Current Approaches to the Management of Hemophagocytic Lymphohistiocytosis (HLH): Recognition, Diagnosis and Treatment

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Objectives

- To help recognize the signs and symptoms of HLH, using a case-based approach.
- To review the work-up and evaluation of a patient with suspected HLH.
- To introduce treatment approaches including targeted therapies, chemotherapy, and transplantation.
- To discuss a unique population of HLH associated with CART

Case Presentation

Jimmy is a 15yr male who presents to the ER with 4 days of fever, fatigue, and extremity pain.

In the ER, the boy is febrile to 40^{o}C with tachycardia (HR 120) and tachypnea (RR35). Blood pressure remains stable at 115/82.

On exam, the boy is interactive but appears ill. Cardiac and respiratory exams are normal (except for vital sign changes). Abdomen appears distended with hepatomegaly of 4cm and splenomegaly of 6cm below the costal margin.

What is in your differential diagnosis?

- Infection/Sepsis
- Hematologic Malignancy
- Rheumatologic Disease
- Cardiac Failure

Data

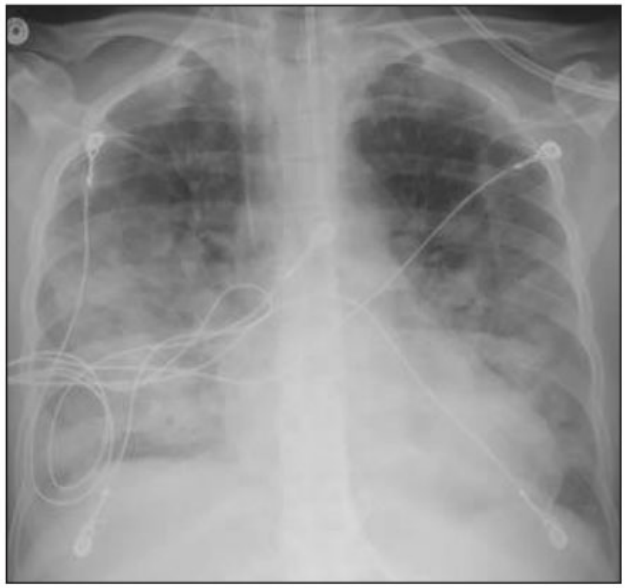
CBC:

- WBC – 2.1 (80%L, 20%N)
- Hb – 7.9
- Plt - 23

CMP:

- Albumin – 3.1
- Bilirubin – 0.8
- AST – 250 ALT – 310
- BUN – 23 Cr – 0.3
- Electrolytes normal

Lactate: 12



ProBNP: normal

Procalcitonin: 0.1

CXR: hazy lung fields concerning for edema

Respiratory Viral Panel: negative

DIC Panel:
INR–1.3 Fibrinogen-110

Shieh et al. 2020

Clinical course

Echo with normal function

AST/ALT remain persistently elevated, and splenomegaly worsens

He is persistently febrile despite negative infectious work up (blood cultures, viral studies all negative)

Pancytopenia persists, requiring plt and pRBC transfusions

DIC screen shows a low and declining fibrinogen of 75. Cryoprecipitate is given

He develops progressive organ dysfunction with AKI, respiratory distress, and is transferred to the ICU

HLH Criteria

Clinical criteria:	Laboratory Criteria:	Pathology Criteria:	Evidence of Inflammation:
• Fever • splenomegaly	• Cytopenias (2 or more cell lines) • High triglycerides OR low fibrinogen	• Hemophagocytosis – bone marrow, spleen, or lymph nodes • CNS HLH = seen in CSF • No evidence of malignancy	• Ferritin >500ng/mL • Soluble IL2R >2400 U/mL • Low or absent NK cell function • Abnormal CD107a degranulation • Absent perforin expression

