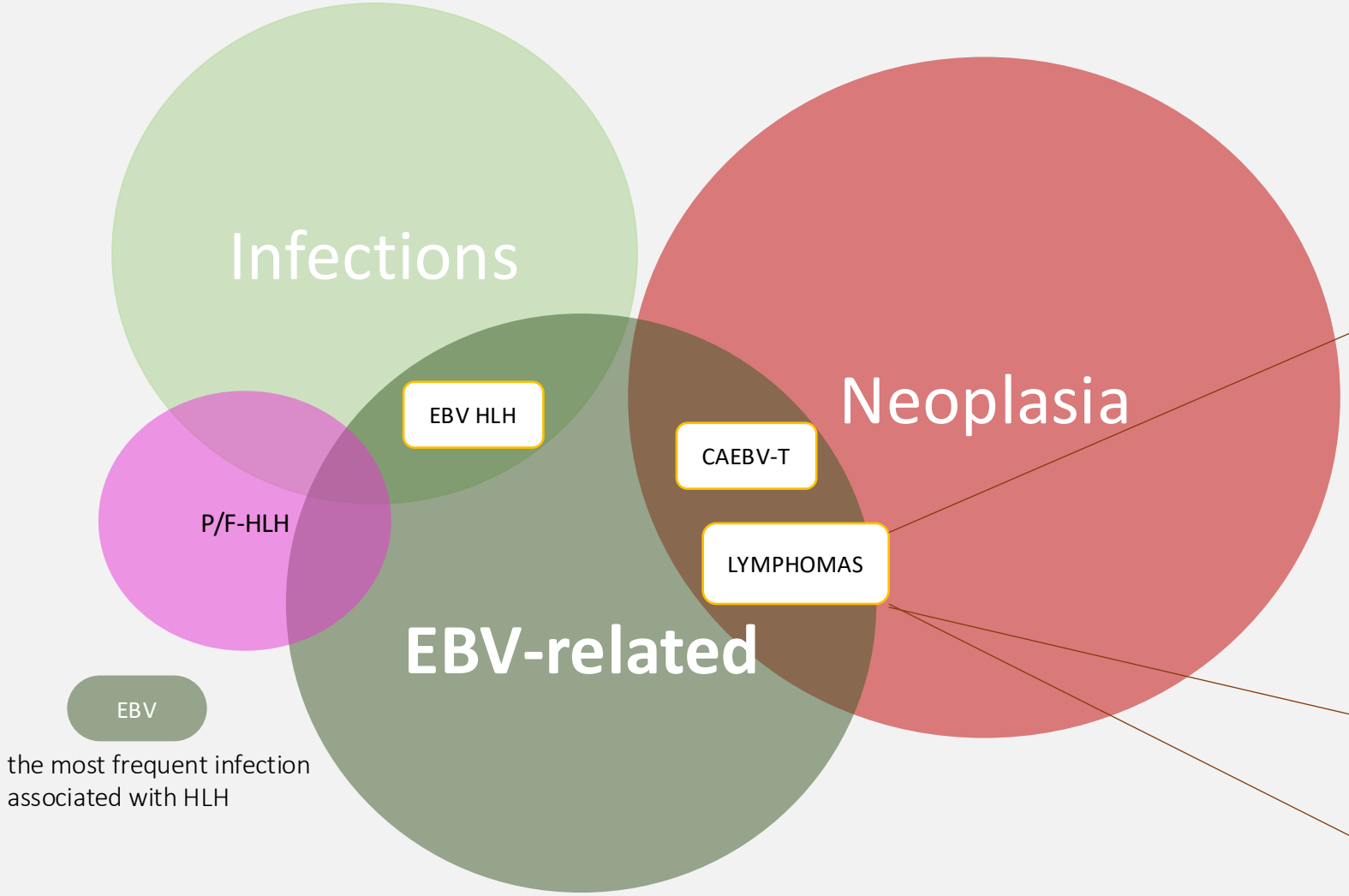


Adi Zoref-Lorenz Blood, 2025

TRIGGERS OF HLH: EBV

HLH with EXTREME ELEVATION OF EBV DNA PCR: cut off?

Nader Kim El-Mallawany BJH, 2021



WHO 2022 DEFINED EBV- RELATED

- EBV-positive **nodal** T- and NK-cell lymphoma
- **Extranodal N**K/T-cell lymphoma

lymphoma

- **Systemic chronic active EBV disease**
- Systemic EBV-positive T-cell lymphoma of childhood

lymphoid proliferations and lymphomas of childhood

OTHER LYMPHOMAS (EBV- RELATED)

LYMPHOMA + EBV REACTIVATION

Treatment outcomes and prognostic factors in adult patients with secondary hemophagocytic lymphohistiocytosis not associated with malignancy

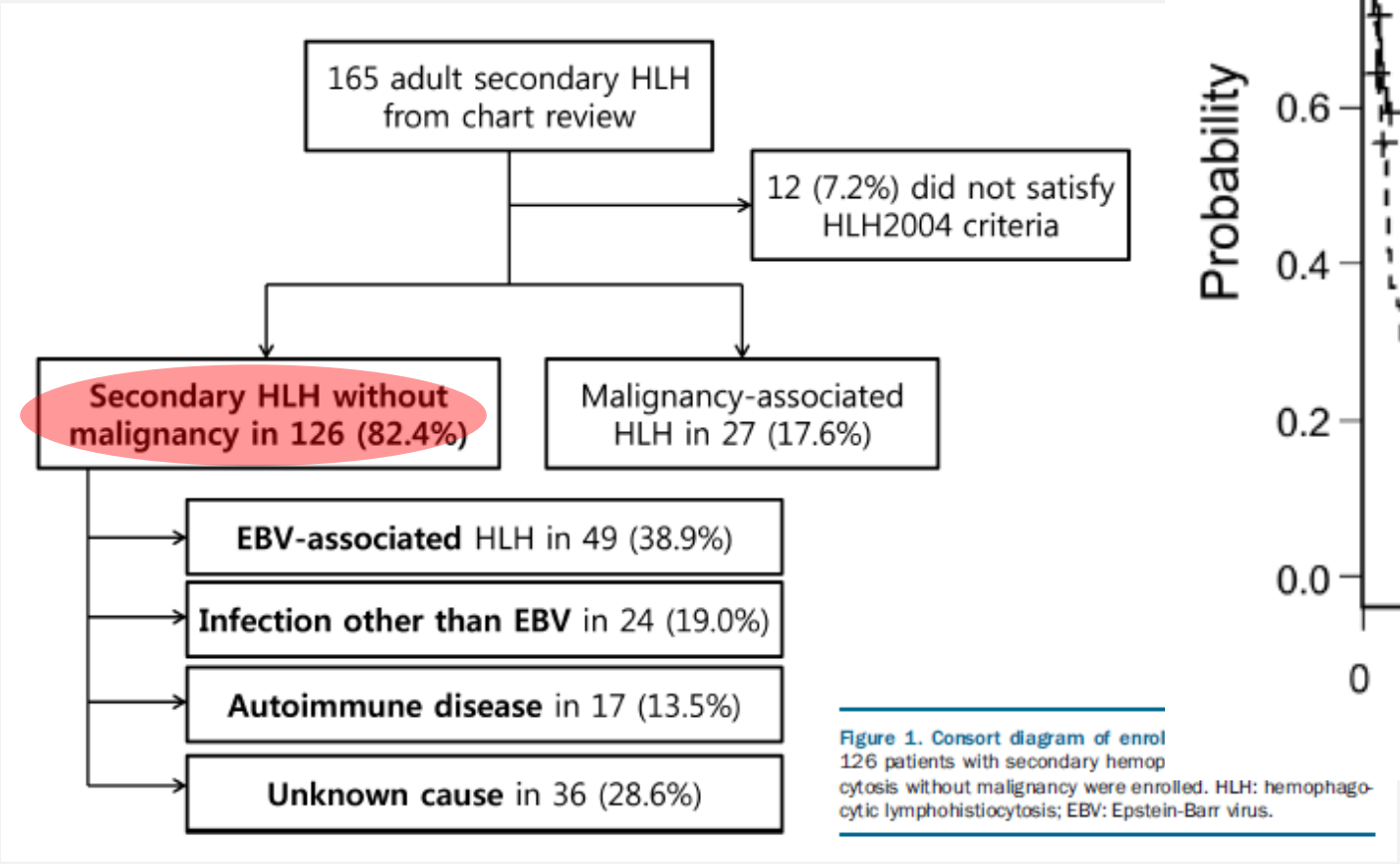
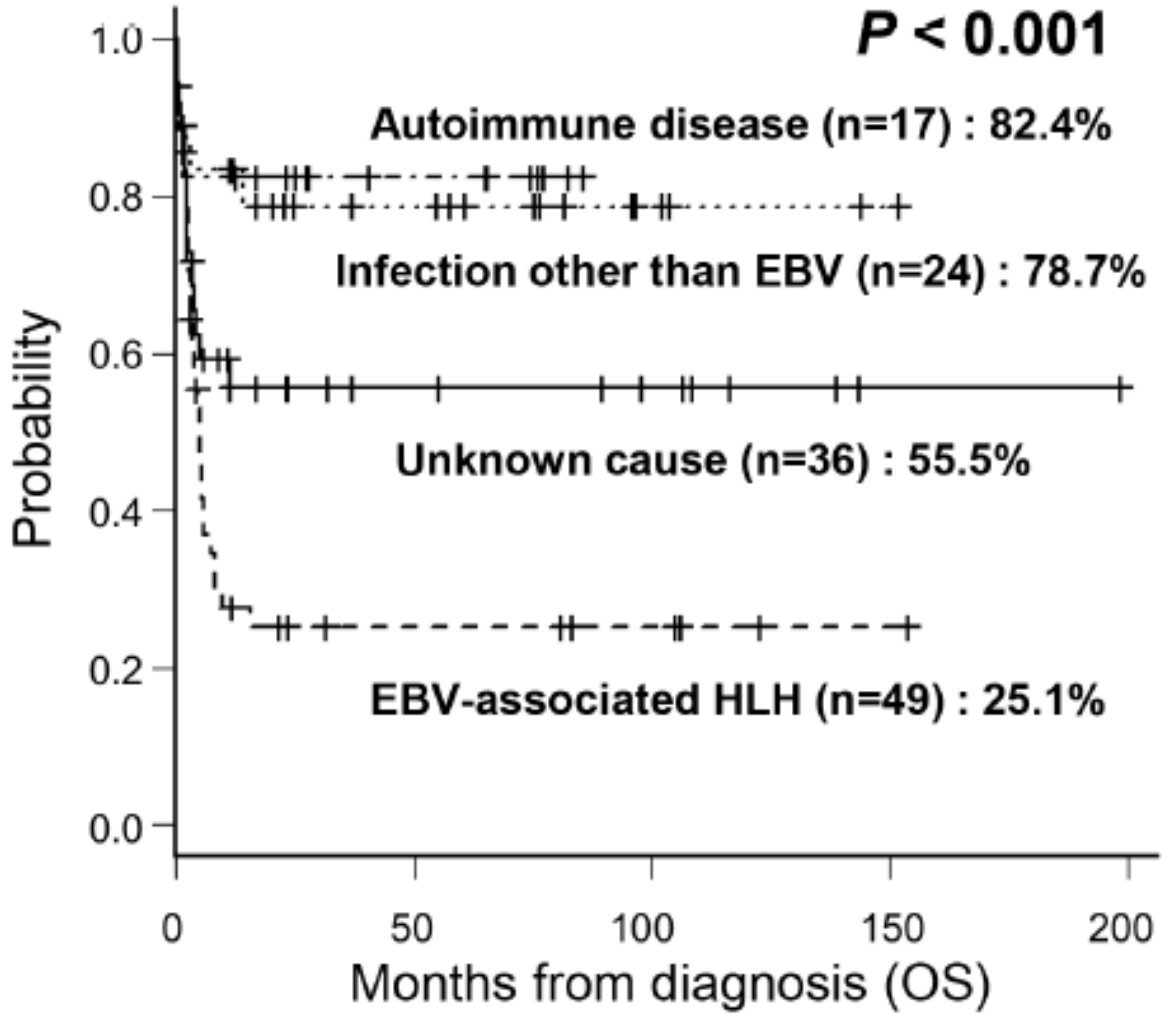


Figure 1. Consort diagram of enrol
126 patients with secondary hemop
cytosis without malignancy were enrolled. HLH: hemophago-
cytic lymphohistiocytosis; EBV: Epstein-Barr virus.



Jae-Ho Yoon,

Haematologica 2019

HLH occurs following immune-activating therapies RxHLH

CAR-T CELL THERAPY

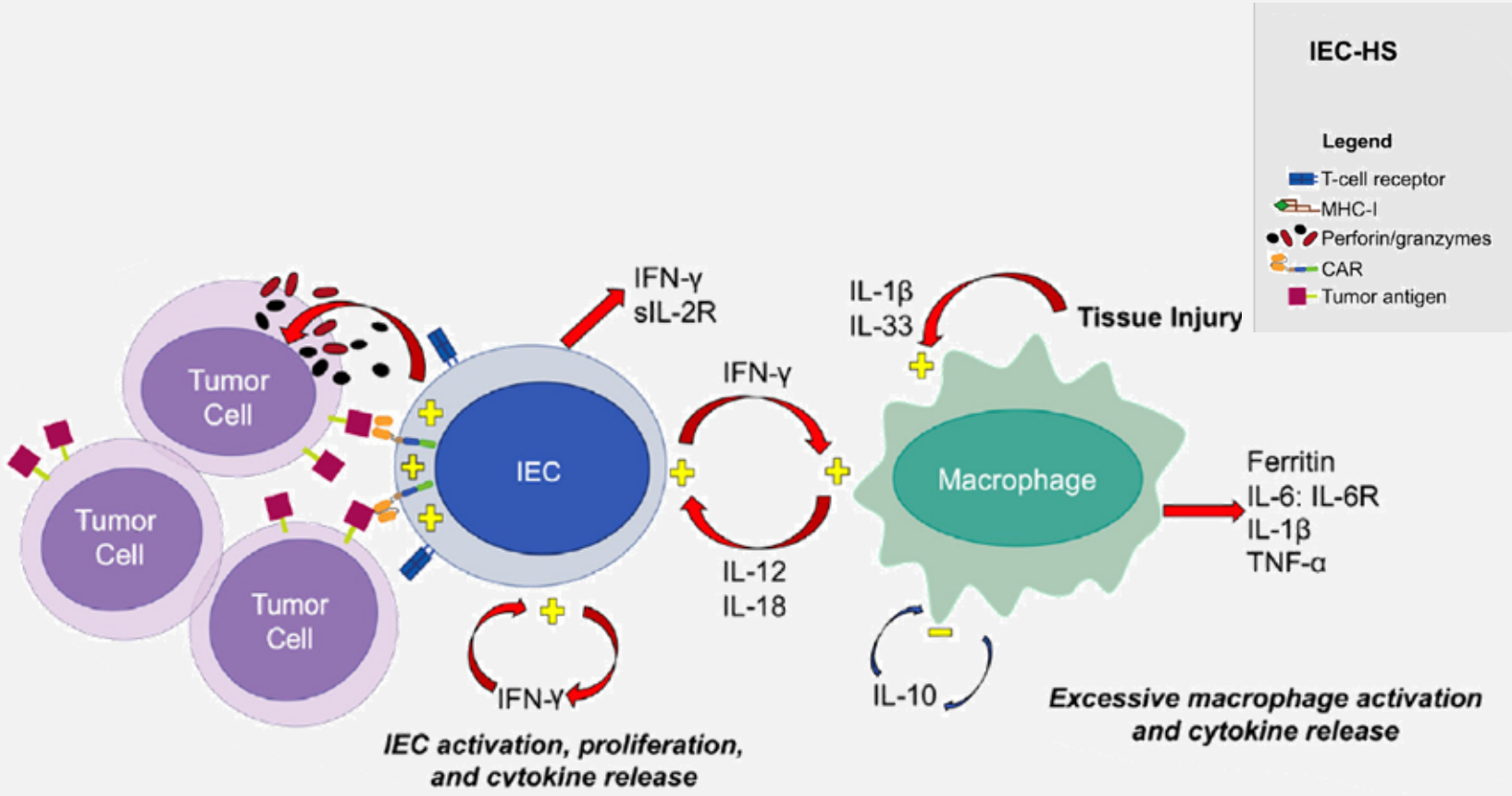
Immune EffectorCell-Associated Hemophagocytic Lymphohistiocytosis-LikeSyndrome. T
Transplantation and Cellular Therapy,2023

CRS and ICANS: CART cells express proteins with antigen-binding,trans membrane, and costimulatory domains, Allowing Tcells to recognize extracellular tumo rantigens,proliferate,and mediate tumorlysis,and cytokine relaease

IEC-HS

Definition

- IEC-HS: **development of a pathological and biochemical hyperinflammatory syndrome** that:
  - manifests with features of macrophage activation/HLH.
  - is attributable to IEC therapy.
  - is associated with progression or new onset of cytopenias
    - hyperferritinemia,
    - coagulopathy wit hypofibrinogenemia, and/or transaminitis.



