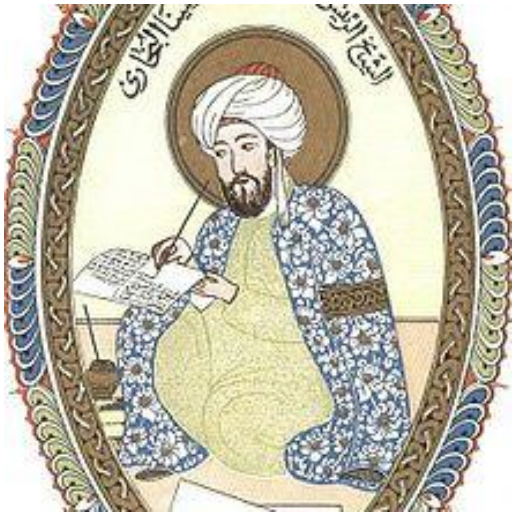
Hemophagocytic LymphoHistiocytosis



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Histiocytic Disorders: Recent Insights into Pathophysiology and Practical Guidelines

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Table 1. Classification of Histiocytic Disorders

Benign disorders of varying biologic behavior

a. Dendritic cell related

Langerhans cell histiocytosis

Juvenile xanthogranuloma and related disorders including:

- Erdheim-Chester disease
- Solitary histiocytomas with juvenile xanthogranuloma phenotype
- Secondary dendritic cell disorders

b. Monocyte/macrophage related

Hemophagocytic lymphohistiocytosis

Familial and sporadic

Secondary hemophagocytic syndromes:

- Infection associated
- Malignancy associated
- Autoimmune associated (MAS)
- Other

HLH

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)

Solitary histiocytoma of macrophage phenotype

Biol Blood Marrow Transplant 16: S82-S89 (2010)

Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency

Genetic HLH

Table 4 | Diseases of immune dysregulation			
Disease	Gene	Inheritance	Associated features
2. Familial hemophagocytic lymphohistiocytosis (FHL) syndromes			
FHL-1	unknown	AR	HLH is the primary and only manifestation
FHL-2	PRF 1	AR	
FHL-3	UNC 13D	AR	
FHL-4	STX 11	AR	
FHL-5	STX BP2	AR	

Al-Herz W, Bousfiha A, Casanova JL et al. Front Immunol 2011;2:54

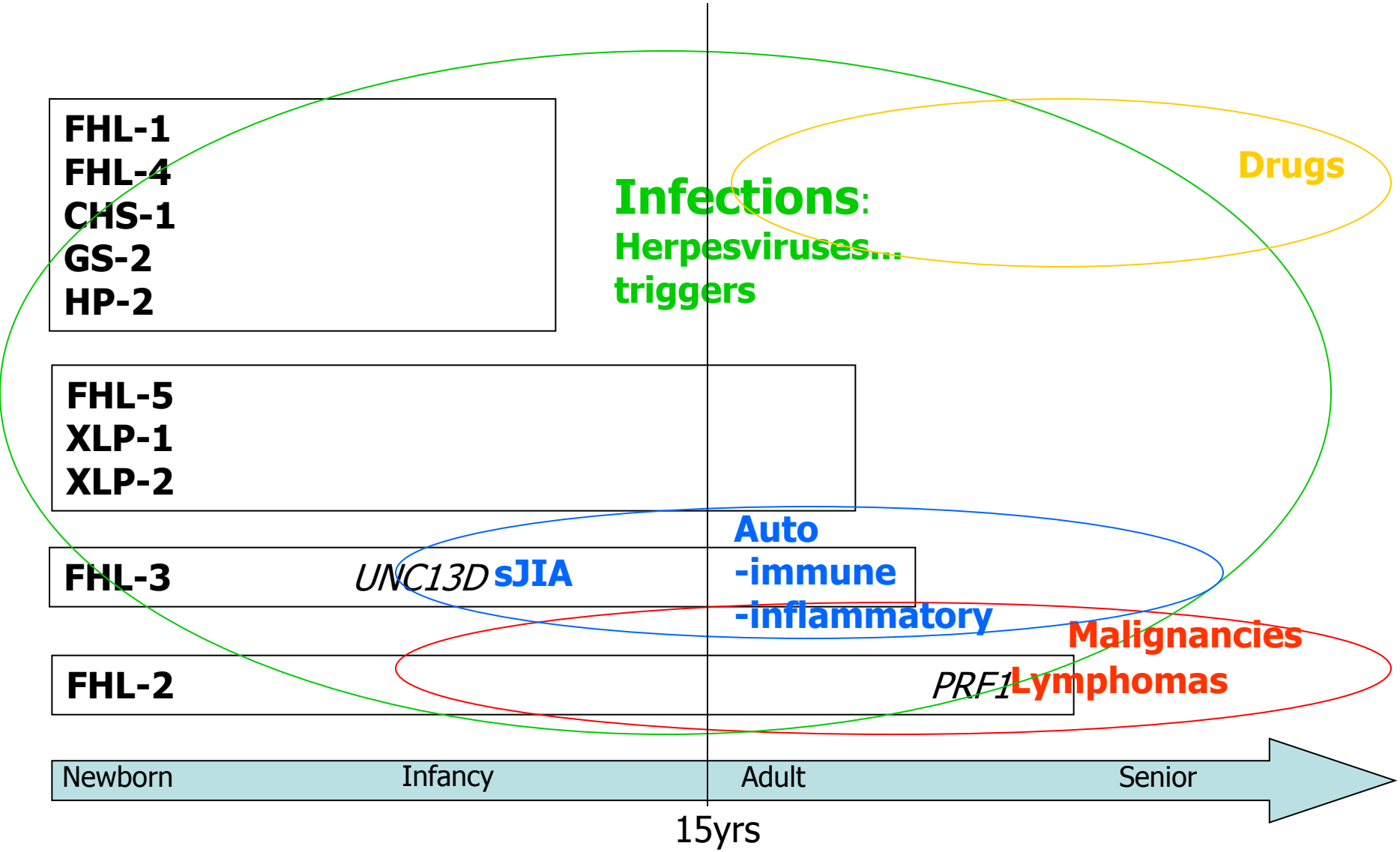
Table 4 | Diseases of immune dysregulation			
1. Immunodeficiency with hypopigmentation			
Chediak-Higashi syndrome	LYST	AR	HLH in the accelerated phases
Griscelli syndrome type2	RAB 27A	AR	
Hermansky-Pudlak syndrome type2	AP3B1	AR	
3. Lymphoproliferative syndromes			
XLP-1	SH2D1A, SAP	XL	HLH trigged by EBV
XLP-2	XIAP, BIRC4	XL	
Table 1 | Combined immunodeficiencies			
20. ITK deficiency	ITK	AR	HLH trigged by EBV

