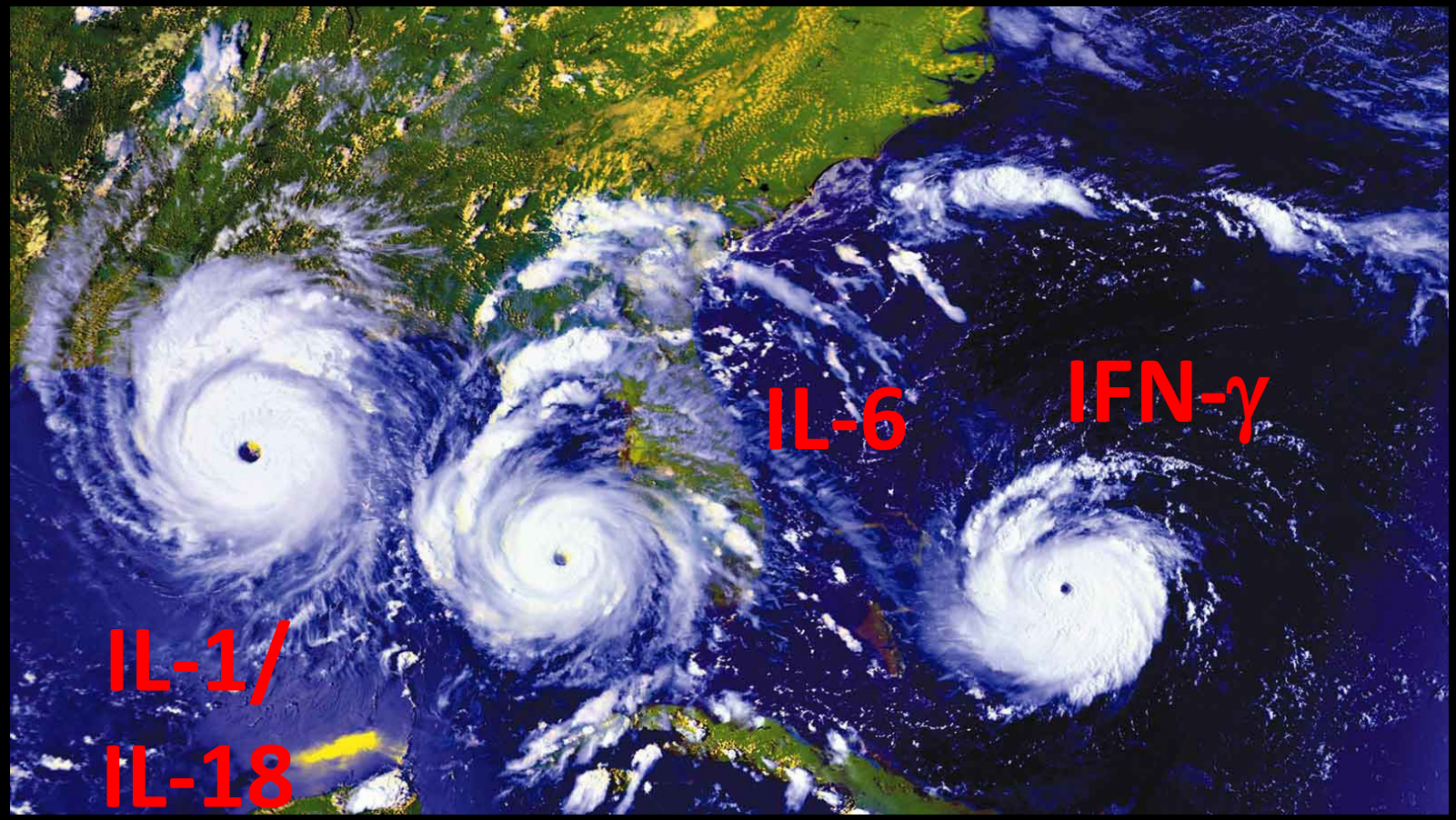
(Cytokine) Storms in our Backyards: Autoinflammation for the General Rheumatologist



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Curing PI. Worldwide.

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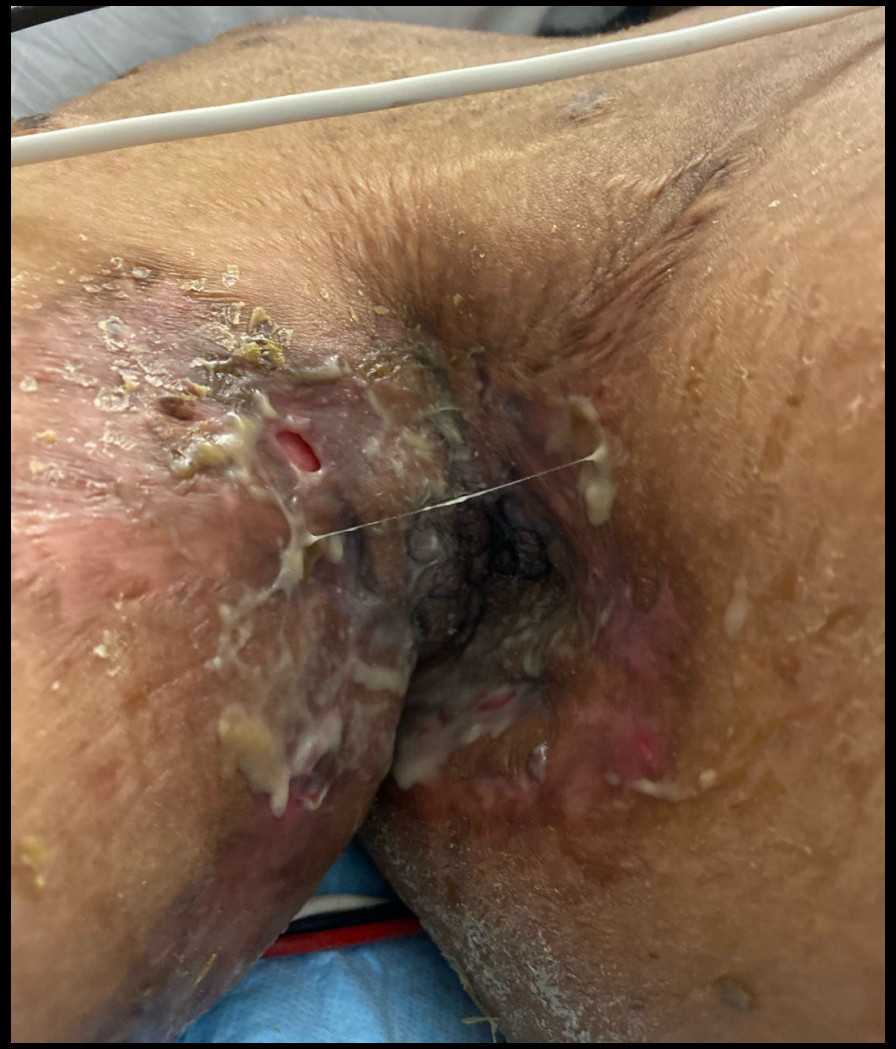
Learning Objectives

- Recognize **red flags** for autoinflammation in adults
- Identify and address barriers to care for patients with autoinflammation and other inborn errors of immunity
- Understand subtypes of cytokine storm and treatment implications

Case 1: 24 yo M with recurrent fevers, hidradenitis, and osteomyelitis

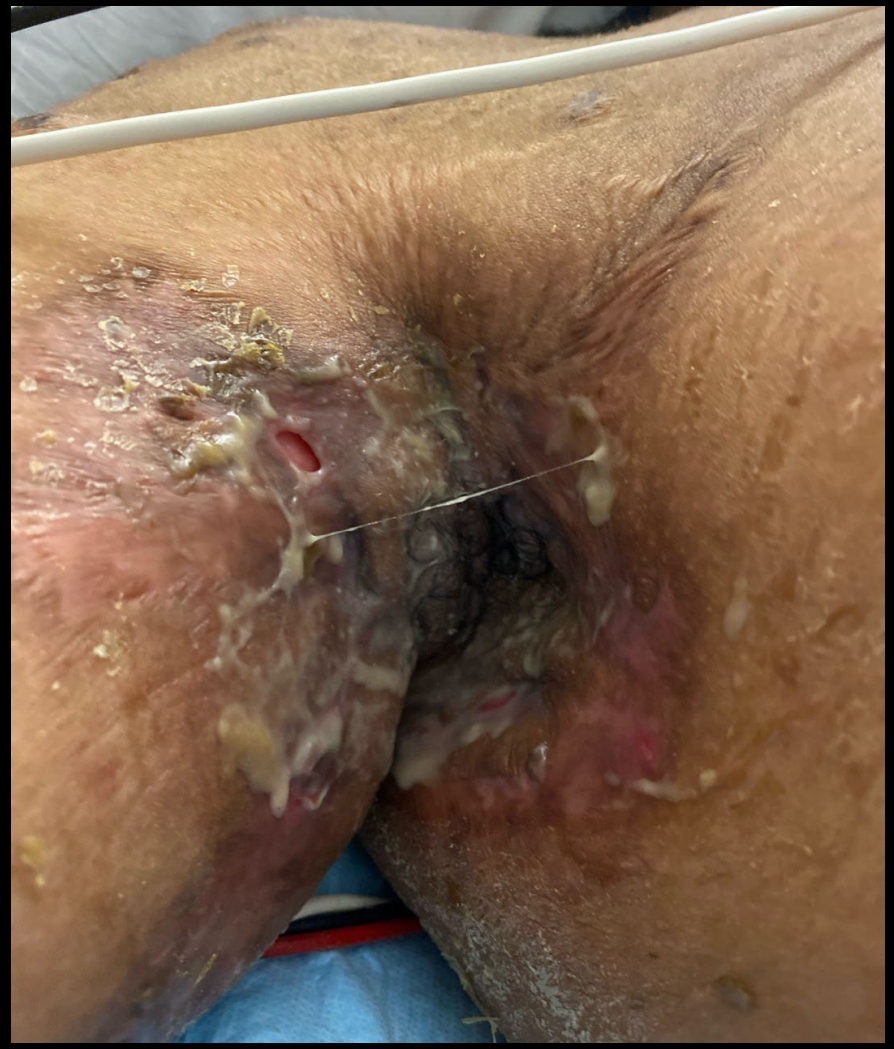
- Age 6-10: mild developmental delay, stuttering
- Age 10-14: periodic fevers, hidradenitis suppurativa, sterile osteomyelitis, inflammatory arthritis → dx **SAPHO syndrome**
- Age 14-23: multiple biologics with incomplete response (3-6 flares/year)
  - Treated/managed at infusion center
  - Multiple steroids/antibiotics
  - Develops brittle diabetes



Case 1: 24 yo M with recurrent fevers, hidradenitis, and osteomyelitis

- Age 23
  - Mother (caregiver) dies (ESRD)
  - Transferred to adult rheumatology
  - **Patient now responsible for his own medical care**

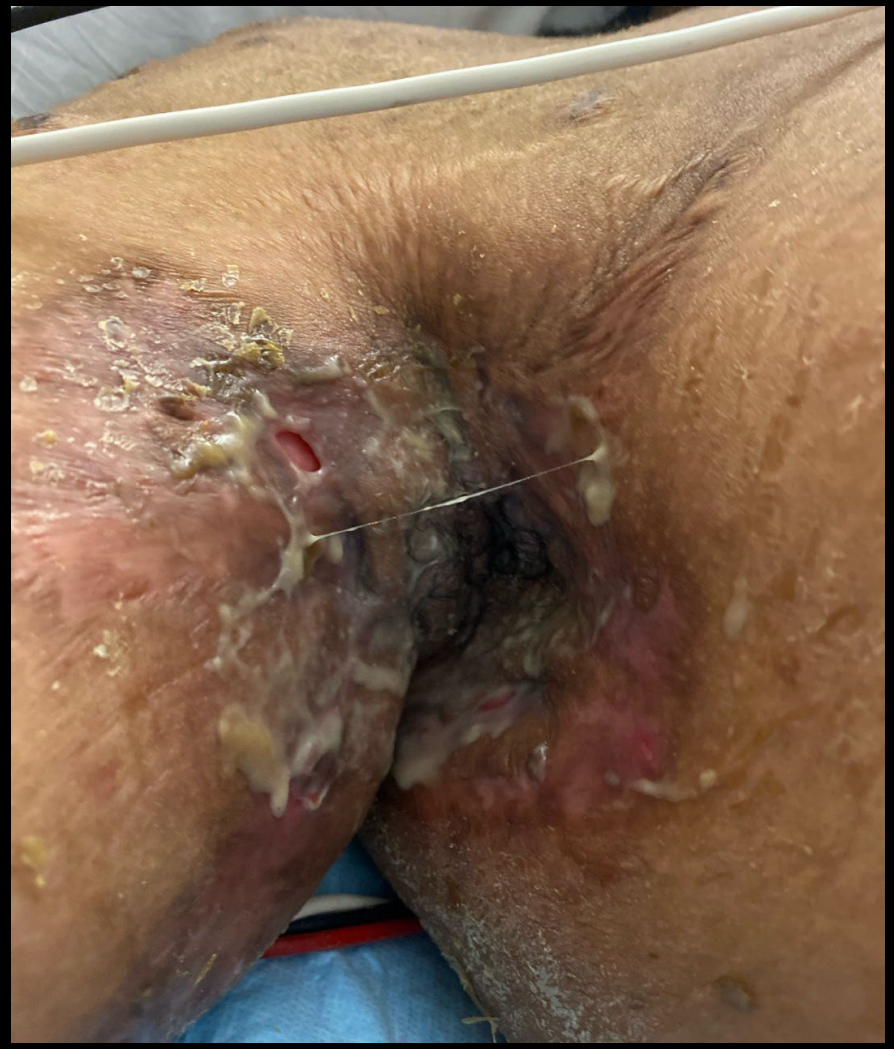
- Continued barriers to care include:
  - Cognitive disability
  - Resource limited
  - Complex, severe disease



Case 1: 24 yo M with recurrent fevers, hidradenitis, and osteomyelitis

- Age 23: admitted **8 times in 10 months** for flare
  - Seen by rheum, ID, derm
  - Treated with steroids/antibiotics
  - Worsening control of diabetes

- Admission #7: Hospitalist requested referral to adult immunogenetics clinic for genetic testing and management



Key questions: Case 1

- What were the **red flags** for a genetic disease in this patient?
  - And why should a general rheumatologist care?
- What to do if you suspect a genetic disease?
- What barriers do genetic disease patients face when pursuing diagnosis and treatment?

Inborn errors of immunity: why should generalists care?

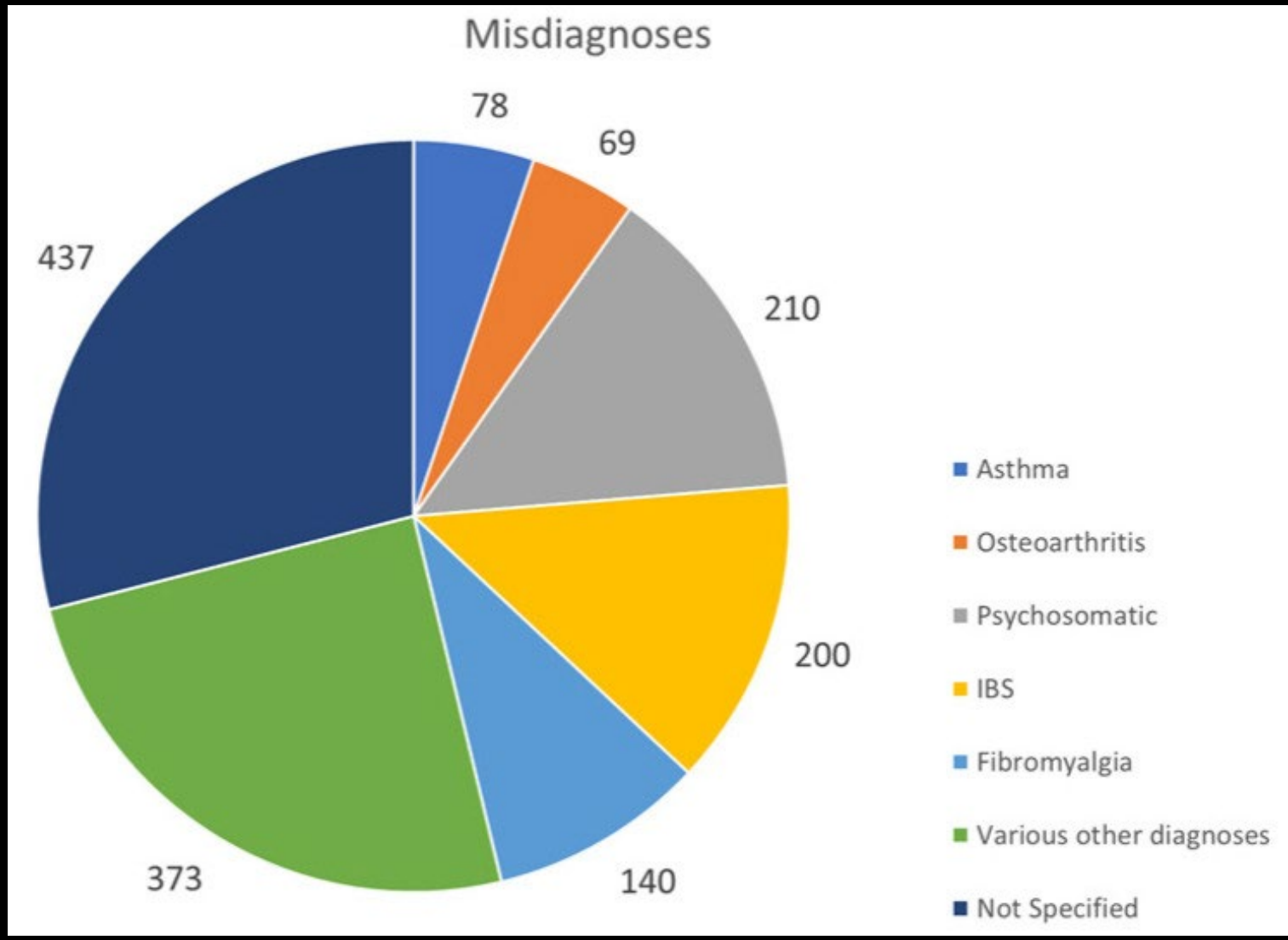
- Inborn errors of immunity are rare individually, **common in aggregate**

- 40% of rare disease patients **are adults**

Thalhammer J, JACI, 2021
Abolhassani, Front Imm, 2022

The burden of IEI/autoinflammatory disease in adults

- **<u>7-14 years</u>** before getting correct diagnosis
- 2-3 misdiagnoses (average)
- Lack of FDA-approved treatments
- High mortality – **<u>up to 60%</u>**



https://globalgenes.org
Bainbridge M, Hum Gen 2020
Rech, J Clin Med 2024

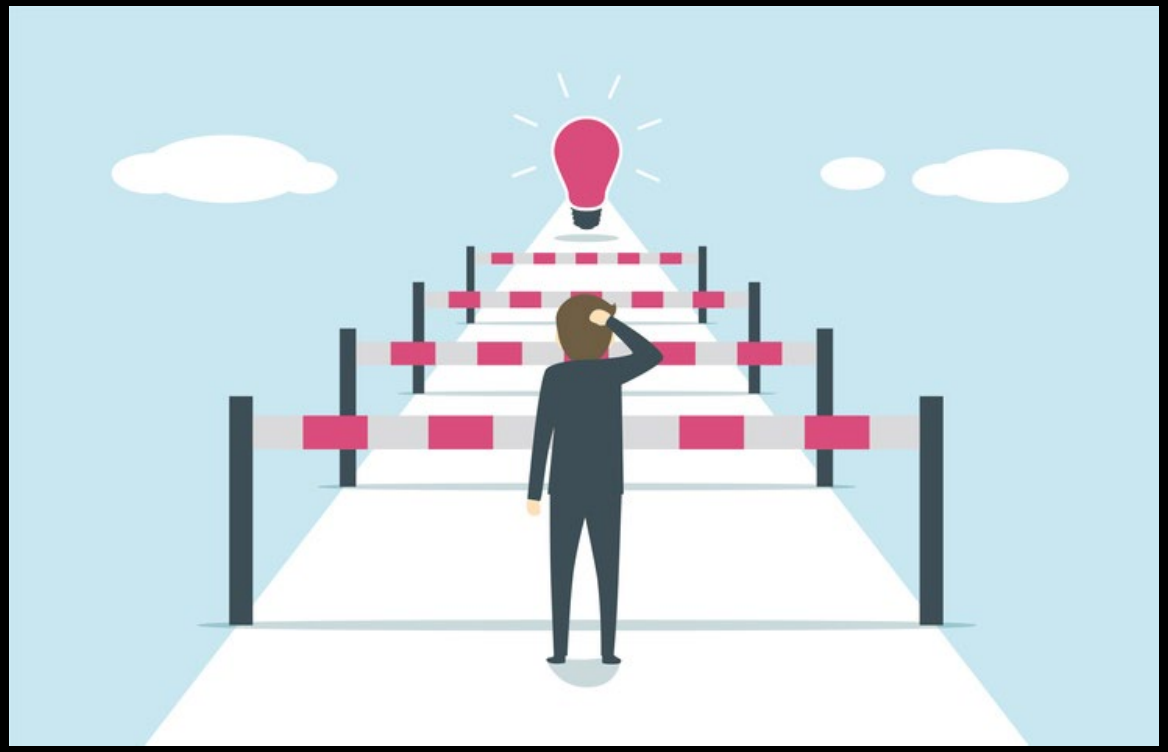
Red Flags for inborn errors of immunity

- Early disease onset
- Multiple family members affected (especially if young)
  - May have different diagnoses but overlapping features
- Atypical/unusual disease features, including unusual or frequent infection
  - JMF “10 warning signs” for immune deficiency
- Recurrent fevers with no identifiable source and elevated APRs DURING FLARE
- Complex (multiple types of) immune dysregulation
  - i.e. autoimmunity plus recurrent infection, severe allergy, and/or lymphoproliferation

Barriers to care: Case 1

- Under-recognition
  - Autoinflammation vs. autoimmunity
  - IEI/genetic disease in adults

- Under-resourced
  - Insurance coverage issues (testing, meds)
  - Caregiver support
  - Cognitive impairment
  - Transitions and expectations – adult vs. peds



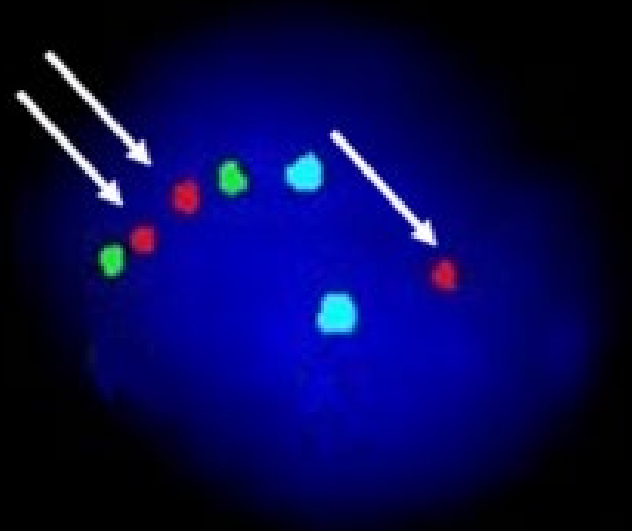
Outcomes: Case 1

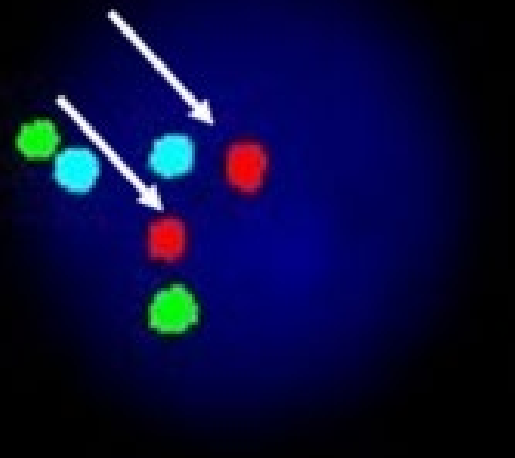
- Genetic testing: **trisomy 8 mosaic (TRIAD)**

- Aggressive treatment
  - Dual biologics
  - Surgical excision
  - Specialized wound care

- Aggressive monitoring
  - Hematology, cardiology, GI, rheum

- Aggressive social support
  - Neuropsychiatric testing
  - Adult protective services





Take home points – case 1

- IEI and autoinflammatory diseases are **common in aggregate**
  - You will probably see them!