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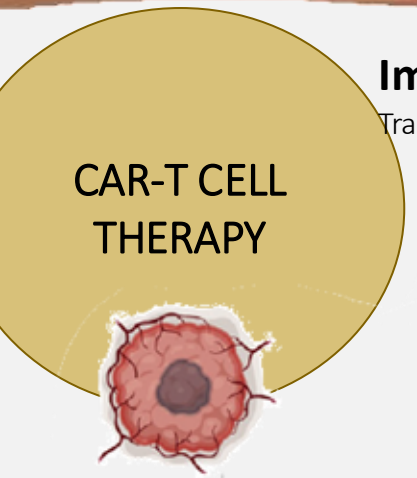
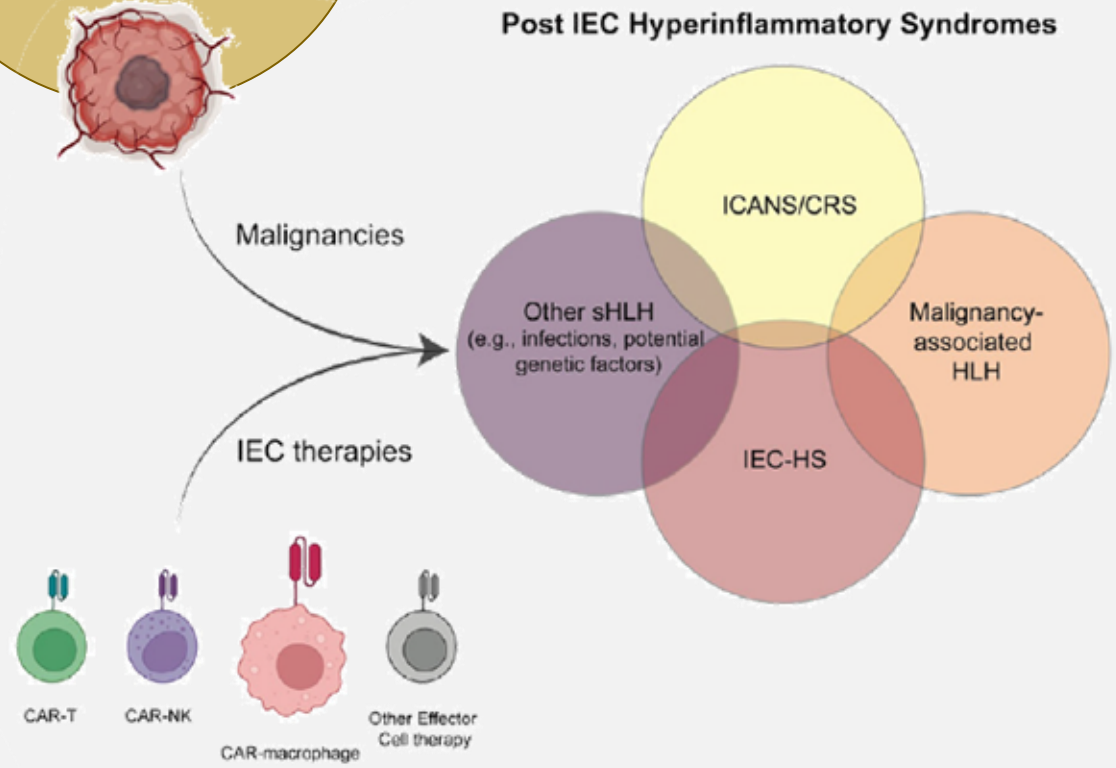
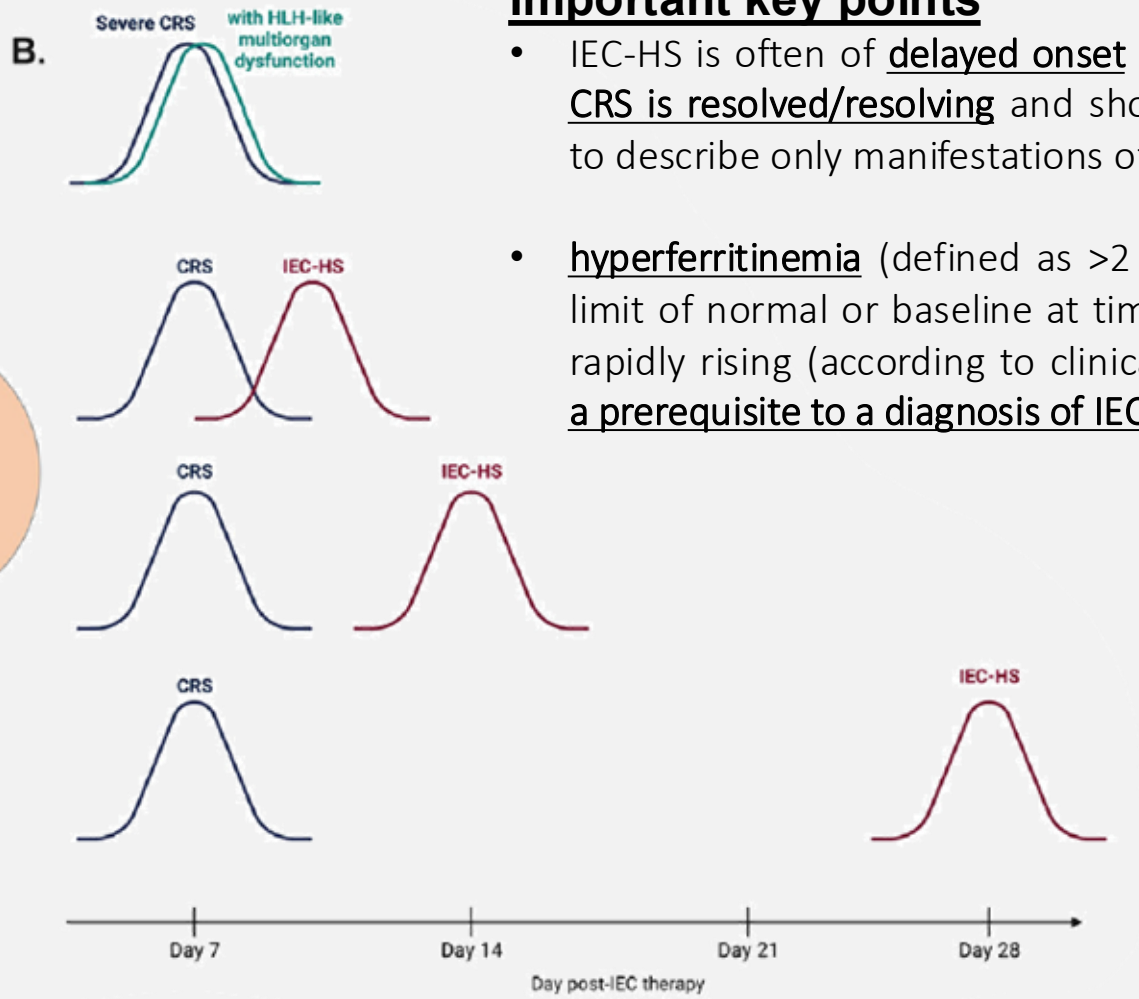
Transplantation and Cellular Therapy,2023







Important key points

- IEC-HS is often of delayed onset and manifests as CRS is resolved/resolving and should not be used to describe only manifestations of severe CRS.
- hyperferritinemia (defined as >2 times the upper limit of normal or baseline at time of infusion) or rapidly rising (according to clinical assessment) is a prerequisite to a diagnosis of IEC-HS

REFLECTIONS BEFORE TURNING TO THERAPY

1. The HLH-2004 criteria: a problem of specificity

Use it as a screening test, not a confirmatory diagnostic test

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Criterion	Limitation(s)
Fever	A common manifestation of immune/inflammatory responses of all etiologies. [10]
Cytopenias	May be a consequence of any profoundly inflammatory state. Among patients hospitalized in ICUs, 50–70% will have anemia to < 9 g/dL, up to 60% thrombocytopenia, and 7% or more will leukopenia. [11]
Hypofibrinogenemia	May result from liver injury or DIC, both common consequences of any/all fulminant inflammatory states, and may occur in over a third of patients admitted to ICUs for any indication. [12]
Hypertriglyceridemia	Non-specific acute phase reactants (not unlike ESR or CRP). The cutoff used in the HLH- 2004 criteria is low enough to be within range of baseline levels among a significant proportion of adults in developed countries. [13, 14]
Splenomegaly	A frequent finding in many of the entities which share a differential diagnosis with HLH including hematologic malignancy, viral infection, and a number of rheumatologic disorders. [15]
Hyperferritinemia	The HLH- 2004 ferritin cutoff demonstrated a specificity of merely 0.3% for HLH (in a critical care population wherein pretest probability may be higher than in lower acuity settings) [16]. Among a cohort of 1055 adult patients with serum ferritin > 5000 ng/mL the prevalence of diagnosed HLH was 6.5%, with prevalence only reaching 50% as serum ferritin approached 90,000 ng/mL [17]. In these cohorts and others, a wide variety of common non-HLH conditions have been associated with profound hyperferritinemia including sepsis, hematologic malignancy, rheumatologic disease, liver injury, and kidney failure
Soluble IL- 2 receptor	May be increased in any process involving T-cell activation (including sepsis, hematologic malignancy, rheumatologic disease, sarcoidosis, and inflammatory bowel disease) [20–24]. Among 132 patients with soluble IL- 2 receptor levels checked for evaluation of HLH, the specificity of the HLH- 2004 cutoff value was 38.8%, with an AUC for the corresponding ROC of 0.69, and no significant difference in levels when comparing patients with HLH, and non-HLH patients with sepsis, hematologic malignancy, or rheumatologic disease [25]
NK-Cell Activity	A cohort of 34 secondary HLH patients demonstrated an "activated NK phenotype profile" similar to inflammatory conditions such as sepsis or rheumatologic disease [27]. Among a cohort of 311 HLH patients, those with primary disease had significantly lower NK cell activity than those with secondary disease, with many secondary HLH patients exhibiting NK activities within the normal range [28]. In primary HLH, the NK-cell cytotoxicity assay has displayed low reliability with a poor AUC of 0.69 at the diagnostic ROC [29]
Bone Marrow Hemophagocytosis	A non-specific finding which may be encountered in a wide array of critically ill patients, including as many as 65% of autopsied ICU deaths, and 44% of autopsied inpatients [30, 31]

This lack of specificity is manifest when examining each individual criterion in earnest

REFLECTIONS BEFORE TURNING TO THERAPY

1. The HLH-2004 criteria: a problem of specificity

Use it as a screening test, not a confirmatory diagnostic test

2. It is **only in primary HLH** that a **definitive diagnosis** can be established.

The absence of any such gold-standard diagnostic in secondary HLH, when combined with the non-specific nature of the syndrome, makes reliable diagnosis a formidable, and to-date inadequately addressed challenge. BUT you can think at secondary HLH as **a a label for excessive and maladaptive inflammation** provoked by any external cause → SO this allows you **to focus more effectively on the underlying trigger.**

HLH: WHAT TO DO IN CASE OF SUSPICION

2023 HiHASC consensus recommendations on the diagnosis and investigatioof suspected Haemophagocytic Lymphohistiocytosis (HLH) in adults

3Fs

Consider HLH in an unwell patient: use the three Fs

Fever | Falling blood counts | Raised ferritin

Consider possible HLH diagnosis: discuss with HLH specialists locally or nationally

Send HLH quick screen
Ferritin, FBC, fibrinogen, electrolytes, renal profile, liver function tests, triglycerides, LDH

Imaging to assess for hepatosplenomegaly and lymphadenopathy

Calculate HLH scores
HLH-2004, HScore

Further tests (panels 1 and 2) to identify a driver and assess for organ involvement

Immediate	• Initial assessment with three Fs • Might need to be repeated
First few hours	• Send HLH quick screen bloods • Calculate HScore **If HLH confirmed or strongly considered:** • Consider where patient best cared for (eg, critical care) • Get baseline echocardiogram • Start to investigate for commoner causes of HLH (panel 1)
Over first 24 to 48 hours	• **Complete panel 1 investigations** • **Start panel 2 investigations as appropriate** • Patient review with clinicians (haematology, rheumatology, or infectious disease) or discussion with multispeciality HLH team if available • Involvement of neurology if neurological symptoms or signs
Within first 5 to 10 days	• **Complete panel 2 investigations if no obvious cause found** • Deep skin biopsy or primary HLH screen

3Fs

Fever + Falling blood counts + Raised ferritin

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discuss with HLH specialists locally or nationally

Send HLH quick screen
Ferritin, FBC, fibrinogen, electrolytes, renal profile, liver function tests, triglycerides, LDH

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HLH-2004, HScore

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1

Haematology	Coagulation screen, blood film, ESR D-dimer, reticulocytes, Bone marrow biopsy
Biochemistry	Renal profile, Lliver fFunction Tests, LDH,CRP, iron profile, vitamin B12/folate, troponin,NT PROBNP, urine -protein-creatinine ratio, ferritin
Immunology	Complement C3/C4, ANA, ANCA, Extractable nuclear antigen/double-stranded sDNA antibody
Microbiology	Bacterial blood cultures x 3, ideally before antibiotics syphilis serology, fungal and tuberculosisTB cultures
Virology	Serum save* Serology* for: EBV/CMV/HIV/ HAV/HBV/HCV/HEV, parvovirus B19 / HTL1 DNA: EBV/DMC/HHV8 * Serum save and serology ideally prior to blood products **Respiratory viral throat swab PCR:** Influenza A&B; Enterovirus, SARSCoV-2 **Swab of ulcers**
Immunology	Soluble CD25, cCytokine testing, lymphocyte subsets and natural killer cellNK cell activity
Imaging	Chest x-ray, PET-CT/CT scan, ultrasound US if delay for cross-sectional imaging, electrocardiogram, echocardiogram
tests for patients with neurological symptoms	**MRI brain with gadolinium** **Lumbar puncture** : cell count, opening pressure, glucose/protein/ matched oligoclonal bands +/- cytospin (min 10mls), bacterial culture, viral PCR. Patient-specific : iImmunoglobulins, , syphilis serology, fungal and TB cultures

2

3

Evaluation for infection	All patients with unclear driver should have an infectious disease (ID) work up. Depending on Infectious DiseasesD consult/travel history, consider: Parasites: • Malaria film or rapid diagnostic test; Toxoplasma and Leishmania serology Other: • Syphilis/Coxiella/Brucella/endemic mycoses/Rickettsia • Consider Quantiferon (unreliable for diagnosing active Tuberculosis) • If Epstein Barr Virus BV viraemia, consider investigating which lymphocyte compartments are harbouring Epstein Barr VirusBV Tissue biopsy infection work up: TuberculosisB, Leishmaniasis Tests to ensure no adverse effects of immune suppression (depending on travel history): Consider Strongyloides and T.cruzi serology
	Additional tests in immunocompromised people
	Recommended: • Adenovirus PCR, HCV RNA, HHV6DNA (if history of HIV, allogenicBMT, CART, SOT) • Parvovirus PCR **Consider:** • HHV8/KSHV DNA • HEV DNA • Cryptococcal antigen • Beta D glucan (note possible false positives after intravenous immunoglobulinIVIg) • Stool microscopy for ova, cysts and parasites

4

	Bone marrow biopsy	Other biopsy sites
Evaluating for malignancy ***Biopsy early*** **Remember, steroids may mask lymphoma**	Aspirate smear • Flow cytometry • Cytogenetics if lymphoma/other malignancy	As determined by imaging: • Lymph node (core or excision) • Deep skin (for intravascular/cutaneous lymphoma) • Liver / Spleen Any FDG avid site
Evaluating for primary HLH	If considering primary HLH • CD107a granule release assay (GRA) • Protein expression ((Perforin/SAP/XIAP)	**Flow cytometry-based assays**

HLH: THERAPY OF f-HLH

Backbone:

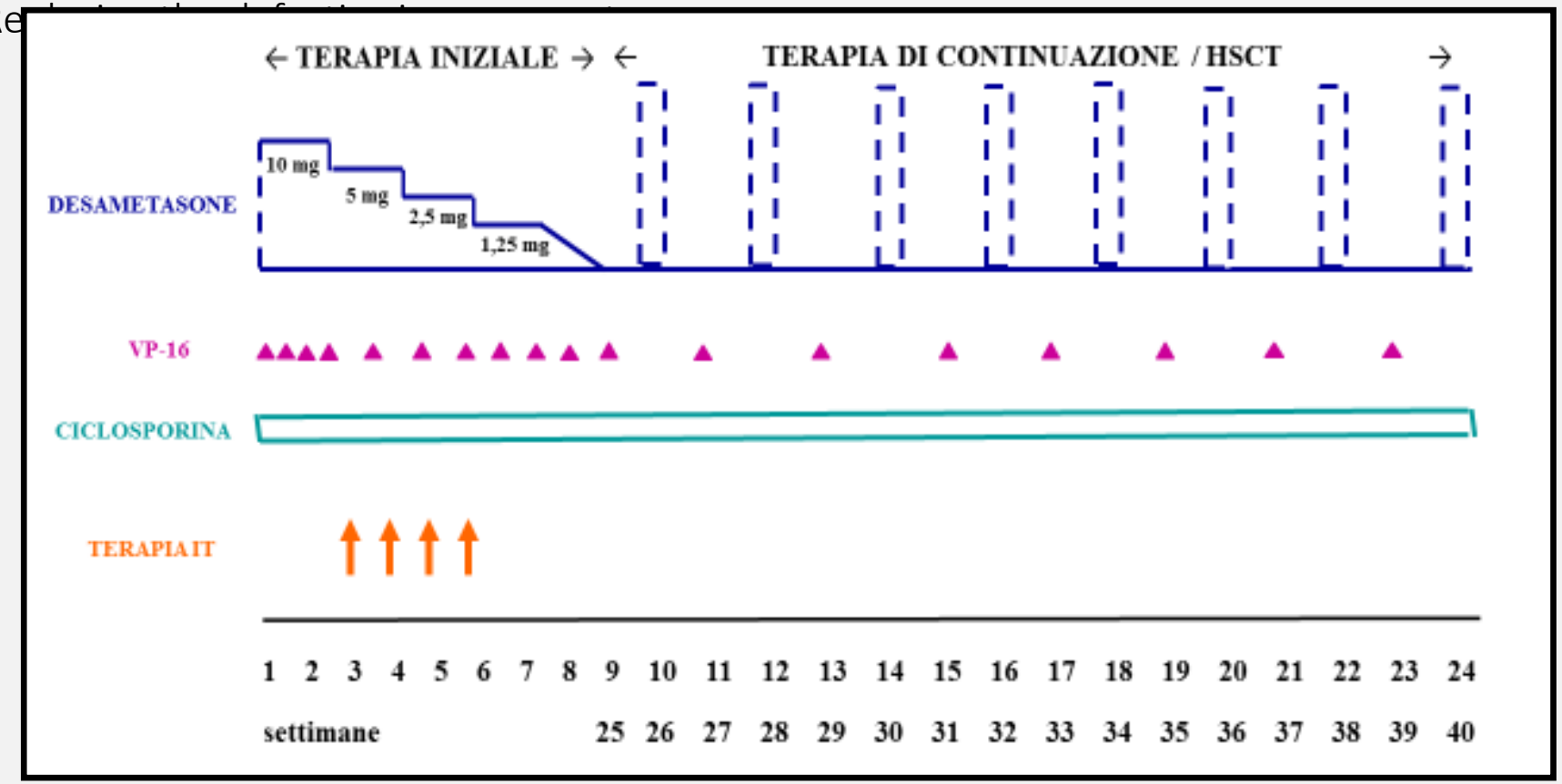
a. Controlling excessive inflammation
b. Replacing the defective immune system

HLH: THERAPY OF f-HLH

Backbone:

a. Controlling excessive inflammation

b. Re



Protocol HLH -94

Protocol HLH 2004

CSPA administered upfront (2004)
Corticosteroid added to IT MTX
HSCT earlier

(HSCT 51% of pts)

