Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Benign White Cell Disorders

Comprehensive Hematology & Oncology Review

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Disclosures

I have no disclosures or conflicts of interest

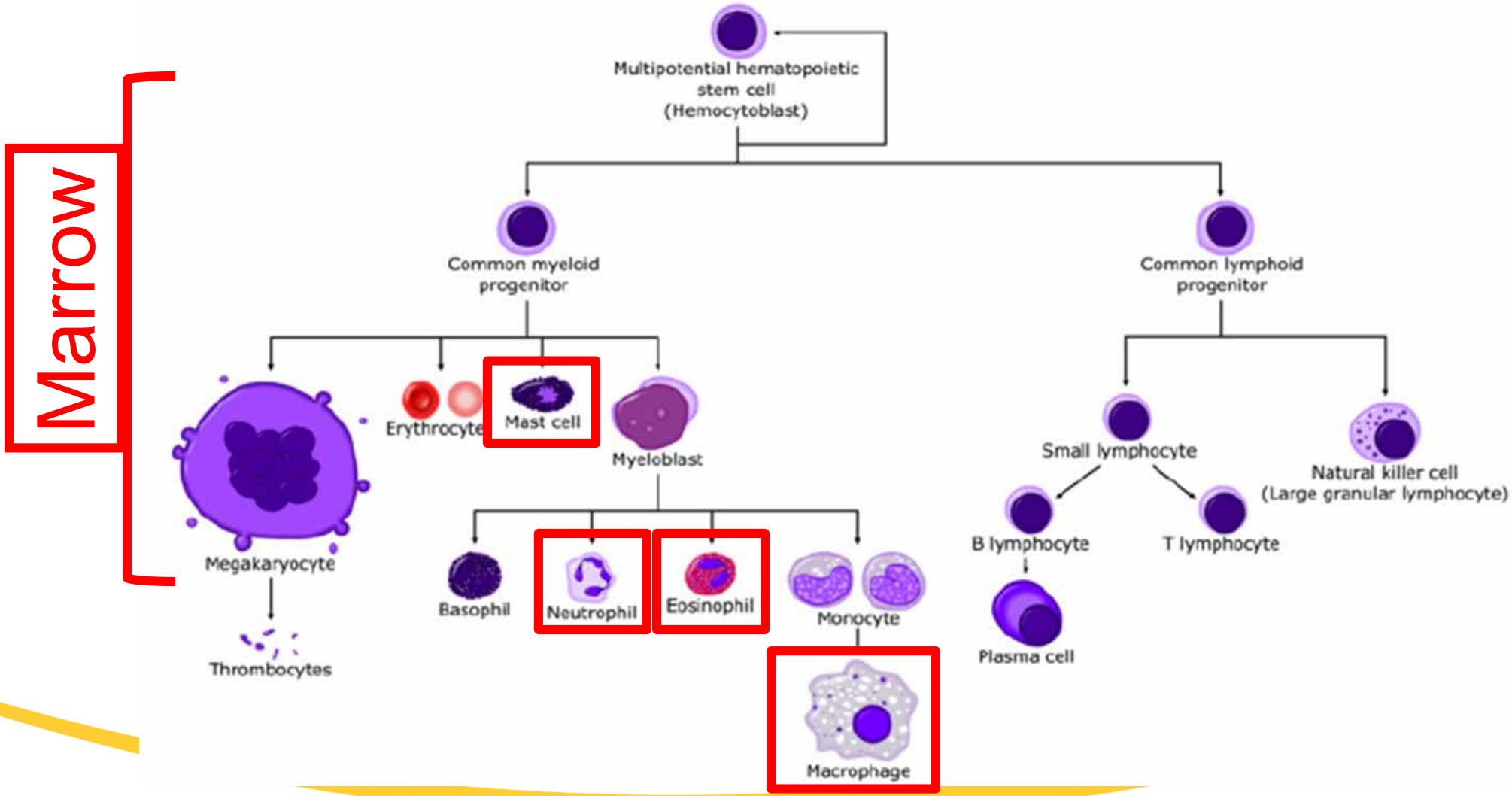
Objectives

- Diagnose and manage congenital and acquired neutropenias and non-clonal neutrophilia
- Recognize the causes, evaluation and treatment of disorders involving eosinophils and mast cells
- Understand the pathobiology and management of HLH and macrophage activation syndromes