- IEI can **present in adulthood**
  - Don’t assume they would have been diagnosed as kids
  - Under-recognition/delays result in severe morbidity

- Adults with IEI frequently have **disease-related barriers to care**
  - Access to providers familiar with disease
  - Access to testing
  - Access to treatments
  - Need for extra caregiver support

Case 2: 34 yo M with recurrent fevers

- Age 5: **recurrent fever to 105**, fatigue, lymphadenopathy, malaise
  - Infectious workup negative
  - Steroid-responsive
  - 5-6 times per year
- Age 14
  - Acute fibrinopurulent **pericarditis** → drainage, pericardial window, steroids
  - **Erythema nodosum**
- Age 14-28: flares 3-6x per year
  - Pericarditis, fever, anterior **uveitis**, abdominal pain, rash, **HSM**, aseptic **meningitis**
  - Multiple DMARDs, TNFi without response
- Age 29: anakinra 100mg daily → partial response
- Age 30: **myasthenia gravis**
  - DMARDs → good response

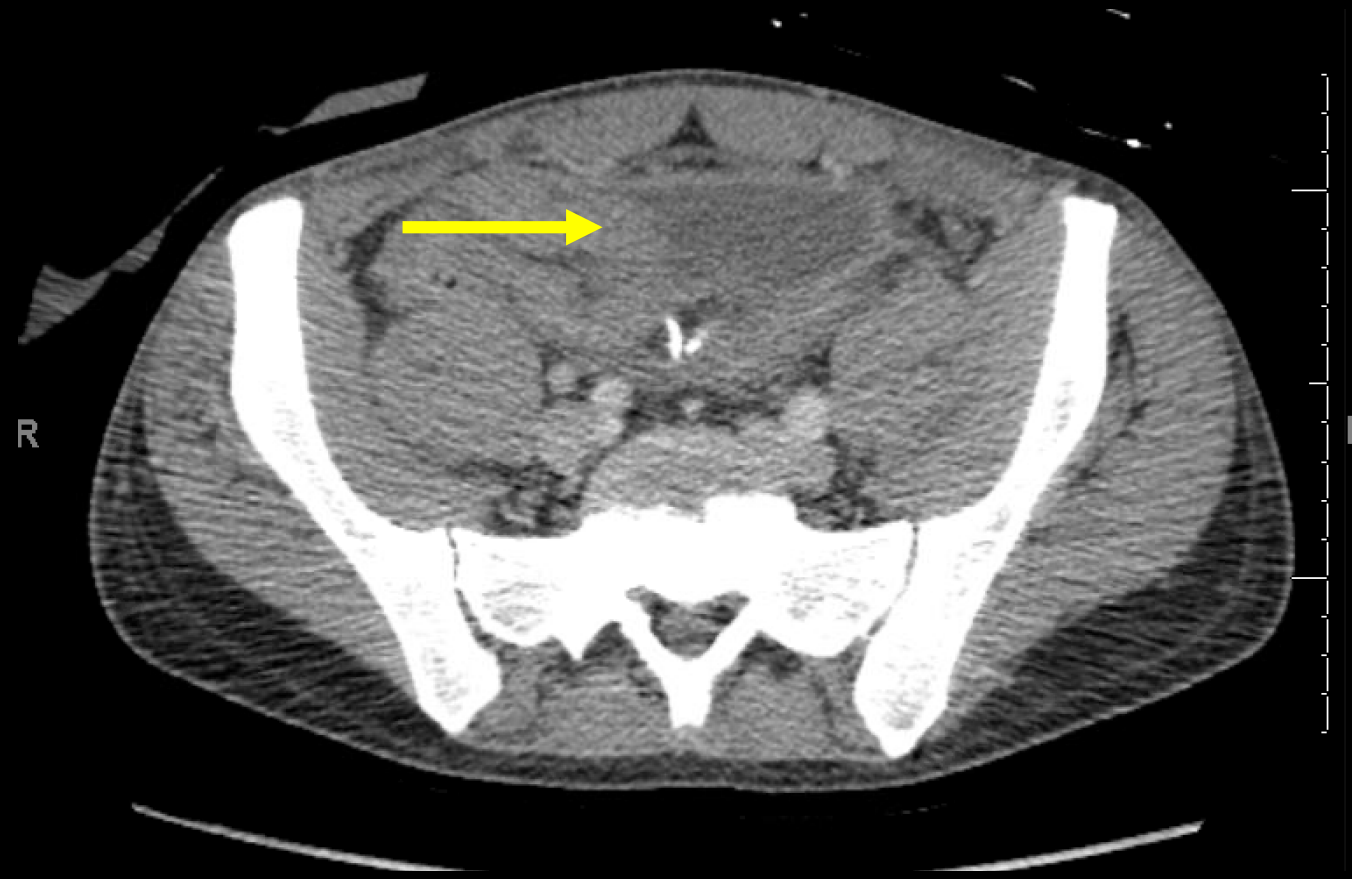
Case 2: 34 yo M with recurrent fevers

- Age 32
  - Acute LLQ pain similar to prior flares, steroid-responsive
  - Colonoscopy → diverticulitis with some **ulcers, not typical of IBD**
    - Antibiotics, observation
  - 1 month later: acute diffuse abdominal pain
    - "**Purulent peritonitis**"
    - EGD negative for leak but **(+) thickened/inflamed sigmoid**
    - Sigmoidectomy with end colostomy → discharged home
    - Readmitted with **pelvic fluid collection** around anastomosis → culture-negative
    - **Anakinra stopped**, antibiotics started
    - Worsening **abdominal pain, fevers** → repeat blood cultures negative

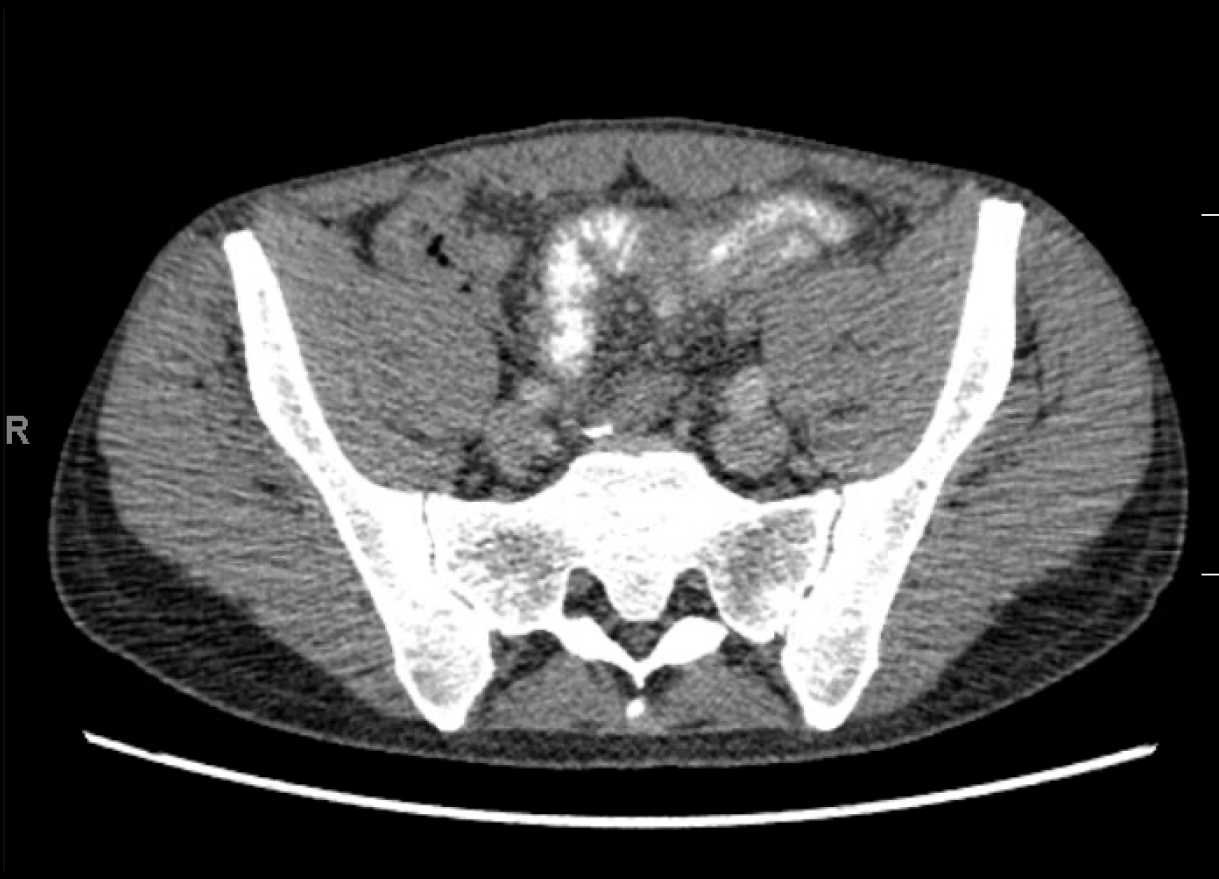
Adult Rheumatology consulted → started prednisone 1mg/kg → no response → called UPMC Autoinflammatory Center

Case 2: 34 yo M with recurrent fevers

Antibiotics



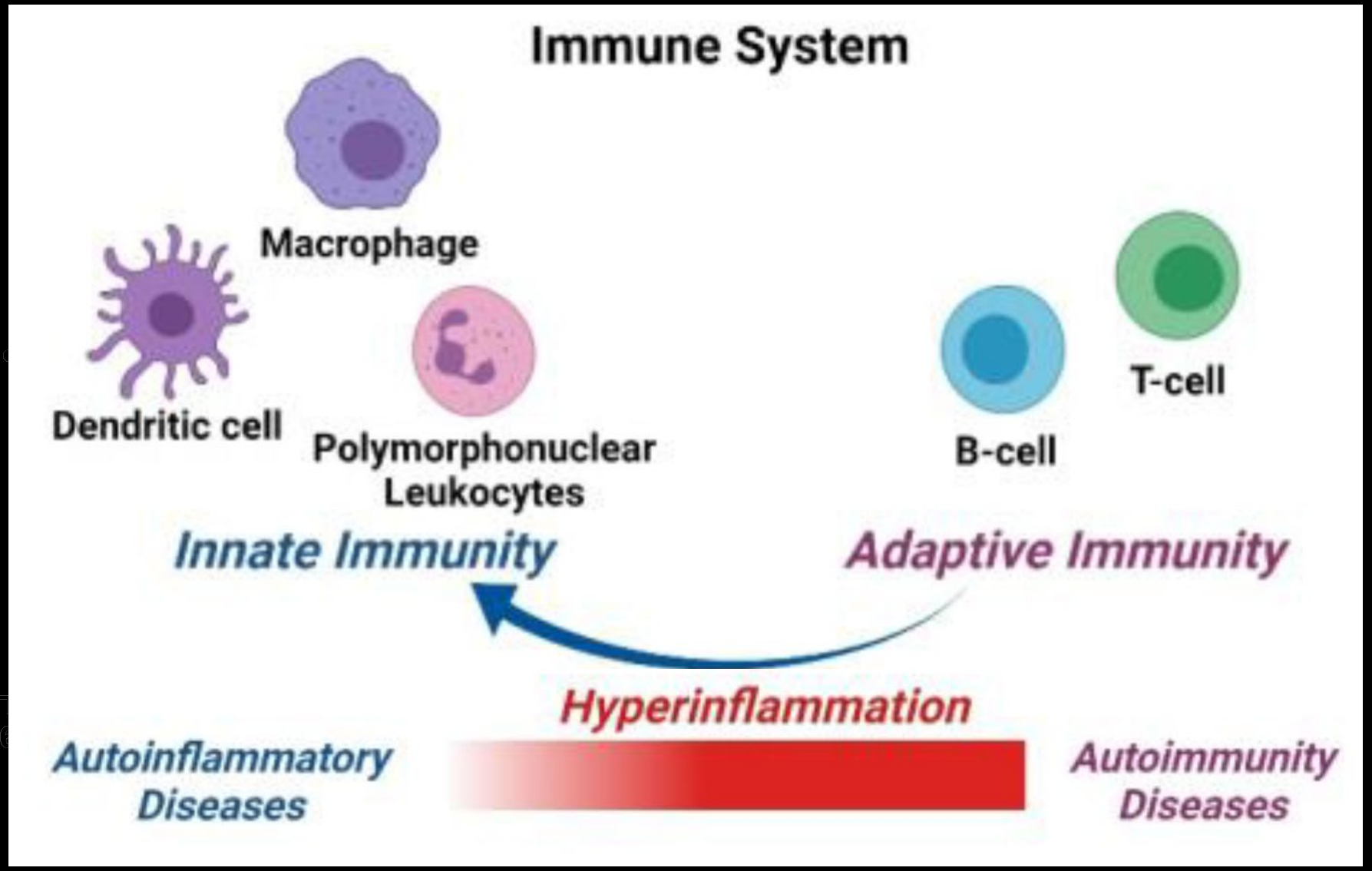
High-dose anakinra



Key questions: Case 2

- What were the **red flags** for autoinflammation?
- How is autoinflammation different from autoimmunity?
- How to treat flares?
  - Could his hemicolectomy have been avoided?

Autoinflammation vs. Autoimmunity

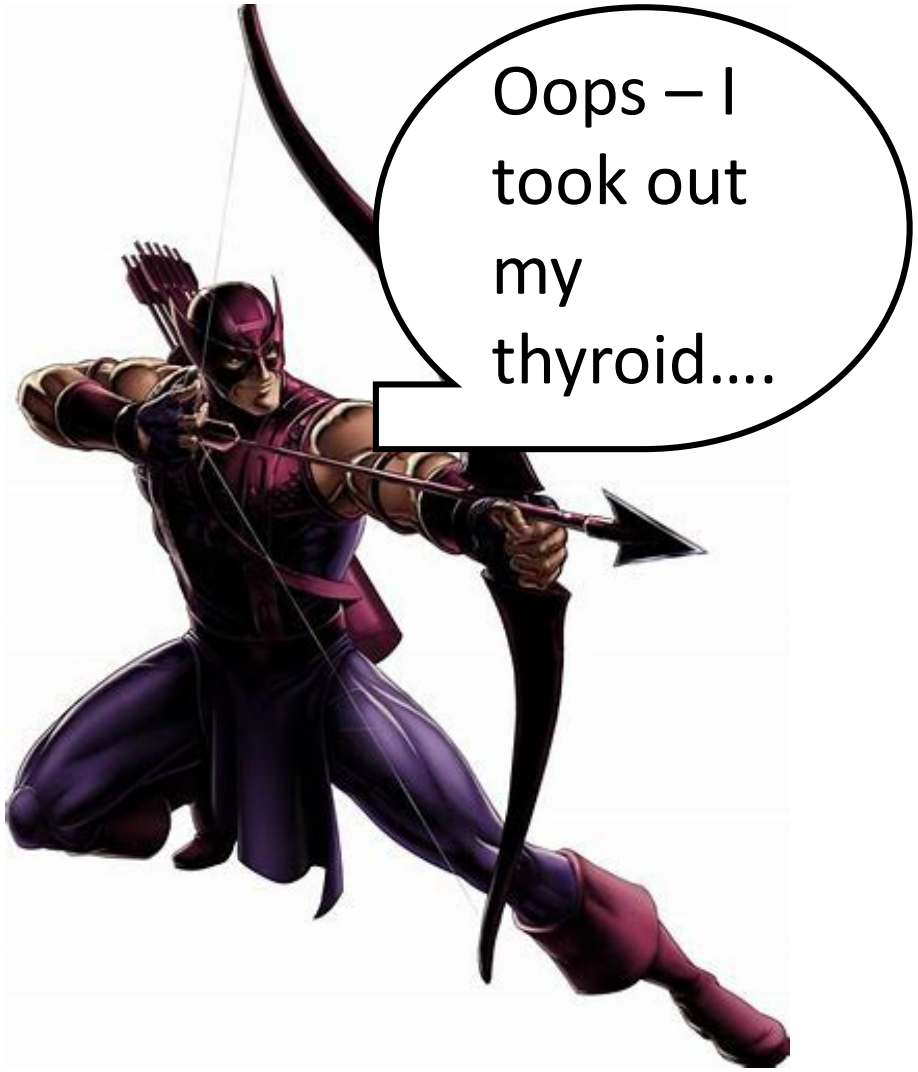


Marcuzzi, Int J Mol Sci 2021

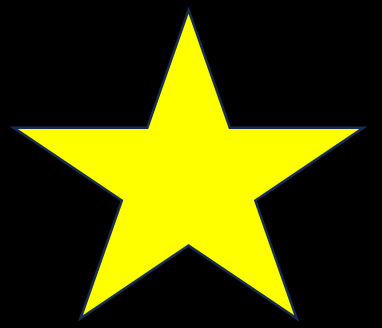
Autoinflammatory diseases

vs.