Acquired HLH :

Infectious agents
Autoinflammatory and autoimmune diseases (macrophage activation syndrome MAS)
Malignant diseases
Immune suppression (drugs), hematopoietic stem cell and organ transplantation, AIDS

Janka GE. Annu Rev Med. 2012;63:233-46.

Genetic HLH may present during Adulthood



HLH: definition

- HLH is:
  - a rare life-threatening disease
  - **a syndromic disorder** defined by a unique pattern of clinical findings
- HLH is characterized by:
  - **severe hyper-inflammation** (cytokines)
  - **multiorgan infiltration and damage** (lymphocyte and macrophage proliferation)

HLH phenotype

Confusion
Headache
Meningitis
Seizures…

lymphadenopathy

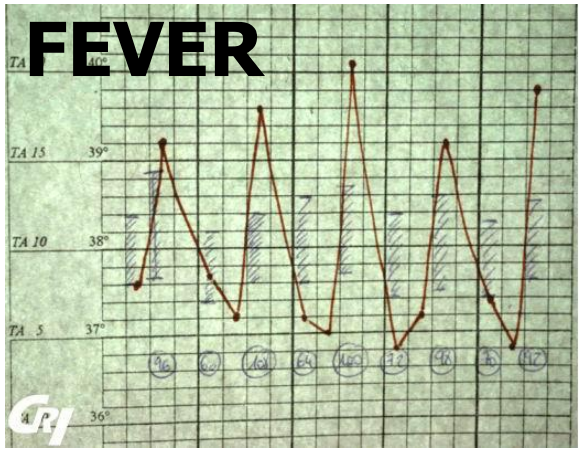
Bone marrow aspiration

Pleural effusion
ARDS

HM/liver biopsy

SM

Ascitis

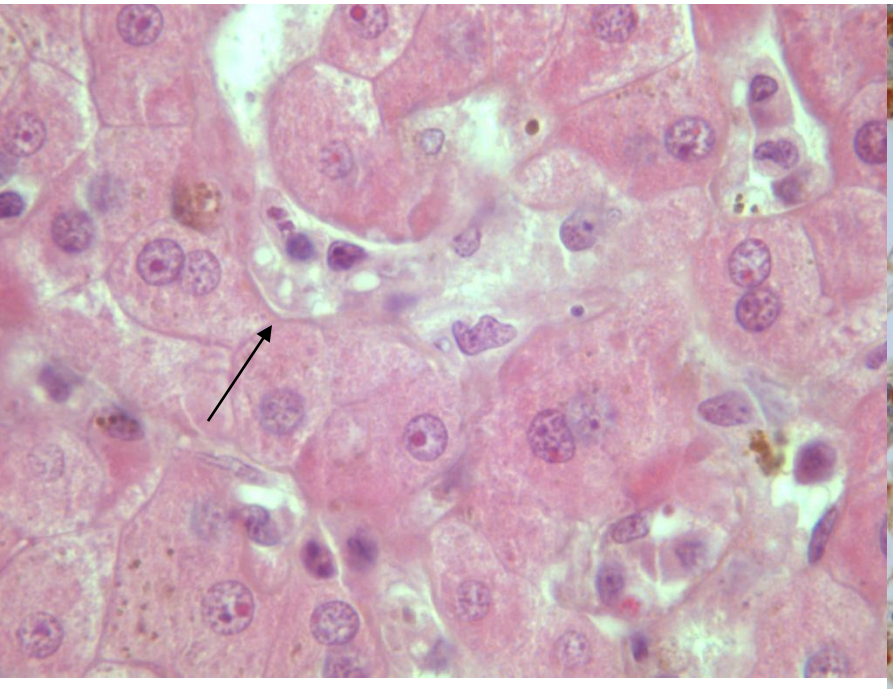


Bi/tri-cytopenias
↗ Ferritin, ↗sCD25
↗ LDH
Cholestasis/cytolysis
↘ Fg
↘Albuminemia
↗ TG, ↗ lipase
↗ β-2m
Lactic acidosis
Renal failure

