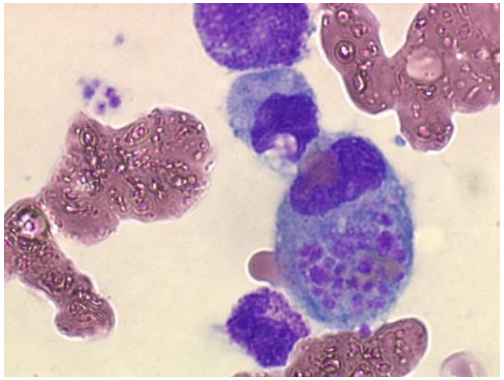
Hemophagocytic syndrome

A better understanding for a better management



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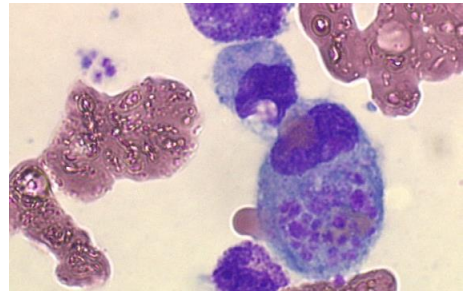
36th International Symposium on Intensive Care and Emergency Medicine

Hemophagocytic syndrome (HS)

1. Clinical features:

- Fever and wasting, organomegaly
- Liver cytolysis, coagulopathy
- Hypertriglyceridemia with hyperferritinemia
- Cytopenias

- Cytologic pictures of hemophagocytosis



2. Associated conditions:

Malignancies

- Lymphoid malignancies
- Other cancers

Immune deficiency

- Hereditary
- Acquired

HIV
Immunosuppressive TTT
Transplantation

Other contexts

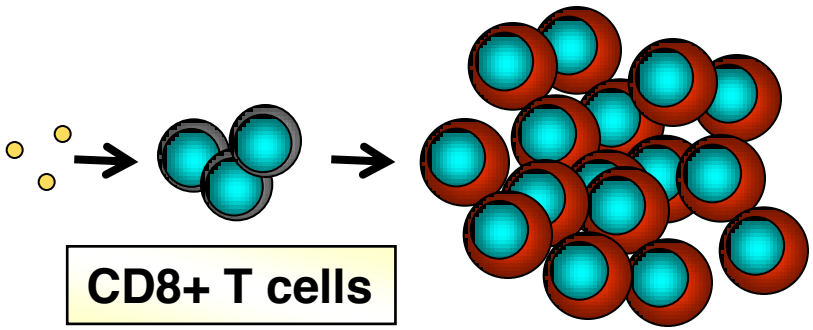
- Autoimmune diseases
- Infections

HS: two main pathophysiological mechanisms I.

- **Hereditary form**

Deficiency in cytotoxicity + infection (trigger)

Failure of the body to clear up (intracellular) infectious agents

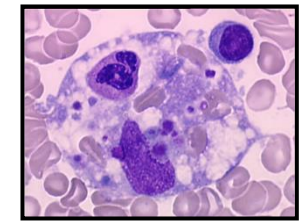


CD8+ T cells

CD8+ T cell expansion

Failure of contraction

Tissue infiltration spleen, liver Bone marrow, CNS



Hemophagocytosis

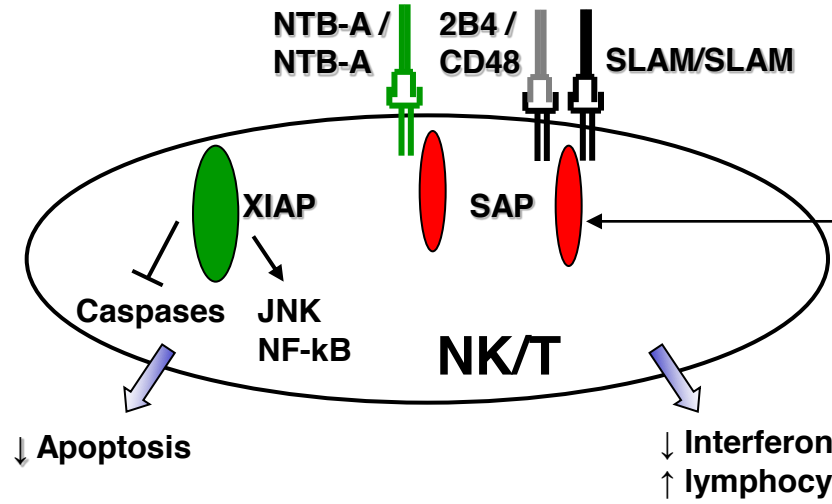
Interferon-γ +++

Macrophage activation

TNFα IL1, IL6 ....