Autoimmune diseases

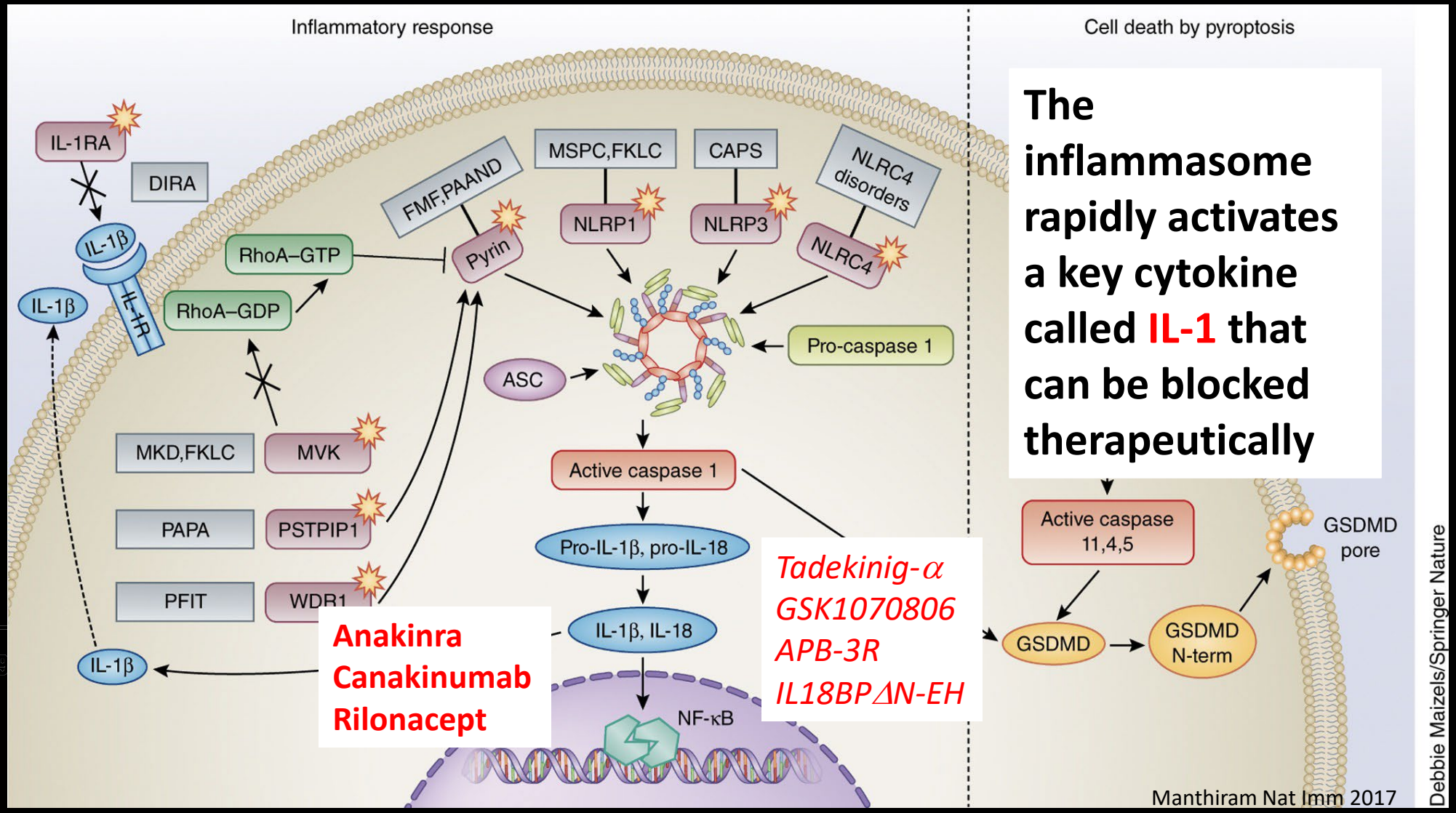


Autoinflammatory diseases look DIFFERENT from autoimmune diseases



Feature	Autoinflammatory	Autoimmune
Immune activation	Innate	Adaptive
Autoantibodies	No	Yes
Elevated ESR, CRP	Yes (only during flare!)	Sometimes
Clinical presentation	**Cyclic (may look normal in clinic)**	**Smoldering (usually look sick in clinic)**
Examples (monogenic)	FMF, TRAPS, CAPS	IPEX, APECED, DiGeorge
Examples (polygenic)	Gout, AOSD	SLE, RA, T1D

Inflammasomes are important for many autoinflammatory diseases



Outcomes: Case 2

- Genetic testing: negative
- Transitioned from anakinra to canakinumab (longer acting IL-1 blocker)
- Continues to need MMF/HCQ for myasthenia gravis
- Colostomy reconnected, in remission

Swanson Nat Rev Immunol 2019

Take home points – Case 2

- Patients with autoinflammatory diseases often look **normal** in clinic
  - ESR/CRP normalize between flares
  - **Critical to check DURING FLARE**

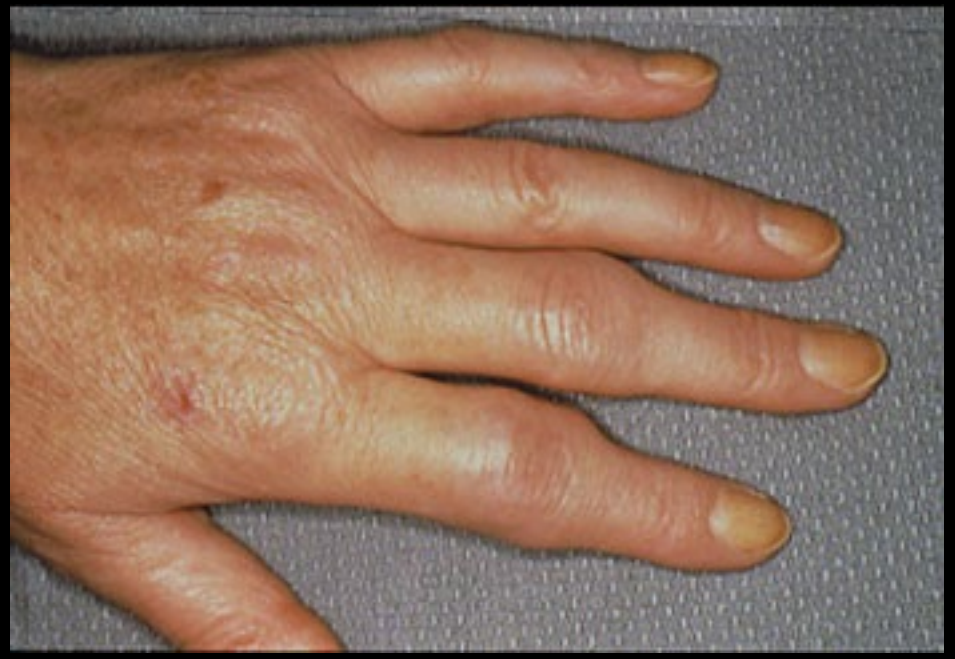
- Patients with autoinflammatory disease often look **septic** in the hospital
  - Inflammasomes are really good at triggering inflammation

- IL-1 blockers are approved at **low doses** but may need to be given at **high doses**
  - Competitive antagonists
  - Studied in RA/gout/pericarditis, not autoinflammatory disease

- Autoinflammatory disease should not be treated like autoimmune disease
  - **Do not stop IL-1 blockers**
  - Avoid aggressive procedures (especially abdominal surgery)
  - Use caution with antibiotics

Case 3 – 61 yo F with recurrent fevers

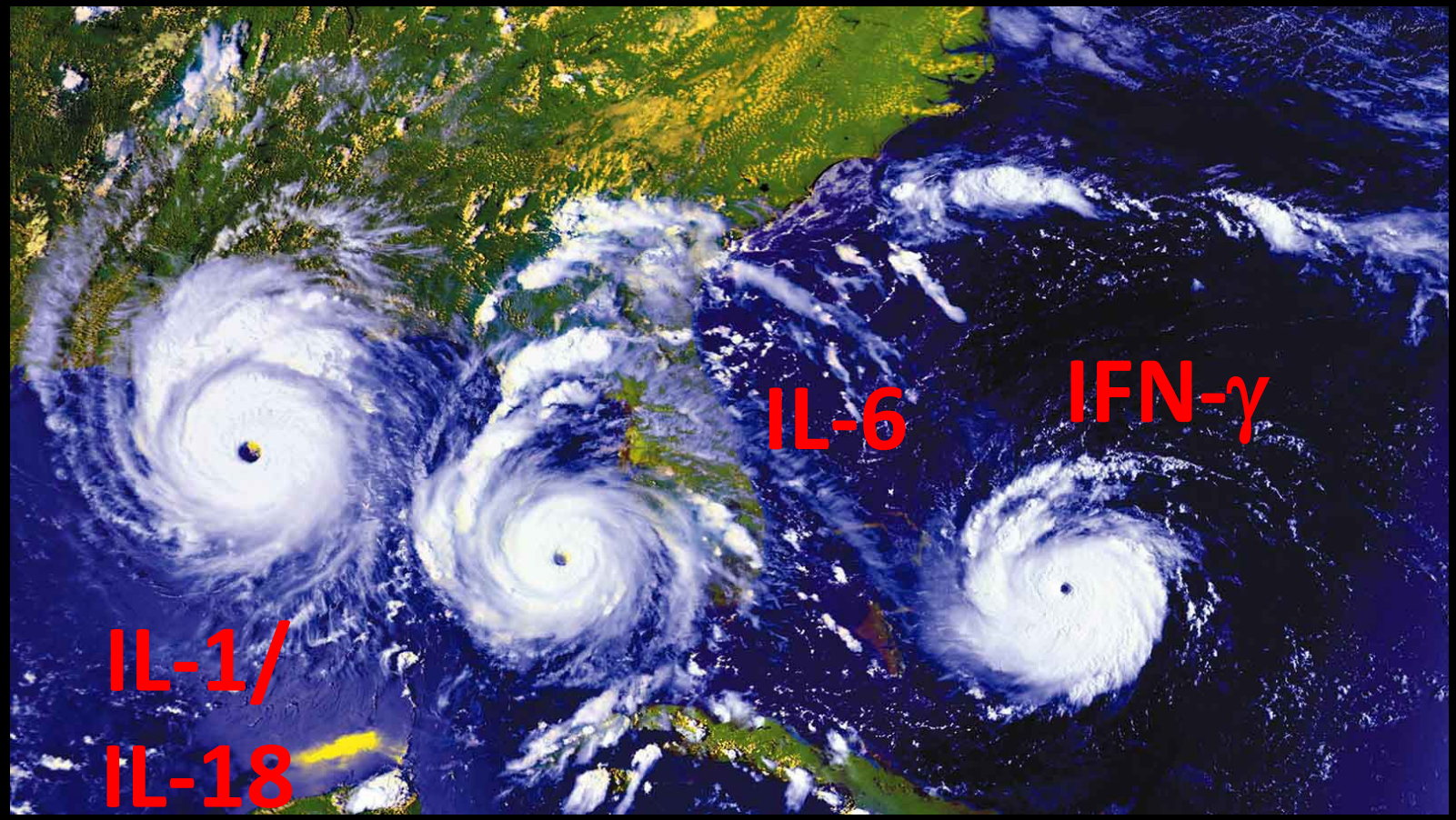
- June 2023-Jul 2023
  - Acute onset inflammatory polyarthritis post COVID
  - Diagnosed with Lyme
  - Treated with doxy x 1 month, prednisone x 2 months
- Aug-Sept 2023
  - Monthly fevers to 104.2
  - Weakness, difficulty swallowing, neck stiffness
  - Unplanned weight loss



Case 3 – 61 yo F with recurrent fevers

- Sept 2023 admission
  - WBC 8.2, ANC 4400, ALC 1400, **Hgb 9.6**, plt 447
  - **ESR > 93**, **CRP 24.6 mg/dL**, **ferritin 826**, **fibrinogen 719, AST 64, ALT 92**
  - **ANA 1:1280 (speckled) with (+) Sm, CCP > 500**
  - **Synovial WBC 40,150**
  - Lyme negative
  - Hand x-rays severe erosive changes at DIP joints
- Sept 2023—Jan 2024: Diagnosed with RA-lupus
  - Treated with pred 30mg/d, HCQ, MTX
  - Unable to taper steroids: recurrent fever to 101, arthritis
- Jan 2024 admission
  - WBC 8.7, ANC 6720, ALC 970, **Hgb 8.3**, plt 447
  - **ESR > 130**, **CRP 28.6 mg/dL**, **ferritin 1587**, **fibrinogen 710**, **AST 87**, **ALT 116**, **LDH 287**, **triglycerides 241**

Does this patient have a cytokine storm syndrome?

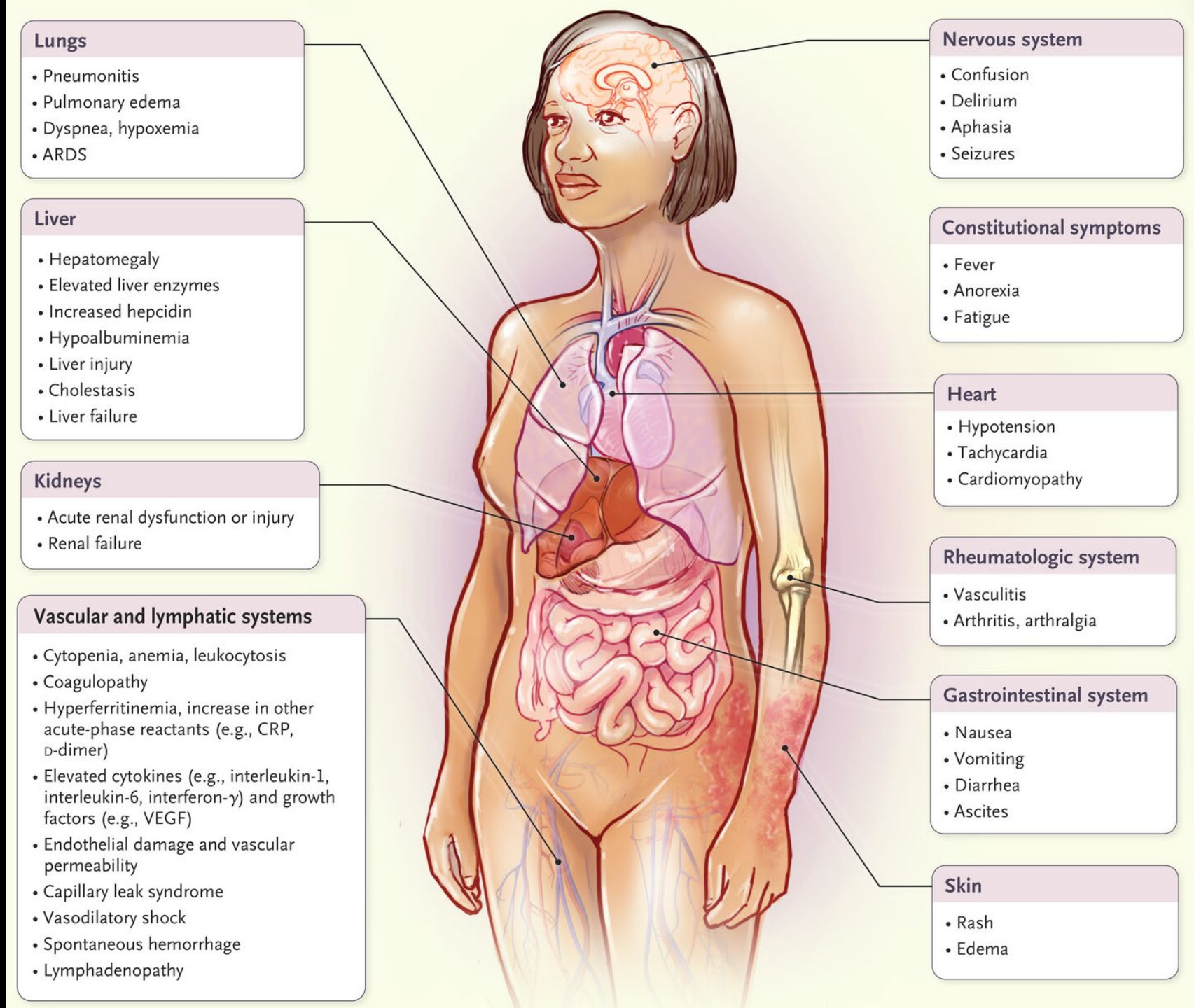


What is cytokine storm?

"***No single definition of cytokine storm or the cytokine release syndrome is widely accepted***, and there is disagreement about how these disorders differ from an appropriate inflammatory response…. the line between a normal and a dysregulated response to a severe infection is blurry, especially considering that certain cytokines may be both helpful in controlling an infection and harmful to the host"