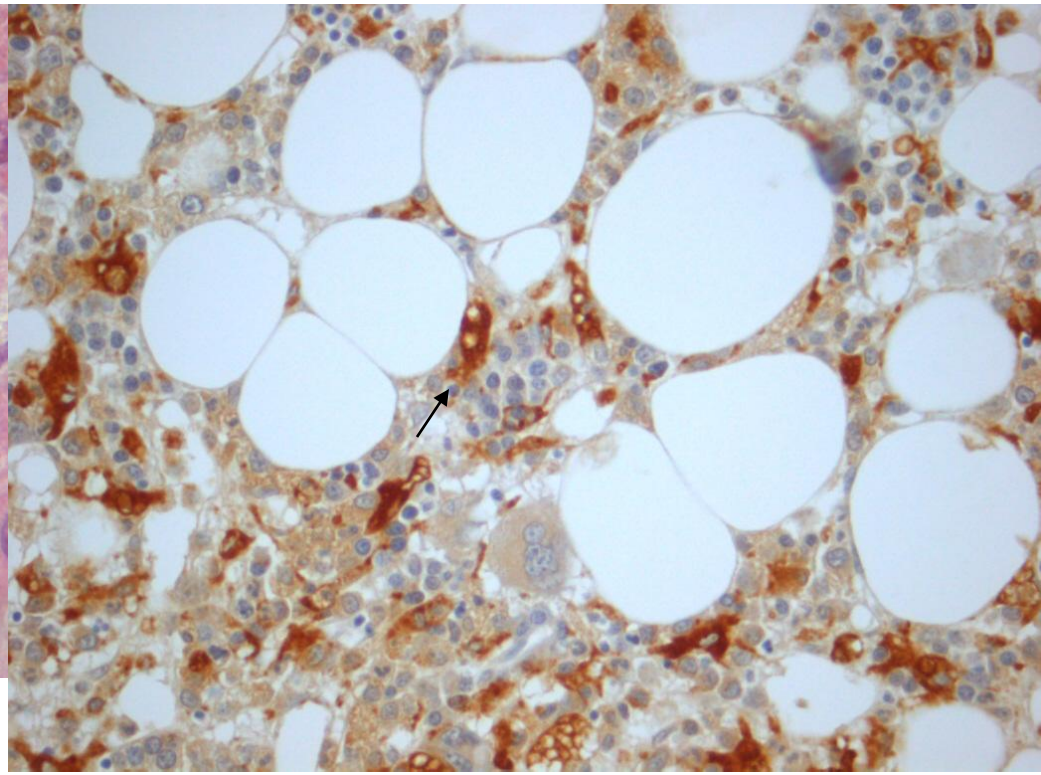
Purpura
Rash
Edema
Jaundice

Cardinal symptoms: prolonged fever, HSM, cytopenias

Histology: hemophagocytosis



LIVER:
Küpffer cells with erythrophagocytosis



BONE MARROW: macrophages with hemophagocytosis (CD68)

Hemophagocytosis is initially absent in half patients
Hemophagocytosis per se is not diagnostic of HLH

Histiocyte Society guidelines

Table 1. Diagnostic criteria for HLH used in the HLH-2004 trial*

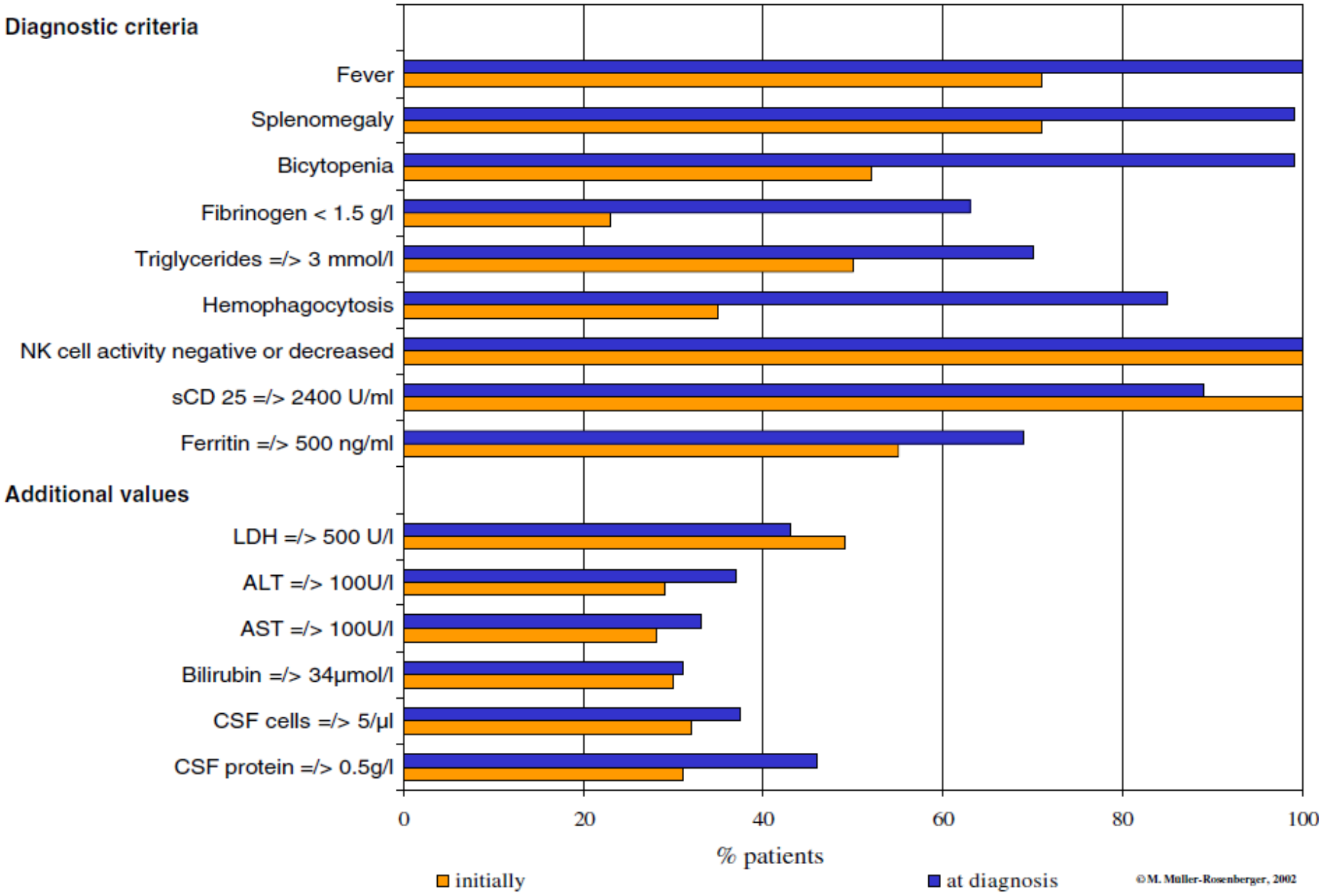
The diagnosis of HLH† may be established:
A. Molecular diagnosis consistent with HLH: pathologic mutations of *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC4*
or
B. Five of the 8 criteria listed below are fulfilled:
1. Fever ≥ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
Hemoglobin < 9 g/dL (in infants < 4 weeks: hemoglobin < 10 g/dL)
Platelets < 100×10^3/mL
Neutrophils < 1×10^3/mL
4. Hypertriglyceridemia (fasting, > 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin > 500 ng/mL‡
8. Elevated sCD25 (α-chain of sIL-2 receptor)§