Peripheral Blood Leukocyte Counts

	Range (#/mcL)	Differential (%)
Total WBC	**4,300 - 10,000**	
Neutrophils	1,800 - 7,000	42 - 70
Neutrophilic Bands	0 - 200	< 2
Monocytes	0 - 800	0 - 8
Lymphs (T, B, NK)	1,000 - 4,800	10 - 40
Eosinophils	0 - 500	0 - 5
Basophils	0 - 200	0 - 2

Hematopoiesis: Normal Blood & Immune Cells



Clinical Case 1: Neutropenia

- 40 yo woman presents with fever, leg sores & flank pain; she was seen 8 days ago for an uncomplicated UTI
- **PMH:** Bipolar affective disorder; illicit substance and alcohol abuse; possible rheumatoid arthritis
- **Medications:** Ciprofloxacin (day 8), lithium, aspirin, risperidone (day 20) for recent acute manic event
- **Exam:** Temp 40.5° C, BP 88/44, Pulse 110. Oriented but lethargic. Nonsuppurative leg ulcers & inguinal adenopathy; left flank & general abdominal pain

Clinical Case 1: Diagnostic Studies

- **Lab Data**

Hemoglobin 12.8 gm/dL	MCV 92 fl
WBC 4,910 /mcL	Plt ct 395,000/mcL
Neutrophils 10 /mcL	Lymphs 3,700 /mcL
Monocytes 900 /mcL	Eosinophils 300 /mcL

- **Urinalysis:** Esterase (+); no WBC; 3+ RBC
  Gram stain: gram negative rods
- **Chest X-ray:** Clear
- **KUB:** No obstruction