HEREDITARY FAILURE OF CYTOTOXICITY: WHY?

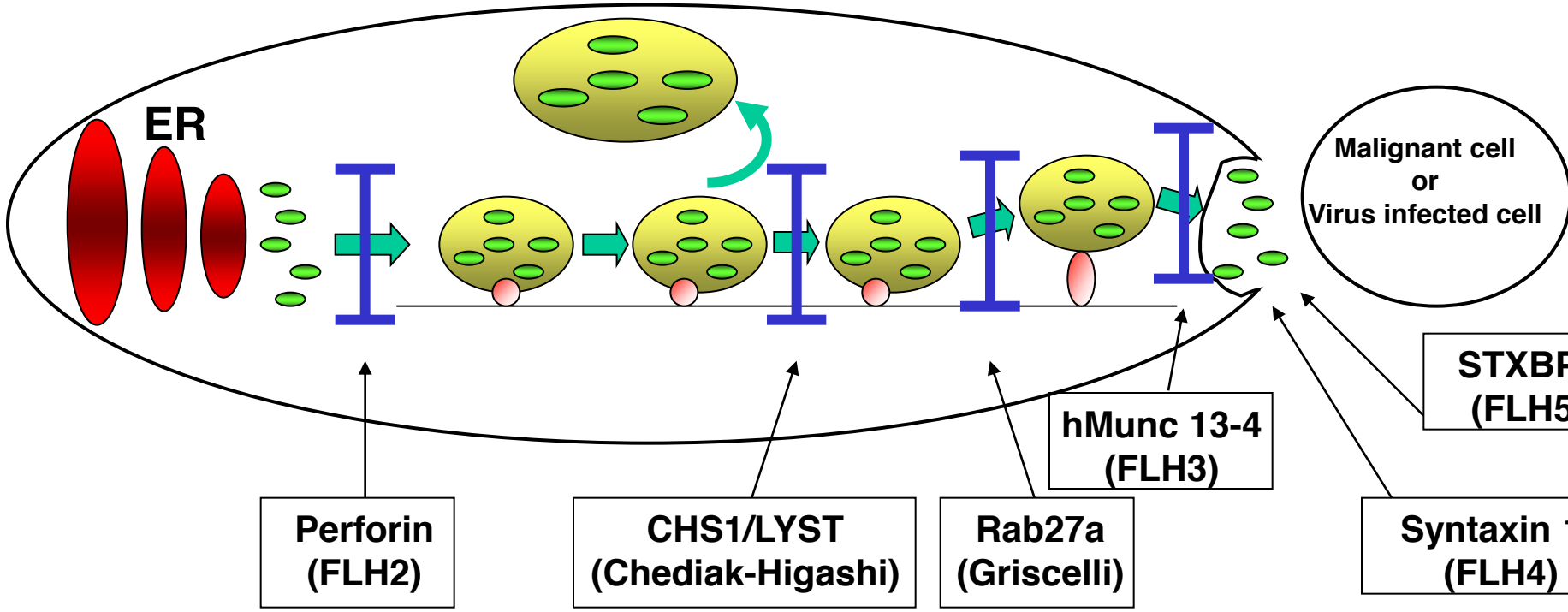
For an optimal cytotoxicity:



SAP: SLAM-associated protein

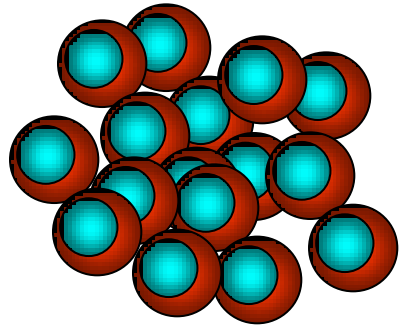
XIAP: X-linked inhibitor of apoptosis

SAP & XIAP (XLP)