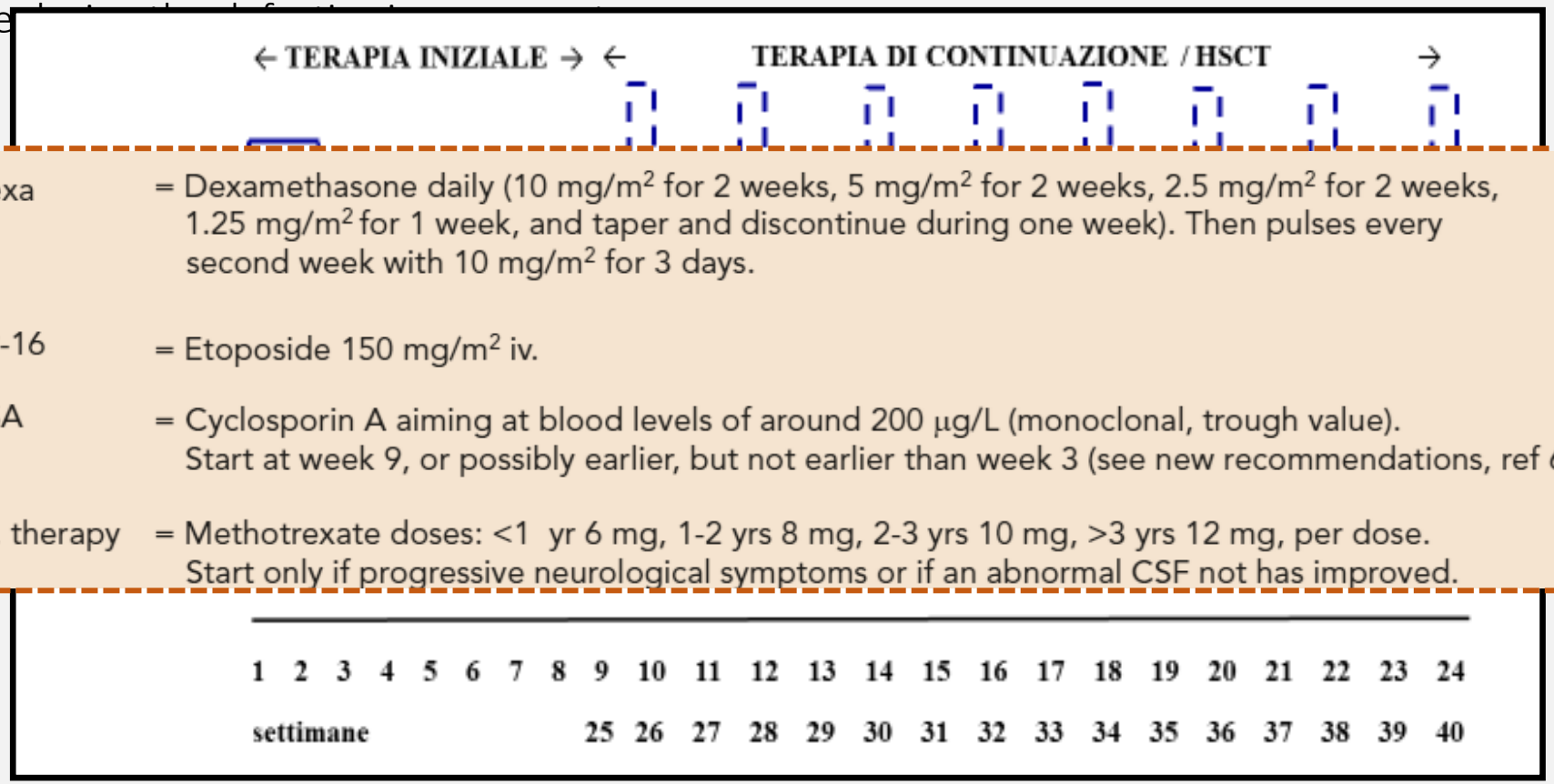
HSCT indicated for pts with familial/genetic, relapsing or severe/persistent disease

HLH: THERAPY OF HLH

Backbone:

a. Controlling excessive inflammation

b. Re



Mixed cohort

no longer reflective of the changing landscape of HLH diagnosis

CSPA administered upfront (2004)
Corticosteroid added to IT MTX
HSCT earlier

(HSCT 51% of pts)

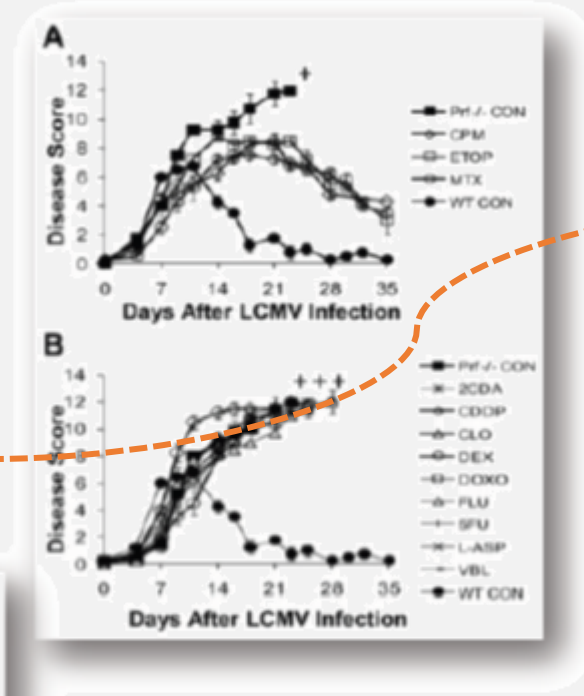
HSCT indicated for pts with familial/genetic, relapsing or severe/persistent disease

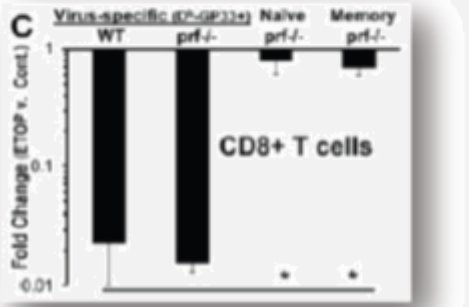
(f)HLH: THE CENTRAL ROLE OF ETO

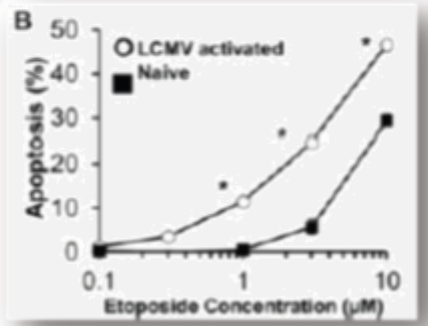
The first reports on the successful use of the epipodophyllotoxin derivatives etoposide and teniposide for FHL (pHLH) came during the 1980s, when they were shown to induce prolonged resolution in combination with corticosteroids

L'etoposide, è tra i pochi chemioterapici (insieme a EDX e MTX) in grado di migliorare il quadro di HLH nel modello murino

L'efficacia del trattamento è legata ad una riduzione dei livelli di IFN-gamma tramite una selettiva eliminazione (per apoptosi) di linfociti CD8 attivati







Johnson et al. J Immunol. 2014; 192: 84–91.

etoposide promotes programmed cell death (apoptosis) rather than proinflammatory lytic cell death (pyroptosis), conceivably ameliorating (f) subsequent systemic inflammation

apoptosis is an energy-dependent cellular process which will not take place when cellular energy is consumed

etoposide should not be administered too late in the disease course

Epidemiology, characteristics, and outcomes of adult haemophagocytic lymphohistiocytosis in the USA, 2006–19: a national, retrospective cohort study

national, retrospective cohort study
2006-2019 -16136 pts-

all adult patients who were admitted non-electively with the diagnosis of HLH
In-Hospital mortality

Malignancy: 4,953 (30·7%)
- Hematologic: 4,619 (28·6%)
  - Lymphoma: 3,171 (19·7%)
    - Non-Hodgkin Lymphomas (NHL): 2,727 (16·9%)
      - B-cell NHL: 935 (5·8%)
      - T-cell NHL: 1,153 (7·1%)
      - Unspecified NHL: 708 (4·4%)
    - Hodgkin lymphoma (HL): 464 (2·9%)
  - Leukemia: 1,463 (9·1%)
    - Lymphoid leukemias: 445 (2·8%)
    - Myeloid leukemias: 752 (4·7%)
    - Myeloproliferative diseases[1]: 231 (1·4%)
    - Unspecified leukemia: 85 (0·5%)
  - Plasma cell dyscrasias: 275 (1·7%)
- Solid: 434 (2·7%)

Autoimmune conditions: 3,362 (20·8%)
- Connective tissue diseases (CTD): 2,998 (18·6%)
  - SLE: 1,088 (6·7%)
  - Rheumatoid arthritis: 1,235 (7·7%)
  - Vasculitis: 374 (2·3%)
  - Other CTD: 404 (2·5%)
- Inflammatory bowel disease: 404 (2·5%)

Organ transplant status: 639 (4%)
- Bone marrow transplant: 204 (1·3%)
- Kidney transplant: 191 (1·2%)
- Other organ transplant: 254 (1·6%)

Congenital immunodefeciency syndromes: 399 (2·5%)

Commonly associated infections: 3,913 (24·3%)[2]
- Viruses: 3,491 (21·6%)
  - EBV: 893 (5·5%)
  - CMV 794 (4·9%)
  - Other herpes viruses: 702 (4·4%)
  - HIV: 710 (4·4%)
  - Viral hepatitis: 818 (5·1%)
  - Influenza: 184 (1·1%)
  - Parvo virus: 109 (0·7%)
- Bacteria: 279 (1·7%)
  - Mycobacterium tuberculosis: 120 (0·7%)
  - Rickettsia and other reicketsial diseases: 159 (1%)
- Fungi: 349 (2·2%)
  - Histoplasma spp: 294 (1·8%)
  - Other endemic fungal infections: 54 (0·3%)[3]
- Protozoan parasites: 70 (0·4%)
  - Toxoplasma spp: 25 (0·2%)
  - Babesia spp: 30 (0·2%)
  - Other protozoa spp: 15 (0·1%)

A. Abdelhay, The Lancet 2023

Epidemiology, characteristics, and outcomes of adult haemophagocytic lymphohistiocytosis in the USA, 2006–19: a national, retrospective cohort study

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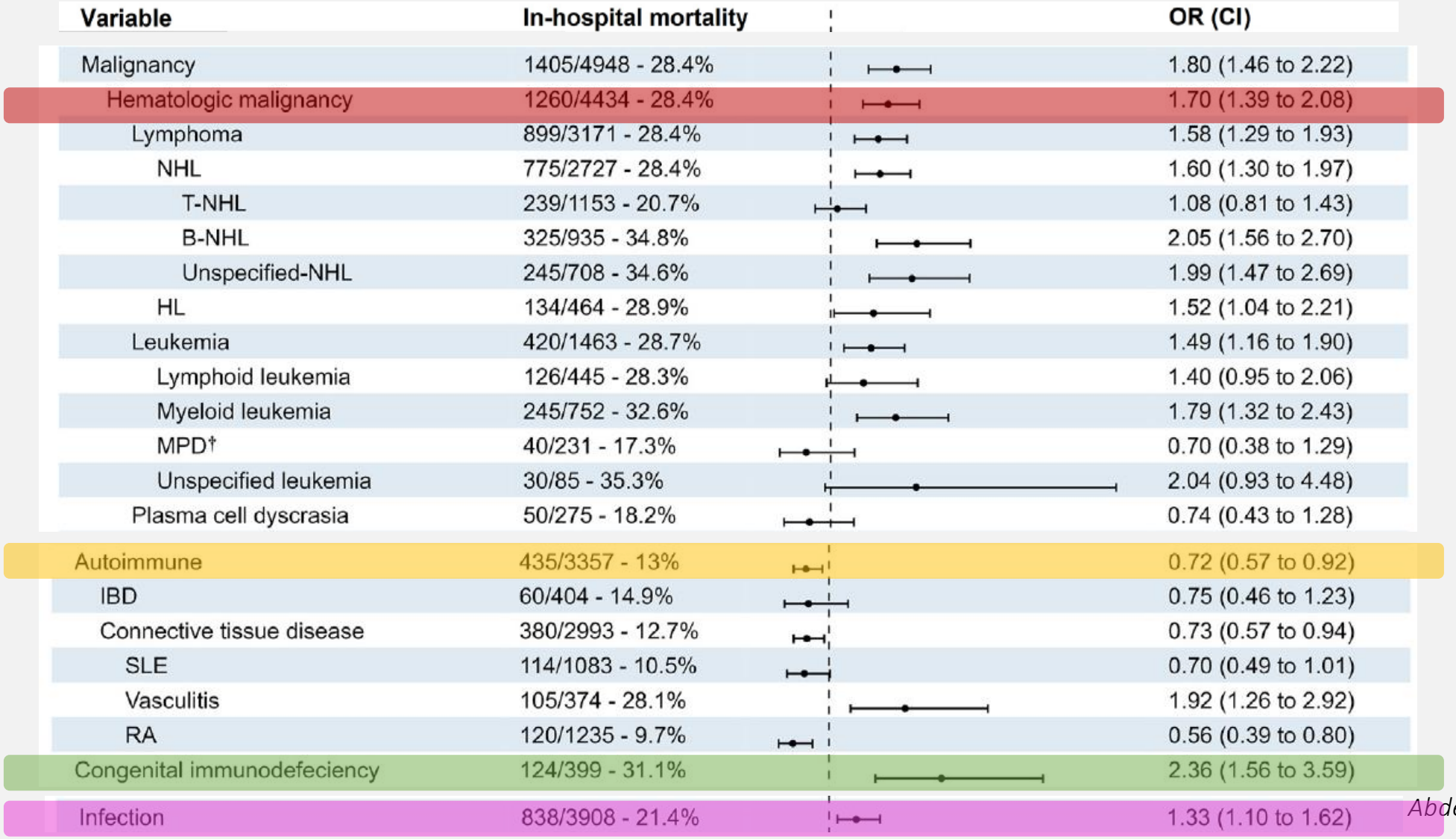

Variable	In-hospital mortality	OR (CI)
Malignancy	1405/4948 - 28.4%	1.80 (1.46 to 2.22)
Hematologic malignancy	1260/4434 - 28.4%	1.70 (1.39 to 2.08)
Lymphoma	899/3171 - 28.4%	1.58 (1.29 to 1.93)
NHL	775/2727 - 28.4%	1.60 (1.30 to 1.97)
T-NHL	239/1153 - 20.7%	1.08 (0.81 to 1.43)
B-NHL	325/935 - 34.8%	2.05 (1.56 to 2.70)
Unspecified-NHL	245/708 - 34.6%	1.99 (1.47 to 2.69)
HL	134/464 - 28.9%	1.52 (1.04 to 2.21)
Leukemia	420/1463 - 28.7%	1.49 (1.16 to 1.90)
Lymphoid leukemia	126/445 - 28.3%	1.40 (0.95 to 2.06)
Myeloid leukemia	245/752 - 32.6%	1.79 (1.32 to 2.43)
MPD†	40/231 - 17.3%	0.70 (0.38 to 1.29)
Unspecified leukemia	30/85 - 35.3%	2.04 (0.93 to 4.48)
Plasma cell dyscrasia	50/275 - 18.2%	0.74 (0.43 to 1.28)
Autoimmune	435/3357 - 13%	0.72 (0.57 to 0.92)
IBD	60/404 - 14.9%	0.75 (0.46 to 1.23)
Connective tissue disease	380/2993 - 12.7%	0.73 (0.57 to 0.94)
SLE	114/1083 - 10.5%	0.70 (0.49 to 1.01)
Vasculitis	105/374 - 28.1%	1.92 (1.26 to 2.92)
RA	120/1235 - 9.7%	0.56 (0.39 to 0.80)
Congenital immunodefeciency	124/399 - 31.1%	2.36 (1.56 to 3.59)
Infection	838/3908 - 21.4%	1.33 (1.10 to 1.62)

Abdelhay, The Lancet 2023

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3. Ok…ok…

If the patient gets worse and we still don't have a diagnosis, good old **etoposide** will bail us out.

Hold on a second, we need to clarify a few things here **"missing the forest or the trees"**

OVERUSE OF ETO-BASED THERAPY(?)

systematic literature review and metaanalysis on the clinical use and effectiveness of etoposide in adult HLH patients.

The role of etoposide in the treatment of adult patients with hemophagocytic lymphohistiocytosis

There is little evidence that etoposide-based therapy Is of benefit in adults with s-HLH

Zondag et al. Experimental Hematology & Oncology 2023

The role of etoposide in the treatment of adult patients with hemophagocytic lymphohistiocytosis

systematic literature review and metaanalysis on the clinical use and effectiveness of etoposide in adult HLH patients.

Author	Year	Reference	Trigger	Total number of adults	Inclusion in meta–analysis	Survival of etoposide–treated patients, % (n)	Survival of non–etoposide–treated patients, % (n)	Additional information	Supporting the effect of etoposide	Risk of bias according to ROBINS–I
Song et al.	2019	[15]	Pregnancy	13	Yes	100% (6)	71% (5)		NS	Critical
Knaak et al.	2020	[16]	Various	40	Yes	14% (1)	45% (15)		NS	Critical
Naymagon et al.	2021	[12]	Various	90	Yes	21% (9)	33% (16)	Log–rank test for difference in the survival distribution (p = 0.41)	No	Critical
Diack et al.	2020	[8]	Various	26	Yes	29% (2)	26% (5)	p = 0.9	No	Critical
Ahn et al.	2010	[17]	Various	26	Yes	31% (4)	69% (9)		NS	Critical
Barba et al.	2015	[9]	Various	71	Yes	54% (15)	67% (29)	p = 0.3	No	Critical
Arca et al.	2015	[3]	Various	162	Yes	85% (69)	74% (60)	p = 0.079, aOR: 0.21, p = 0.04	Yes	Serious
Bigenwald et al.	2018	[4]	Malignancy	71	No			uHR: 0.55 (p = 0.04), aHR: 0.50 (p = 0.04)	Yes	Critical
Bubik etal.	2020	[5]	Various	31	No			HR: 0.22 for ≥ 5 doses of etoposide (p = 0.003)	Yes	Critical
Li et al.	2020	[7]	B–cell lymphoma	31	No			Log–rank test for difference in survival distribution (p = 0.0183)	Yes	Critical
Song et al.	2019	[6]	EBV	58	No			Etoposide as 1st line therapy vs. no etoposide or 2nd line therapy (p = < 0.001)	Yes	Critical
Buyse et al.	2010	[10]	Various	56	No			EIT for non–survivors 6 h vs. survivors 4 h (p = 0.19)	No	Serious
Schram et al.	2015	[11]	Various	68	No			OS etoposide: 9.5 months, OS no etoposide: 1.9 months (p = 0.78)	No	Critical

Zondag et al. Experimental Hematology & Oncology 2023

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Li et al.	2020	[7]	B–cell lymph					if- dis-	Yes	Critical
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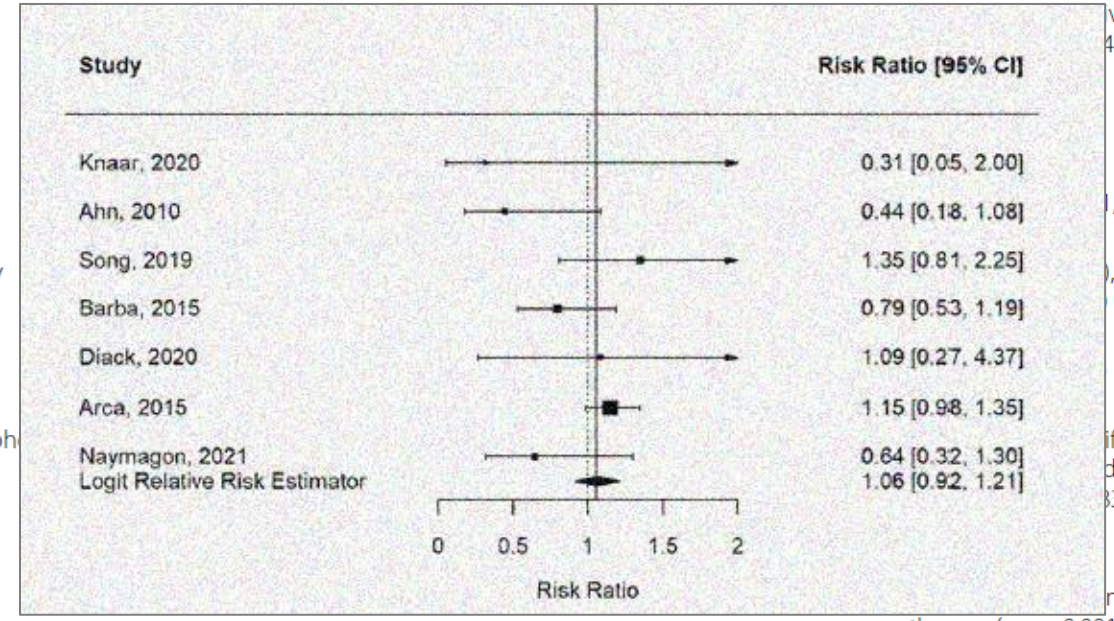
Schram et al.	2015	[11]	Various	68	No			OS etoposide: 9.5 months, OS no etoposide: 1.9 months (p = 0.78)	No	Critical