Acquired Neutropenia

Disorders of Granulopoiesis

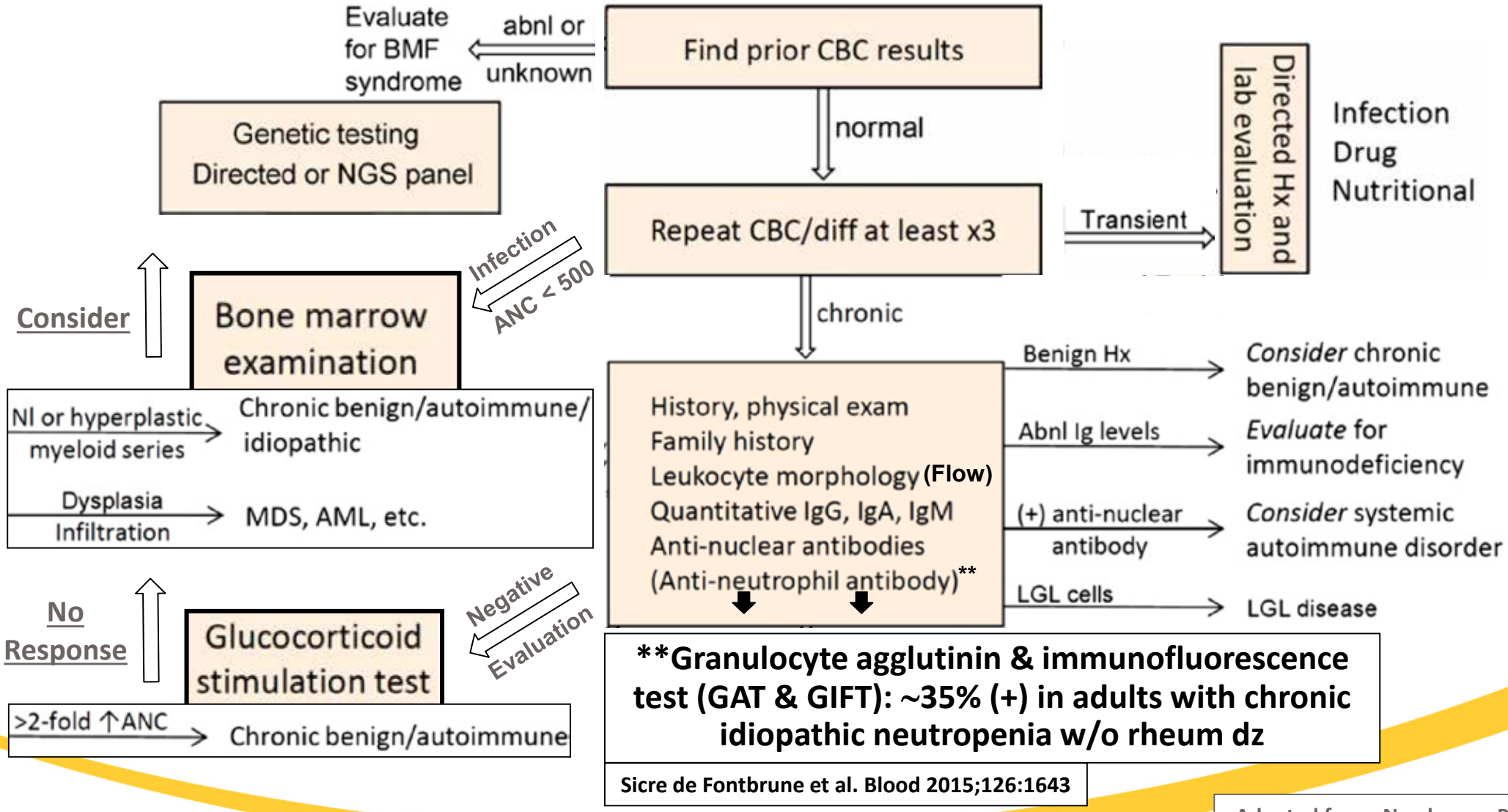
- Drugs (dose-dependent and idiosyncratic)
- Chronic idiopathic neutropenia
- Nutritional deficiency (B12, folate)
- Infections (HIV, CMV, EBV, parvovirus, others)
- 1º hematopoietic disorder (MDS, aplastic anemia)

Peripheral Destruction

- Immune / autoimmune (RA, SLE)
- Large granular lymphocytic (LGL) leukemia
- Infection (EBV, HIV, *H pylori*)
- Drugs (idiosyncratic immune-mediated)