Established on pediatric cohortes

Not included liver, CNS involvement

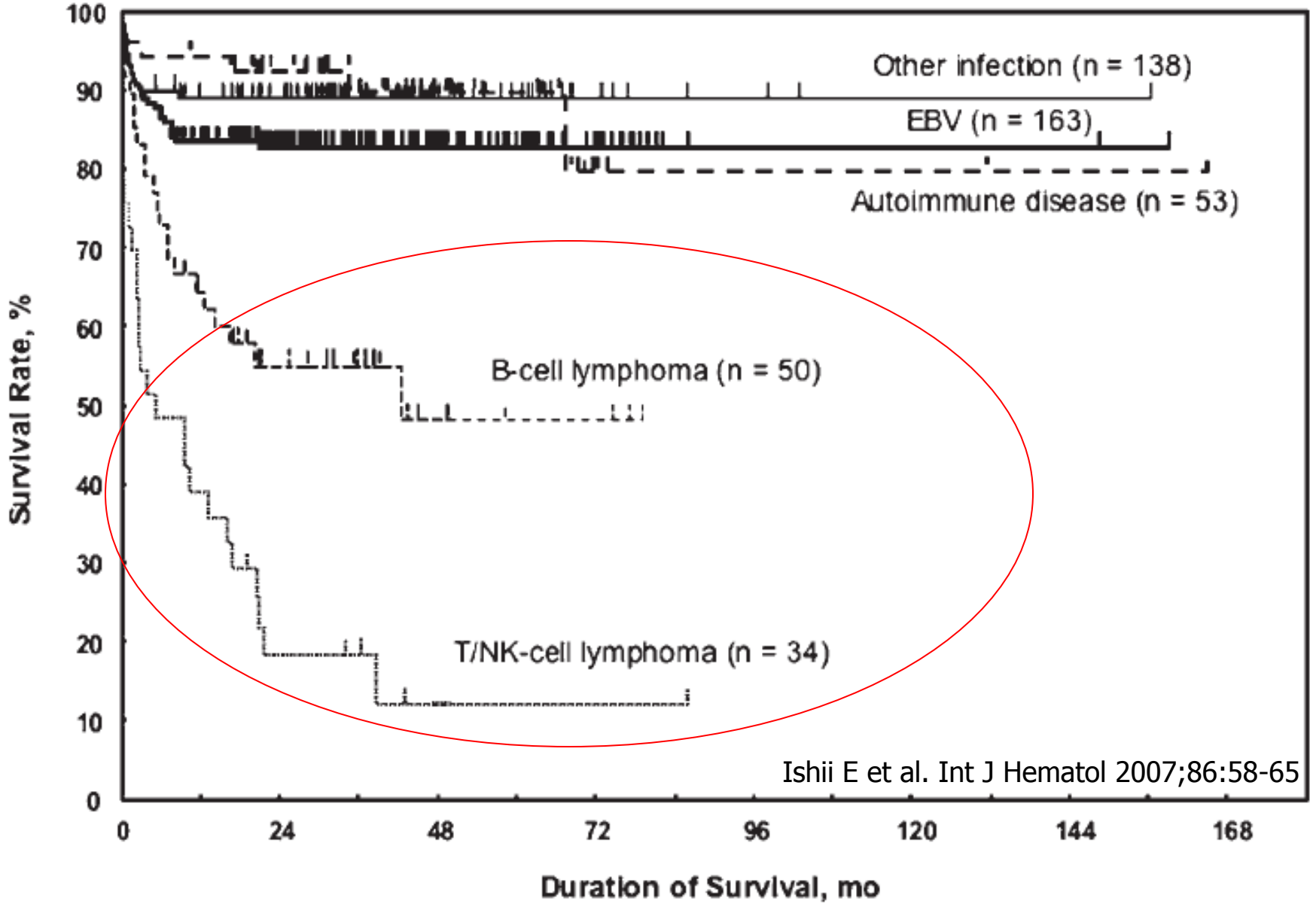
What issues should arouse suspicion of HLH ?