Bergsten et al. 2017; Jordan et al. 2011

HLH from a historical perspective

Without treatment, HLH is fatal

1986 was the first successful HCT for HLH

Following initial treatment, HCT using myeloablative conditioning

Overall Survival Rates of 50-70%, but with early transplant related mortality

Toxicities associated with myeloablation

- VOD
- Pulmonary complications
- Recurrence of HLH

Seo, JJ. 2015; Jordan 2011

HLH can be primary or secondary

Primary HLH = Familial HLH

- Genetic Defects often identified

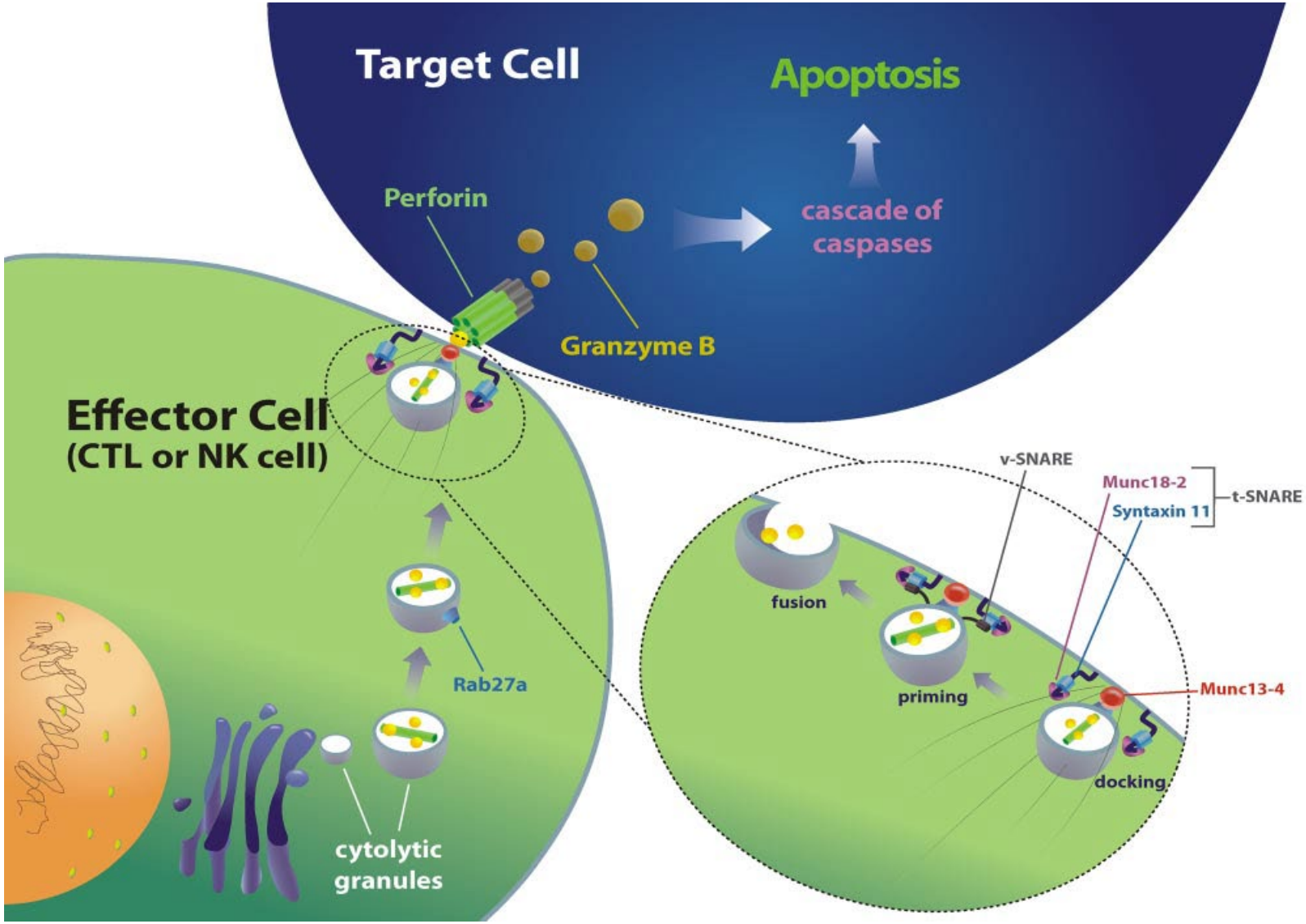
Secondary HLH

- Can be associated with infectious trigger (EBV, COVID)
- Can be secondary to malignancy
- Can be secondary to other immune deficiency/dysregulation syndromes

Macrophage Activation Syndrome

- Hyperinflammatory syndrome associated with rheumatologic disease

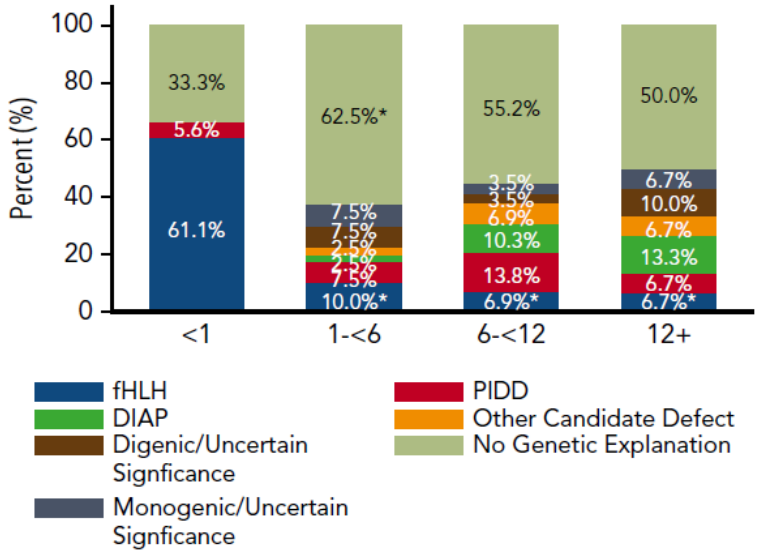
HLH is a disorder of immune activation



Jordan MB et al. 2011

Primary Immune Deficiencies can present with HLH-like syndromes

C



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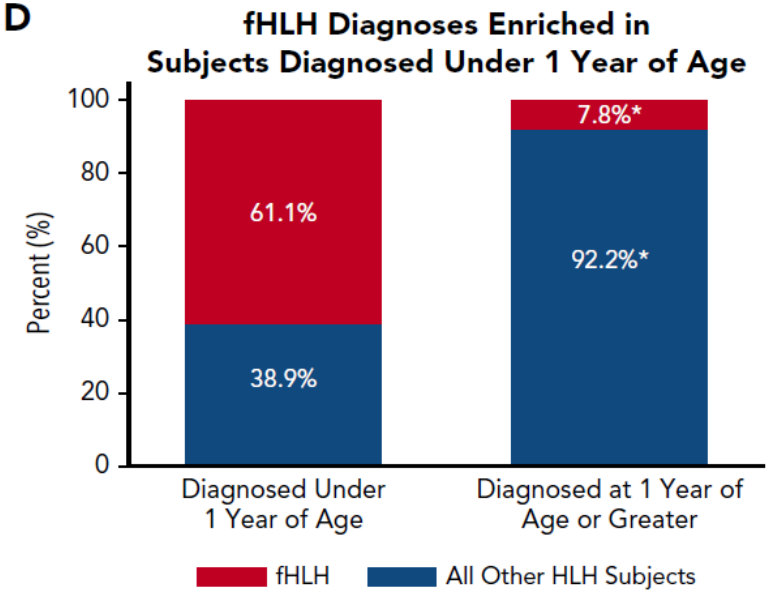


*Significantly different from those <1 year old with same genetic profile at $p < 0.0001$.