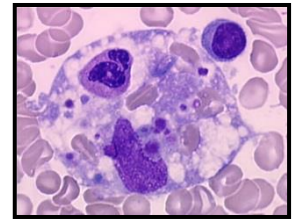
Pathophysiology of reactive HS: less clear

Dysrégulation of secretion / synthesis of interferon-γ



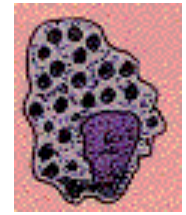
T-, NK- or regulatory B-cell (?) lymphoma

Interferon-γ
+++



Hemophagocytosis

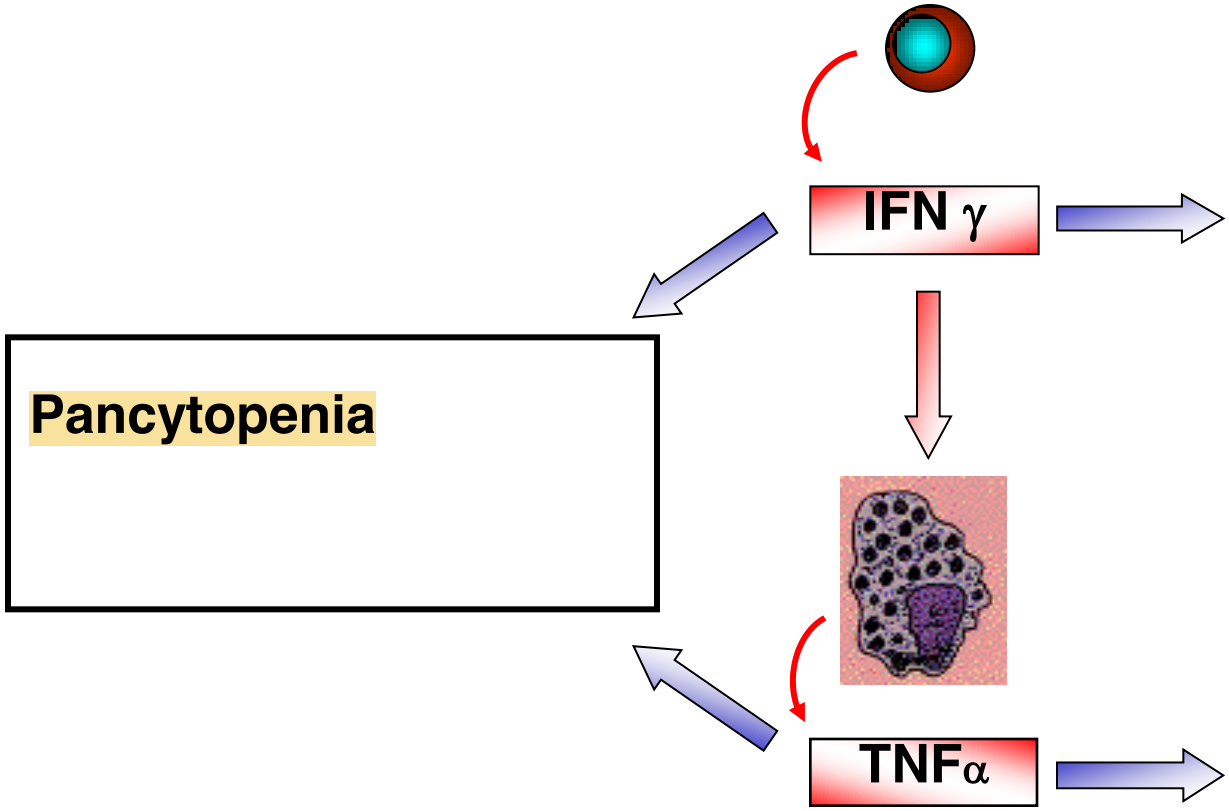
TNFα
IL1, IL6
....