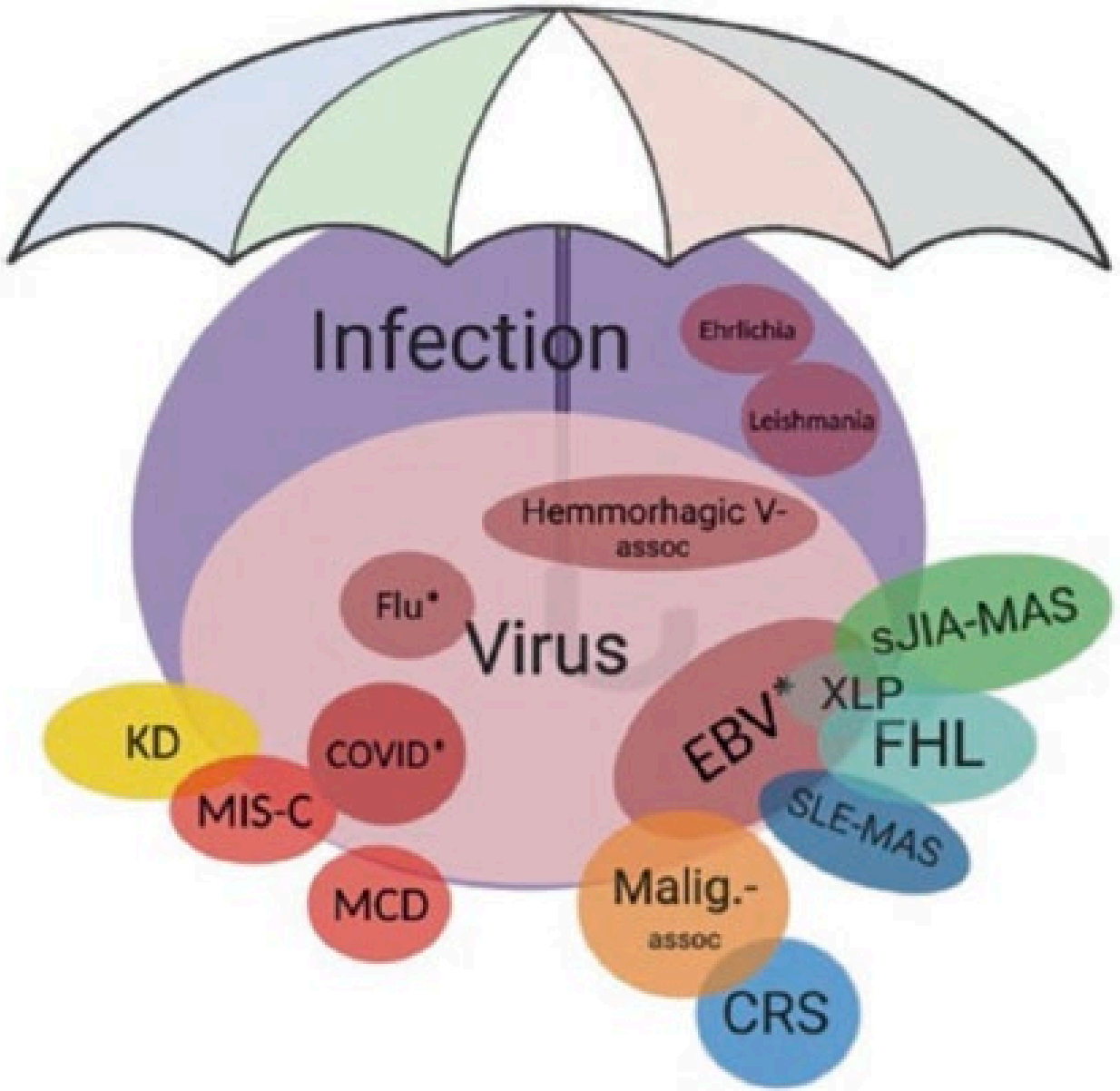
Faigenbaum D and June C,
NEJM 2020

Clinical features of cytokine storm are heterogeneous



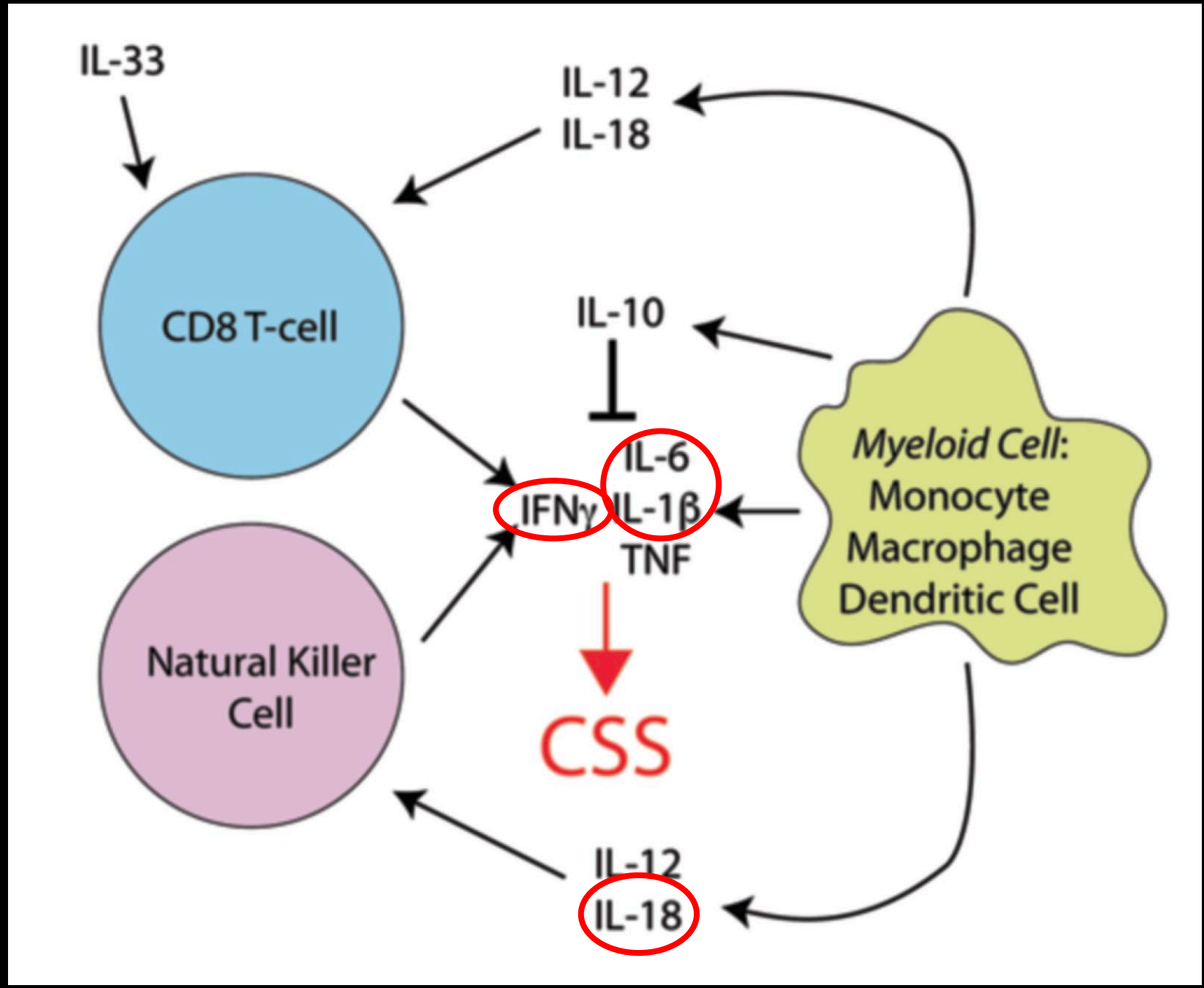
Faigenbaum D and June C,
NEJM 2020

Triggers of cytokine storm



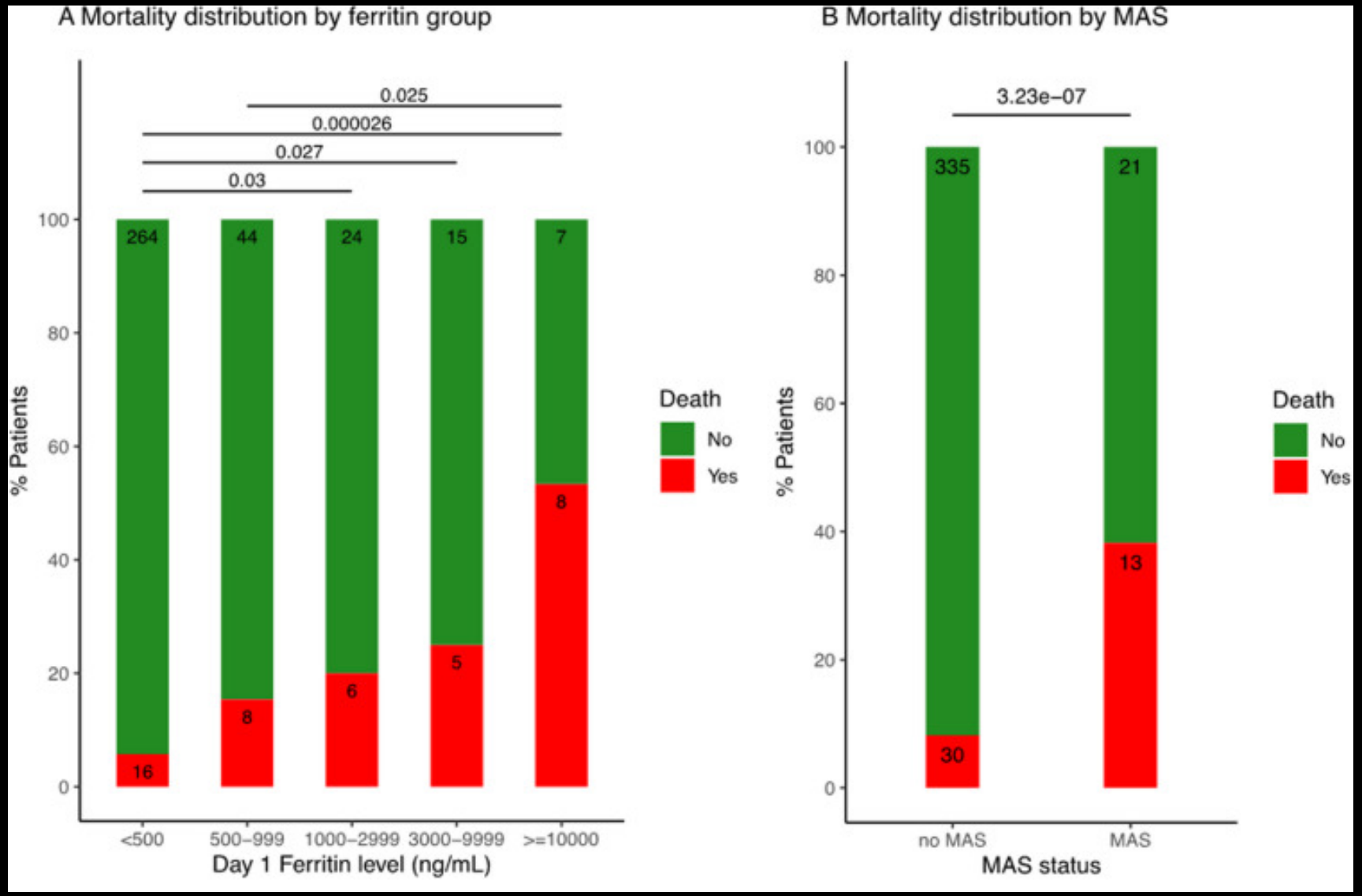
Behrens, Cron, *Cytokine Storm Syndrome* 2024

Immunologic drivers of cytokine storm syndromes



Behrens, Cron, *Cytokine Storm Syndrome* 2024

HLH/MAS: a lethal “flavor” of cytokine storm that can be seen in sepsis

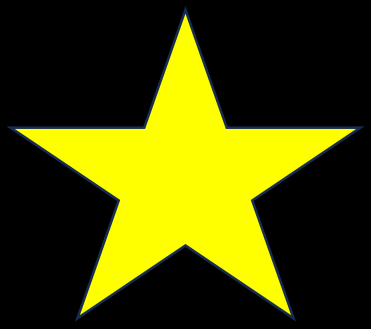


Fan, Crit Care 2023

Key questions: Case 3

- What are the **red flags** for HLH/MAS?
- How to work up HLH/MAS?
- How to treat HLH/MAS?
  - Does it depend on the underlying cause?

Trending ferritin is key to recognizing HLH



Consider HLH in an unwell patient: Use the '3Fs'		
Fever	**R**ising **F**erritin	**F**alling blood counts

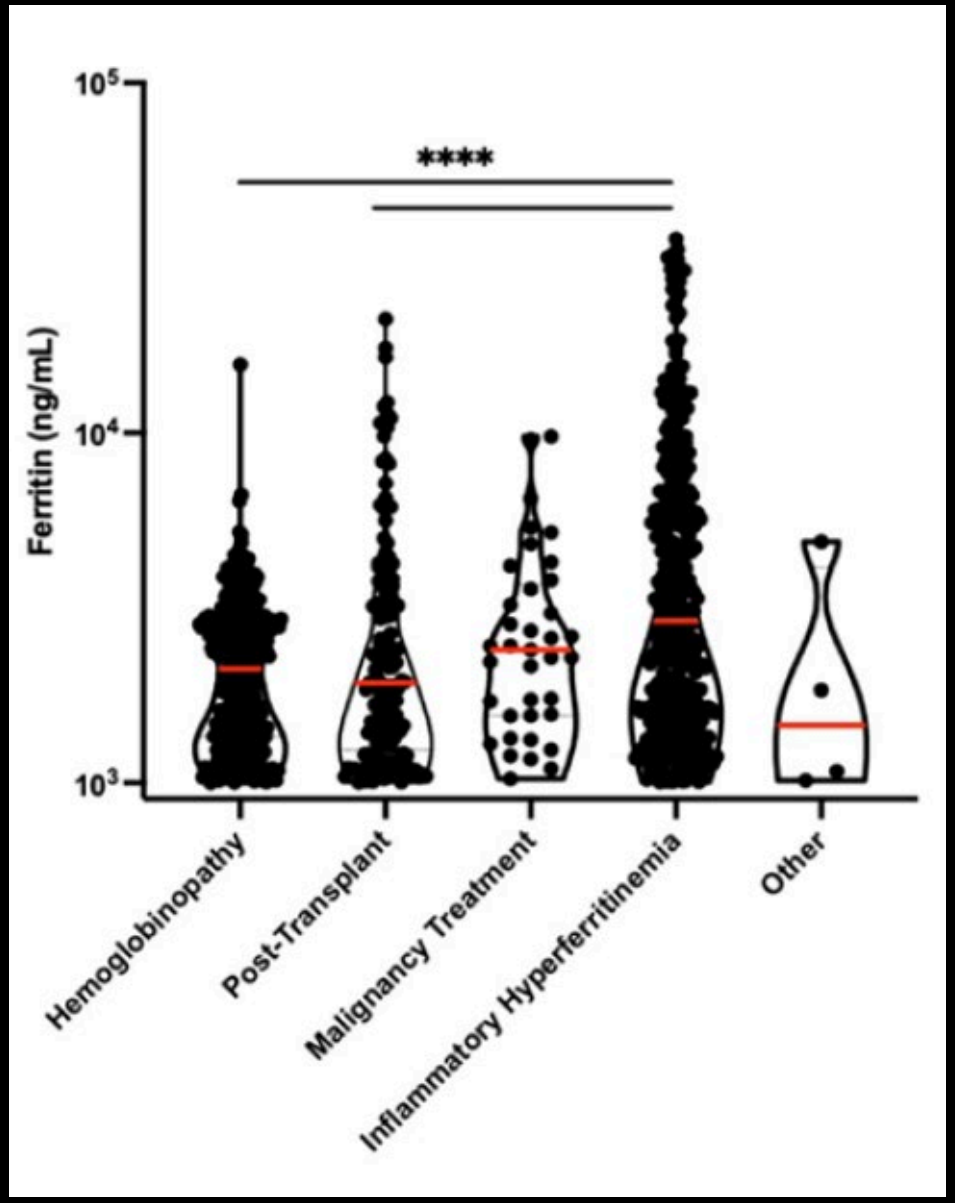
Cox, Lancet Rheum 2023
Shakoory, Ann Rheum Dis 2022

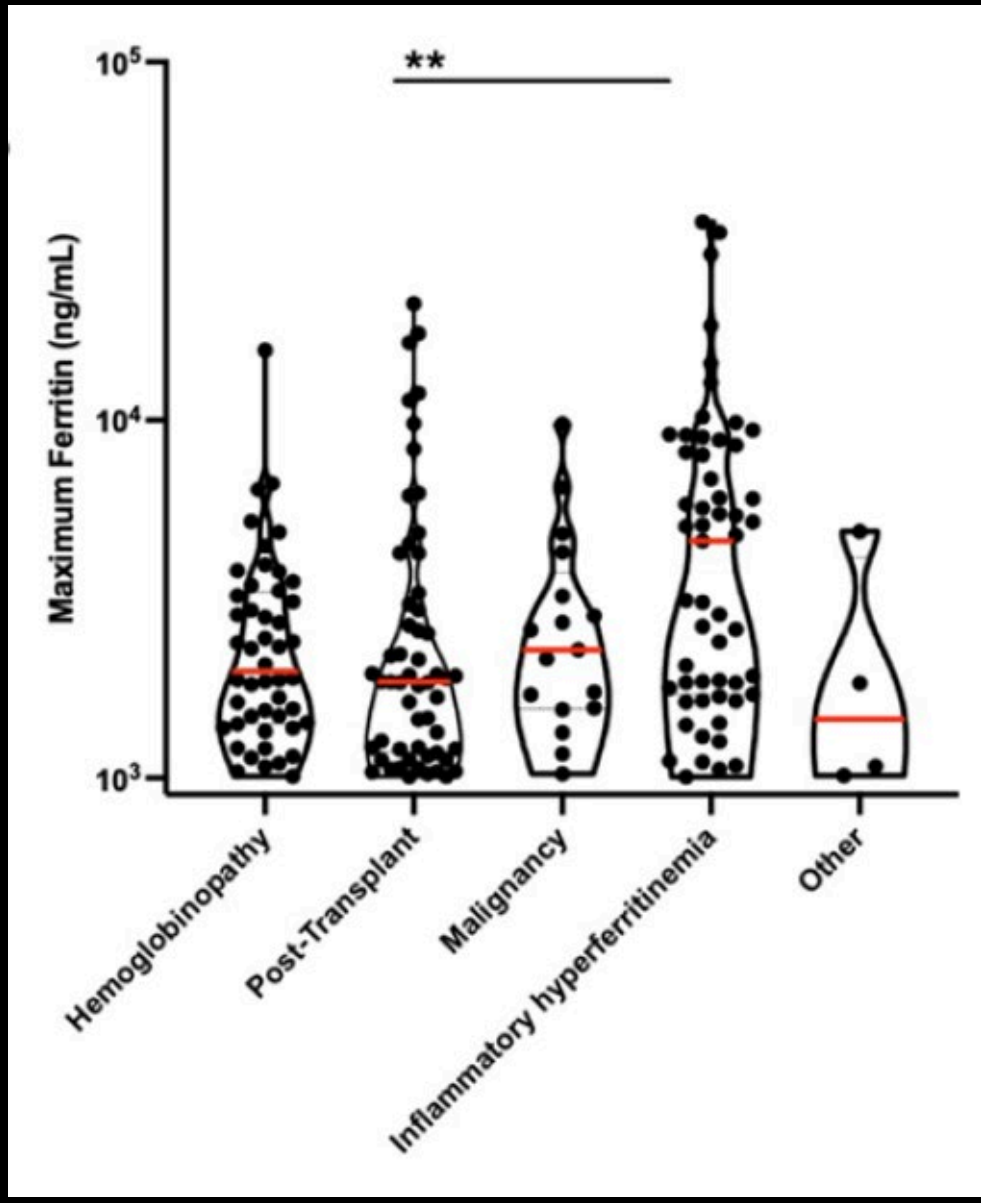
Hyperferritinemia is a marker of HLH/MAS

Sensitive, but not specific

Needs followup

- **TREND** levels
- Confirmatory testing





Carol, JOCI, 2025

(Lots of) clinical disease scores are used in HLH/MAS

Table 1: H Score (Patients Findings)

Findings		Score
Fever (°C)	<38.4	0
	38.4.039.4	33
	>39.4	**49**
Organomegaly	Absent	0
	Hepatomegaly or Splenomegaly	23
	Hepatomegaly and Splenomegaly	**38**
Cytopenia	Single Cell Line	0
	Two Cell Lines	**24**
	Three Cell Lines	34
Triglycerides (mg/dL)	<132.7	0
	132.7-354	44
	>354	**64**
Fibrinogen (mg/dL)	**>250**	**0**
	<250	30
AST (IU/L)	<30	0
	>30	**19**
Ferritin (ng/L)	<2,000	0
	2,000-6,000	35
	>6,000	**50**
Hemophagocytosis	**Absent (Not Tested)**	**0**
	Present	35
Immunosuppression	**Absent**	**0**
	Present	18
		Total Score: 244*

Table 1: New Classification Criteria for MAS

A febrile patient with known or suspected systemic JIA is classified as having MAS if patient has ferritin >700 ng/L *and* at least two of the following laboratory abnormalities:

- Platelets <180 x 10^9/mL
- Aspartate aminotransferase (AST) >50 U/L
- Triglycerides >160 mg/dL
- Fibrinogen <360 mg/mL

Table 2. HLH-2004 diagnostic criteria

The diagnosis of HLH can be established if Criterion 1 or 2 is fulfilled.

1. A molecular diagnosis consistent with HLH

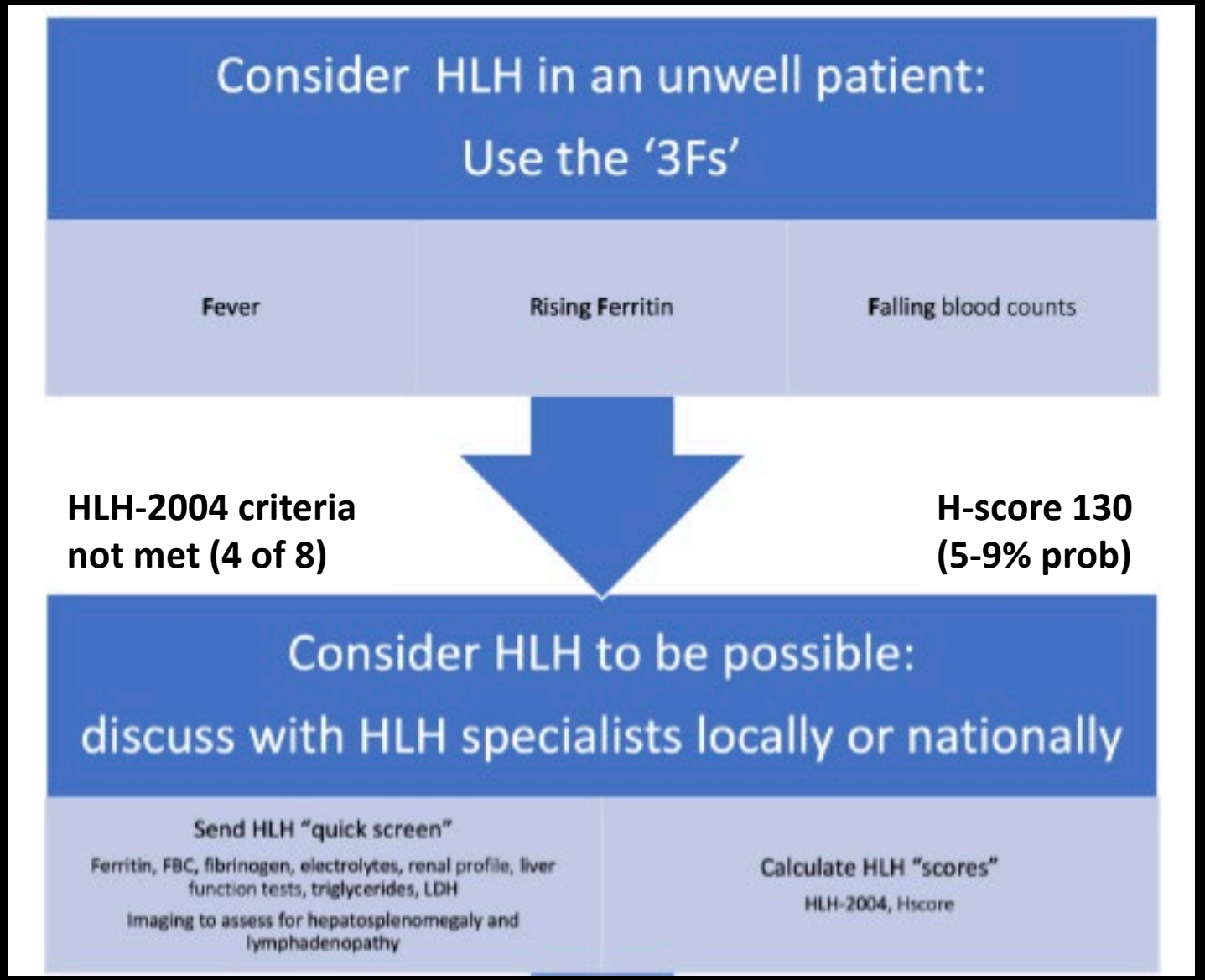
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)
   - Fever
   - Splenomegaly
   - Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood)
     - Hemoglobin <90 g/L (hemoglobin <100 g/L in infants <4 wk)
     - Platelets <100 × 10^9/L
     - Neutrophils <1.0 × 10^9/L
   - Hypertriglyceridemia and/or hypofibrinogenemia
     - Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL)
     - Fibrinogen ≤1.5 g/L
   - Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy.
   - Low or no NK cell activity (according to local laboratory reference)
   - Ferritin ≥500 μg/L
   - sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL

Cox, Lancet Rheum 2023
Shakoory, Ann Rheum Dis 2022

Case presentation 3: Clinical disease scores say no

Table 1 Recognisable clinical features/patterns in HLH/MAS

Features		Criteria*
1	Systemic inflammation (elevated or rising)	
	Fever	All
	CRP	–
	LDH	–
2	Hyperferritinemia (elevated or rising)	All
3	Cytopenias (low or dropping)	
	Platelet count†	All
	Leucocyte count (particularly neutrophil count)	HLH04, HScore
	Haemoglobin	HLH04, HScore
4	Disseminated intravascular coagulopathy	
	Increased d-dimer	–
	Low/Dropping fibrinogen†	All
	Prolonged PT/INR, PTT	–
5	Liver dysfunction	
	Hepatomegaly	HScore
	Increased ALT, AST, bilirubin	MAS16, HScore
	Increased triglycerides	All
6	Splenomegaly	HLH04, HScore
7	CNS dysfunction	–
	Encephalitis, encephalopathy, altered mental status, seizure	
	CSF pleocytosis, elevated CSF protein, increased ICP	
	Radiological evidence of inflammation	



Cox, Lancet Rheum 2023
Shakoory, Ann Rheum Dis 2022

Are there any alternatives to clinical disease scores?