Familial HLH genes identified	*PRF1, RAB27A, STX11, UNC13D*
PIDD-associated genes identified	*CARMIL2, CASP10, CYBB, DOCK8, LRBA, MCM3AP, MCM9, NCF1, PIK3CD, RAG1, RAG2, STAT1, STAT2, STAT3, TTC7A, WAS*
DIAP-associated genes identified	*NLRC3, NLRC4, NLRP12, NLRP13, NLRP4, NRAS*
Other candidate genes	*ARHGEF6, ERCC4, G3BP1, IL16, RASGRP3, STAT4, TREM2*

Chinn et al. 2018

Secondary HLH

Viral Associated HLH

Develops as the result of infection

Viral (most common), bacterial, fungal, parasites

Often in immunocompromised hosts (HIV, oncologic, Crohn’s disease)

HLH is not an infrequent diagnosis in adults

Can occur in young adults and older adults

- Bimodal distribution: 16-30yo and 56-70yo

Secondary HLH is most common in adults

- 30.7% associated with malignancy
- 24.3% associated with infection
- 20.8% associated with autoimmune conditions
- Other associations – organ transplant (4%), immune deficiencies (2.5%), no trigger identified (35.8%)

Hospital Utilization

- The incidence of HLH has noted to increase from 2006 to 2019
- Mean length of stay was 14 days
- In-Hospital mortality of almost 20%

Abdelhay et al. 20

Case Presentation

Testing for perforin was normal but NK cell degranulation was abnormal

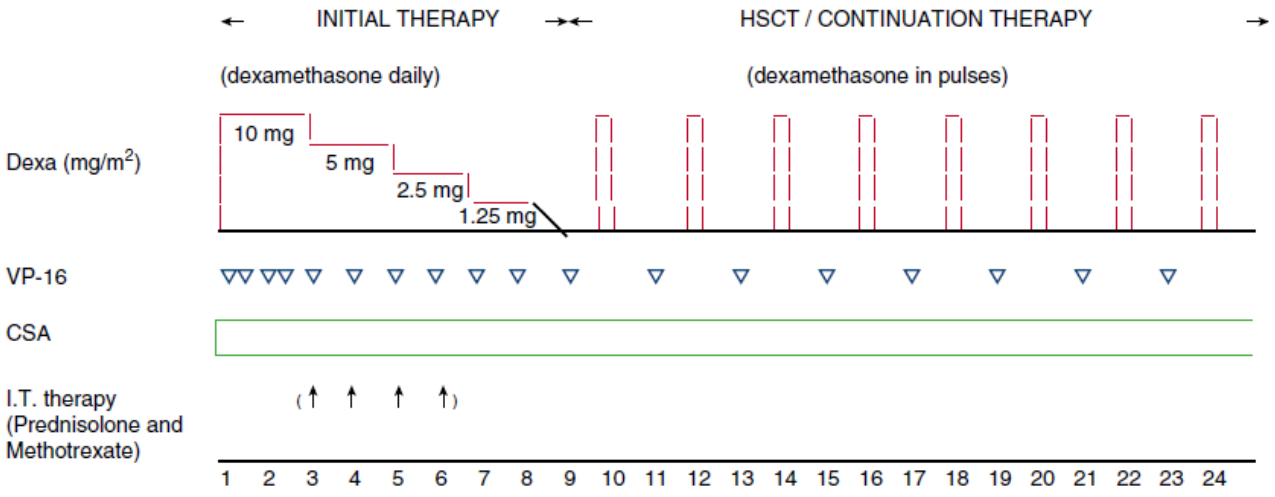
Infectious studies were positive for EBV.

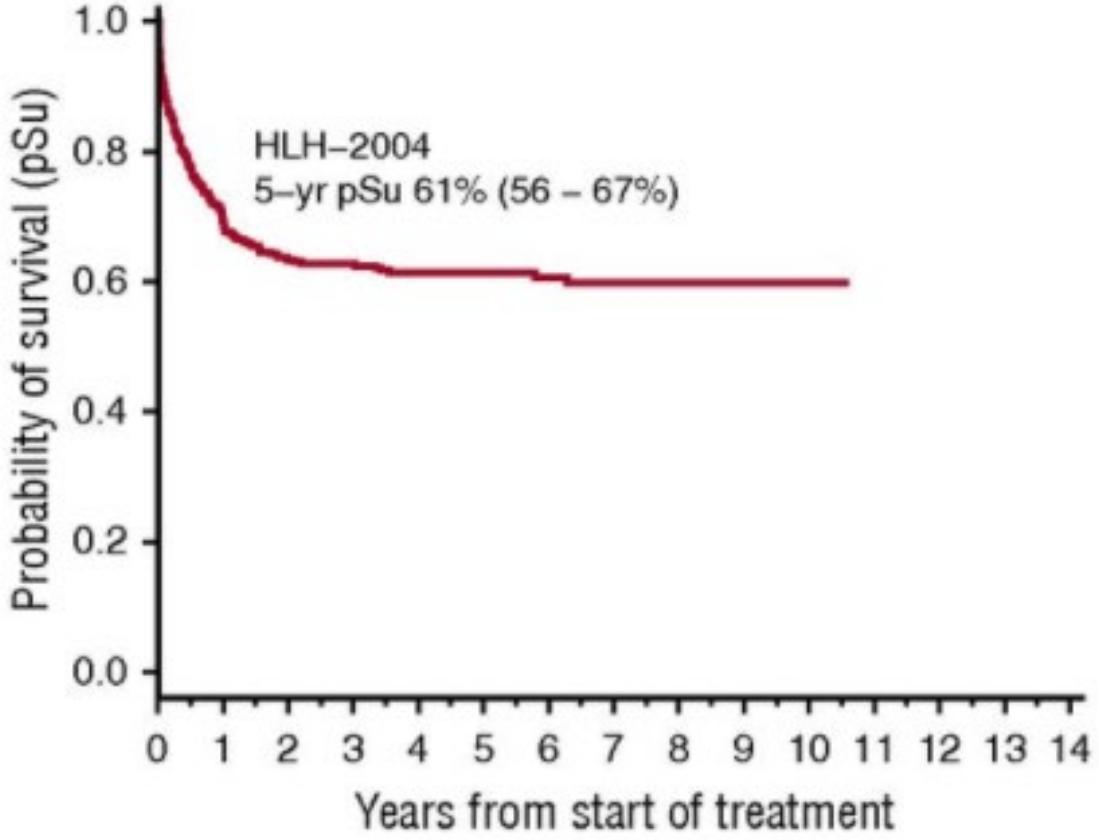
Genetic studies sent and identified an STXBP2 mutation