RRL 1,06

Zondag et al. Experimental Hematology & Oncology 2023

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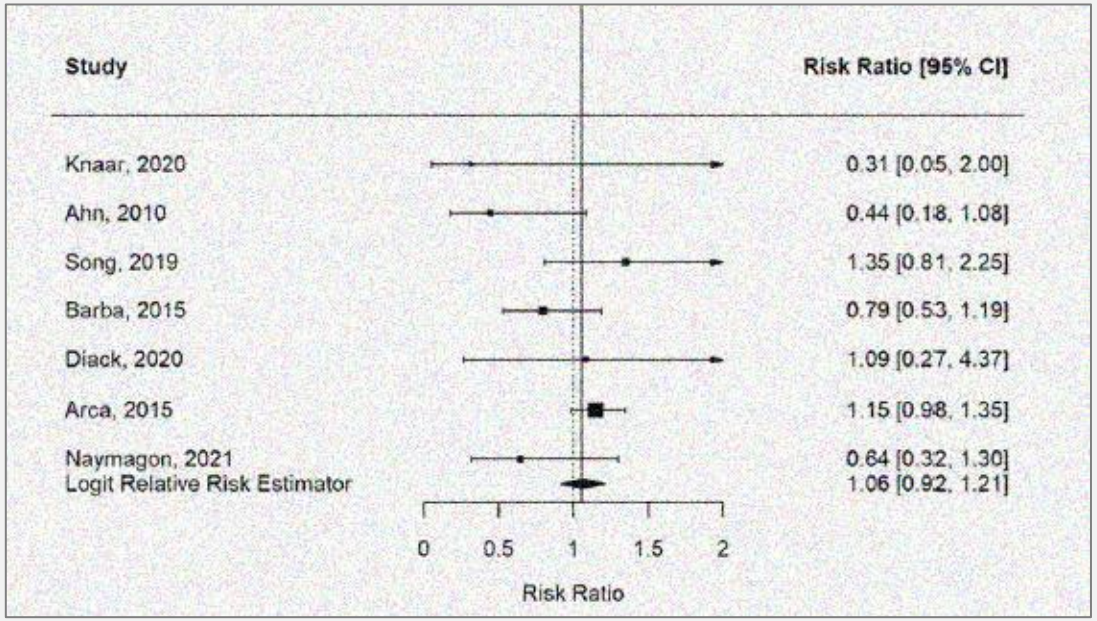


RRL 1,06

TO CONSIDER:

- Patients receiving ETO: <u>more severe cases</u>
  → prior lower survival probability
- within individual groups, high degree of heterogeneity
- several <u>confounders</u> are assumed to effect outcome

etoposide might be especially beneficial in EBV and lymphoma associated HLH

Zondag et al. Experimental Hematology & Oncology 2023

HLH and HLH-spectrum key features: fever /Falling cytopenia/ HyperFerritinemia
HLH-2024: fulfilled 5/7

KEY considerations:
Pt Hystory
Family History
Preexisting IS (a or IEI)

Hscore >169
OHI

Ferritin and other markers

CLINICALLY STABLE

Act and monitor

Urgent diagnostic testing to detect trigger

CLINICALLY UNSTABLE

Supportive therapy
Antimicrobial
Prophylaxis
Call RRT
Biopsy

CS+/- IVIgs

SI DG

NO DG

Ferritin and other markers

No ETO!

CLINICALLY UNSTABLE

Supportive therapy
Antimicrobial
Prophylaxis
Call RRT
REPEAT BIOPSY!

CS+/- IVIgs

Ferritin and other markers

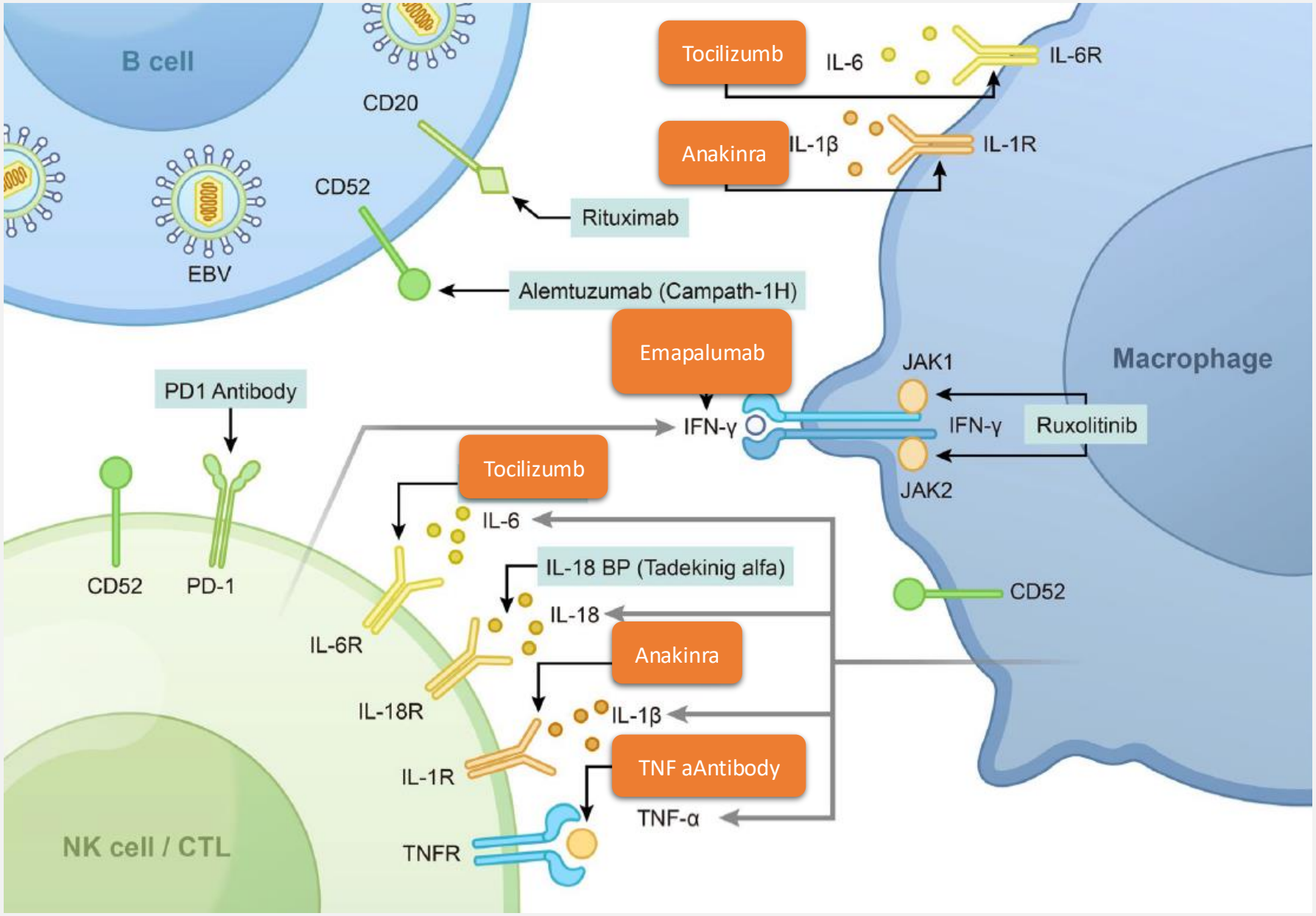
Treat the underlying disease

Remember the CSS concept before ETO!

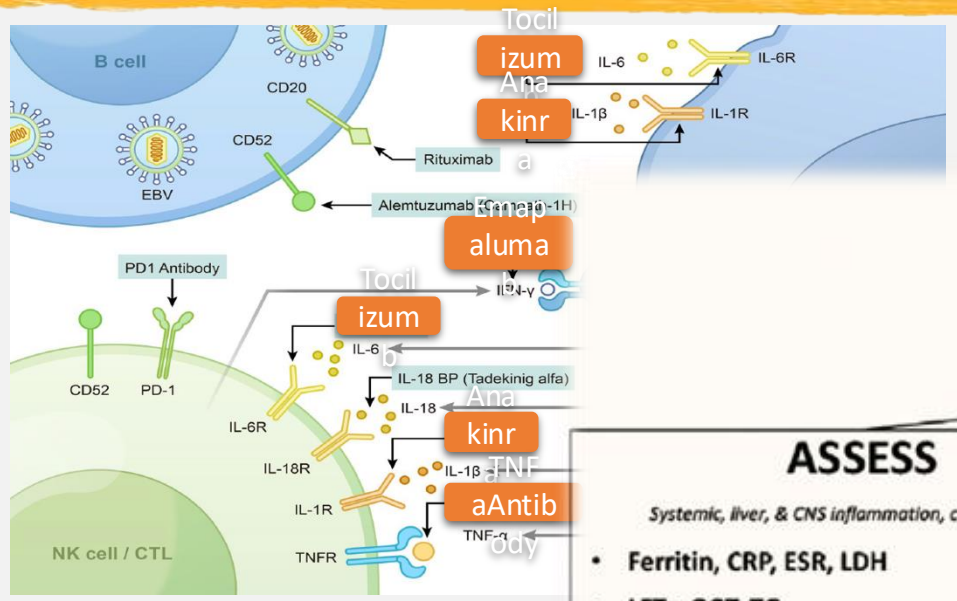
NO DG

The potential of cytokine directed therapy: more rational approach

TARGETING CYTOKINES



The potential of cytokine directed therapy: more rational approach



TARGETING CYTOKINES

HYPERINFLAMMATION SUSPECTED HLH/MAS

ASSESS

Systemic, liver, & CNS inflammation, cytopenias, DIC

- Ferritin, CRP, ESR, LDH
- LFTs, GGT, TG
- Brain MRI, CSF
- CBC+diff
- D-dimer, fibrinogen, PT/PTT

(See tables 3 & 4)

INVESTIGATE

genetic causes, predisposing conditions, acute triggers

- **Infection**
  Blood cultures, viral PCRs (EBV, CMV, adeno, Resp, ...), other studies
- **Malignancy**
  Bone marrow aspirate/biopsy, pan-imaging, other biopsies as indicated
- **Other**
  Rheumatic, Inborn Errors of Immunity or Metabolism, ...

(5)

TREAT

- **Supportive Care***
  Anti-pyretics, fluids, nutrition, blood products Per local/national organ failure, DIC, shock guidelines
- **Empiric Anti-Microbial Therapies**
- **Prophylaxis**
  bacterial, viral, fungal, gastric, DVT, etc. as indicated

If persistent, severe, or worsening inflammation or organ dysfunction & etiology unclear, consider empiric immunomodulation:

• **Glucocorticoids**$^{mod \rightarrow pulse}$ • **Anakinra** • **IVIg** (7)

MONITOR

Inflammation, Organ Damage, Toxicity (4)

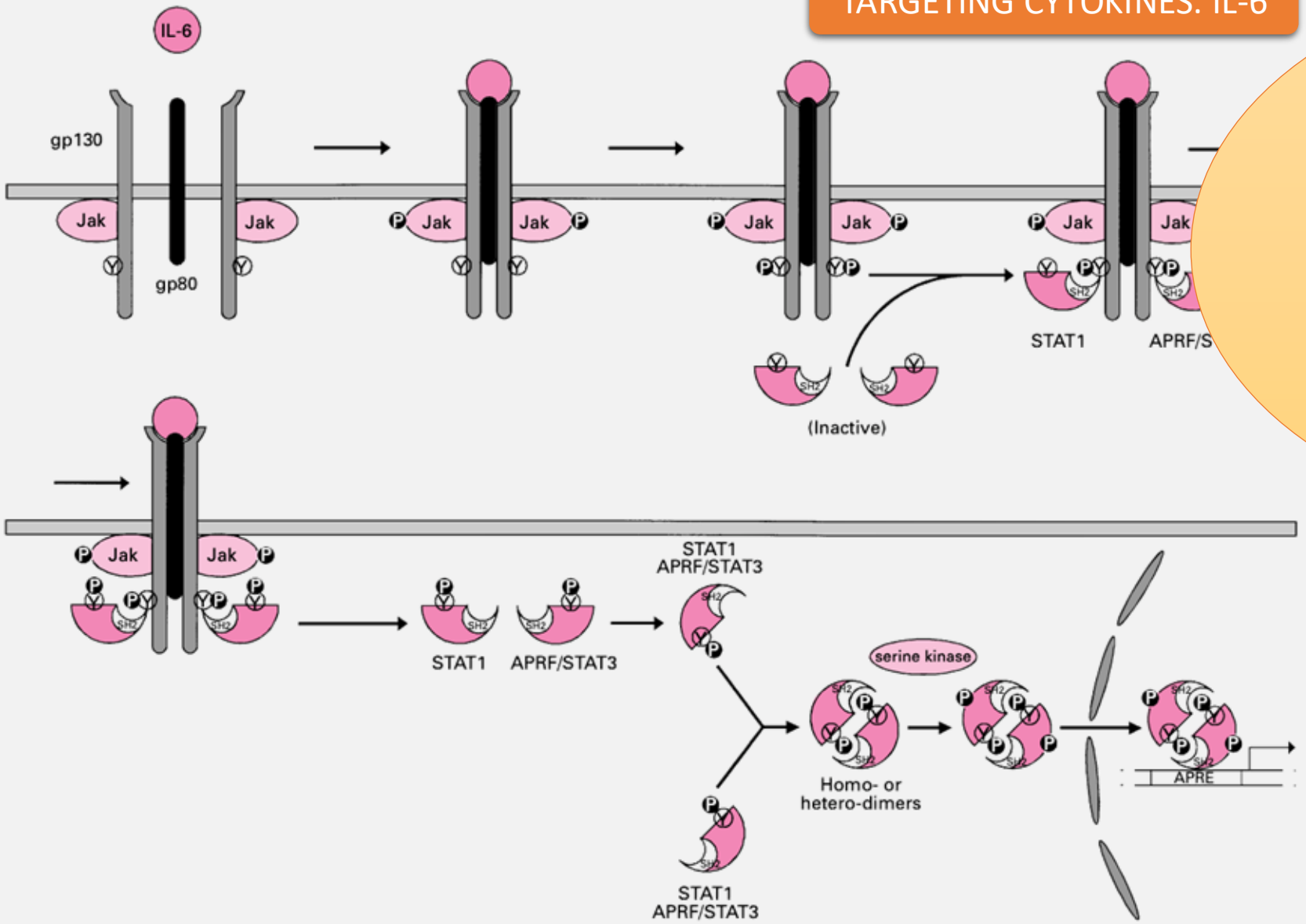
REASSESS

Contributors, Treatments, Prophylaxis

The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)

The potential of cytokine directed therapy: more rational approach

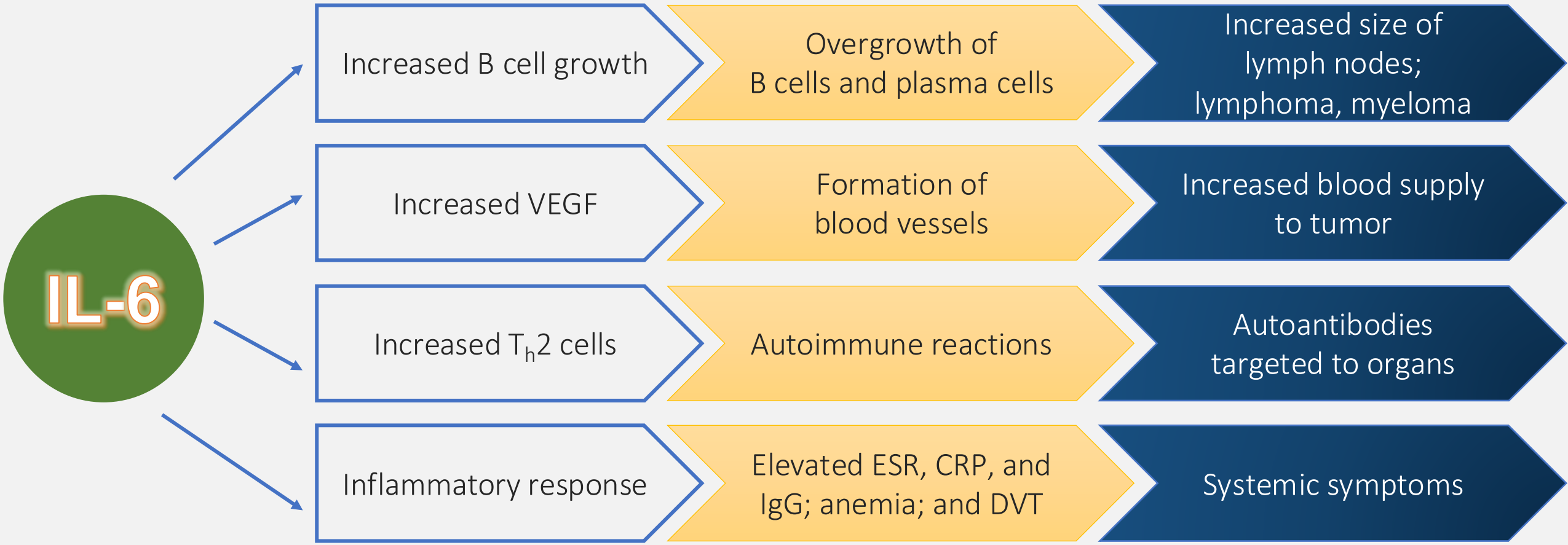
TARGETING CYTOKINES: IL-6



IL-6 is synthesised in a local lesion at the first stage of inflammation and then moves to the liver via the bloodstream, where it results in a **rapid increase** in **levels of acute phase proteins**

- CRP), a key marker of IL-6
- Serum amyloid A
- Fibrinogen and haptoglobin
- Hepcidin
- Vascular endothelial growth factor (VEGF)