*"Systemic hyperinflammation is an **immunopathological continuum**; the characteristic clinical and laboratory findings are individually non-specific, but when viewed collectively and longitudinally are recognisable and warrant prompt diagnostic evaluation. **Therapeutic intervention may be warranted even when not satisfying specific classification/diagnostic criteria** for HLH/MAS."*

Shakoory et al, Ann Rheum Dis 2023
Cox et al, Lancet Rheum 2024

Hemophagocytosis on bone marrow biopsy is NEITHER sensitive nor specific for HLH

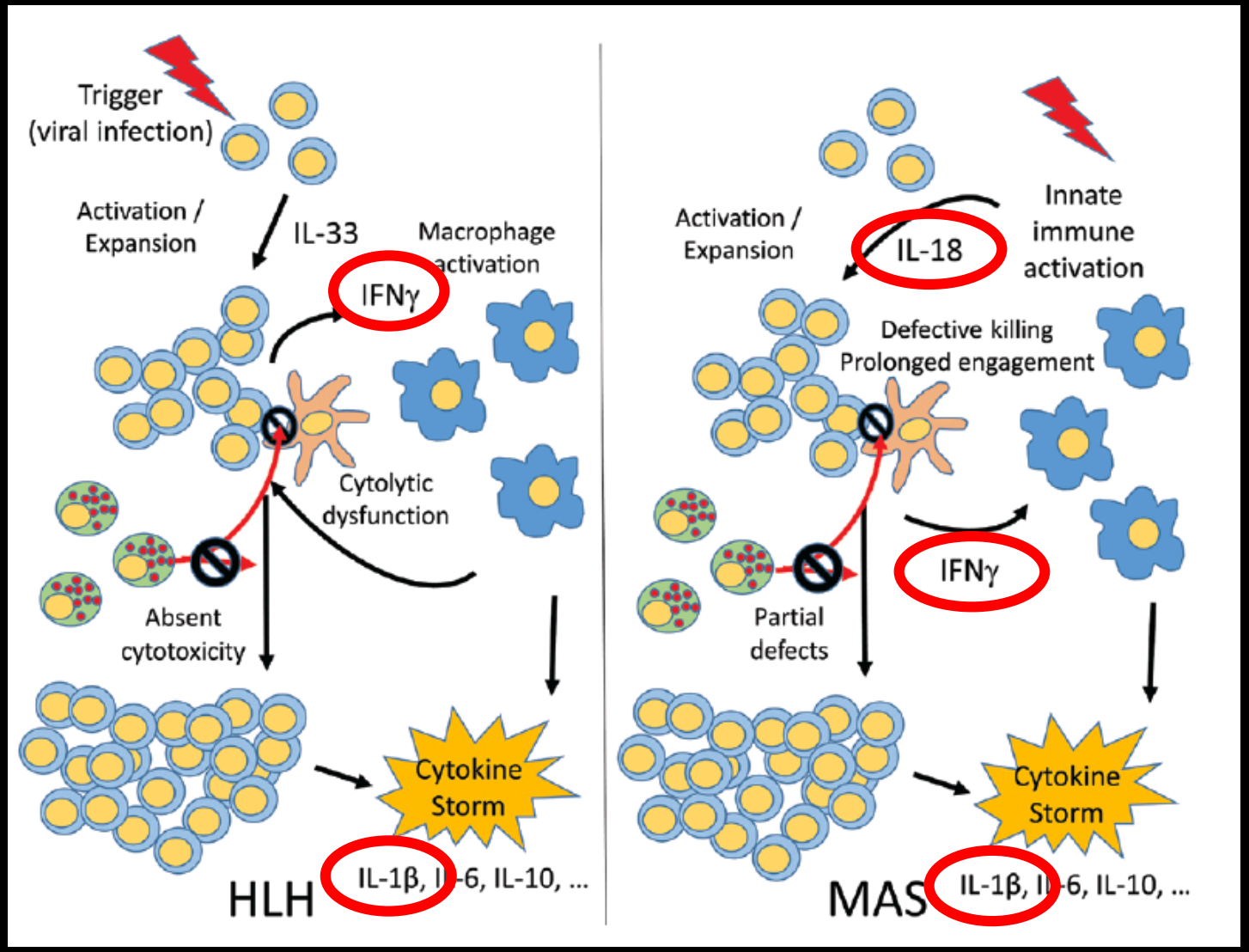
Table 4.2 Comparison of clinical features of each cytokine storm syndrome

Clinical features	FHL (%)	s-JIA-associated MAS (%)	SLE-associated MAS (%)	EBV-associated HLH (%)
Fever	91	96.1	96.9–100	100
Hepatomegaly	94	70.0	18.80	87.8
Splenomegaly	98	57.9	27.2–56.3	64.3
Lymphadenopathy	17	51.4	31.30	50.0
CNS involvement	47–73	35.0	36.90	18.4
Hemophagocytosis in the bone marrow	85	60.7	60.7–100	92.7
References	[10–12]	[13]	[14, 15]	[16]

FHL familial hemophagocytic lymphohistiocytosis, *SLE* systemic lupus erythematosus

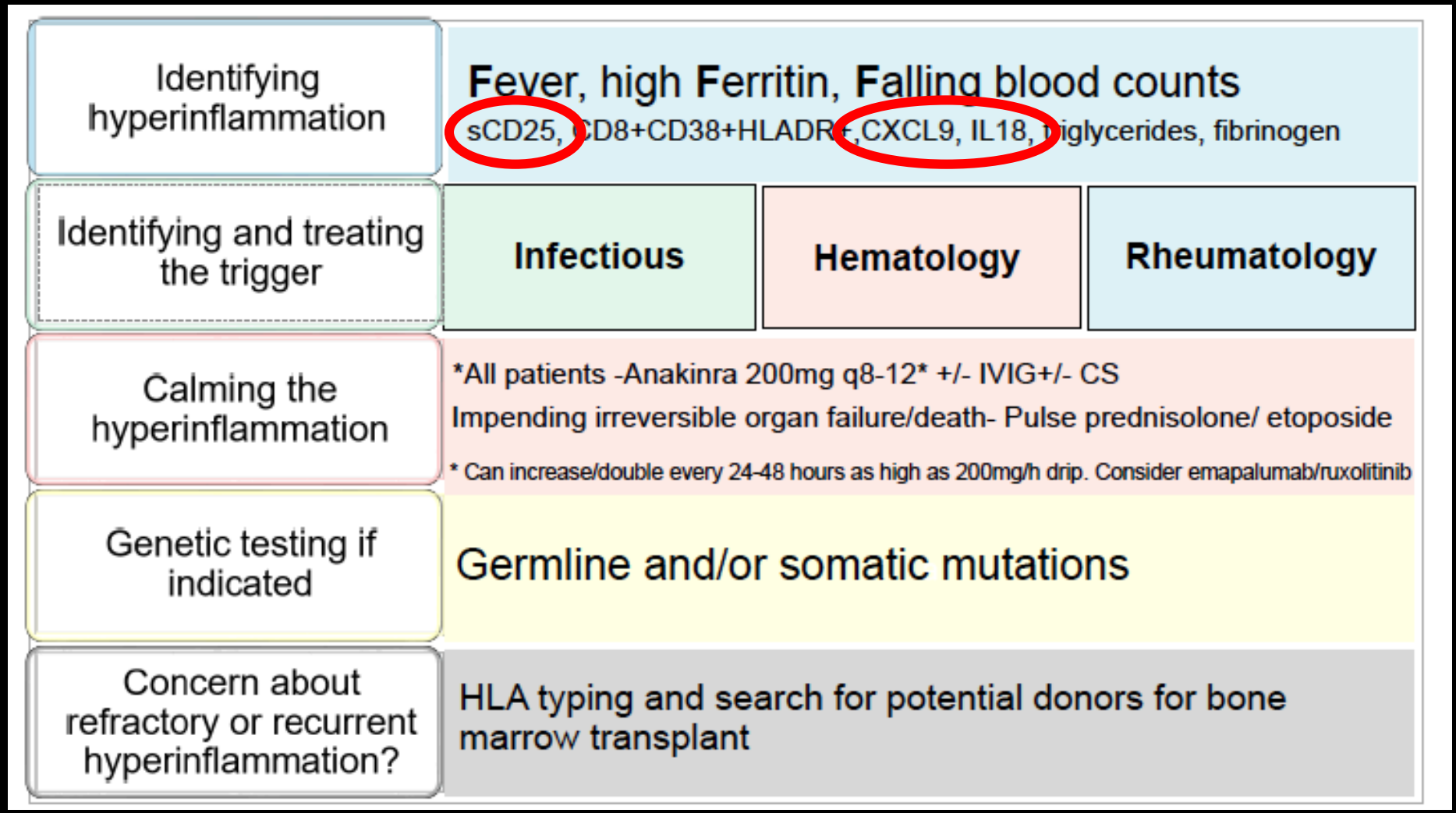
Shimizu, in *Cytokine Storm Syndrome* 2024

HLH-MAS is one “flavor” of cytokine storm with conserved terminal effectors



Canna et al, Int Immunol 2018

Patients with hyperferritinemia should be tested for classic terminal effector cytokines:



sIL2R = T cell activation marker

CXCL9 = marker for IFN-γ

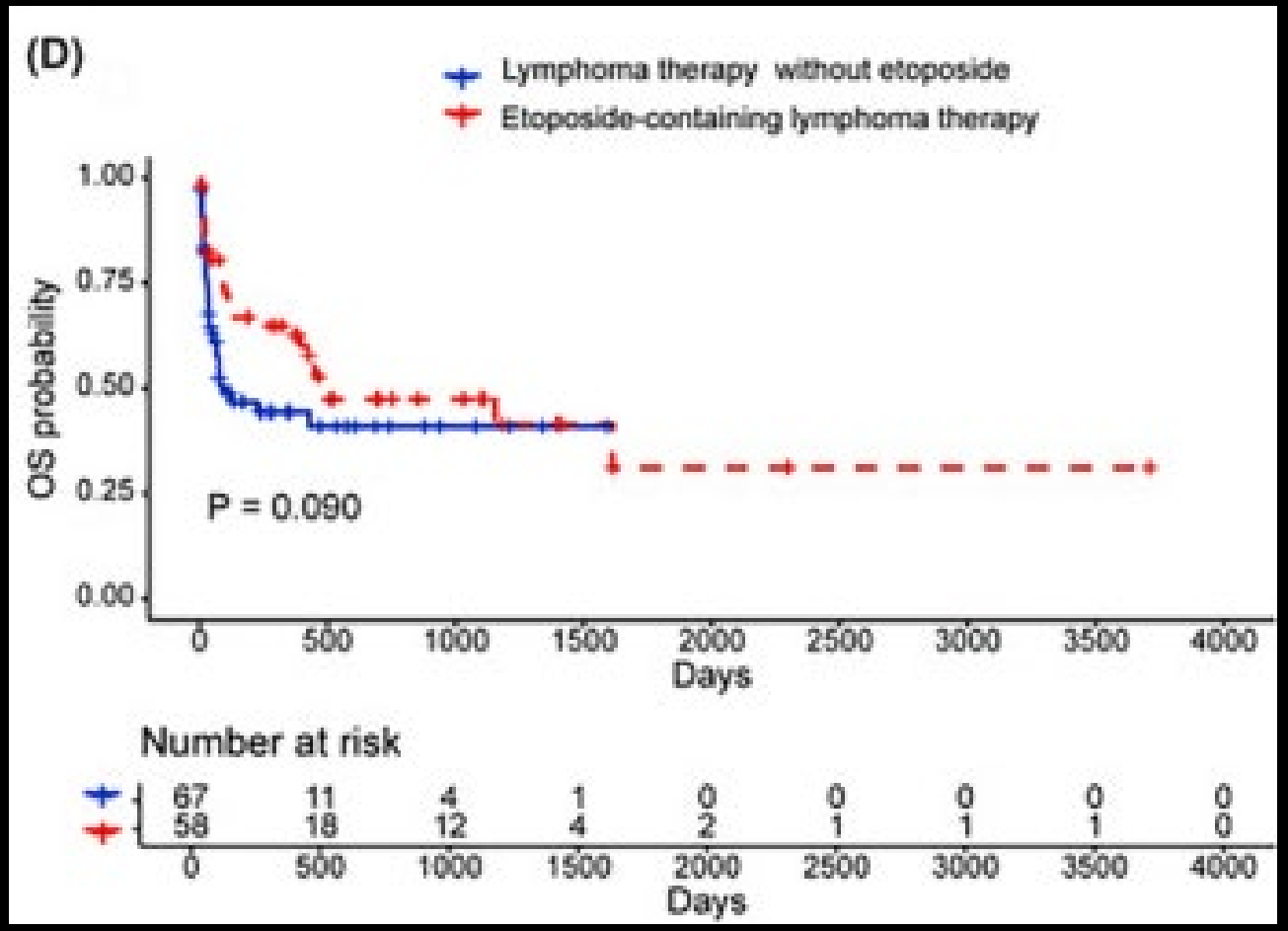
IL-18 = marker for Still's disease as a cause/trigger

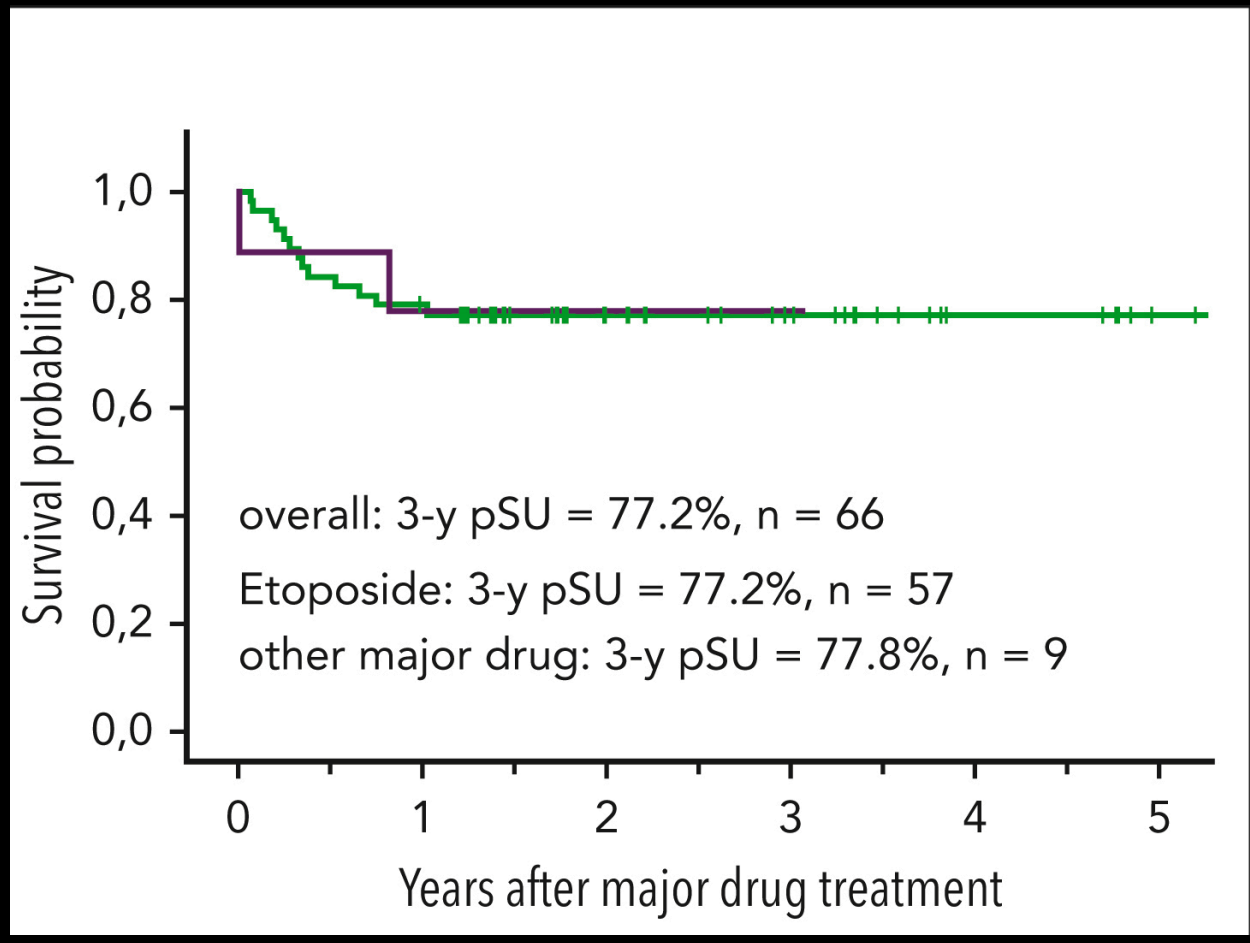
Zoref Lorenz, Jordan, Rocco, Schwartz (in revision)
Carol, JOCI 2025

Case 3: using biomarkers to guide diagnosis

- March 2024 referral to UPMC (outpatient clinic)
  - **CXCL9: 28,594** (ref <647), **IL-18: 747** (ref <477), **sIL2R: 2,885** (ref <1891)
  - Diagnosis: HLH/MAS
  - Now what?
    - (How to treat?)

Etoposide – a mainstay for fHLH (and traditionally for sHLH)





Bohm, Blood 2024
Miao Cancer Med 2024

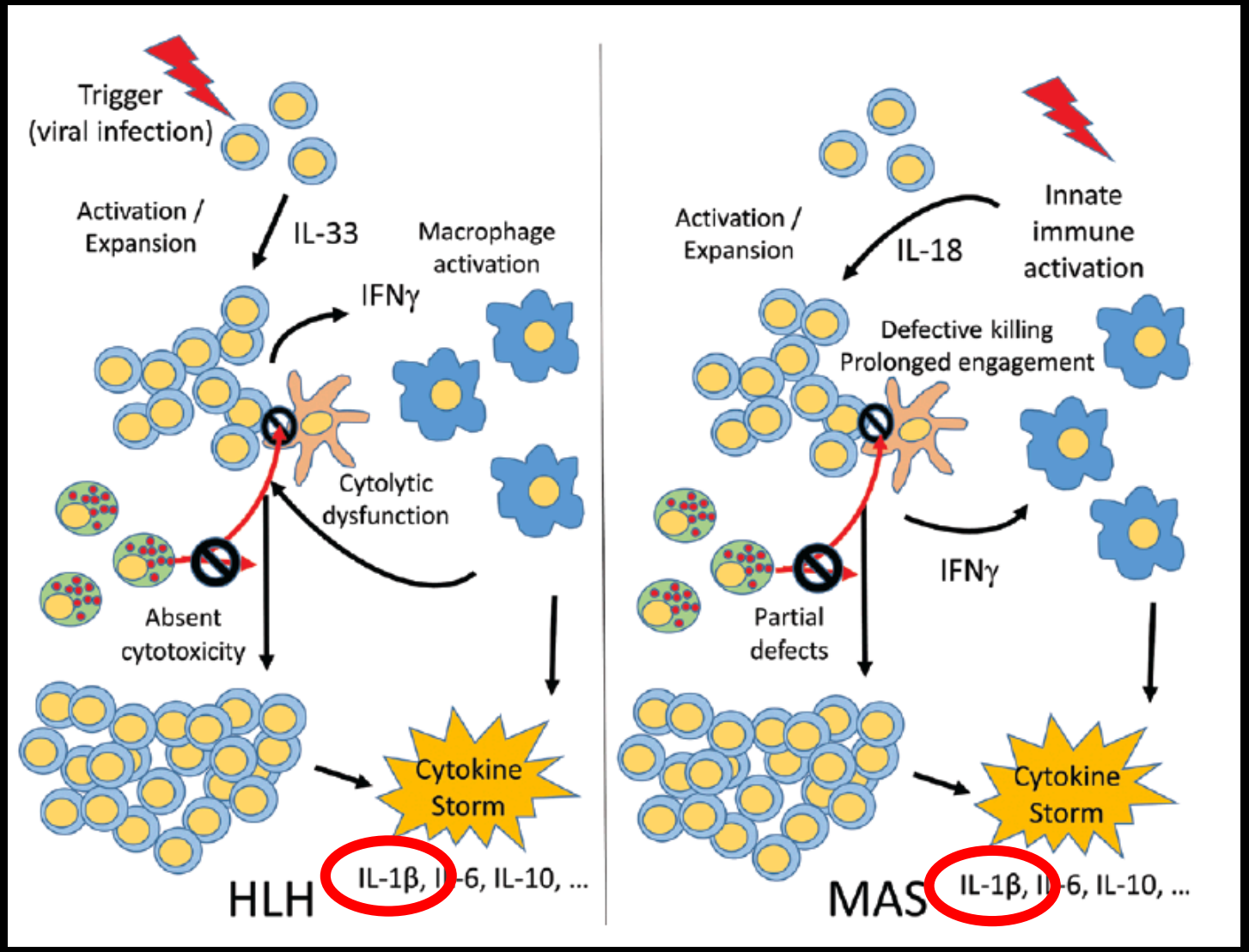
However, etoposide is NOT FIRST LINE for many causes

Table 30.1 Differences between sepsis-related MAS/MALS, rheumatology-associated MAS, and familial HLH

	MAS	p HLH	Sepsis-induced MODS	Hyperferritinemic sepsis
Cytokine pattern	Hyperferritinemia Very high IL-18 Increased interferon-γ	Extreme Hyperferritinemia Increased interferon-γ Increased IL-18	Increased ferritin, Absent interferon-γ	Increased ferritin, Somewhat increased IL-18 Low interferon-γ
NK cell numbers/ function	Normal numbers, Decreased cytolytic function	Normal numbers, Absent cytolytic function	Low numbers, Normal cytolytic function per cell	Less than 10% of Normal numbers, Normal cytolytic function per cell
T-cell numbers/ function	T-cell activation/No proliferation	T-cell activation/ Proliferation	Decreased T-cell numbers	Profound lymphopenia and T-cell exhaustion
Putative therapies	Corticosteroids, IVIg Anakinra, Emapalumab (Interferon-γ blocker)	Etoposide dexamethasone, Emapalumab (interferon-γ blocker	Remove source of infection GM-CSF? [117] Checkpoint inhibitors? [118] IL-7? [119]	Remove source of infection IVIg, Methylprednisolone, anakinra, plasmapheresis