He developed mental status changes and an LP was performed, showing hemophagocytosis in CSF

Treatment was initiated with Dexamethasone and Etoposide

Etoposide and Dexamethasone: Outcomes for patients on the HLH-2004 trial





Bergsten et al. 2017

HLH treatment includes calming the inflammation

Stop the hyperinflammatory state

- Steroids (Dexamethasone crosses BBB) and Etoposide
- If refractory:
  - Emapalumab – anti-interferon gamma antibody
  - Alemtuzumab – anti-CD52, targets lymphocytes
  - Ruxolitinib – JAK pathway inhibitor
  - Anakinra – targets IL1-beta

2) If secondary → treat underlying cause (infection, malignancy)

- If recurs, then consider BMT

3) If genetic cause identified → proceed to bone marrow transplant

Emapalumab – targeted treatment for HLH

- Emapalumab is an anti-interferon γ monoclonal antibody
- N=34 with active HLH (previously treated or untreated), given with Dexamethasone
- Overall response of 63% of previously treated and 65% of untreated
- CXCL9 levels declined with treatment

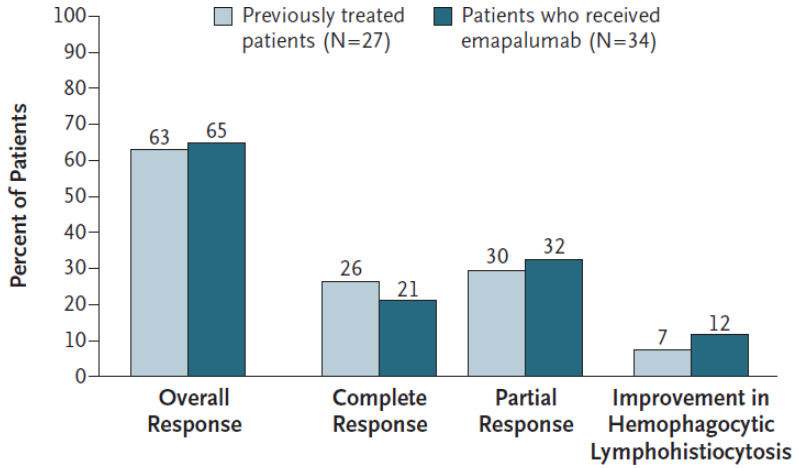
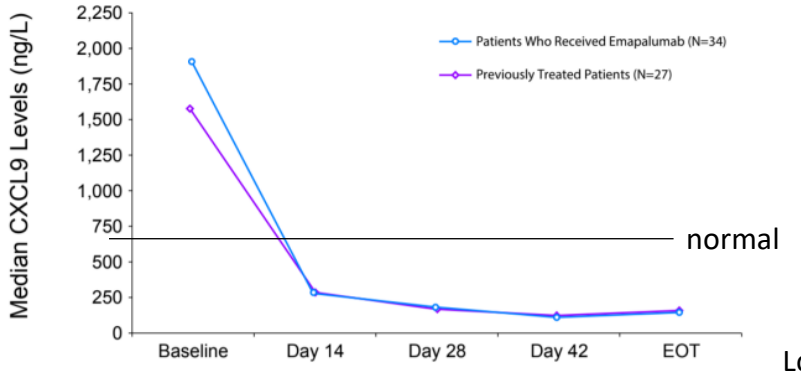


Figure S5. CXCL9 serum levels



Locatelli et al. 2020

Emapalumab – targeted treatment for HLH

FDA approves emapalumab for hemophagocytic lymphohistiocytosis

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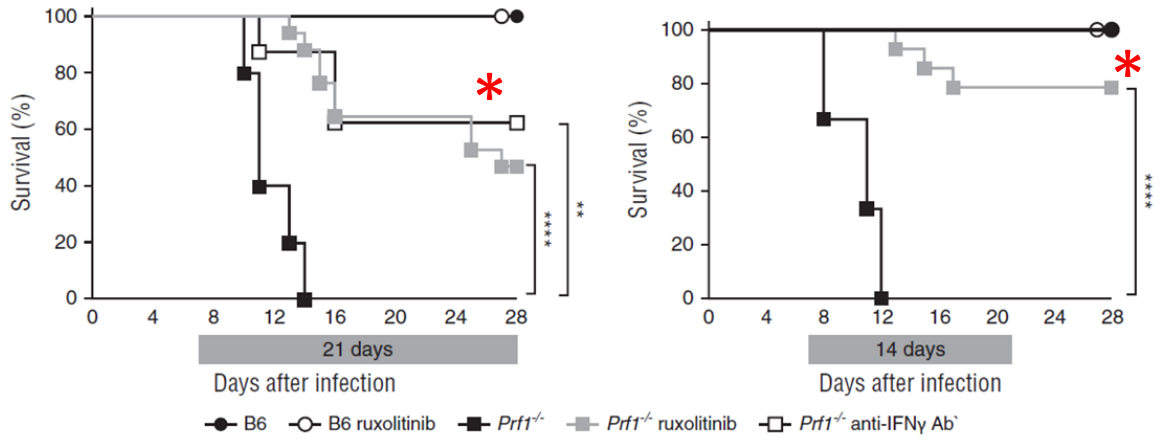
On November 20, 2018, the Food and Drug Administration approved emapalumab (GAMIFANT, Novimmune SA), a monoclonal antibody that binds and neutralizes interferon gamma, for adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.