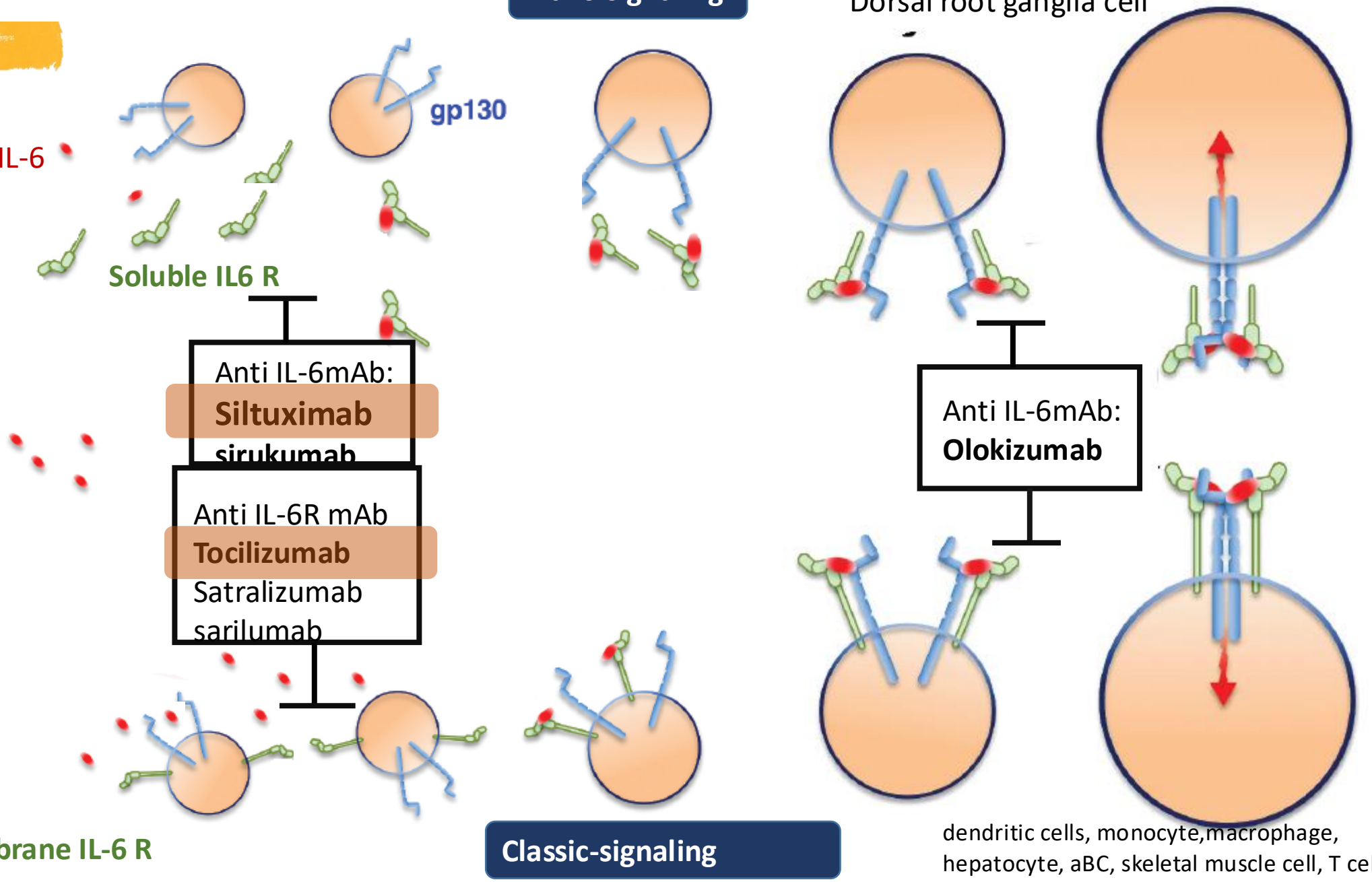
The potential of cytokine directed therapy: more rational approach



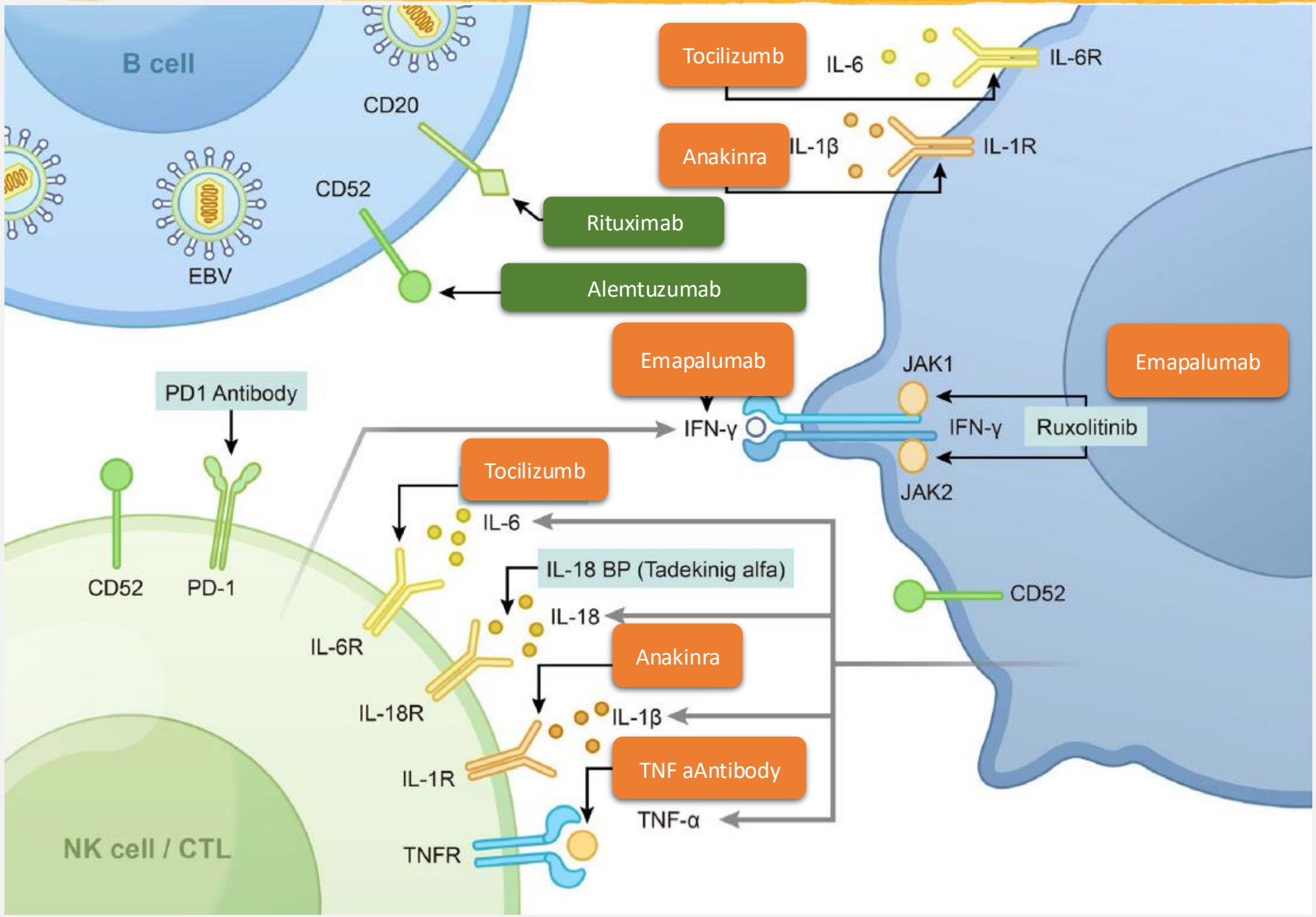
IL-6

Monocyte
Macrophages
Neutrophils
dendritic cells
activated B cells
T cells

Fibroblasts
Keratinocytes
Astrocytes
endothelial cells
neurons



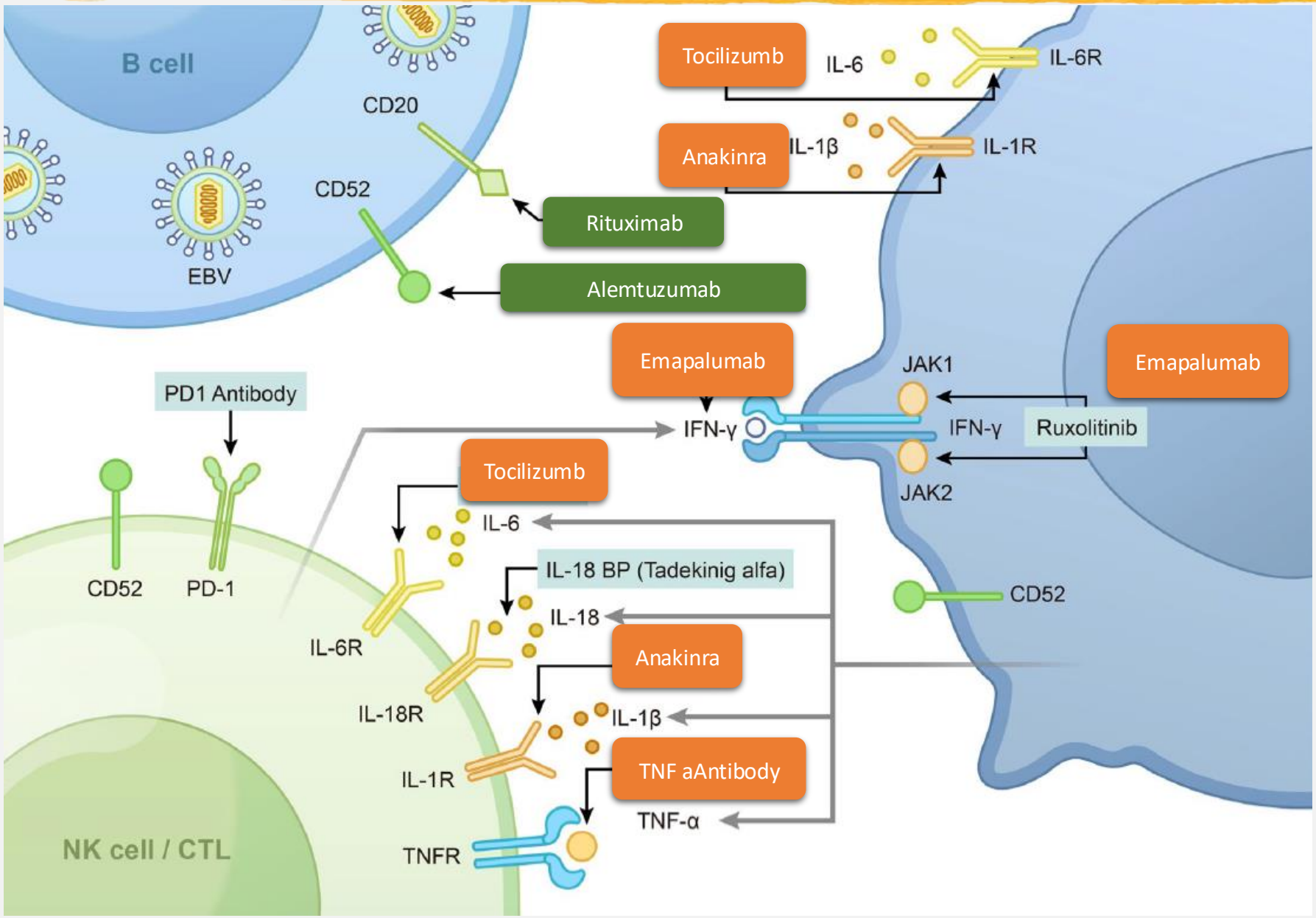
The potential of cytokine directed therapy: more rational approach



TARGETING CYTOKINES

TARGETING IMMUNOCYTES

The potential of cytokine directed therapy: more rational approach



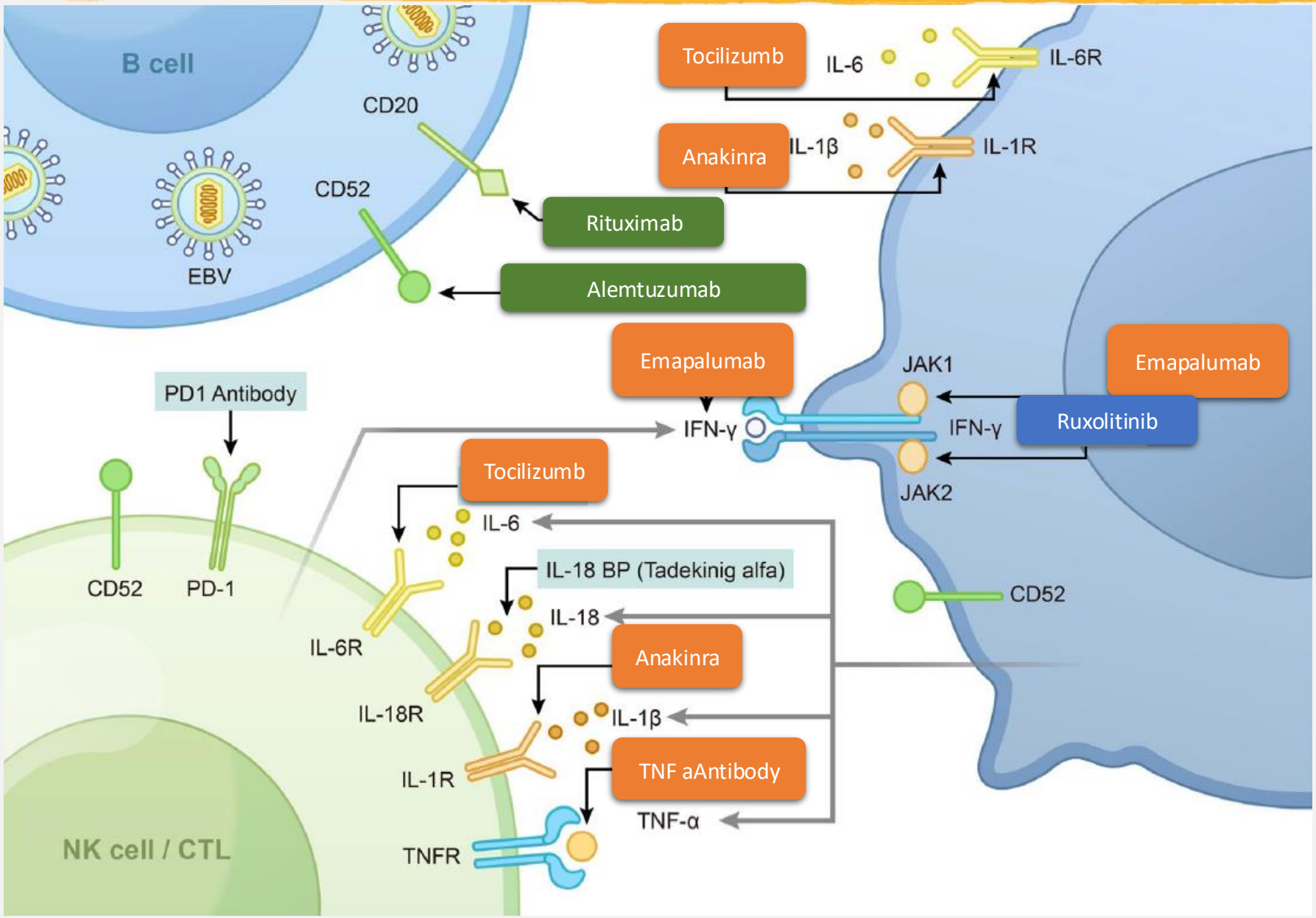
TARGETING IMMUNOCYTES

Rituximab-based chemotherapeutic regimens have been used for EBV-HLH

There were also one report of two cases of central nervous system involvement in patients with EBV-HLH on which alleviated symptoms were rapidly observed with the use of rituximab as a monotherapy

Reducing EBV activation and decreasing its viral load has been shown to help control clinical symptoms and improve survival.

The potential of cytokine directed therapy: more rational approach

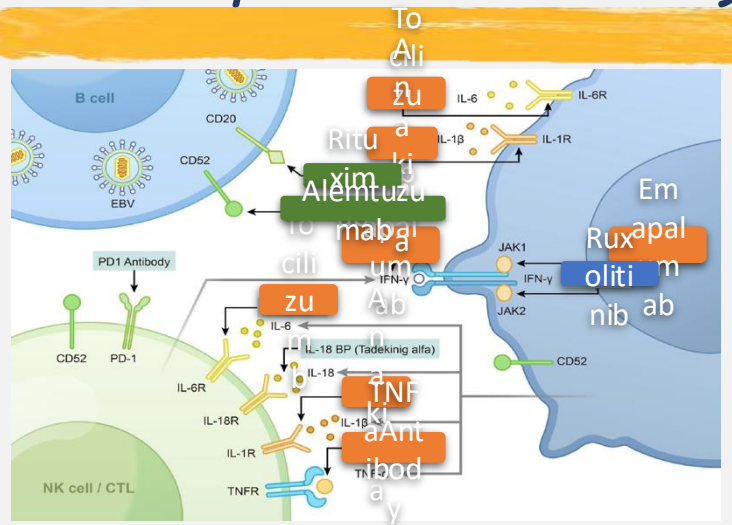


TARGETING CYTOKINES

TARGETING IMMUNOCYTES

TARGETING PRO-INFLAMMATORY SIGNAIING PATHWAYS

The potential of cytokine directed therapy: more rational approach



TARGETING PRO-INFLAMMATORY SIGNAIING PATHWAYS

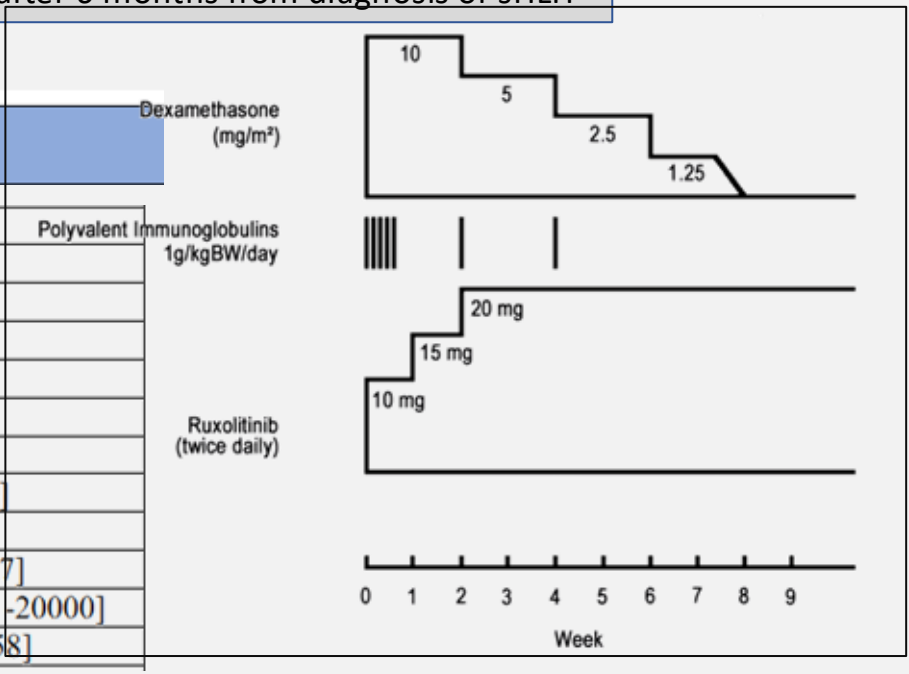
Ruxolitinib, IV Immunoglobulin, and High-Dose Glucocorticoids for Critically Ill Adults With Secondary Hemophagocytic Lymphohistiocytosis: A Single-Center Observational Pilot Study