Macrophage activation

FROM PATHOPHYSIOLOGY TO CLINICAL PRESENTATION

Hemophagocytic syndrome : an inappropriate secretion of cytokines



Fever

Macrophage activation

Hyperferritinemia

Liver cytolysis : Fas/FasL

Pancytopenia

wasting, cachexia

Cardiac failure

Hypoalbuminemia, amyotrophy

Hyponatremia (ADH-mediated)

Hypertriglyceridemia

Tissue plasminogen activator

To diagnose an hemophagocytic syndrome

Suspicion of HS (fever + wasting + cytopenias, with no other obvious etiology)

No specific biological test : the diagnosis is based on an association of criteria

Δ criteria of the « Histiocyte Society 2004 »:

Henter et al., Pediatr Blood Cancer 2004

Typically used for HS in children; used by default in adults+++

1. Familial context / Genetic abnormality
2. 5/8 following criteria:

- Fever
- Splenomegaly
- ≥ 2 cytopenias
- Hypertriglyceridemia or hypofibrinemia
- Ferritin > 500 ng/mL
- sCD25 > 2400 U/mL
- Decreased NK cell activity
- Hemophagocytosis

Uneasy to use in emergency…

The diagnosis of HS is frequently underestimated; a delayed diagnosis is frequent

A tool for the diagnosis of adult reactive HS: the HScore

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)

9 variables used

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

HScore = 230 (IQR, 203-257) for a PPV of 98%

125 (IQR, 91-150) for a NPV of 93%

The probability of HS ranges from < 1% with a HScore ≤ 90 to > 99% with a HScore ≥ 250

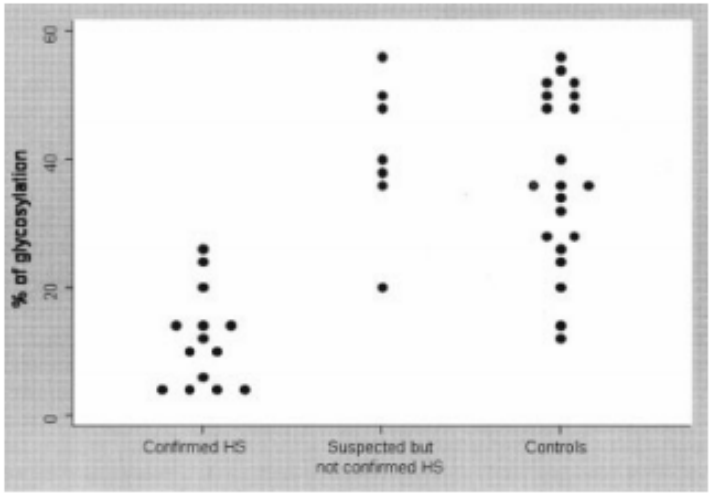
Score freely available online: http://saintantoine.aphp.fr/score/

Fardet et al., Arthritis Rheumatol 2014

A potentially interesting tool: glycosylated ferritin

Low Glycosylated Ferritin, a Good Marker for the Diagnosis of Hemophagocytic Syndrome

Laurence Fardet,[1] Paul Coppo,[1] Adrien Kettaneh,[1] Monique Dehoux,[2] Jean Cabane,[1] and Olivier Lambotte[3]



	Patients with confirmed hemophagocytic syndrome (n = 14) vs. patients with suspected but unconfirmed hemophagocytic syndrome (n = 7)		Patients with confirmed hemophagocytic syndrome (n = 14) vs. controls (n = 21)	
	Apparent performance	Cross-validation performance	Apparent performance	Cross-validation performance
Optimal cutoff, %†	26	25	26	25
Sensitivity	1.00 (0.77–1.00)	1.00 (0.77–1.00)	1.00 (0.77–1.00)	0.86 (0.57–0.98)
Specificity	0.86 (0.42–1.00)	0.71 (0.29–0.96)	0.76 (0.53–0.92)	0.76 (0.53–0.92)
Positive predictive value	0.93 (0.68–1.00)	0.88 (0.62–0.98)	0.74 (0.49–0.91)	0.71 (0.44–0.90)
Negative predictive value	1.00 (0.54–1.00)	1.00 (0.48–1.00)	1.00 (0.80–1.00)	0.89 (0.65–0.89)

* Values in parentheses are 95% confidence intervals.
† The optimal cutoff value is the one that gives the higher total sensitivity and specificity.

Value of glycosylated ferritin : certain HS: 10% [3-14] vs 40% [36-47] (uncertain HS) (p<0.001) vs controls (36% [26-49]) (p<0.001)

Fardet et al., Arthritis Rheumatol 2008

Therapeutical principles: 3 points

1. Management in emergency and ressuscitation measures:

- Correct ionic troubles and coagulopathy, transfusions
- Typically need preemptive antibiotherapy (febrile neutropenia)
- Organ failure: ventilation, catecholamins, anti-epileptic drugs…

2. Symptomatic treatment: « to calm the immune system down »

- Steroids 0.3 to 1 mg/kg
- Most efficient treatment: etoposide+++: rapidly efficient
  efficacy > steroids > IgIV
  > leukemogenic risk (+++ if > 2 g/m^2 !)