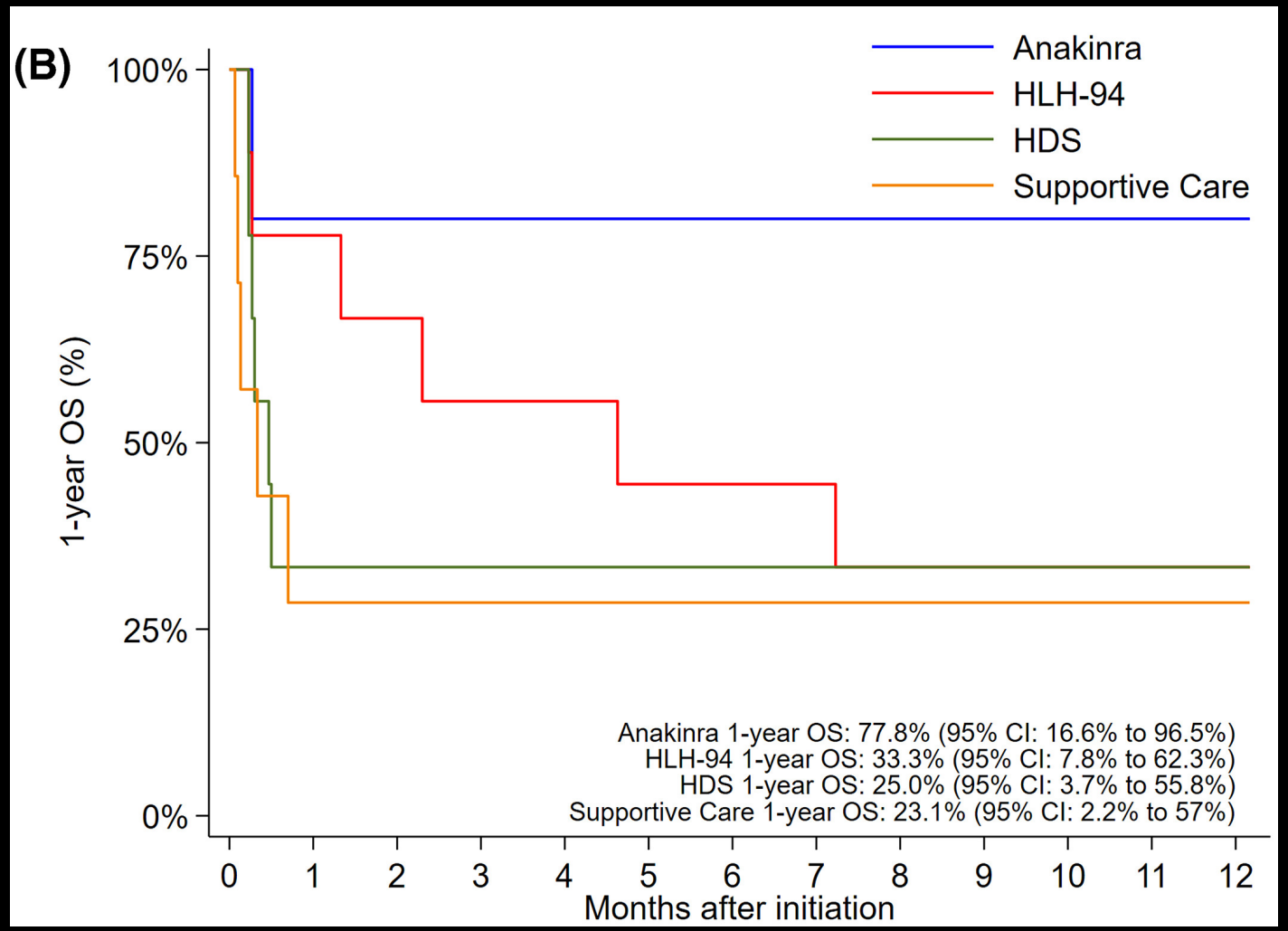
Carcillo, Shakoory, in *Cytokine Storm Syndrome* 2024

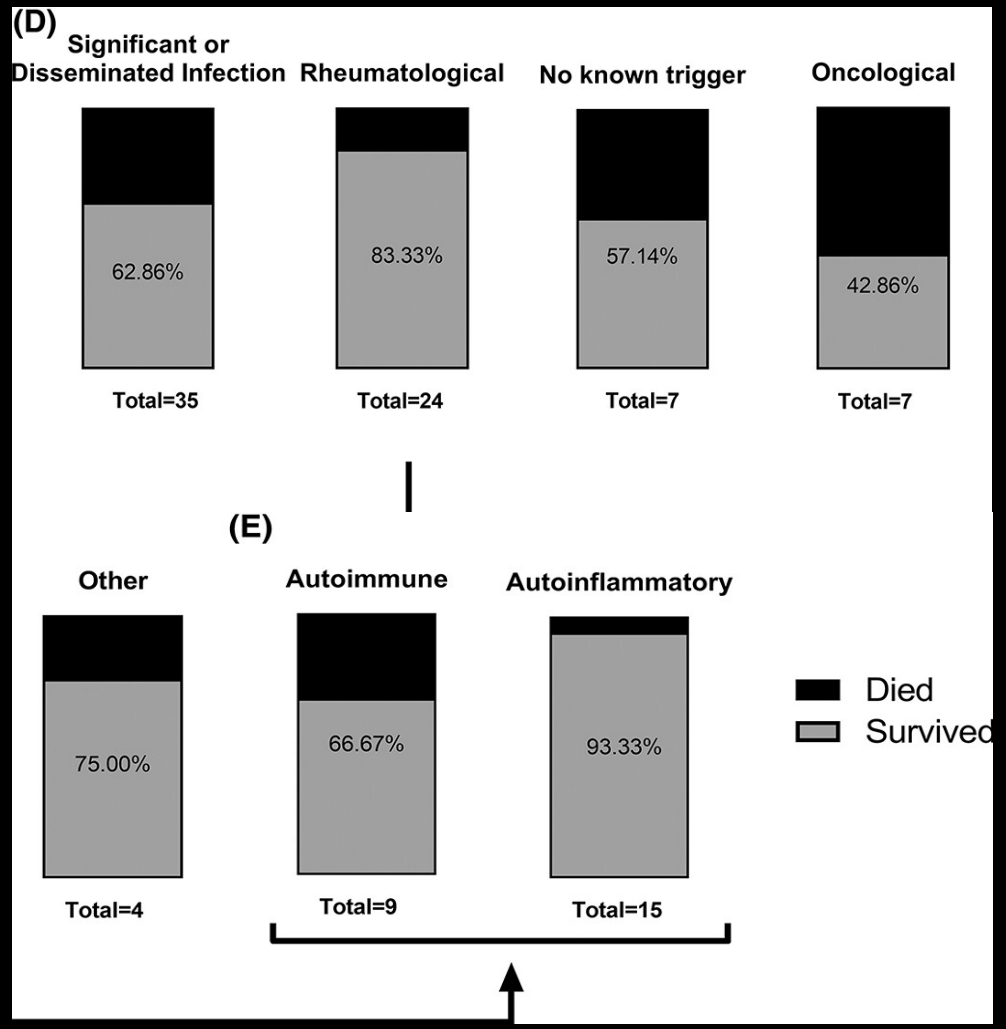
Blocking **conserved terminal effectors: IL-1**



Canna et al, Int Immunol 2018

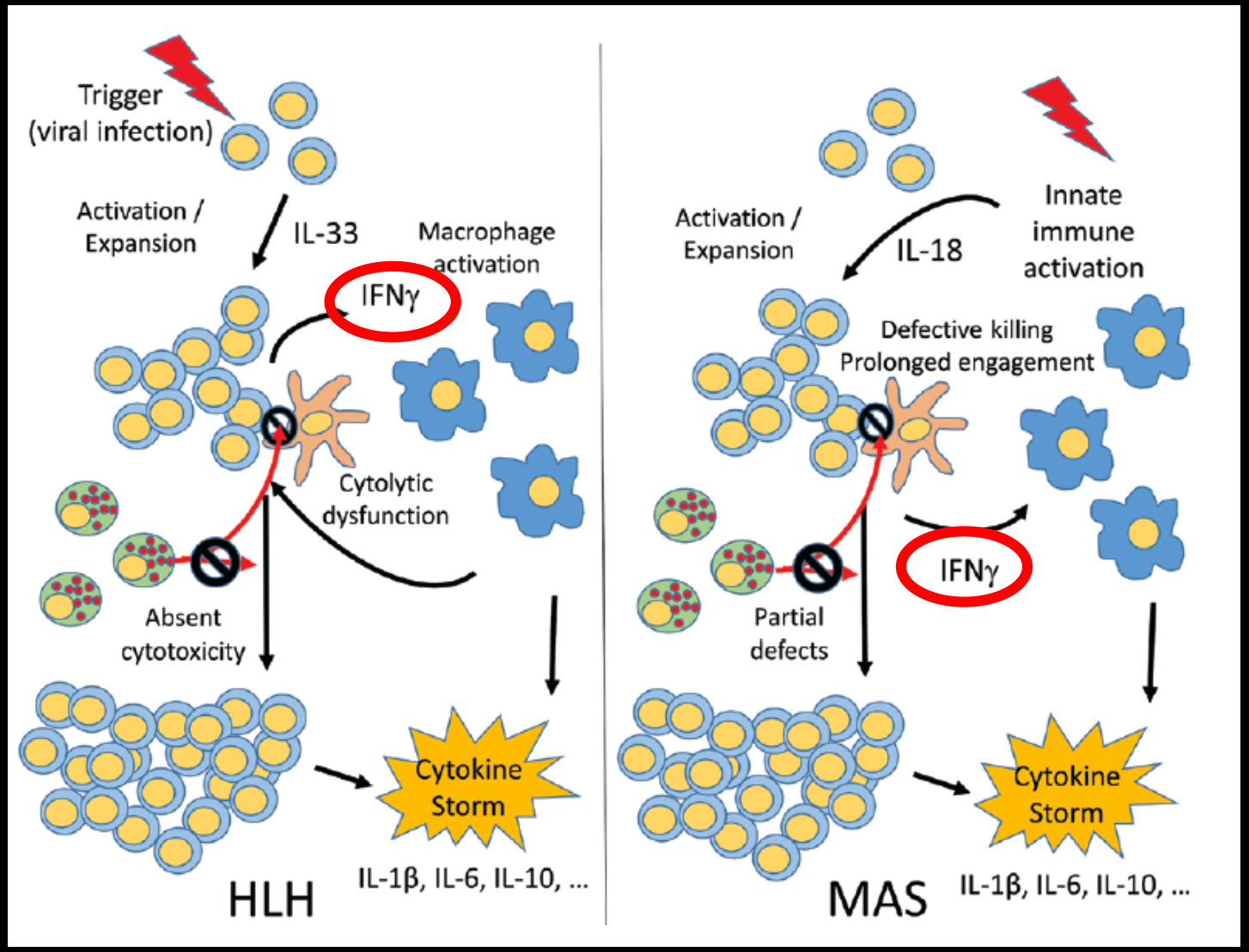
Anakinra: a mainstay in sHLH and MAS





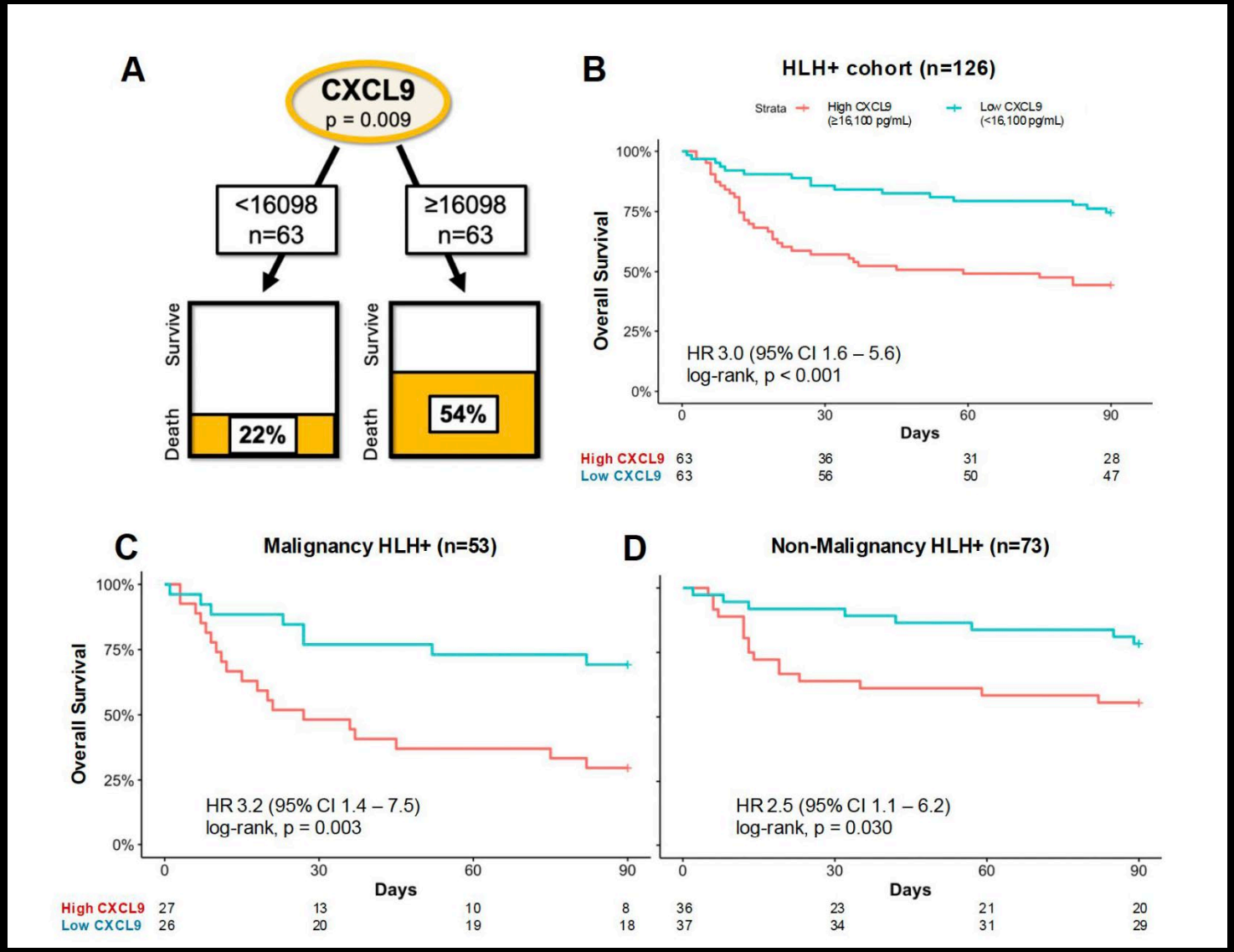
Lee, Eur J Hematol 2023
Charlesworth, Eur J Hematol 2023

Blocking **conserved terminal effectors: IFN-γ**



Canna et al, Int Immunol 2018

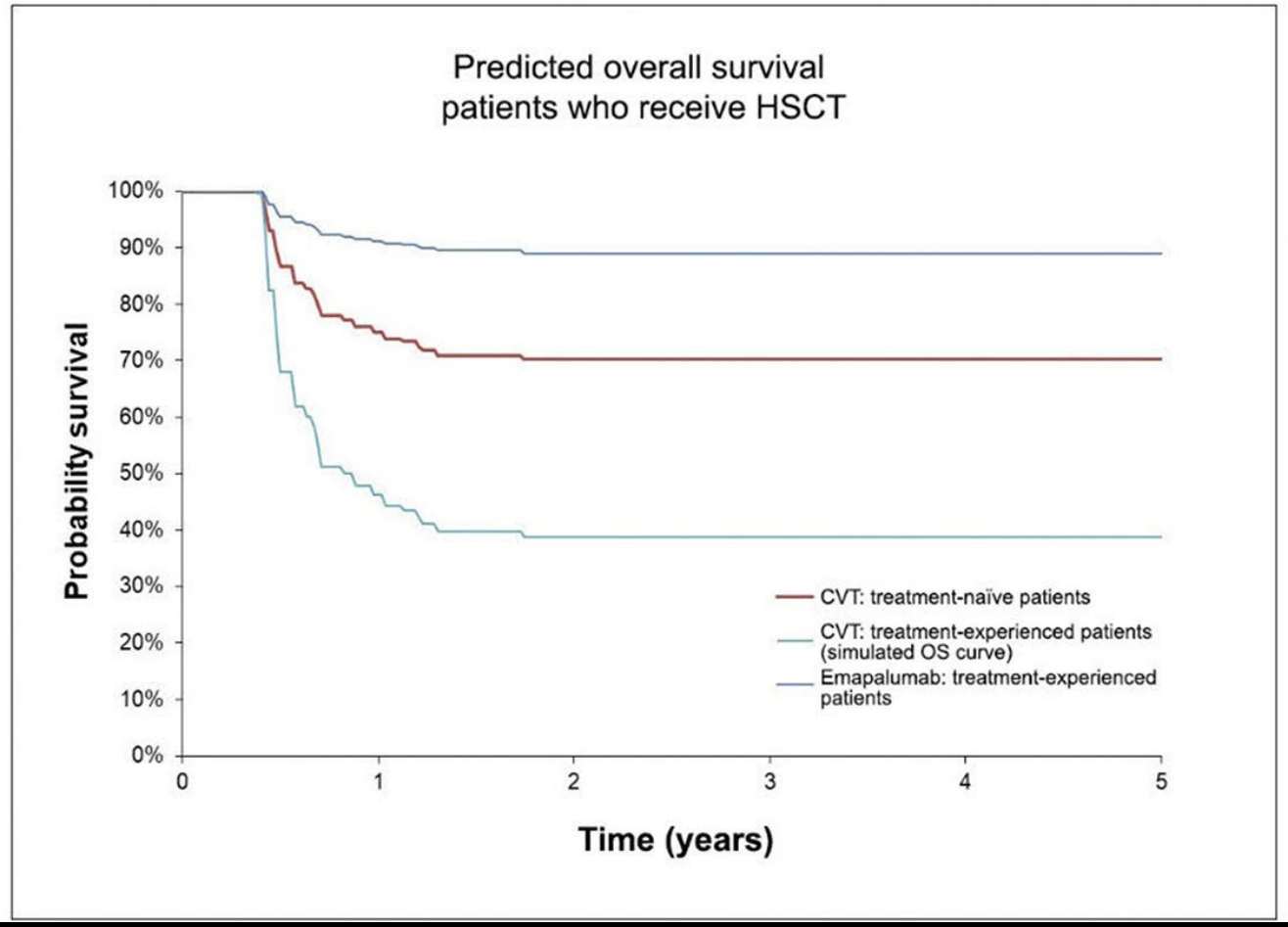
IFN-γ and CXCL9: important mortality markers!



Rocco et al, Blood 2026

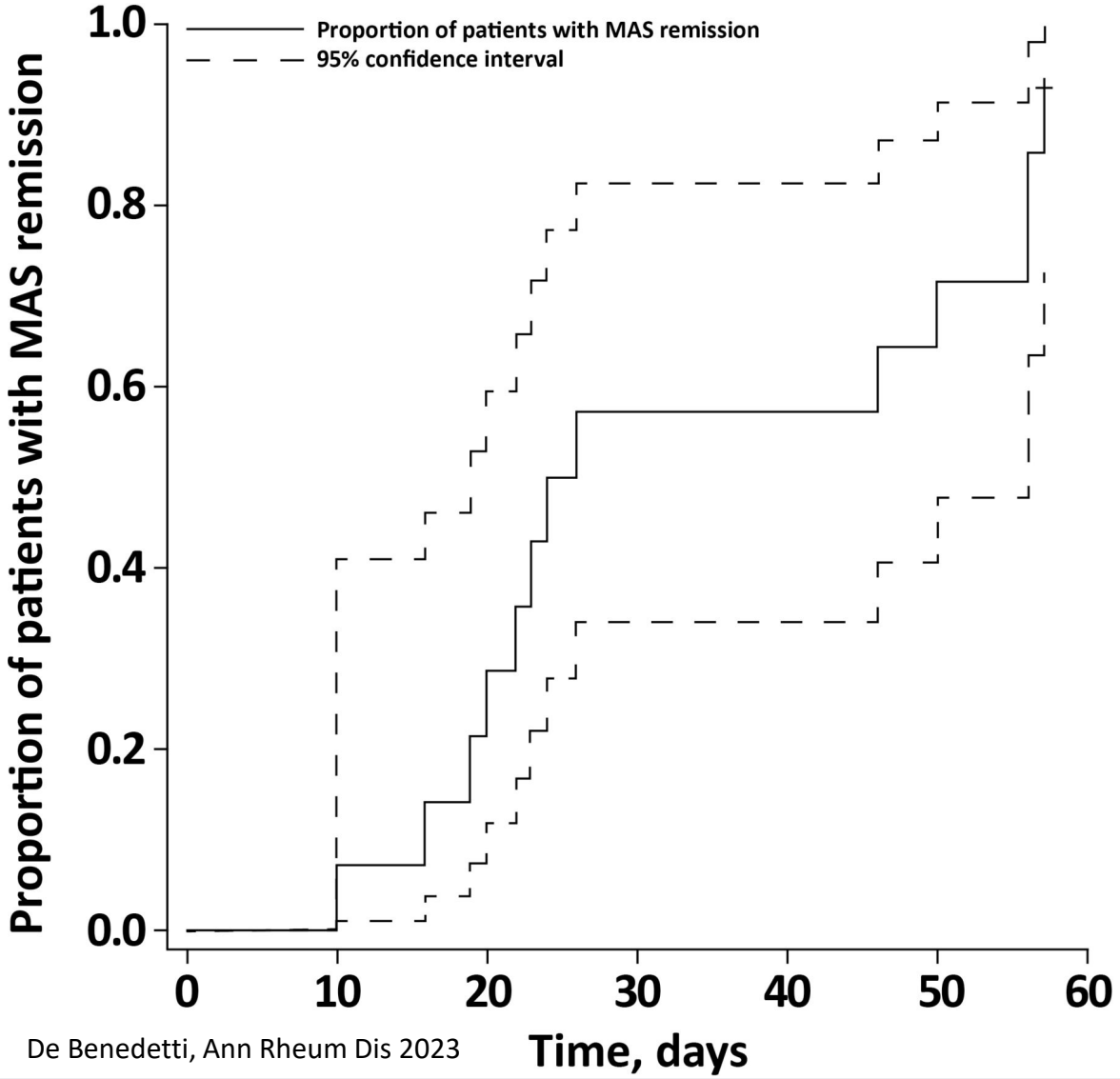
Emapalumab: a new first-line drug for pHLH