Pilot study -9 pts

Primary endpoint: OS) after 6 months from diagnosis of sHLH

Variable	Overall (n=9)
Female	3 (33%)
Age	43 [32-54]
BMI	24.6 [22.6-26.9]
Underlying cause of HLH	
----EBV	3 (33%)
----Hodgkin´s lymphoma	1 (11%)
----CAEBV/ Hodgkin's lymphoma	1 (11%)
----HIV	1 (11%)
----Legionella pneumophilia	1 (11%)
----PUUV	1 (11%)
----unknown/idiopathic	1 (11%)
Time to HLH diagnosis[days]	0 [0-15]

Variable	Overall (n=9)
Ventilation	
----vvECMO	1(11%)
----IV	3 (33%)
----NIV	2 (22%)
----O_2-support	4 (44%)
Vasopressor	4 (44%)
Renal replacement therapy	2 (22%)
H-score	299 [255 -304]
HLH-probability [%]	99 [99-99]
Ferritin [µg/L]	27.8 [14.4-46.7]
sIL-2 receptor [pg/mL]	20000 [17295 -20000]
LDH [U/L]	1126 [364-2558]



The potential of cytokine directed therapy: more rational approach

TARGETING PRO-INFLAMMATORY SIGNAIING PATHWAYS

Ruxolitinib, IV Immunoglobulin, and High-Dose Glucocorticoids for Critically Ill Adults With Secondary Hemophagocytic Lymphohistiocytosis: A Single-Center Observational Pilot Study

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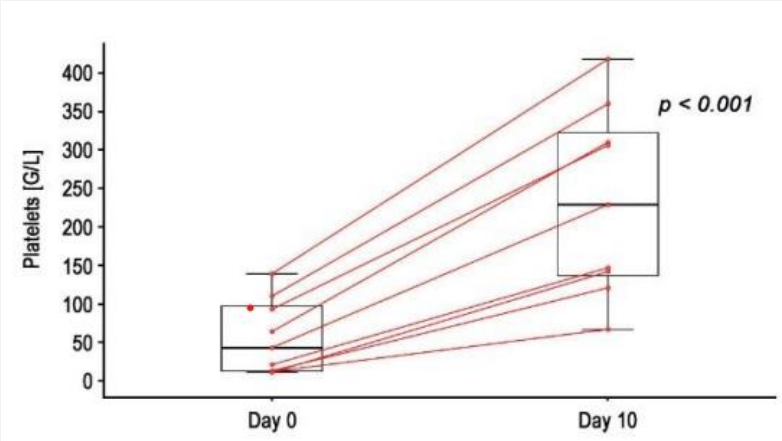
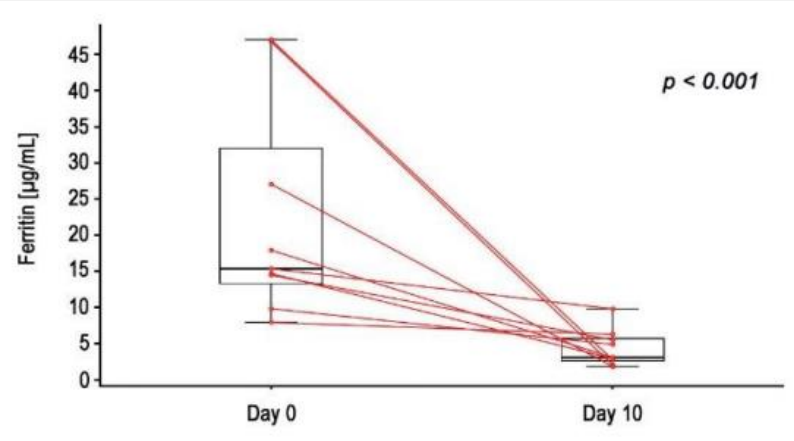
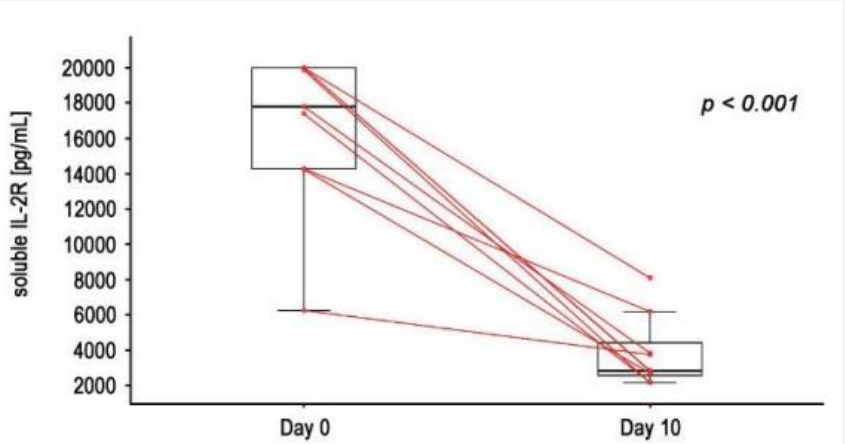






Criteria for discontinue ruxo: if no relapse at 374 and 937 dd

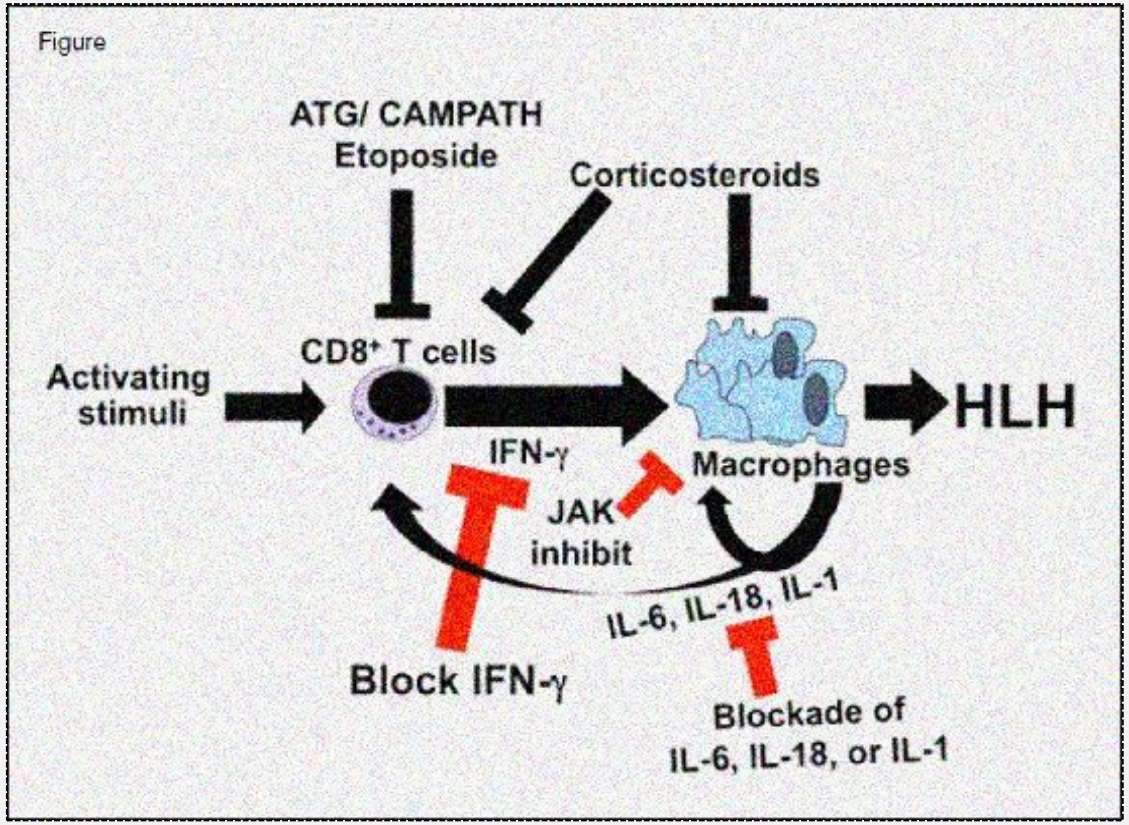
Median time to administration: dd 208

One death, due to traumatic intracerebral hemorrhage due to a fall in context of delirium and confusion, which occurred 14 days after ICU discharge.

The potential of cytokine directed therapy: more rational approach

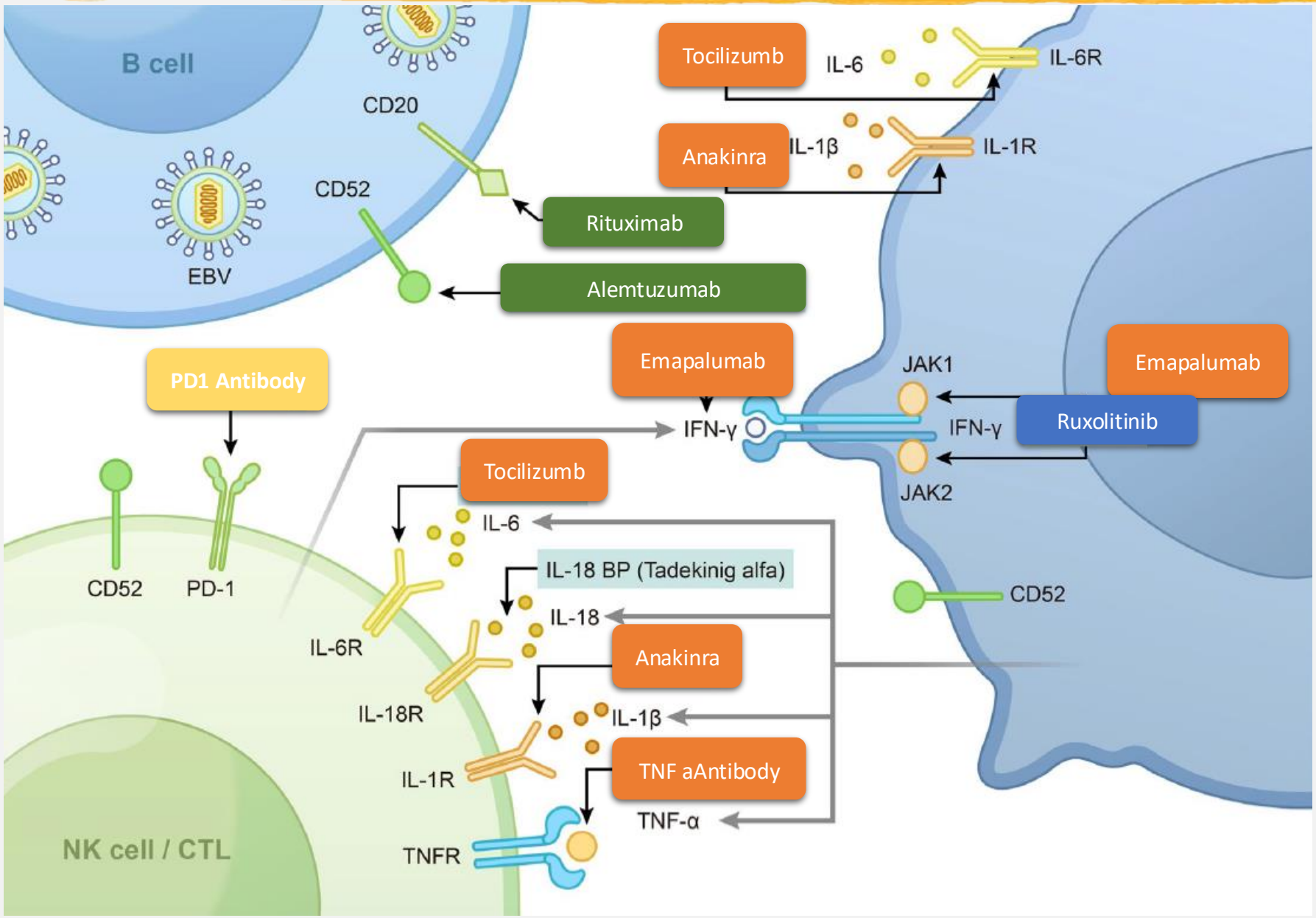
TARGETING CYTOKINES

- IFNγ has a key role in HLH → activates the JAK/STAT pathway
- **Emapalumab is a fully human IgG1 monoclonal antibody that binds to and neutralizes IFNγ**
- First targeted therapy approved for HLH treatment (spp pt unresponsive to conventional treatment)



Combined emapalumab and ruxolitinib in patients with haemophagocytic Lymphohistiocytosis

The potential of cytokine directed therapy: more rational approach



TARGETING CYTOKINES

TARGETING IMMUNOCYTES

TARGETING PRO-INFLAMMATORY SIGNAIING PATHWAYS

TARGETING IMMUNE CHECKPOINT

HLH and HLH-spectrum key features: fever /Falling cytopenia/ HyperFerritinemia
HLH-2024: fulfilled 5/7

KEY considerations:
Pt Hystory
Family History
Preexisting IS (a or IEI)

Hscore >169
OHI

Ferritin and other markers

Urgent diagnostic testing to detect trigger

Act and monitor

SI DG

CLINICALLY UNSTABLE

Supportive therapy
Antimicrobial
Prophylaxis
Call RRT
Biopsy

CS+/- IVIgs

NO DG

Ferritin and other markers

CLINICALLY UNSTABLE

Supportive therapy
Antimicrobial
Prophylaxis
Call RRT
REPEAT BIOPSY!

CS+/- IVIgs

Ferritin and other markers

CS-ivIG+Anakinra

NO DG

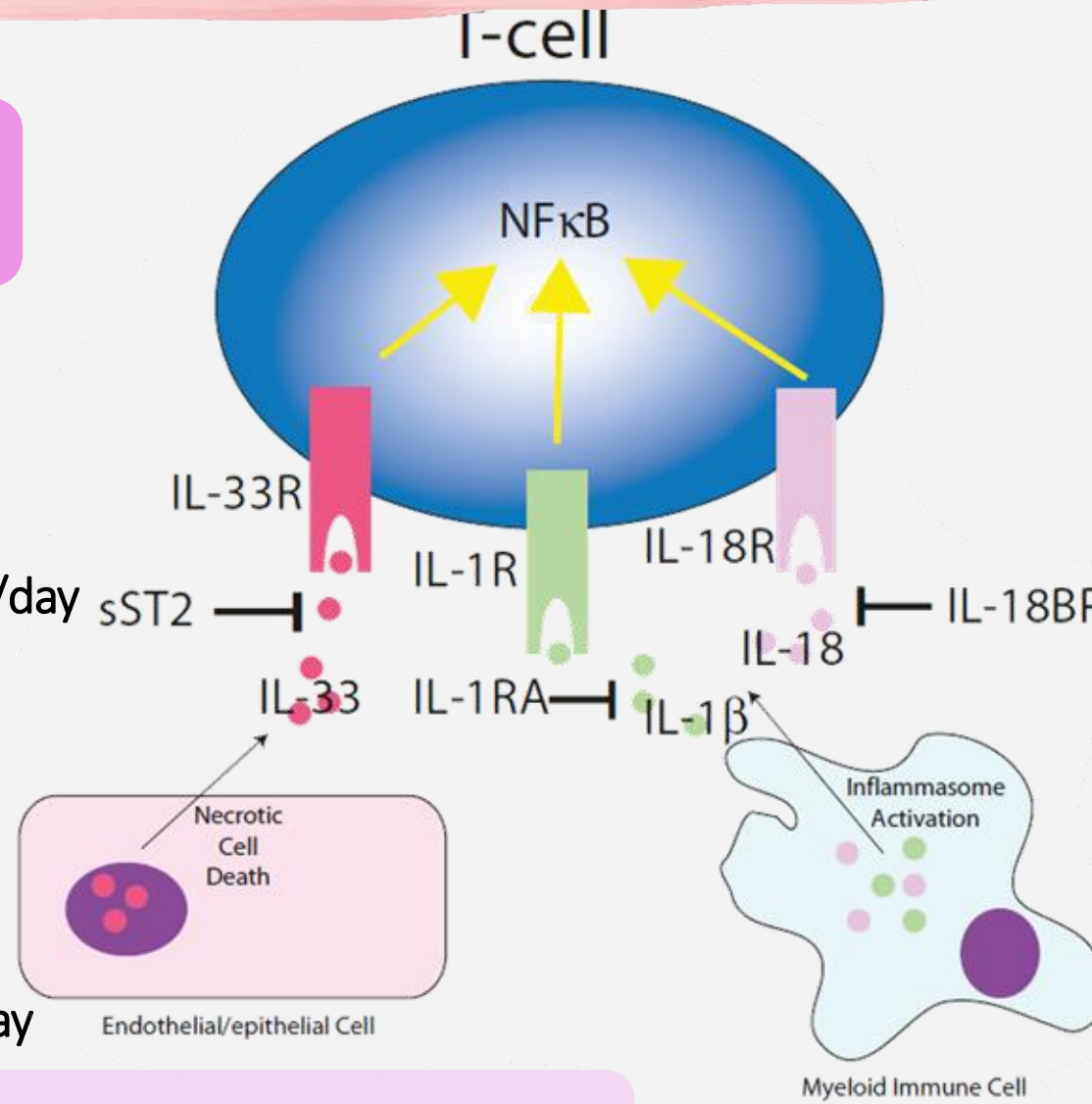
HLH: initial THERAPY -(not) severe -notEBV driven

Glucocorticoids+ Anakinra+ ivIG

- 6Mpdn i,v, 1-2 mg/kg/day
- Dexamethasone iv 10mg/2 per day
- High –dose 6Mpdn iv 10-30mg/Kg/day (max 1gr/day) for 1-3 dd

- 0.4-1gr/kg/day x 2-5 days

- iv (preferred) or s.c. 5-10mg/kg/day



Potential new approach:

CS +ivIG + Ruxolitinib or
Ruxolitinib+ Emapalumab +/- CS +/- ivIG

HLH and HLH-spectrum key features: fever /Falling cytopenia/ HyperFerritinemia
HLH-2024: fulfilled 5/7

KEY considerations:
Pt Hystory
Family History
Preexisting IS (a or IEI)

Hscore >169
OHI

Ferritin and other markers

CLINICALLY STABLE

Act and monitor

Urgent diagnostic testing to detect trigger

CLINICALLY UNSTABLE

Supportive therapy
Antimicrobial
Prophylaxis
Call RRT
Biopsy

CS+/- IVIgs

SI DG

NO DG

Ferritin and other markers

CLINICALLY UNSTABLE/ICU pt

Supportive therapy
Antimicrobial
Prophylaxis
Call RRT
REPEAT BIOPSY!