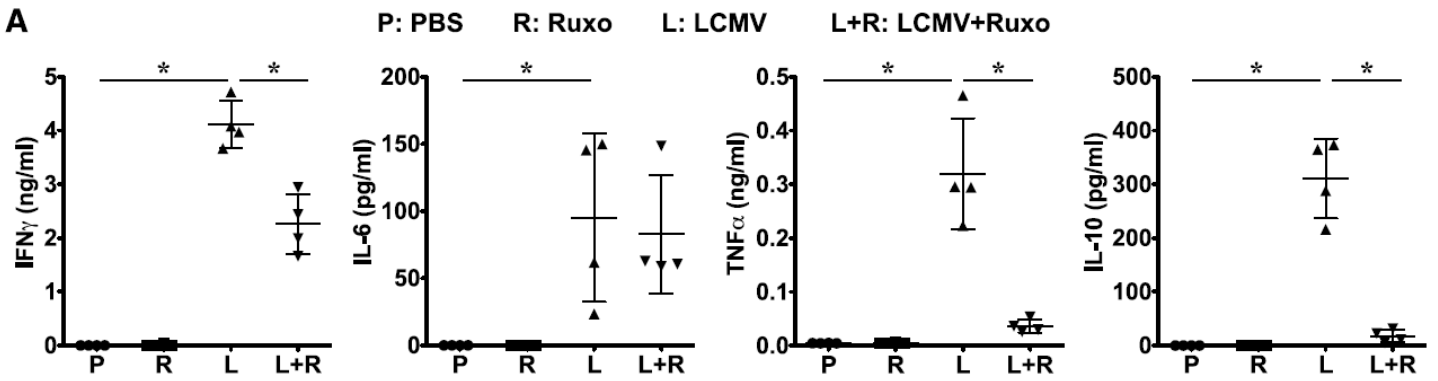
Baseline Day 14 Day 28 Day 42 EOT

Locatelli et al. 2020

Ruxolitinib – broad cytokine blockade for HLH

- HLH in vitro – elevated IFNγ, IL-6, IL-], IL-10, IL-12
- Ruxolitinib inhibits JAK1/2 and decreases cytokines during inflammation





Maschalidi et al 2016; Das et al 2016; Broglie et al 2017

Ruxolitinib – broad cytokine blockade for HLH

EXCEPTIONAL CASE REPORT

blood advances

Ruxolitinib for treatment of refractory hemophagocytic lymphohistiocytosis

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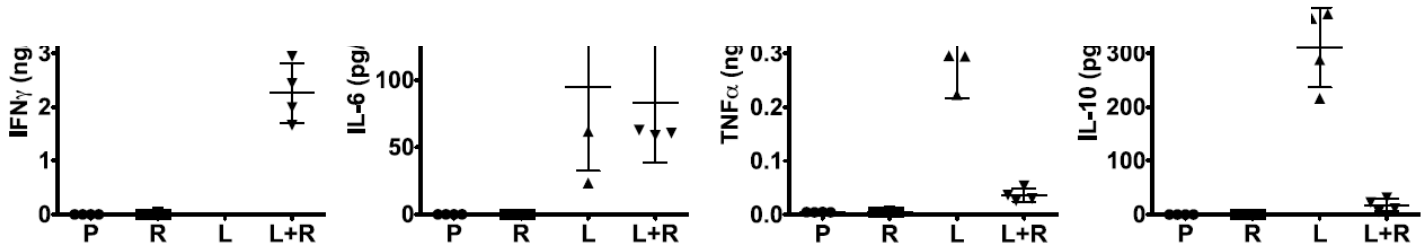
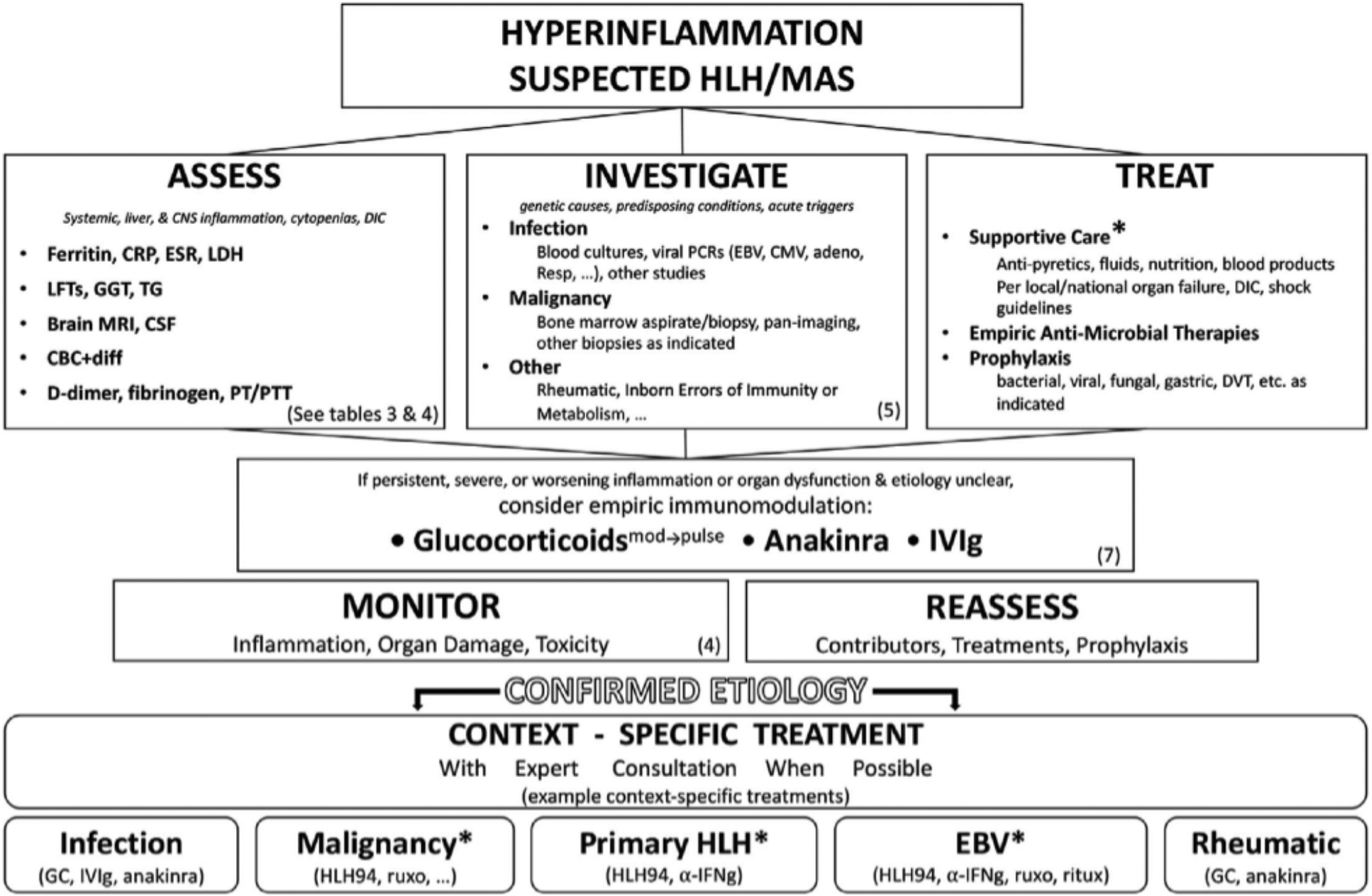
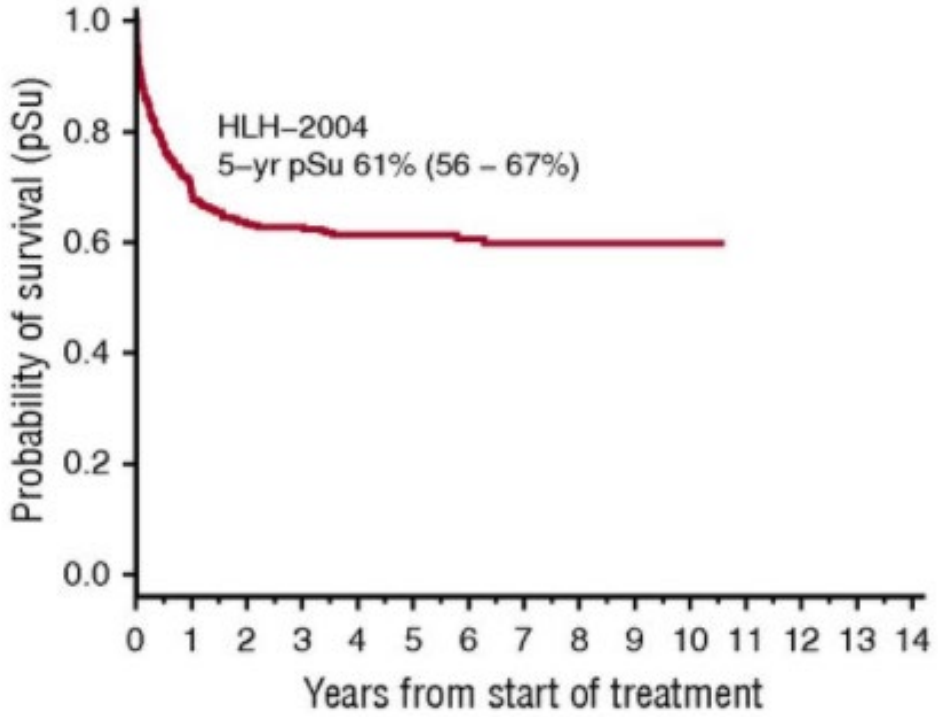