Figure 2. Overall survival: emapalumab versus conventional treatment (CVT) in hematopoietic stem cell transplantation patients (adjusted analysis of emapalumab and CVT treatment-experienced patients)

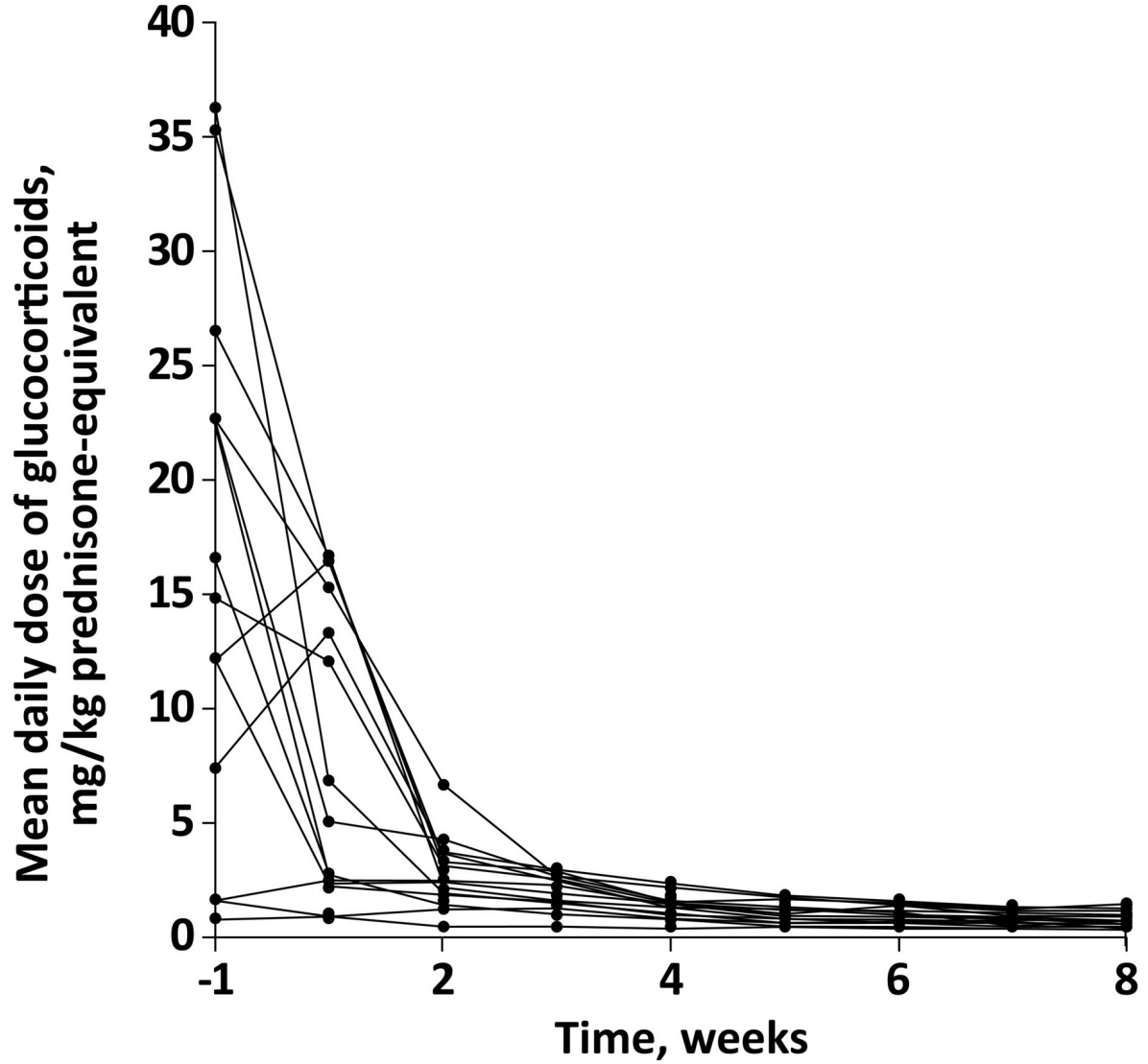


Dewilde, Blood 2020

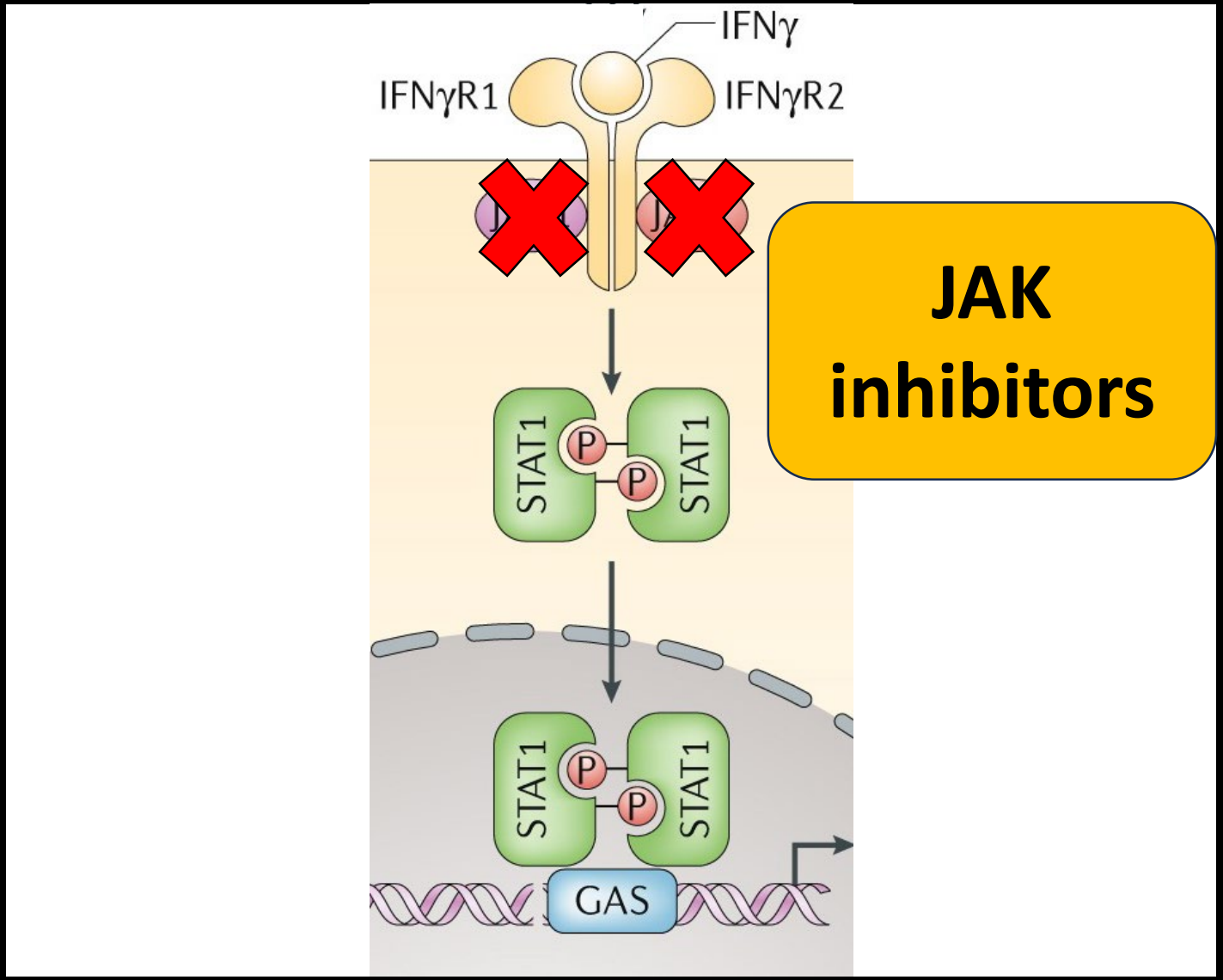
Emapalumab is also effective for MAS



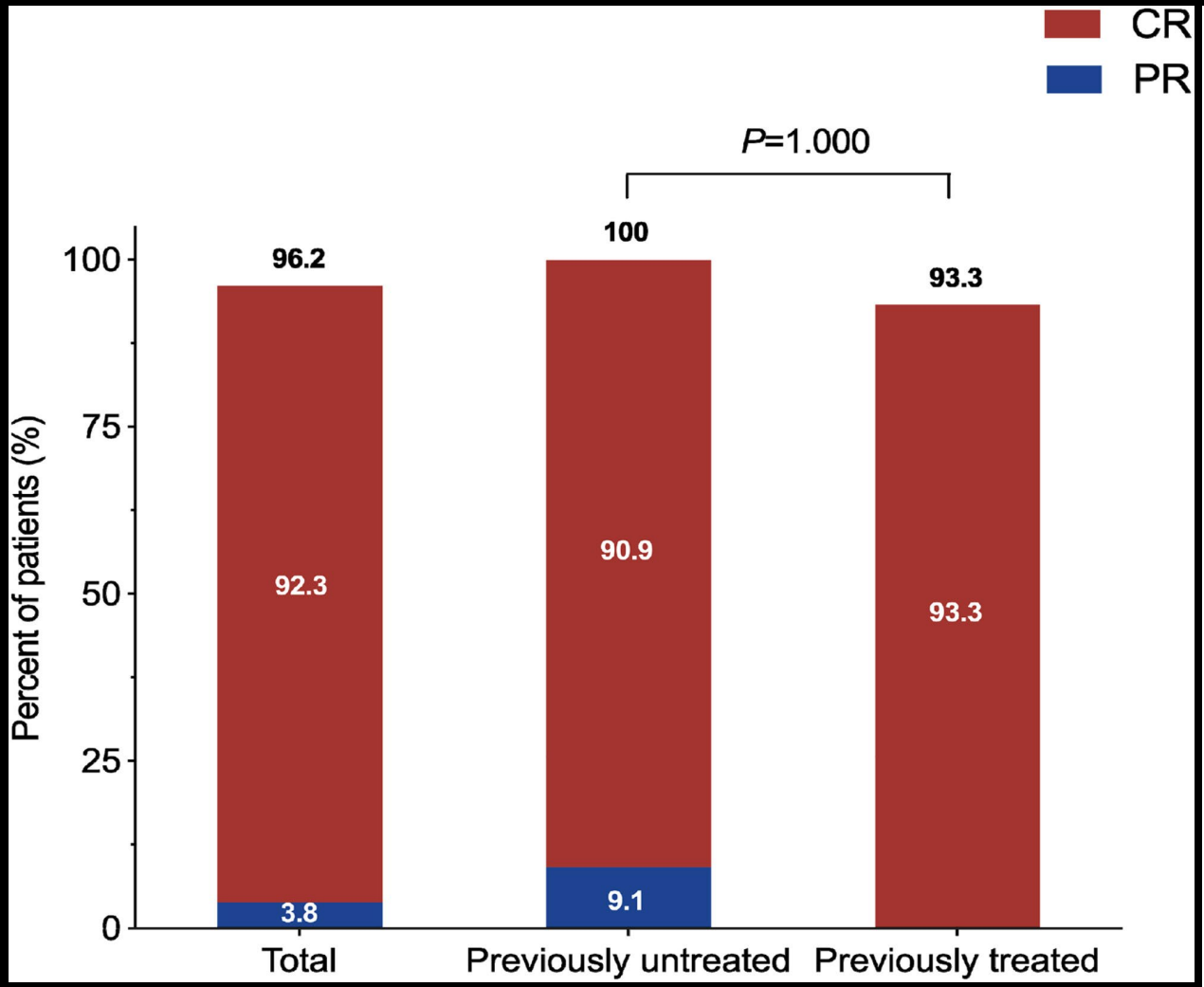
De Benedetti, Ann Rheum Dis 2023

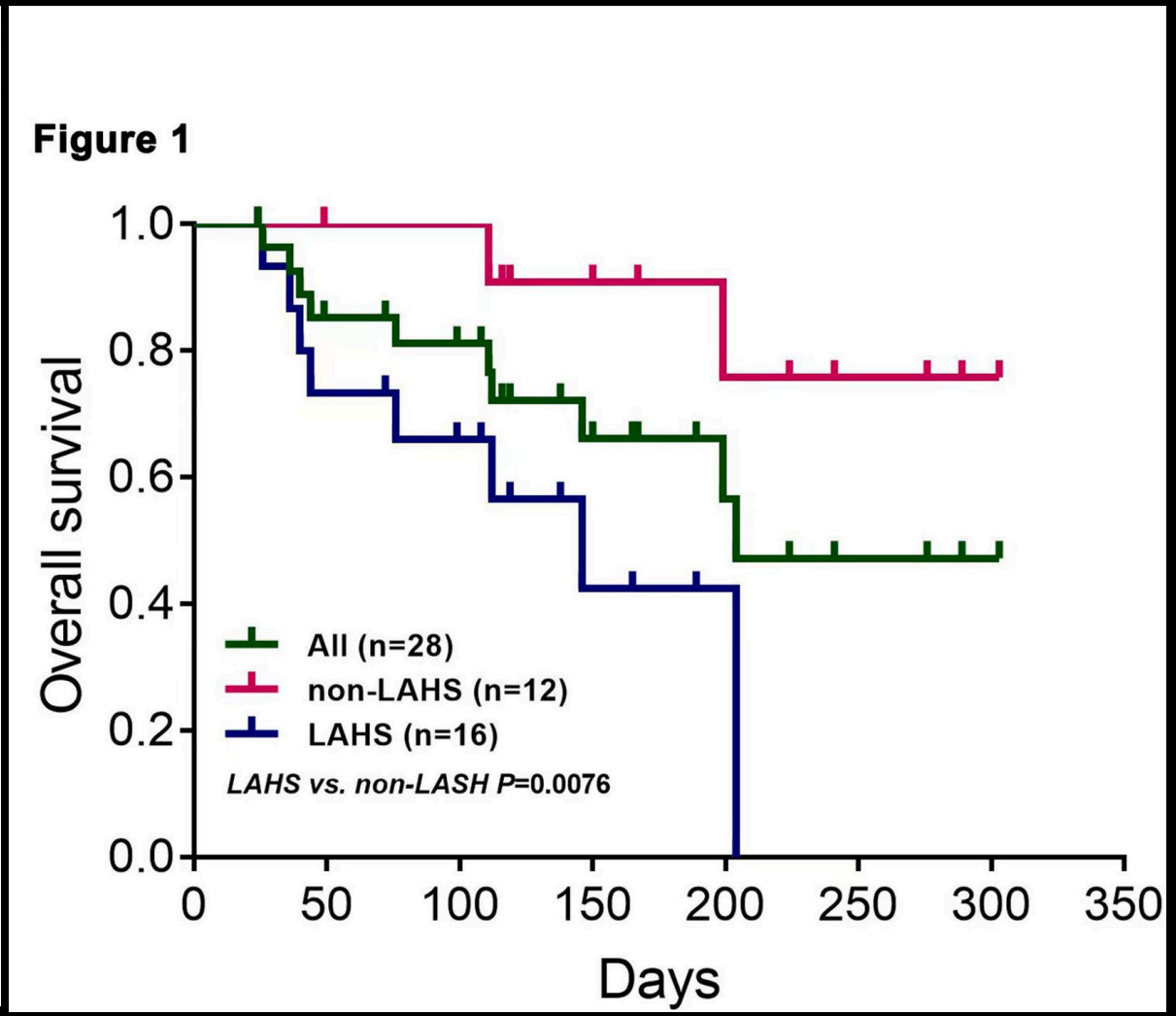


JAK inhibitors indirectly block IFN-γ



Ruxolitinib: another emerging therapy for sHLH





De Zhou, Blood 2022
Fang, Br J Hem 2024

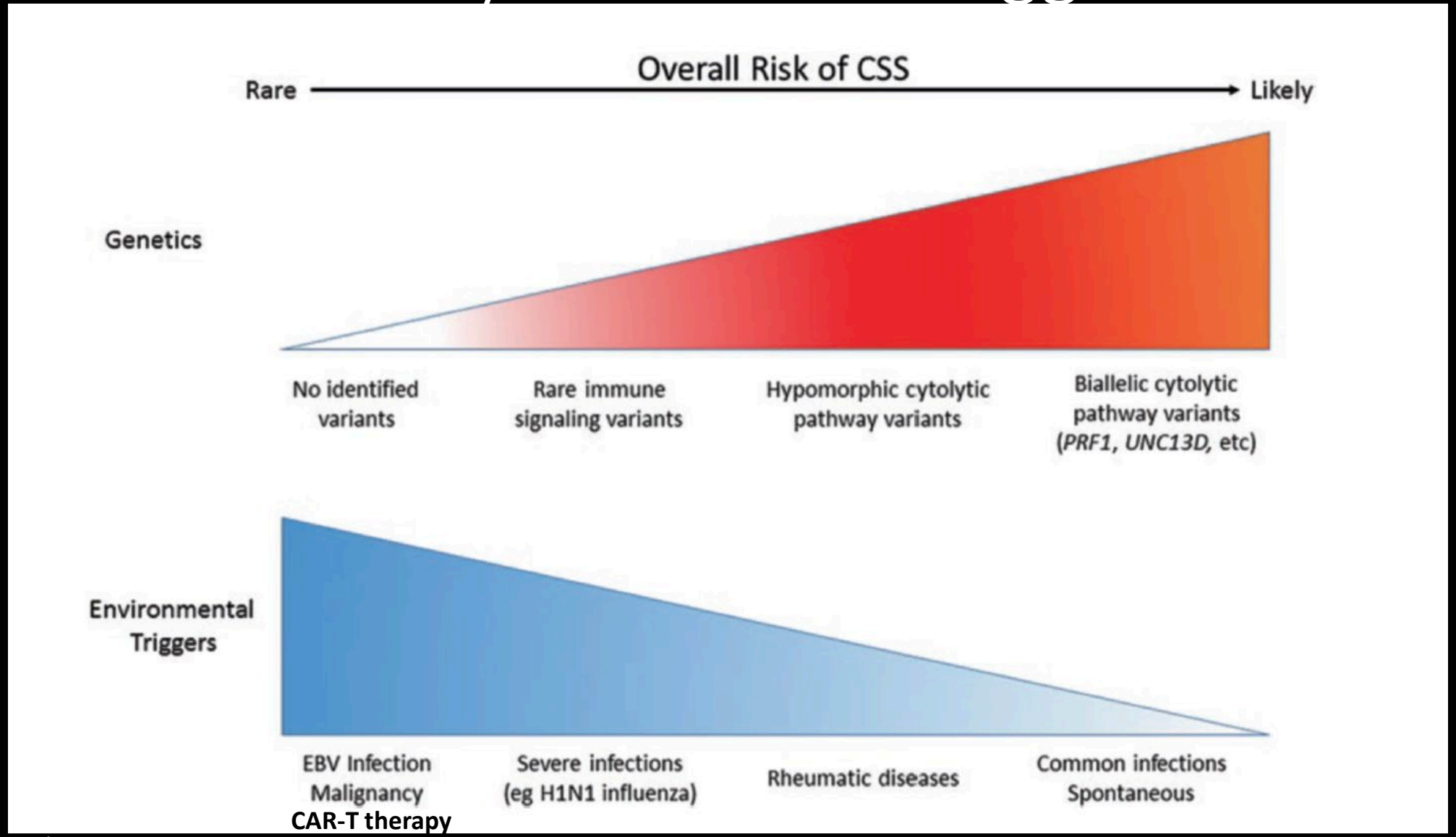
Case 3: using biomarkers to guide diagnosis

- March 2024 referral to UPMC (outpatient clinic)
  - **CXCL9: 28,594** (ref <647), **IL-18: 747** (ref <477), **sIL2R: 2,885** (ref <1891)
  - Diagnosis: HLH/MAS
  - Anakinra → partial response
- March 2024-July 2024
  - Dose escalate anakinra → partial response
  - Unable to taper below prednisone 10-15mg daily
  - Symptoms now starting to **worsen**

Back to the key questions: Case 3

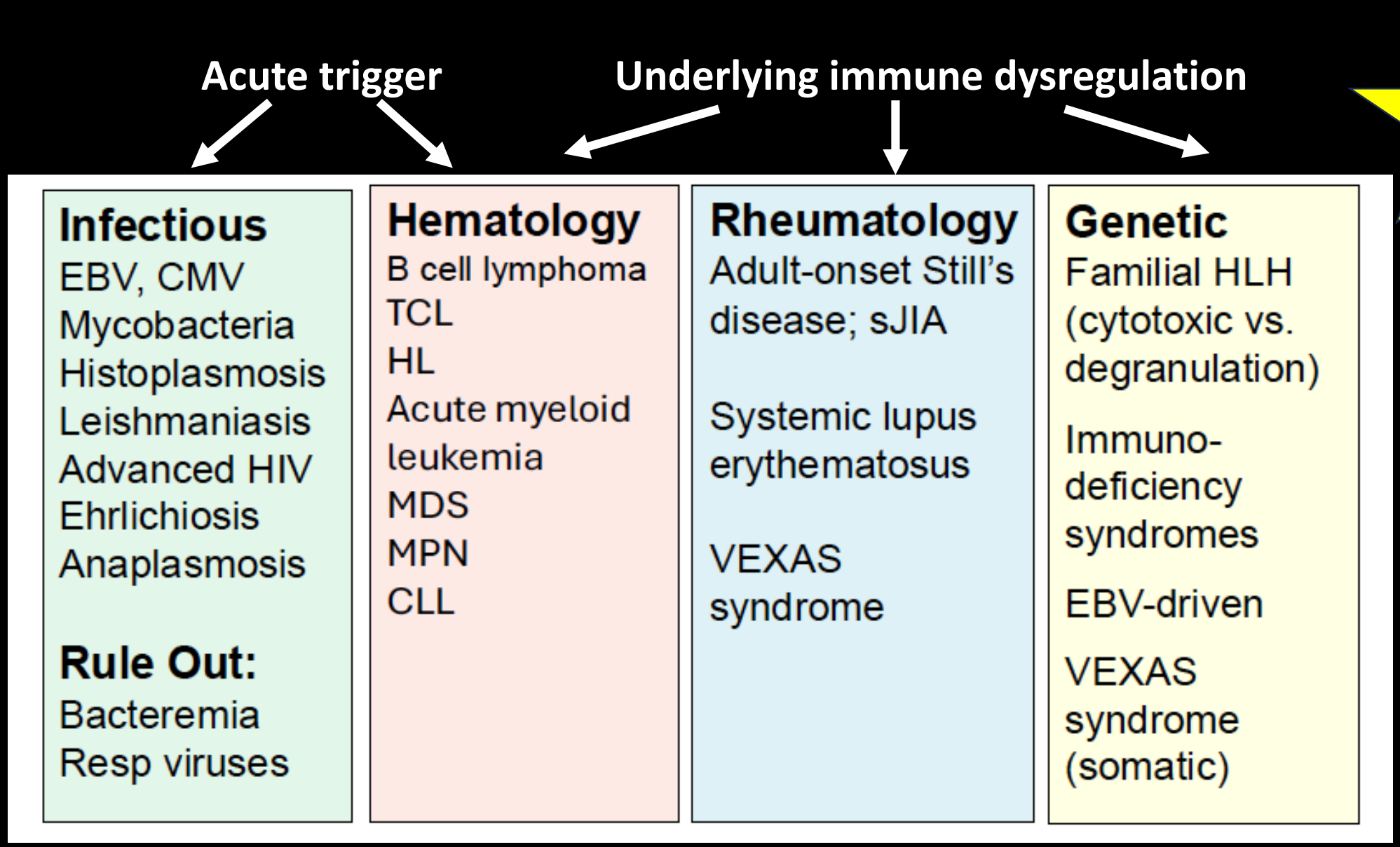
- *What are the red flags for HLH/MAS?*
- How to work up HLH/MAS?
- How to treat HLH/MAS?
  - **Does it depend on the underlying cause?**

HLH-MAS has many causes and triggers



Canna et al, Int Immunol 2018
Jordan et al, Pediatr Blood Cancer 2019
Schulert, Zhang, in *Cytokine Storm Syndrome* 2024

Calming the hyperinflammation ≠ source control



Zoref Lorenz, Jordan, Rocco, Schwartz. Hematol Oncol Clin North Am, 2025

The ID workup of HLH is based on genetic and environmental risk

First Pass:

EBV, CMV (including PCR)
→Mycobacteria (TB), Histoplasmosis
If in an endemic area:
→Leishmaniasis, Ehrlichiosis, Anaplasmosis

Screen for common triggers:
→Bacteremia, Candidemia
Respiratory viruses (Flu, COVID, etc.)