- Patients treated with etoposide during the 4 first weeks have a better pronosis ($p < 0.01$)
- 1-2 or more infusions…, 100 to 150 mg/m^2

Shinsaku et al., J Clin Oncol 2001

3. Specific therapies:

- Treat an associated disease+++: autoimmune disease, lymphoid malignancy, HIV infection…

PROGNOSIS OF REACTIVE HS

Assessment of parameters on admission associated with day-30 mortality in 162 patients with reactive HS

Variable	Odds ratio	95% CI	*P*-value
Age (per 10 years increase)	1·59	1·06–2·38	0·03
Platelets (per 1 × 10^9/l increase)	0·97	0·95–0·99	0·01
Underlying immunodeficiency (HIV infection)	0·19	0·03–1·03	0·06
Triggering condition			
Infection or other condition*	1	–	–
Lymphoma	11·9	2·4–60·5	0·003
Multicentric Castleman disease	–	–	–
Treatment use			
No specific treatment or glucocorticoid or IVIG alone	1	–	–
Etoposide	0·21	0·05–0·94	0·04

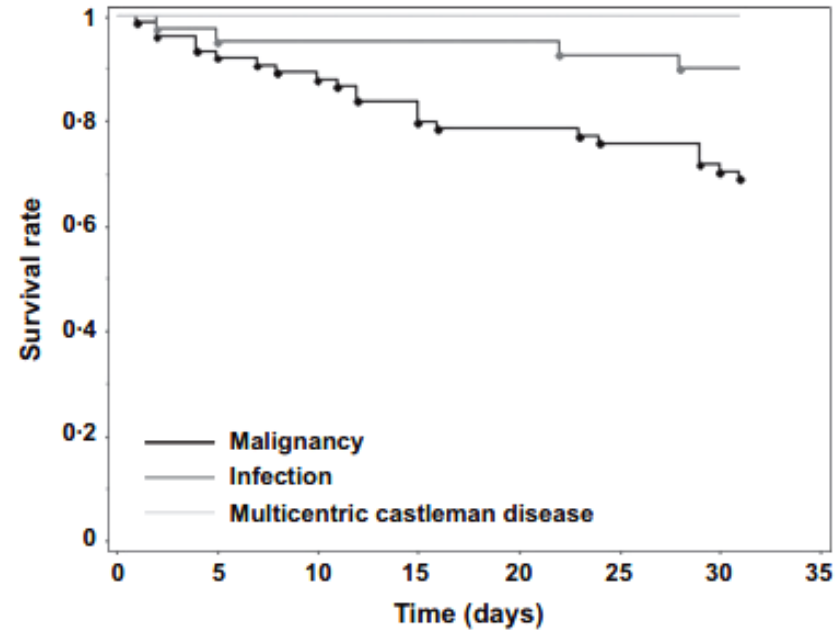


Fig 1. Kaplan–Meier survival estimates of survival rate in patients with reactive haemophagocytic syndrome according to the underlying condition.

Age, thrombocytopenia, an underlying lymphoid malignancy and lack of etoposide in the treatment negatively impact prognosis

Arca et al., Br J Haematol 2014

Conclusion: future directions for 2016

1. HS: at the junction of immune deficiency, infections and malignancies:

- Are there susceptibility genes shared by these conditions?
- hMunc13.4, perforine (lymphoma or CTD + HS)

2. Improvement of diagnostic criterias:

- Confirmation of the Hscore by other groups
- Glycosylated ferritin should be evaluated in emergency: a reliable tool?
- An « aggressive » consensual diagnostic work up should be proposed in reactive HS

3. Consensual recomendations should be developed:

- First line therapy: what one should do beyond empiricism? Etoposide: how and how much?
- Therapeutical trials should evaluate targeted therapies: anti-interferon, alemtuzumab, anti-IL1/anakinra…

Bruck et al., J Clin Rheumatol 2011; Ideguchi et al., Rheumatology 2007; Tomoko et al., Am J Hematol 2006

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