- The **magnitude** of the symptoms: long-lasting fever, marked hepatosplenomegaly, and low blood counts, high ferritin, low fibrinogen
- The **progression** of the symptoms with time



Median time to Dg = 3.5 months

Gritta E. Janka Eur J Pediatr (2007) 166:95–109



Ishii E et al. Int J Hematol 2007;86:58-65

The most urgent is to rule out lymphoma

Lymphoma-associated HLH

- B-cells :
  - Diffuse large B-cell lymphoma
  - Intravascular large B-cell lymphoma
  - Hodgkin's lymphoma
- T- or NK/T- cells :
  - Peripheral T-cell lymphoma, NOS
  - Extranodal NK/T-cell lymphoma
  - Anaplastic large cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Enteropathy-associated T-cell lymphoma

EBV-HLH

- Infectious mononucleosis
- Chronic active EBV infection (CAEBV)
- XLP-1 and XLP-2 (trigger)
- FHL (trigger)

- T, NK, NK/T lymphoma
- Hodgkin lymphoma
- EBV^{+}B-cell LPD in immunodeficient patients

Whole-blood EBV DNA levels (PCR)

ISH in tissus (EBER, LMP)

EBV-specific antibody titers

NKT-cell quantification

Molecular diagnosis (SAP, XIAP, PRF, ITK)

MAS

Pediatric MAS:

- **sJIA**
- Juvenile SLE
- Juvenile DM
- Kawasaki disease
- CINCA, FMF

Adult MAS:

- **SLE** ± Kikuchi
- Still's disease
- IBD (Crohn), DM, RA, MCTD, systemic sclerosis, vasculitis, Sjögren

⇨**search for underlying infection and drug triggers**

Bennett TD et al. Arthritis Rheum 2012;64:4135-4142
Ravelli A et al. Genes and Immunity 2012;13:289-298

SLE-associated HLH

- Juvenile and adult SLE-HLH
- At the disease onset
- What is highly suggestive of HLH ?
  - thrombopenia
  - high ferritin
  - high frequency of lymphadenopathy
- Heart involvement adults / CNS children
- Corticosteroids are usually sufficient

Parodi A et al. Arthritis Rheum 2009;60:3388-3399
Lambotte O et al. Medicine 2006;85:169-182

In practice :

- Clinical daily evaluation
- Repeated Hb platelets, ferritin, fibrinogen, bilirubin… (results in 1day) ⇨ table
- Glycosylated ferritin (result in 7d, 56€)
- sCD25 (result in 4-7d, 75€)
- CD8+DR+ T-cells (result 5d, 82€)
- EBV PCR, other herpesviruses, HIV, mycobacterium tuberculosis
- Bone marrow aspiration/biopsy, liver, skin (IVL), adenopathy…repeated biopsies
- Inclusion in HLHObs/HLHgenes

Date						
Leucocytes						
Neutrophils						
Lymphocytes						
Hemoglobin						
Platelets						
Coagulation PT, Fg, DD						
CRP						
ASAT / ALAT						
Bilirubin						
Alkalin phosphatase						
GGT						
LDH						
Triglycerides						
Ferritin (glycosylated)						
Creatinin						
Natremia						
Protein / albumin						
Gammaglobulin						
Lipase						
Lactic acid						
β-2m / sCD25						
Procalcitonin /haptoglobin						
Treatment / transfusions						