Risk Factor based Assessment

Immunosuppressed (Heme malignancy, Transplant, etc.)
→Adenovirus, Parvovirus-B19, VZV
→Toxoplasmosis
→Screen for Hepatitis viruses

Advanced HIV (CD4 <200)
→Mycobacteria (TB/NTM), Histoplasmosis
→EBV-lymphoma, KSHV-related syndrome
→Rare: Cryptococcus, Toxoplasmosis, Bartonella, Salmonella

If Epidemiologic Exposure:
→Malaria, Babesiosis, Leishmaniasis
→Hemorrhagic fevers (ie. Dengue)
→Other Rickettsia, Leptospirosis

Rare Etiologies

Appropriate Syndrome + Possible Exposure
→Coccidioidomycosis, Blastomycosis
→Talaromycosis, Melioidosis
→Brucellosis, Q fever
→Heartland/Bourbon virus

PID + Pathogen Associations
→SCID – Viruses (Adeno, Parvo, VZV, etc.)
→CGD – Burkholderia infections
→Gata-2 or IL12R Deficiency – Mycobacteria

Zoref Lorenz, Jordan, Rocco, Schwartz. Hematol Oncol Clin North Am, 2025

Outcomes: case 3 HLH “triggers” workup

- EBV, CMV, HGE/HGA, flu/COVID checked 3/24 → negative
- PET-CT with PET-avid lung and vertebral lesions
- Bronchoscopy with budding yeast
  - Histo, Blasto, Aspergillus negative
  - **Cryptococcal antigen 1:16, BAL culture positive for Cryptococcus**
- Fluconazole initiated 11/2024
  - Rapid resolution of symptoms
  - Tapered off prednisone successfully to 3mg daily
- Viral-triggered flare 3/2025
  - Re-initiated high dose steroids, started ruxolitinib 10 mg BID
  - Tapered off prednisone successfully to 3mg daily

Take home points – case 3

- **HLH is a continuum** of IL-1/IFN-γ driven hyperinflammation
  - Do not over-rely on criteria
  - **Use biomarkers** to characterize the cytokine storm and aid workup
- HLH usually involves a **chronic underlying disease** and an **acute trigger**
  - Rheumatology/immunology workup may not be enough
- Infectious triggers may be **disease-specific**
  - Inborn and somatic disorders
  - Acquired/iatrogenic disorders
- The cytokine storm **may recur** with new infectious triggers

Case 4: 64 yo M with “hyperinflammatory syndrome"

- Age 63: gradual decline
  - Fatigue, exertional dyspnea, night sweats (Tmax 100)
  - Myalgia, arthralgia
  - Microcytic anemia, thrombocytosis, high ESR/CRP
  - Presumed PMR vs. GCA → temporal artery biopsy negative
  - Steroids ineffective (IV dex) and caused anxiety
  - Bone marrow biopsy: 7-8% plasma cells, MGUS

Case 4: 64 yo M with “hyperinflammatory syndrome"

- WBC 6.7, ANC 4400, ALC 1400, **Hgb 7, MCV 65.3, plt 906**
- **ESR > 130**, **CRP 207.9 mg/L**, ferritin 264, C3 191, C4 39
- **IgG 4,427** (751-1560) , **IgM 27** (40-274), **IgA 517** (82-453)
- **Albumin 2.3**

Key questions: Case 4

- What are the **red flags** for non-HLH cytokine storm syndromes?
  - Especially if the ferritin is normal?

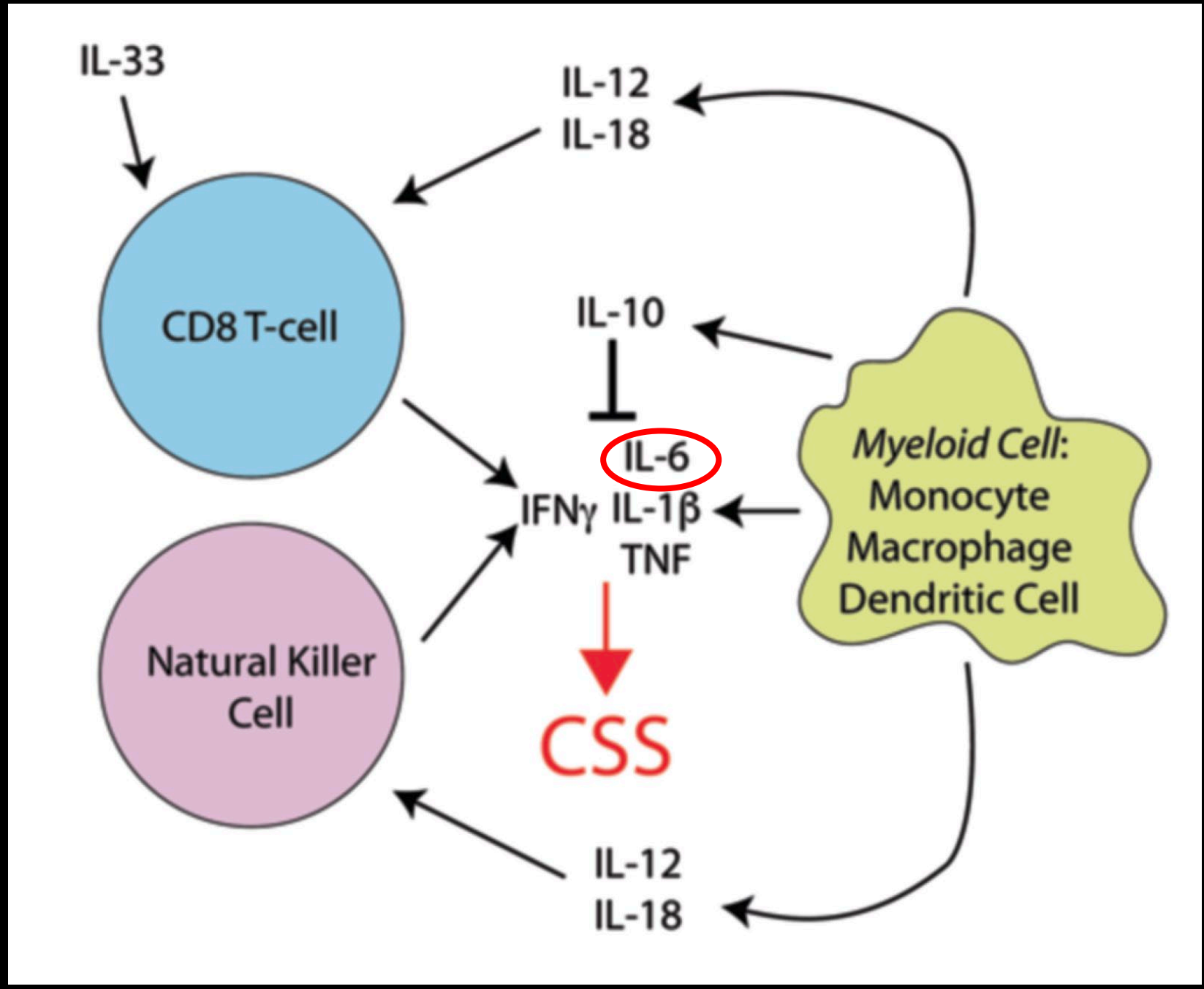
- How to work up hyperinflammatory disease in the elderly?
  - What are the immune drivers?
  - What is the underlying cause?

Case 4: 64 yo M with “hyperinflammatory syndrome"

- WBC 6.7, ANC 4400, ALC 1400, **Hgb 7, MCV 65.3, plt 906**
- **ESR > 130**, **CRP 207.9 mg/L**, **ferritin 264**, C3 191, C4 39
- **IgG 4,427** (751-1560) , **IgM 27** (40-274), **IgA 517** (82-453)
- **Albumin 2.3**

Immunologic drivers of cytokine storm:

IL-6 is directly upstream of CRP



Behrens, Cron, *Cytokine Storm Syndrome* 2024

Case 4: 64 yo M with “hyperinflammatory syndrome"

- Back to labs – any clues?
  - WBC 6.7, ANC 4400, ALC 1400, **Hgb 7, MCV 65.3, plt 906**
  - **ESR > 130**, **CRP 207.9 mg/L**, ferritin 264, C3 191, C4 39
  - **IgG 4,427** (751-1560) , **IgM 27** (40-274), IgA 517 (82-453)
  - **Albumin 2.3**

- **IL-6 240 pg/mL** (ref <5 pg/mL)

Hyper IL-6 syndromes

- Viral CRS
  - COVID-19
  - Herpesviruses (CMV, HHV8)
- Chemotherapy-related CRS
  - Tumor immunotherapy
  - CAR T cell therapy
  - T cell activating therapy
- Rheumatologic diseases
  - AOSD
  - VEXAS
  - (some GCA)
- Hematologic Diseases
  - Castleman disease

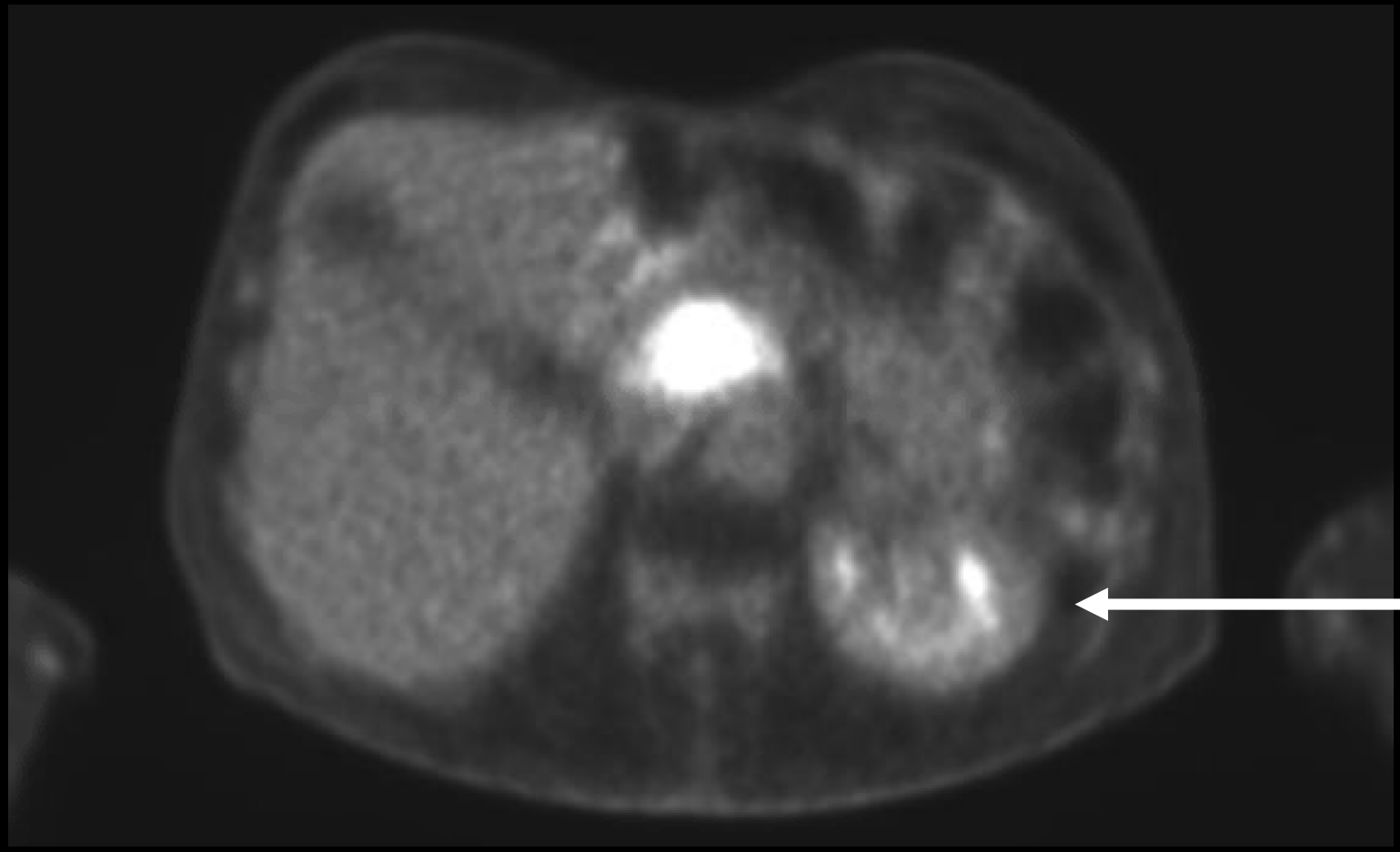
Case 4: 64 yo M with “hyperinflammatory syndrome"

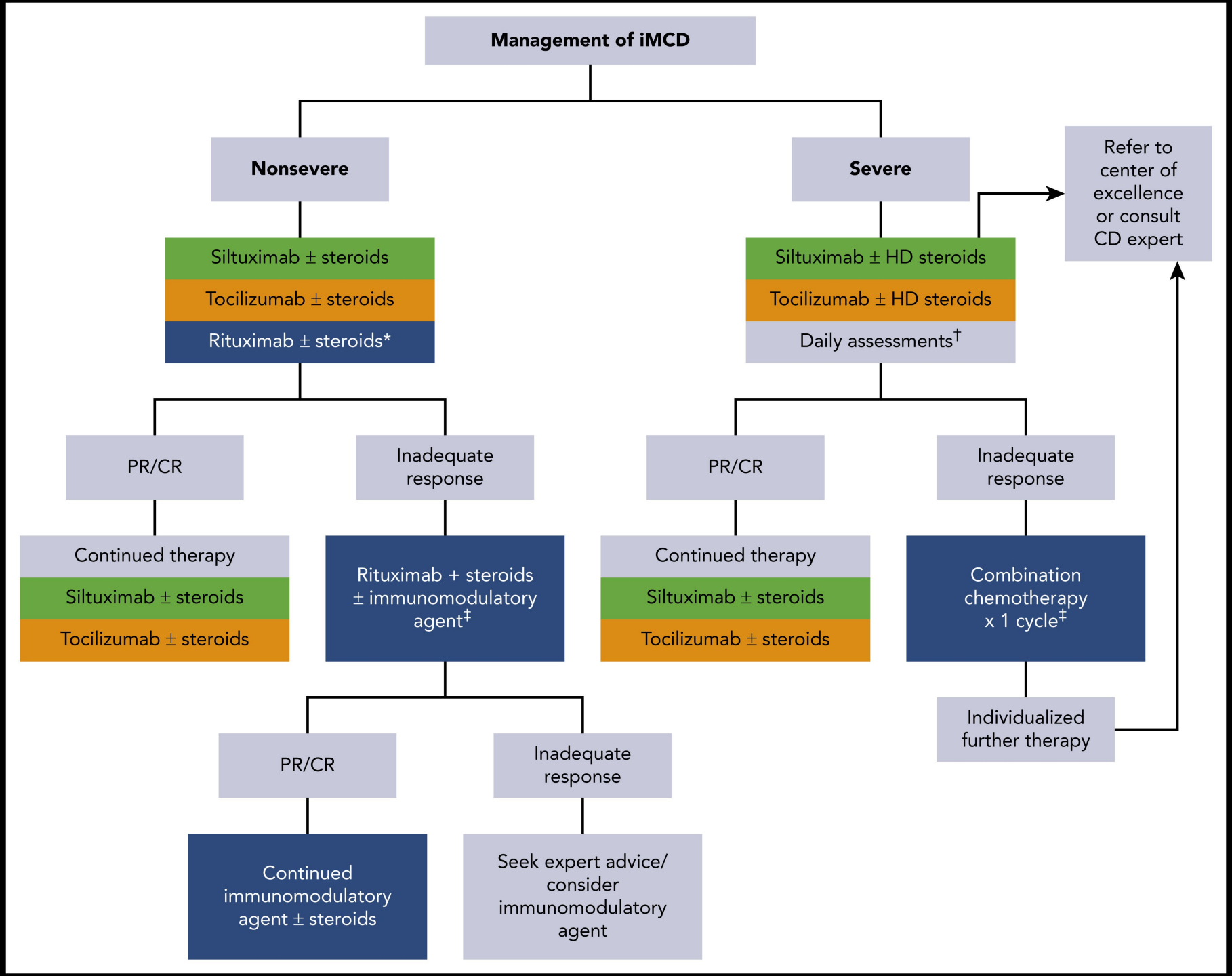
- Negative
  - HIV, HBV, HCV, HGA, HE, syphilis, lyme serologies
  - HIV, EBV, CMV PCR
  - QFN (indeterminate, no response to mitogen)
  - RF, CCP, ANA (1:40), ENA
  - Whipple disease testing (tissue based)
  - SPEP, UPEP, IFE
  - CT C/A/P
  - Temporal artery biopsy (B/L)
  - Bone marrow biopsy
  - UBA1 testing (VEXAS)

Hyper IL-6 syndromes

- ~~Viral CRS~~
  - ~~COVID-19~~
  - ~~Herpesviruses (CMV, HHV8)~~
- ~~Chemotherapy-related CRS~~
  - ~~Tumor immunotherapy~~
  - ~~CAR T cell therapy~~
  - ~~T cell activating therapy~~
- Rheumatologic diseases
  - AOSD
  - ~~VEXAS~~
  - ~~(some GCA)~~
- Hematologic Diseases
  - Castleman disease

Case 4: FDG PET-CT should be considered early if standard workup is negative





Van Rhee, Blood 2018

Outcomes: Case 4

- Diagnosed with probable unicentric CD
- Started **IL-6 blockade** (siltuximab) 11/24 → **rapid improvement**
- Unable to get lymph node excised at UPMC (**curative!**)
  - Referral to UPenn ongoing
  - Re-image pancreas/node

Take home points – case 4

- Persistent hyperinflammatory syndromes **should be worked up as FUO/cytokine storm**
  - Even if there is no fever, it's still innate immune activation
- **Using biomarkers** to a characterize a cytokine storm can narrow ddx
  - IL-6/IL-10/IL-8 vs. IL-1/IL-18/IFNγ
- **FDG-PET-CT** should be considered relatively early
  - Insurance approval generally available after pan-CT and bloodwork negative
- If something doesn't fit, it often pays to **dig deeper**
  - FDG-PET-CT
  - Lymph node biopsy
  - Bone marrow biopsy
  - Somatic variant testing including UBA1 (CCUS)

Summary and take home points

- Autoinflammation **is not autoimmunity**
  - Totally different clinical picture, biomarkers, and management
- Autoinflammation and IEI are **more common than you think**
  - But need better recognition and more resources
- Cytokine storm syndromes are high-mortality yet treatable
  - Like septic shock, they are **syndromes and not end-diagnoses**
- Cytokine storm has multiple (sometimes overlapping) immunologic subtypes with **biomarkers and targeted therapies**

Acknowledgements and Questions

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Daniel Barnett

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Jeffrey Modell Foundation

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NIH National Human Genome Research Institute

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