CS+/- IVIgs

Ferritin and other markers

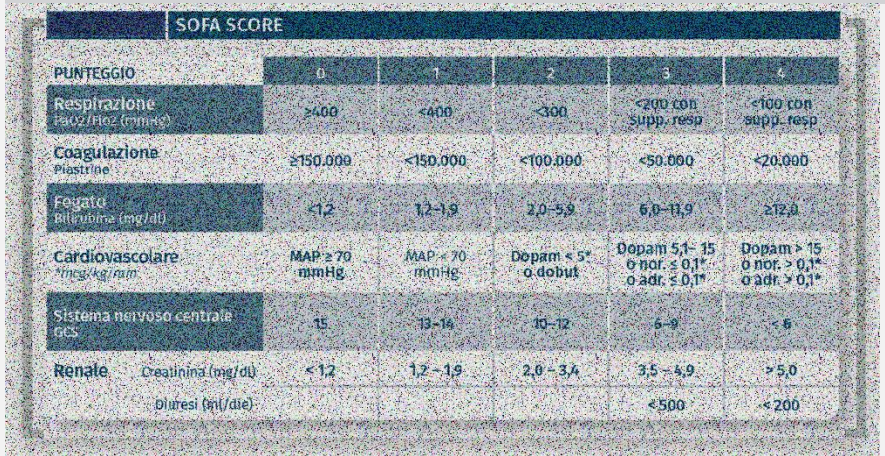
TREAT UNDER DISEASE

CRITICALLY ILL GUIDELINES

NO DG

CRITICALLY ILL PTS WITH HLH -ICU-

Mild	No evidence of organ dysfunction except coagulation/ hematologic system
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
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



SOFA SCORE					
PUNTEGGIO	0	1	2	3	4
Respirazione PaO2/FiO2 (mmHg)	≥400	<400	<300	<200 con supp. resp	<100 con supp. resp
Coagulazione Piastrine	≥150.000	<150.000	<100.000	<50.000	<20.000
Fegato Bilirubina (mg/dl)	<1,2	1,2–1,9	2,0–5,9	6,0–11,9	≥12,0
Cardiovascolare *mcg/kg/min	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopam < 5* o dobut	Dopam 5,1– 15 o nor. ≤ 0,1* o adr. ≤ 0,1*	Dopam > 15 o nor. > 0,1* o adr. > 0,1*
Sistema nervoso centrale GCS	15	13–14	10–12	6–9	< 6
Renale Creatinina (mg/dl)	< 1,2	1,2 – 1,9	2,0 – 3,4	3,5 – 4,9	> 5,0
Diuresi (ml/die)				< 500	< 200

Consider addition of corticosteroid therapy

Dexamethasone 10 mg/m2 daily every 12h
or equivalent methylprednisolone 2 mg/kg/d
+
anakinra 2–10 mg/kg/d, two to four daily doses (subcutaneous or IV)

Addition of etoposide with dose reduction as follows
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.
dose reduction for hypoalbuminemia, hyperbilirubinemia alone, other evidence of liver dysfunction, and/or cytopenias is not recommended

M.R. Hines, Crit care Med 2022

HLH: initial THERAPY - SEVERE -notEBV driven

high likelihood of MA-HLH

Glucocorticoids+ ETO+ /-ivIg+ antiinfectious thpy

- Dexamethasone iv 10mg/2 per day
- (better penetration into CNS)

AFTER BIOPSY
IF IT'S POSSIBLE

- ETO 150mg/m2 x2/week
- ETO 100mg/m2 x2/week in adolescents and young adults
- ETO50-75mg/m2 in middle aged and elderly pts

in these severe life-threatening cases, the potential side effects of a few age-adjusted doses of etoposide, in particular in patients with acceptable blood counts and good empirical supportive care, may be a reasonable risk to take, even if the full diagnostic picture is not complete, in order to halt a potentially life-threatening CSS or a CSS that may result in severe permanent sequelae such as neurological complications

- PCP prophylaxis
- Antiviral prophylaxis
- IGV 0.5gr/kg iv once every 4 weeks
- Antibiotic/antifungal –selected cases-

Invasive aspergillosis and disseminated candidiasis

How I treat High likelihood MA/LA-HLH

BEFORE MALIGNANCY DIAGNOSIS:

- Anti-inflammatory therapies **SHOULD NOT compromise the diagnosis** or curative therapy for the underlying malignancy itself
- Always remember that delayng or compromising treatment for malignancy, infection may be potentially catastrophic
- ETO with high suspicious of LA-HLH is lifesaving and must not be withheld even when confirmation by pathology is still awaited
- if treatment is initiated in a patient **without a firm diagnosis**, the **diagnosis should be re-evaluated once the patient is stable**

GENERAL CONSIDERATIONS

therapy is guided mainly by expert opinion due to a paucity of prospective trials in this heterogeneous patient population

HLH and HLH-spectrum key features: fever /Falling cytopenia/ HyperFerritinemia
HLH-2024: fulfilled 5/7

KEY considerations:
Pt Hystory
Family History
Preexisting IS (a or IEI)

Hscore >169
OHI

Ferritin and other markers

CLINICALLY STABLE

Act and monitor

Urgent diagnostic testing to detect trigger

CLINICALLY UNSTABLE

Supportive therapy
Antimicrobial
Prophylaxis
Call RRT
Biopsy

CS+/- IVIgs

SI DG

NO DG

Ferritin and other markers

CLINICALLY UNSTABLE

Supportive therapy
Antimicrobial
Prophylaxis
Call RRT
REPEAT BIOPSY!

CS+/- IVIgs

Ferritin and other markers

TREAT UNDER DISEASE

.....

YES DG!!

REFLECTIONS BEFORE TURNING TO THERAPY

1. The HLH-2004 criteria: a problem of specificity

Use it as a screening test, not a confirmatory diagnostic test

2. It is **only in primary HLH** that a **definitive diagnosis** can be established.

The absence of any such gold-standard diagnostic in secondary HLH, when combined with the non-specific nature of the syndrome, makes reliable diagnosis a formidable, and to-date inadequately addressed challenge. BUT you can think at secondary HLH as **a a label for excessive and maladaptive inflammation** provoked by any external cause → SO this allows you **to focus more effectively on the underlying trigger.**

3. Ok…ok…

If the patient gets worse and we still don't have a diagnosis, good old **etoposide** will bail us out.

Hold on a second, we need to clarify a few things here **"missing the forest or the trees"**

4. **And now, should I treat the cancer or the HLH?**

How I treat MA-HLH

AFTER DIAGNOSIS OF MALIGNANCY

MD Andrerson's two STEPS approach

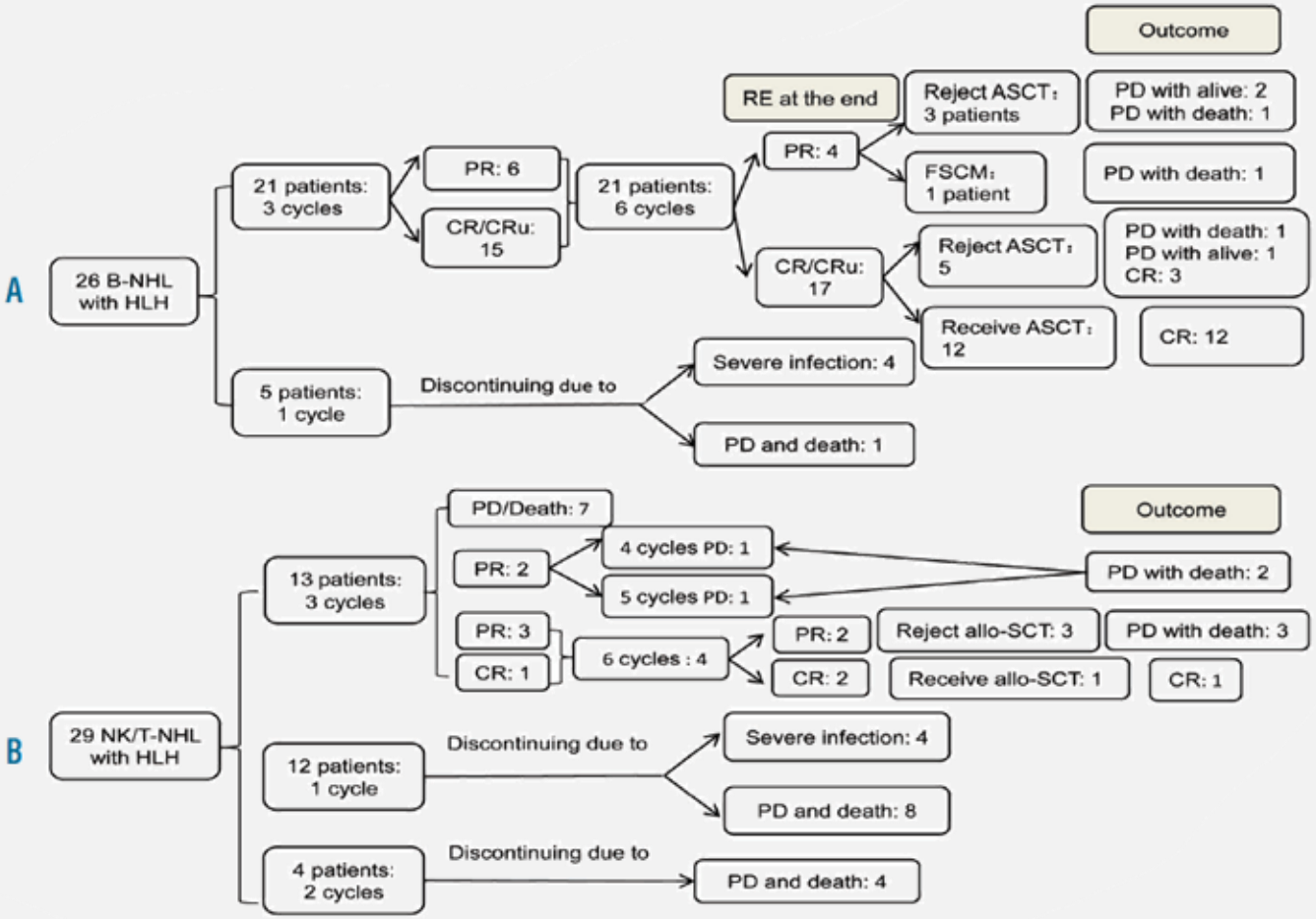
FIRST STEP:
targeting the cytokine storm and proliferating T cells using etoposide and corticosteroids

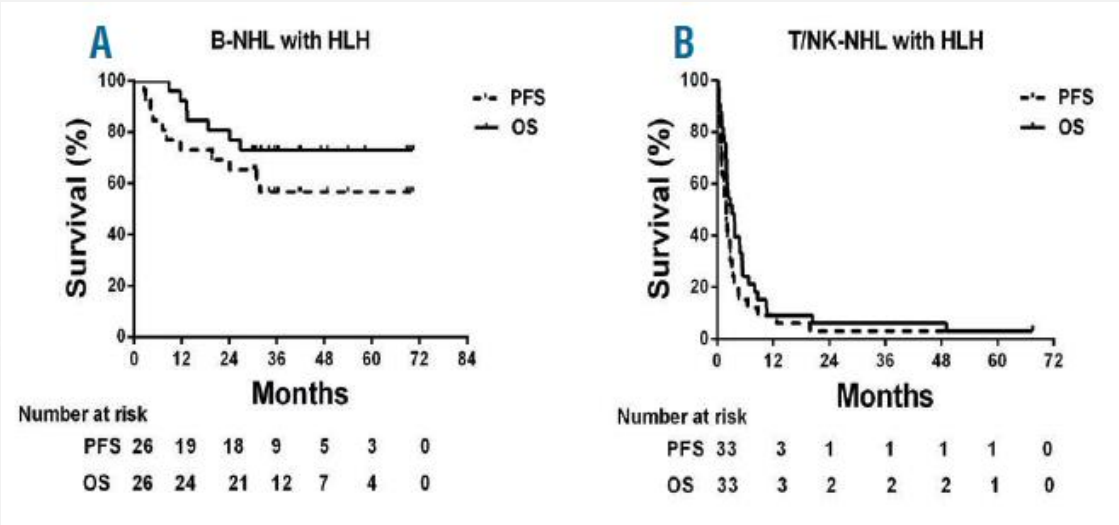
SECOND STEP:
starting a tumour-specific therapy once organ function improves and the patient is relatively stable

TRIAL WITH DOSE –ADJUSTED EPOCH REGIMEN

REMEMBER OHI: AUTOASCT in FIRST REMISSION

Dose-adjusted EPOCH regimen as first-line treatment for non-Hodgkin lymphoma-associated hemophagocytic lymphohistiocytosis: a single-arm, open-label, phase II trial





CONCLUSIONS:

DA-EPOCH-R regimen as front-line treatment followed by ASCT as consolidation treatment demonstrates a **high efficacy and safety for B-NHL patients with HLH**. However, DA-EPOCH cannot improve outcomes for T/NK-NHL patients with HLH

2020

How I treat MA-HLH/EBV DRIVEN

DIAGNOSIS OF MALIGNANCY "ONGOING"

EBV-infected T/NK-cell population in pts with EBV-HLH is often **phenotypically atypical a**nd difficult to define along a spectrum of malignant transformation

Clonal T-cell expansion in the setting of acute EBV infection is common,
and therefore does not necessarily equate with underlying malignancy

those patients that do not improve with empiric HLH directed
therapy typically die after a fulminant disease
cours

HLH: THERAPY. THAT STRANGE CASE OF EBV

While universal evidence-based treatment guidelines for the spectrum of disease encompassed by EBV-associated HLH do not yet exist,
a consensus agrees to start with HLH94-based therapy including dexamethasone and etoposide.
No benefit effect of CSA

Search for other viruses!
KSHV/HHV8
HIV

HLH: initial THERAPY - SEVERE -EBV driven

Glucocorticoids+ ETO+Rituximab+ + antiinfectious thpy

- **Rituximab 375mg/m2 once /week**

EBV can replicate in NK and T cells and thus a lack of response or recurrence after rituximab treatment is a possibility

Requirement for etoposide in the initial treatment of Epstein-Barr virus–associated haemophagocytic lymphohistiocytosis

Song Y, 2019

Features	Group 1† (n = 52)	Group 2‡ (n = 41)	P value
Age, years			
Median	22·5	30	0·088
Range	[1–70]	[4–70]	
Gender (n)			
Male	31	23	0·83
Female	21	18	
Fever (>38·5°C)	52	41	
Splenomegaly (n)	45 (86·5%)	35 (85·4%)	1·00
Hepatomegaly (n)	22 (42·3%)	15 (36·6%)	0·67
Haemophagocytosis (n)	38 (73·1%)	21 (51·2%)	0·49
WBC ($\times 10^9$/l)	1·8 [0·37–40·65]	2·33 [0·2–10·1]	0·097
Hb (g/l)	98 ± 21·41	104 ± 18·61	0·105
PLT ($\times 10^9$/l)	49 [2–255]	62 [13–365]	0·070
ALT (u/l)	122 [10·0–2142·3]	101 [26–998]	0·623
AST (u/l)	132·5 [17·1–1744·0]	135·3 [23·3–695·8]	0·952
Total bilirubin (μmol/l)	17·99 [4·85–254·08]	27·53 [7·15–367·24	0·074
Creatinine (μmol/l)	52·7 [23·0–291·9]	70·53 ± 40·36	0·080
Triglycerides (mmol/l)	3·05 ± 1·66	2·92 [0·59–16·77]	0·891
Fibrinogen (g/l)	1·62 ± 0·95	1·53 [0·21–7·69]	0·607
Ferritin (μg/l)	8·40 [4·48–12·56]	7·68 [5·32–11·23]	0·070
sCD25 (pg/ml)	9·07 [7·13–10·69]	10·24 [7·11–10·69]	0·623
EBV-DNA (lg copies/ml)	5·13 ± 0·92	4·90 ± 1·51	0·406

Values are given as median [range] or mean ± standard deviation. ALT, alanine aminotransferase; AST, aspartate aminotransferase; EBV-HLH, Epstein–Barr virus-associated haemophagocytic lymphohistiocytosis; Hb, haemoglobin concentration; PLT, platelet count; WBC, white blood cell count.
†Patients whose initial therapy included etoposide.
‡Patients whose initial therapy did not include etoposide.

HLH: initial THERAPY - SEVERE -EBV driven

Glucocorticoids+ ETO+Rituximab+ + antiinfectious thpy

- **Rituximab 375mg/m2 once /week**

<u>EBV can replicate in NK and T cells</u> and thus a lack of response or recurrence after rituximab treatment is a possibility

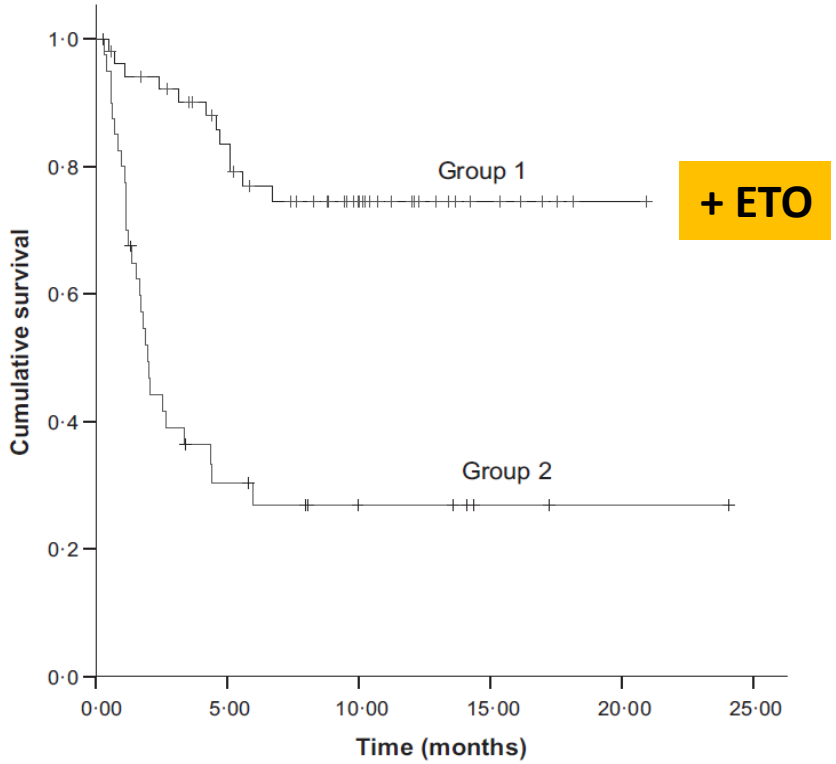
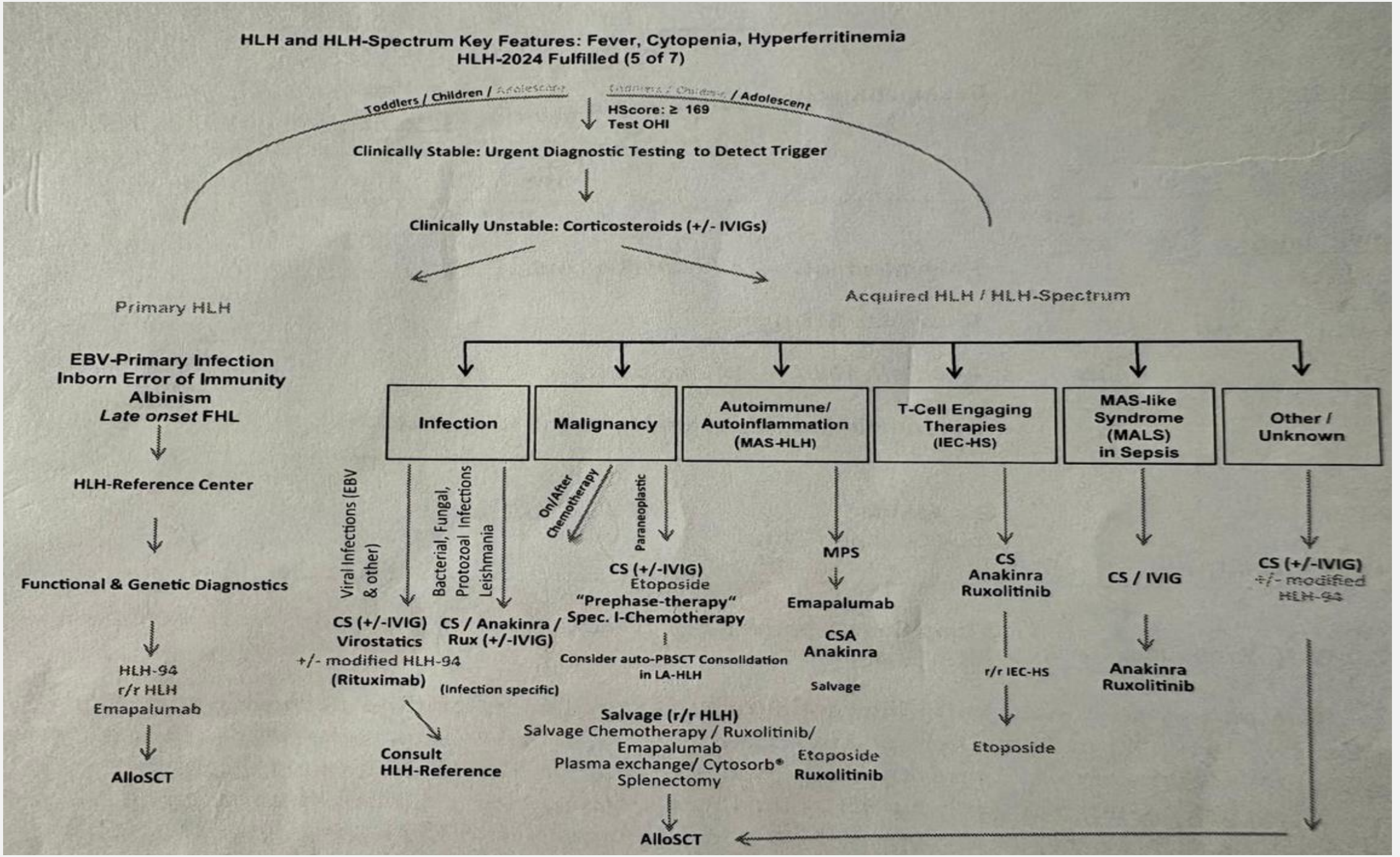