Maschalidi et al 2016; Das et al 2016; Broglie et al 2017



Shakoory et al 2023

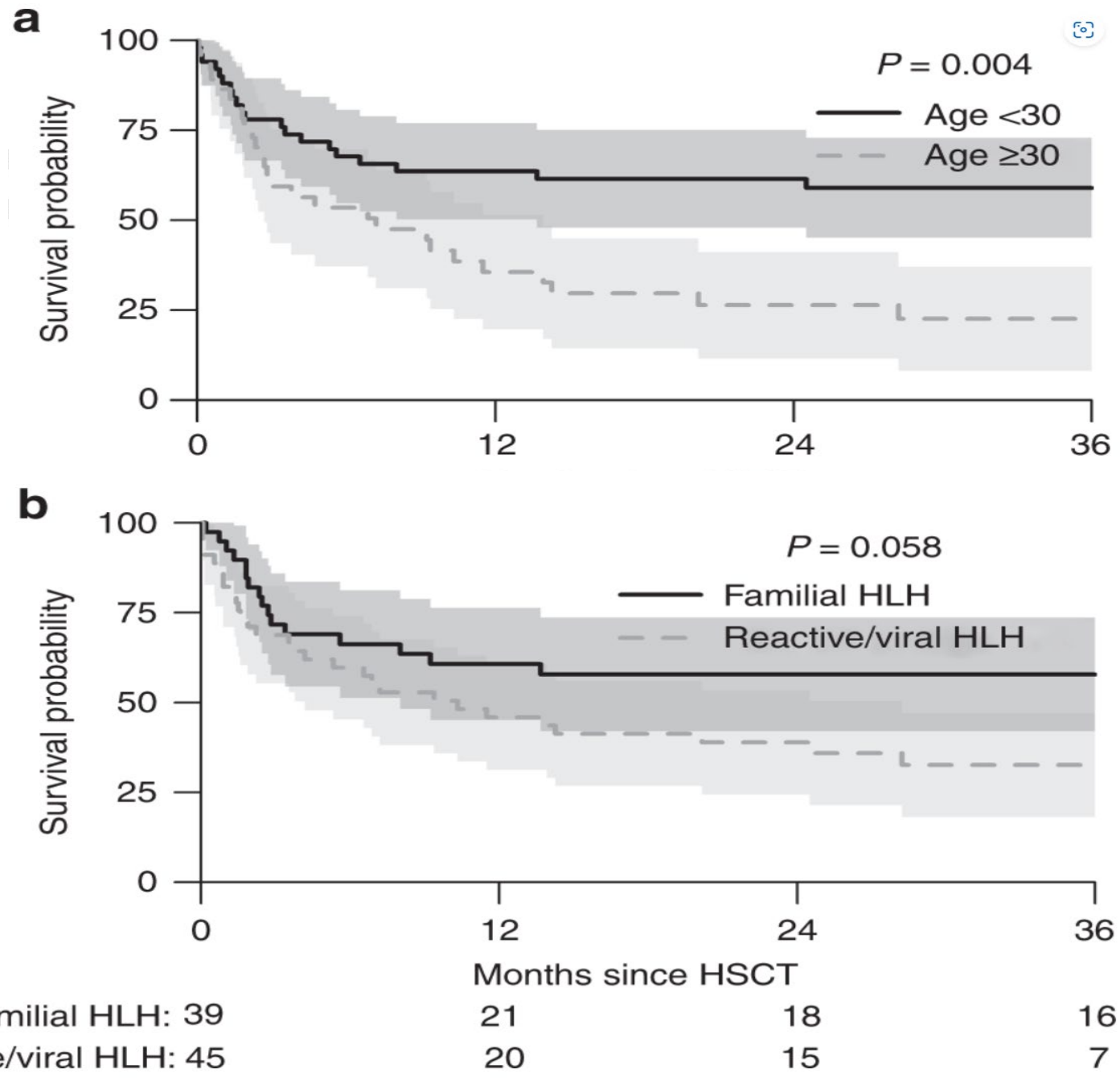
AlloHCT is necessary for patients with primary HLH