The aim in the treatment

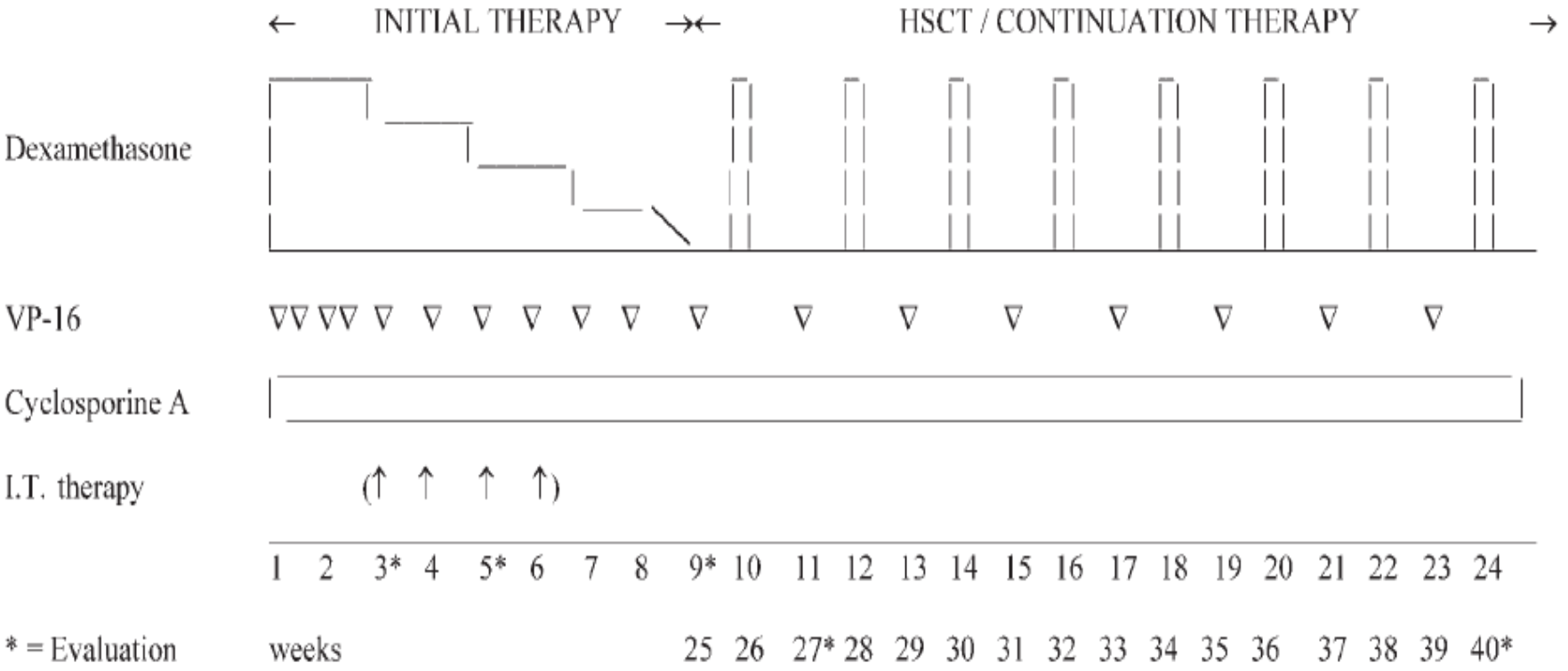
- Suppress severe hyperinflammation
- Remove trigger(s) for the ongoing T-cell activation

⇨ ALWAYS search for underlying disease triggers in all patients

Supportive care

- Intensive Care Unit if appropriate: acute respiratory failure, confusion-coma, shock, acute renal failure, fulminant liver failure, acute bleeding
- Baseline cardiac function, serial cardiac studies in selected patients
- No need for antibiotic-fungal-antiviral prophylaxis, and IVIG in acquired adult HLH

HLH-2004: primary, any severe form on HLH in patients <18yrs



We have no experience of HLH-94/-04 in acquired adult HLH

Etoposide = VP16

- podophyllotoxin-derived DNA inhibitor
- pro-apoptotic in T-cells from FHL in vitro
- acts via cytotoxic effects on dividing T-cell in perforin-deficient mice
- inhibits EBV-induced transformation, by the inhibition of DNA and EBNA synthesis

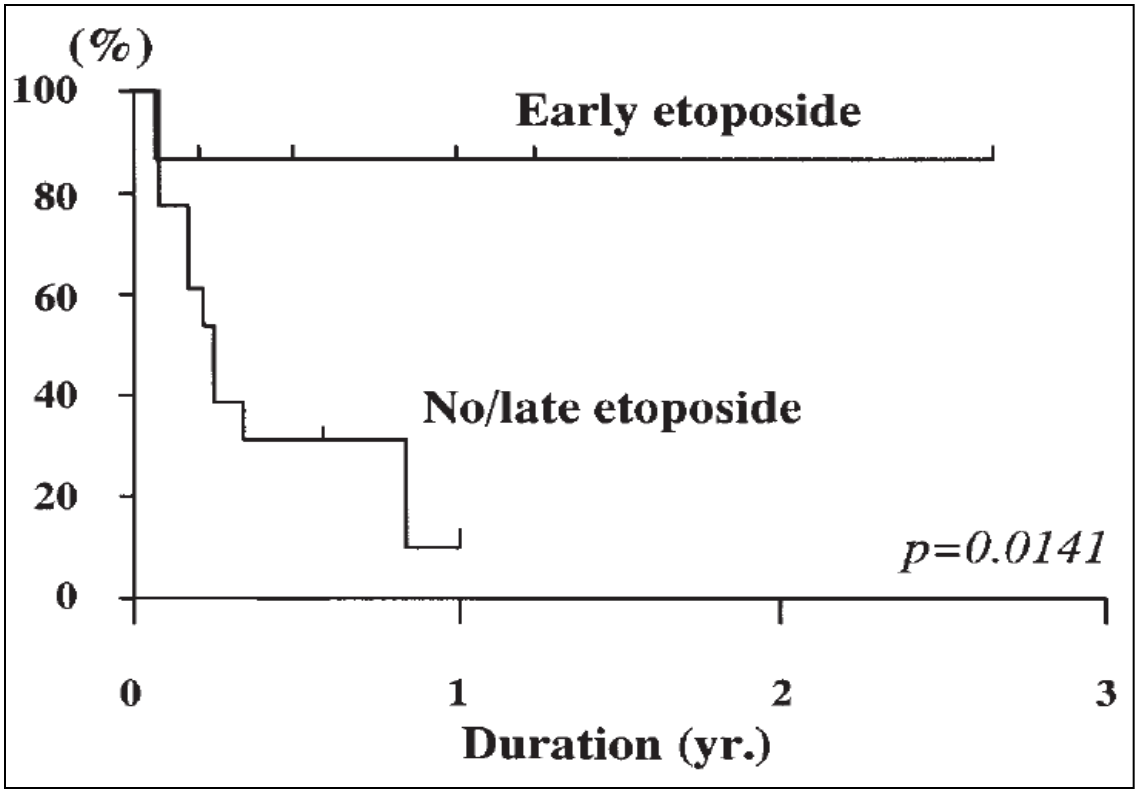
Fadeel B et al. Br J Hematol 1999;106:406-415
Johnson TS et al. Blood 2009;114:abstract 714
Kikuta H, Sakiyama Y. Blood 1995;90:971-973