Fig 1. The survival curves of the two groups. Group 1: patients whose initial therapy included etoposide. Group 2: patients whose initial therapy did not include etoposide.

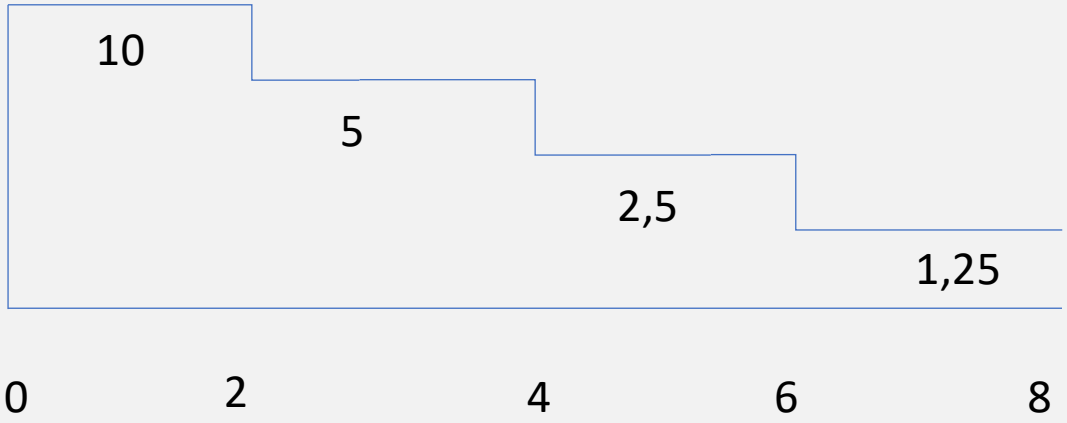
Requirement for etoposide in the initial treatment of Epstein-Barr virus–associated haemophagocytic lymphohistiocytosis

Song Y, 2019


HLH and HLH-Spectrum Key Features: Fever, Cytopenia, Hyperferritinemia
HLH-2024 Fulfilled (5 of 7)
Toddlers / Children / Adolescent
Toddlers / Children / Adolescent
HScore: ≥ 169
Test OHI
Clinically Stable: Urgent Diagnostic Testing to Detect Trigger
Clinically Unstable: Corticosteroids (+/- IVIGs)
Primary HLH
Acquired HLH / HLH-Spectrum
EBV-Primary Infection
Inborn Error of Immunity
Albinism
Late onset FHL
HLH-Reference Center
Functional & Genetic Diagnostics
HLH-94
r/r HLH
Emapalumab
AlloSCT
Infection
Malignancy
Autoimmune/
Autoinflammation
(MAS-HLH)
T-Cell Engaging
Therapies
(IEC-HS)
MAS-like
Syndrome
(MALS)
in Sepsis
Other /
Unknown
Viral Infections (EBV & other)
Bacterial, Fungal, Protozoal Infections
Leishmania
On/After Chemotherapy
Paraneoplastic
CS (+/-IVIG)
Virostatics
+/- modified HLH-94
(Rituximab)
CS / Anakinra /
Rux (+/-IVIG)
(Infection specific)
CS (+/-IVIG)
Etoposide
"Prephase-therapy"
Spec. I-Chemotherapy
Consider auto-PBSCT Consolidation
in LA-HLH
MPS
Emapalumab
CSA
Anakinra
Salvage
CS
Anakinra
Ruxolitinib
r/r IEC-HS
Etoposide
CS / IVIG
Anakinra
Ruxolitinib
CS (+/-IVIG)
+/- modified
HLH-94
Consult
HLH-Reference
Salvage (r/r HLH)
Salvage Chemotherapy / Ruxolitinib/
Emapalumab
Plasma exchange/ Cytosorb®
Splenectomy
Etoposide
Ruxolitinib
AlloSCT

Backbone

DEXAMETASHONE
mg/m2



Individualized

EBV-HLH
LA-HLH/MA-HLH
Ch-HLH
MAS-like sepsis
MAS-HLH
IEC-HS

Polyvalent IGG 1-1.6 g/kg (3-5 d split)

Rituximab 375mg/m2

Anakinra 100-800mg/d s.c./ev

Ruxolitinib 5mg to 40mg/d per os (ng tube if need)

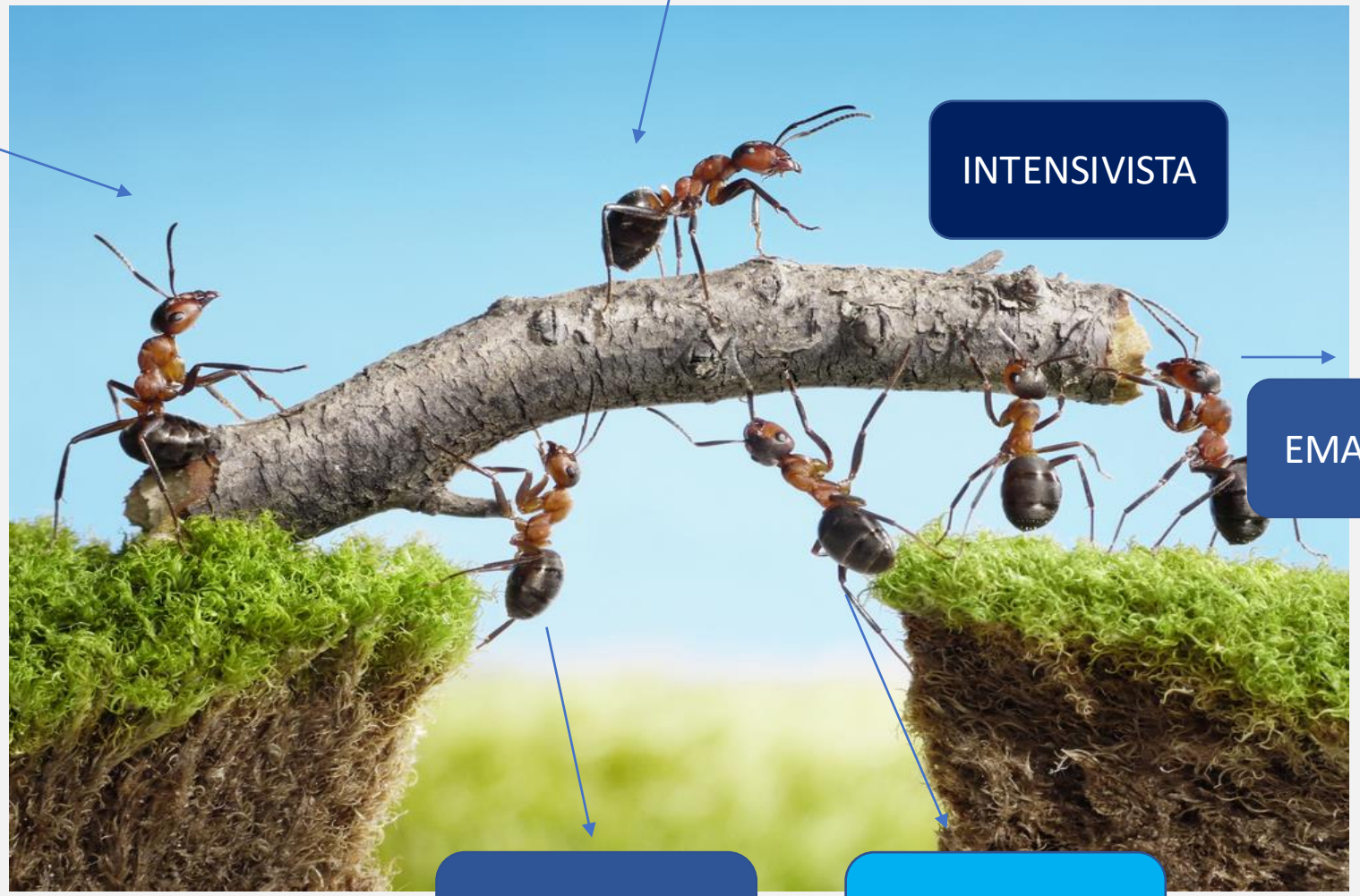
LA-HLH
EBV-HLH
r/r HLH
r/r MAS-HLH

Etoposide 50-150mg/m2 biw

Lesson learned

INFETTIVOLOGO

PATOLOGO



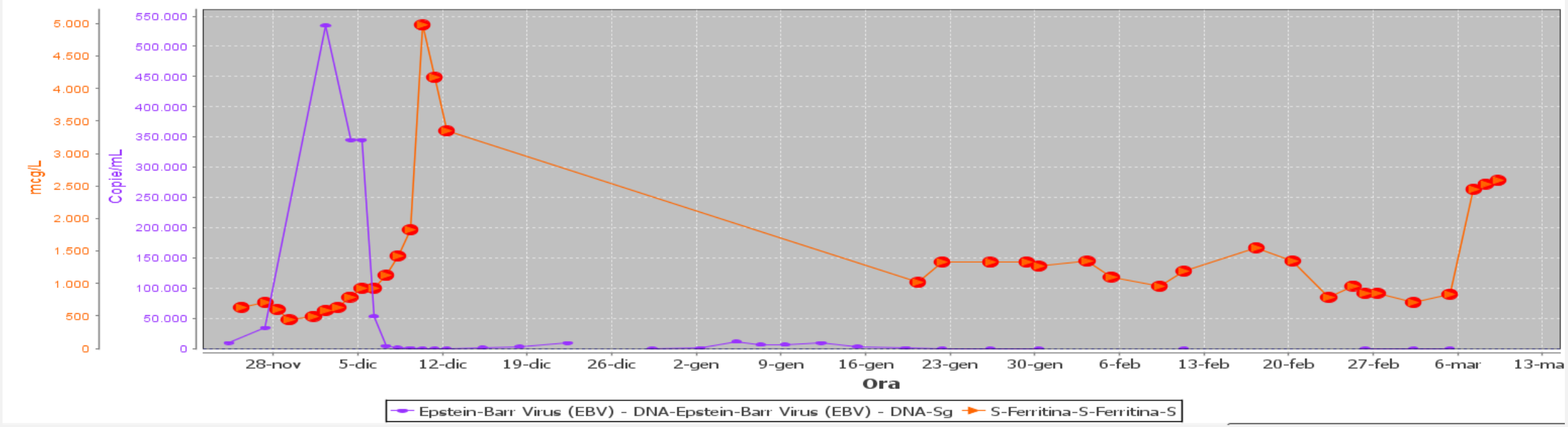
INTENSIVISTA

EMATOLOGO

INTERNISTA

.....

Special thanks to all the patients who are still with us and to those who were part of our journey.


mcg/L
Copie/mL
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4.500
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28-nov
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16-gen
23-gen
30-gen
6-feb
13-feb
20-feb
27-feb
6-mar
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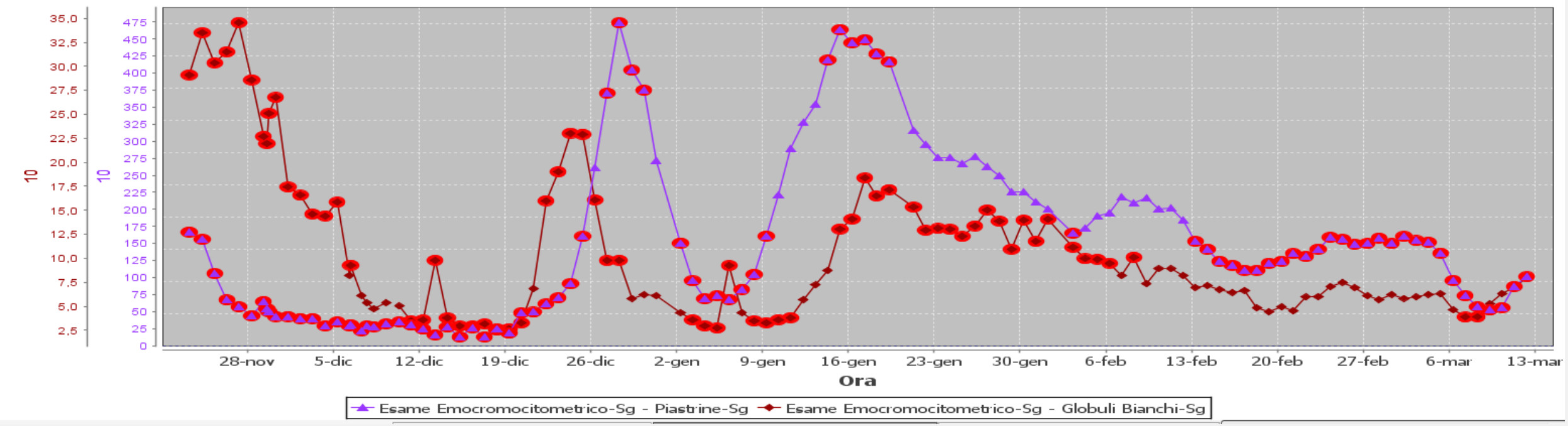
Ora
Epstein-Barr Virus (EBV) - DNA-Epstein-Barr Virus (EBV) - DNA-Sg
S-Ferritina-S-Ferritina-S


10
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28-nov
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26-dic
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23-gen
30-gen
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20-feb
27-feb
6-mar
13-mar
Ora
Esame Emocromocitometrico-Sg - Piastrine-Sg
Esame Emocromocitometrico-Sg - Globuli Bianchi-Sg

HEMATOLOGISTS AND INFLAMMATION

SYSTEMIC BUT CLINICALLY INAPPARENT

- inflammaging

CHRONIC SYMPTOMATIC INFLAMMATION

- HM with inflammation or systemic autoimmune/inflammatory disorders

HEMATOLOGISTS AND INFLAMMATION: DD

SYSTEMIC BUT CLINICALLY INAPPARENT

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CHRONIC SYMPTOMATIC INFLAMMATION

- HM with inflammation or systemic autoimmune/inflammatory disorders

TOO MUCH INFLAMMATION

- Sepsis
- Macrophage activation like syndrome (MALS)
- Cytokine release syndrome (CRS)
- MAS-HLH
- Immune effector cell-associated HLH-like syndrome
- HLH

HEMATOLOGISTS AND INFLAMMATION: DD

Macrophage activation like syndrome (MALS)

sepsis → an inadequate host response to infection

High mortality rates in sepsis complicated by MALS (79%)

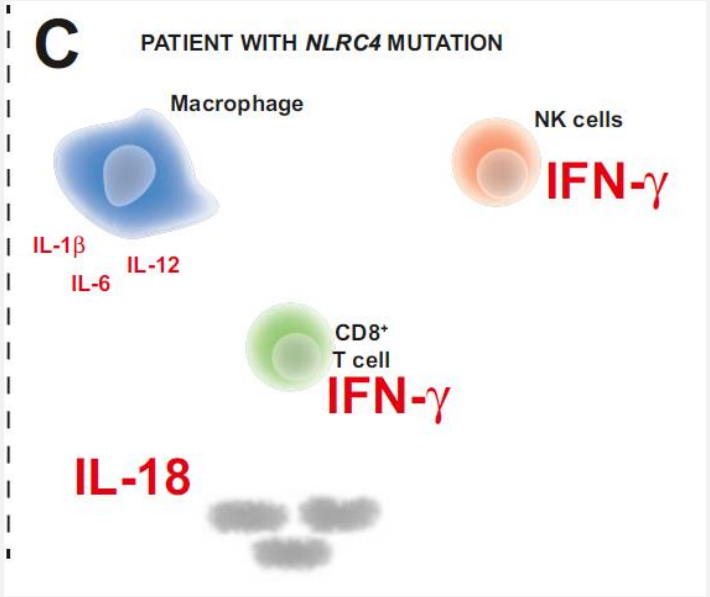
MALS:
Sepsis+
hyperinflammatory phenotype

excessive release of proinflammatory cytokines, IL-6,TNF-a, IFN-g, hyperferritinemia

MALS definition:

- ferritin cut-off of 4420 mg/ L in sepsis patients
- hepatobiliary dysfunction and DIC

MAS-HLH



The CSSs associated with sJIA and AOSD are essentially identical, consistent with the increasing recognition of these disorders as a single entity extending across age groups.
Hyperinflammation is driven primarily by a dysregulated IL-1 inflammasome, resulting in excess release of both IL-1 and IL-18; gain-of-function inflammasome mutations are becoming more widely recognized in affected patients with sJIA or AOSD