- Without HCT, HLH will recur
- Familial donor selection requires genetic testing, even if asymptomatic
- Pre-transplant evaluation requires consideration of:
  - liver function (risk of VOD),
  - infection and cardiac function (long term steroid use)

Bergsten et al. 2017

AlloHCT for adult patients is feasible: but younger is better



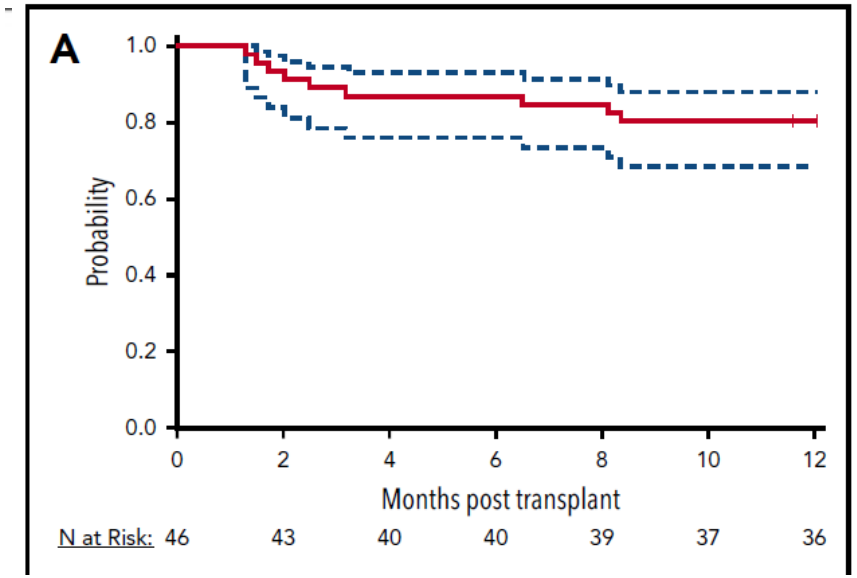
Machowicz et al. 2022

Balancing Toxicity: MAC versus RIC

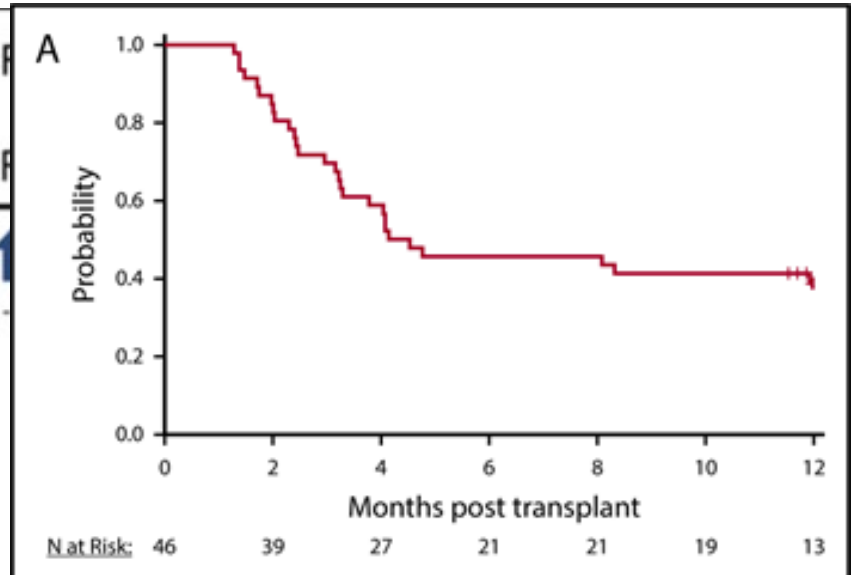
- Single center reports of using Fludarabine/Melphalan/Alemtuzumab: OS 85-95%, less toxicity

- BMT-CTN 1204:

Probability of Overall Survival



Probability of Intervention-free Engraftment

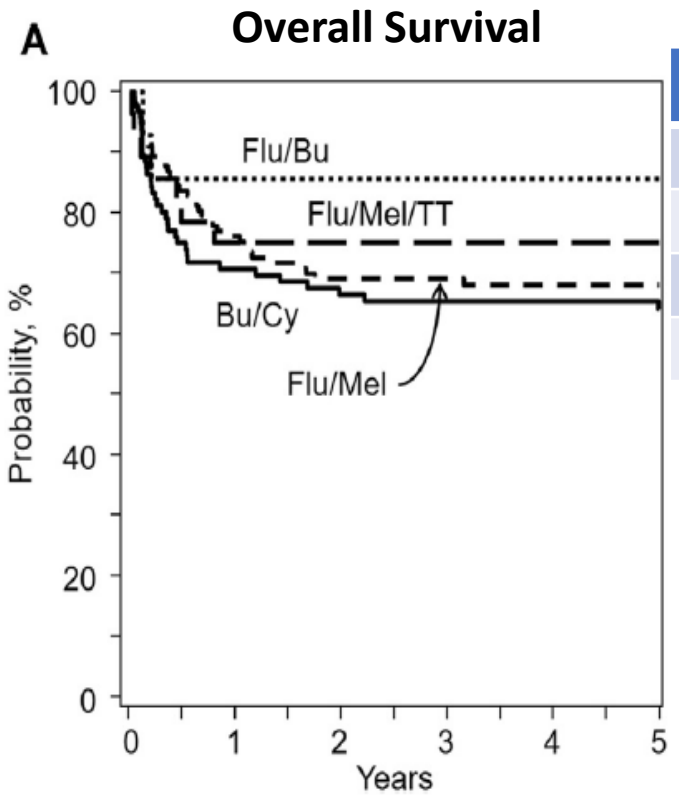


Allen et al. 2018

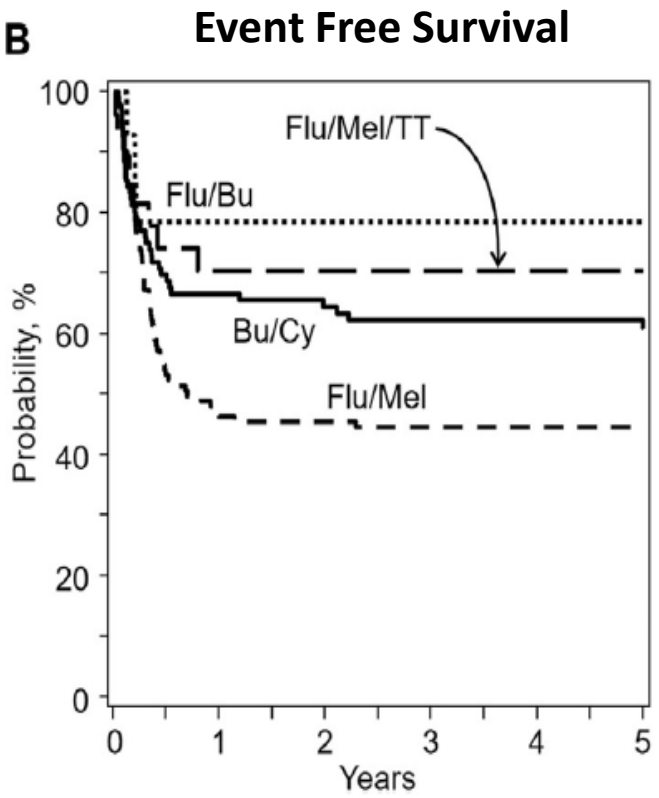
Balancing Toxicity and Engraftment: What is the best conditioning regimen?

- CIBMTR study compared 4 conditioning regimens:

Bu/Cy (n=96) Flu/Mel (n=123) Flu/Mel/Thiotepa (n=28) Flu/Bu (n=14)



2 year	5 year
86%	86%
75%	75%
69%	68%
67%	64%



2 year	5 year
79%	79%
70%	70%
65%	61%
45%	44%

Marsh et al. 2022

Case Presentation

Following induction with Etoposide and Dexamethasone, markers of HLH normalized

Given weekly IT methotrexate and steroids for CNS HLH

Received a myeloablative transplant from matched unrelated donor with Bu/Flu/ATG

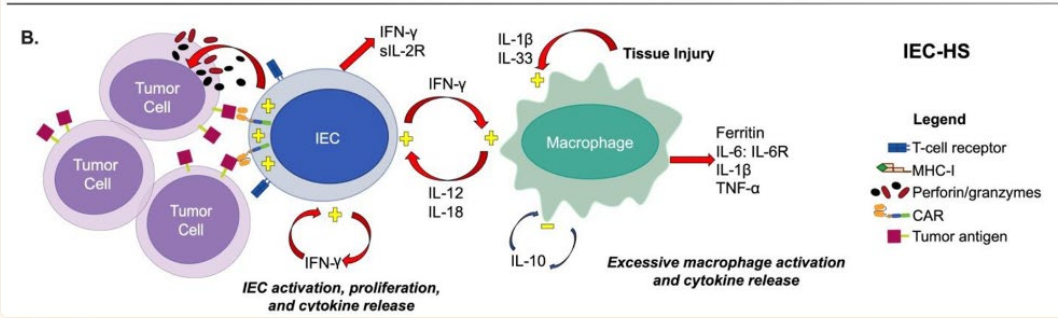
Transplant course complicated by VOD requiring Defibrotide treatment

Weaned off Immune Suppression by 7 months post-HCT, alive and well 3 years later

Special HLH Circumstances

Immune Effector Cell Associated HLH: overlap syndrome with CRS

Criteria for identification of IEC-HS ^	Clinical or laboratory manifestations
Most common manifestations $	**REQUIRED**: Elevated ferritin (> 2 × ULN or baseline (at time of infusion)) and/or rapidly rising (per clinical assessment)
	Onset with resolving/resolved CRS or worsening inflammatory response after initial improvement with CRS directed therapy*
	Hepatic transaminase elevation** (> 5 × ULN (if baseline was normal) or > 5 x baseline if baseline was abnormal)
	Hypofibrinogenemia (< 150 mg/dL or < LLN)^^
	Hemophagocytosis in bone marrow or other tissue^^
	Cytopenias (new onset, worsening, or refractory&)



Hines et al. 2023