Etoposide = VP16

- Prolonged remissions first achieved with VP16 introduction in 1980
- High-dose etoposide in HLH-94 and HLH-2004 : 1500mg/m^2 (w0-w8) → 4500mg/m^2 w40
- Risk of etoposide-related t-AML if cumulative dose > 3000mg/m^2

Ambruso D.Cancer 1980;45:2516-20
Henter JI.Pediatr Blood Cancer 2007;48:124-31
Imashuku S. Pediatr Blood Cancer 2007;48:121-123

VP16 in EBV-HLH

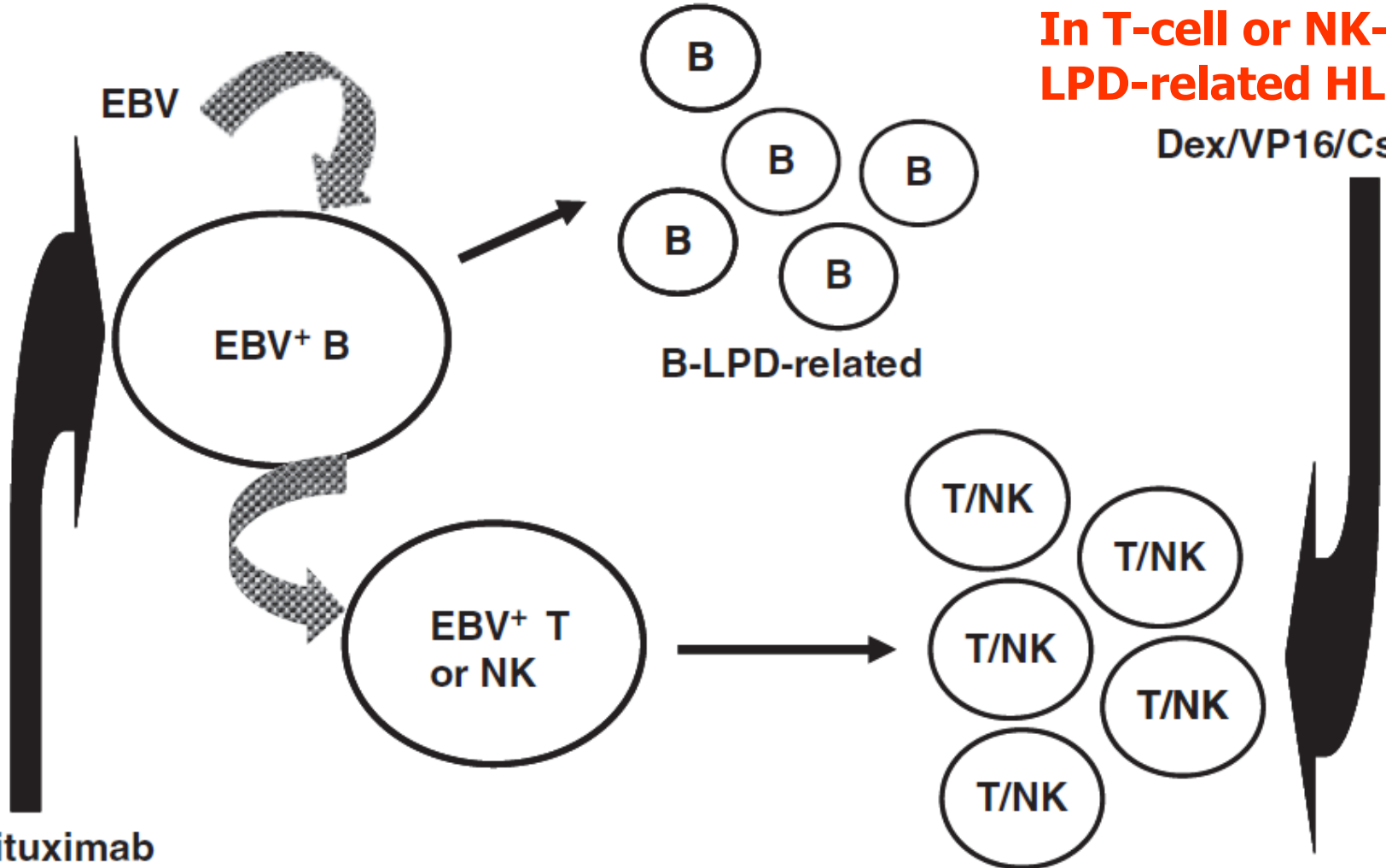


Start VP-16 ≤ 4 weeks after diagnosis ⇨ major effect on OS

Imashuku S et al. JCO 2001;19:2665-73
Imashuku S et al. Med Pediatr Oncol 2003:41:103-9

Treatment of Epstein-Barr Virus-related Hemophagocytic Lymphohistiocytosis (EBV-HLH); Update 2010

Shinsaku Imashuku, MD



What does Jan-Inge Henter recommend today?

- Prompt and aggressive therapy in CNS-MAS, *including etoposide*
- **LESS etoposide than in primary HLH** :
  - Lower doses:
    - 100 mg/m^2 age 0-10y
    - 75 mg/m^2 age 10-39y
    - 50 mg/m^2 age $\geq$40y
  - Less frequent interval: once weekly
  - Less duration: may not need 8 weeks

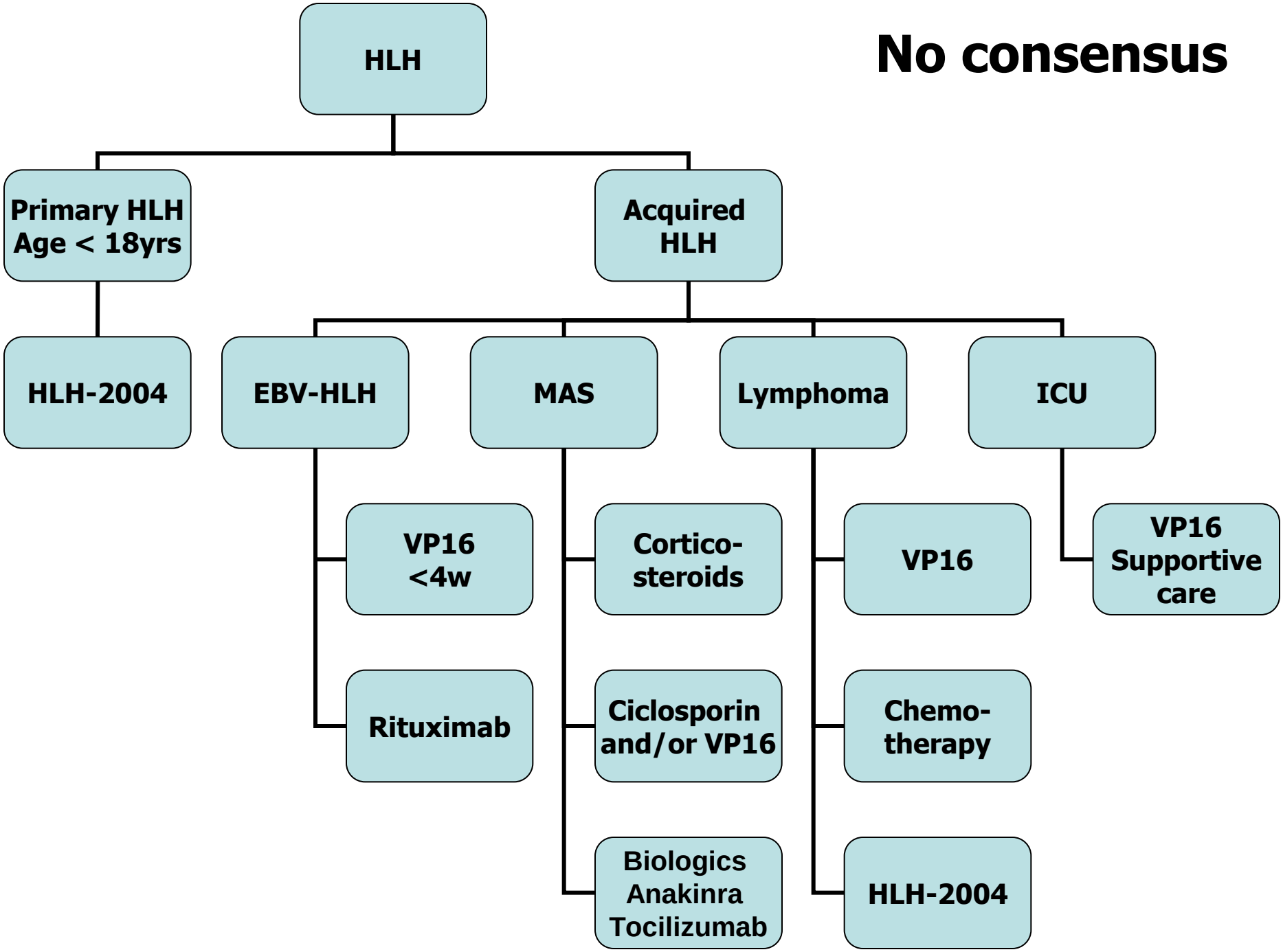
EULAR 2012, PReS Session

What is our experience ?

- Low-dose etoposide:
  - 100 mg/m^2
  - ≤ 200 mg total dose
  - ≤ 100 mg if : albumin < 20g/l, bilirubin> 40 µM/l, GFR < 30 ml/min
- Usually 1 dose is enough
- VP16 *not* removed by hemodialysis

A retrospective study of all patients treated by low-dose etoposide is ongoing

No consensus



HLHObs/HLHgenes

- French observational registry
- Acquired HLH > 12 yrs, now open to pediatric cases > 2 yrs
- Prospective cohort study – DNA collection (HLHgenes)
- First patient 01/2010
- 111 patients (to date)

HLHObs/HLHgenes

The aims of these studies :

- characterize acquired HLH in a large cohort
- study new prognostic factors, eg CD8+DR+ T-cells
- study NKT-cells phenotype
- find hypomorphic mutations of known HLH genes
- validate expert therapeutic recommendations

Take home messages in adult acquired HLH

1. High index of suspicion
2. Find the triggers and treat them with no delay
3. The more we wait, the more HLH becomes obvious, and the patient critically ill
4. Low-dose Etoposide is effective, and cheap (100mg = 2€)

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

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Marc Michel…

And all participating MD in France in HLHObs/HLHgenes