Splenic Sequestration

Diagnostic Approach to Neutropenia

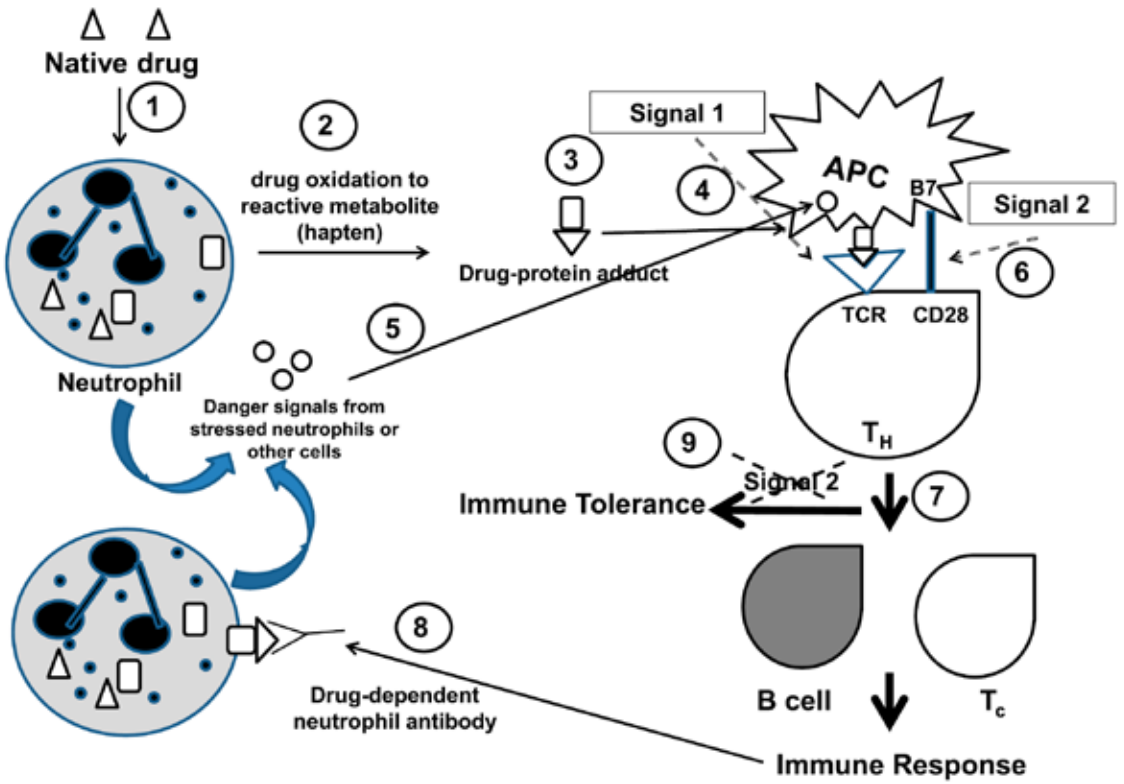


****Granulocyte agglutinin & immunofluorescence test (GAT & GIFT): ~35% (+) in adults with chronic idiopathic neutropenia w/o rheum dz**

Sicre de Fontbrune et al. Blood 2015;126:1643

Adapted from: Newburger P. Hematology Am Soc Hematol Educ Program **2016;38**

Idiosyncratic Drug-Induced Neutropenia



Curtis BR Hematology Am Soc Hematol Educ Program 2017(1):187

Table 2. Drugs most frequently reported to cause IDIN

Huber et al[7]	Medrano-Casique et al[5]
Carbamazepine†	Benzylpenicillin†
Clozapine†	Cefipime†
Metamizole (dipyrone)†	Linezolid
Sulfasalazine†	Meropenem†
Thiamazole†	Metronidazole
	Piperacillin-tazobactam†
	Teicoplanin
	Tobramycin
	Torsemide
	Vancomycin†

Andrés et al[9]	Curtis*
Amoxicillin†	Cefipime
Carbimazole†	Ceftriaxone‡
Clozapine†	Ciprofloxacin‡
Cotrimoxazole†	Clindamycin
Cefotaxime	Ibuprofen
Noramidopyrine	Levetiracetam
Piperacillin-tazobactam	Piperacillin-tazobactam‡
Salazopyrine	Quetiapine
Ticlopidine†	Sulfamethoxazole/trimethoprim‡
Valganciclovir	Tacrolimus
	Vancomycin‡
	Venlafaxine

†Five most frequently associated drugs. ‡Five most suspected drugs.

Management of Drug-Induced Neutropenia

- Withdraw all nonessential drugs, herbals, OTC meds
- **Expect ANC recovery within 1-2 wk of drug removal;** slower for ANC <100/mcL, sepsis, severe infection
- Broad-spectrum antibiotics as indicated for fever and infection or prophylaxis (case-by-case basis)
- **Marrow Biopsy: If abnormal RBC/plts or delayed recovery**
- **G-CSF:** Beneficial for ANC < 100/mcL (even w/o infection); consider with ANC < 500/mcL in elderly ± infection, severe comorbidity, sepsis

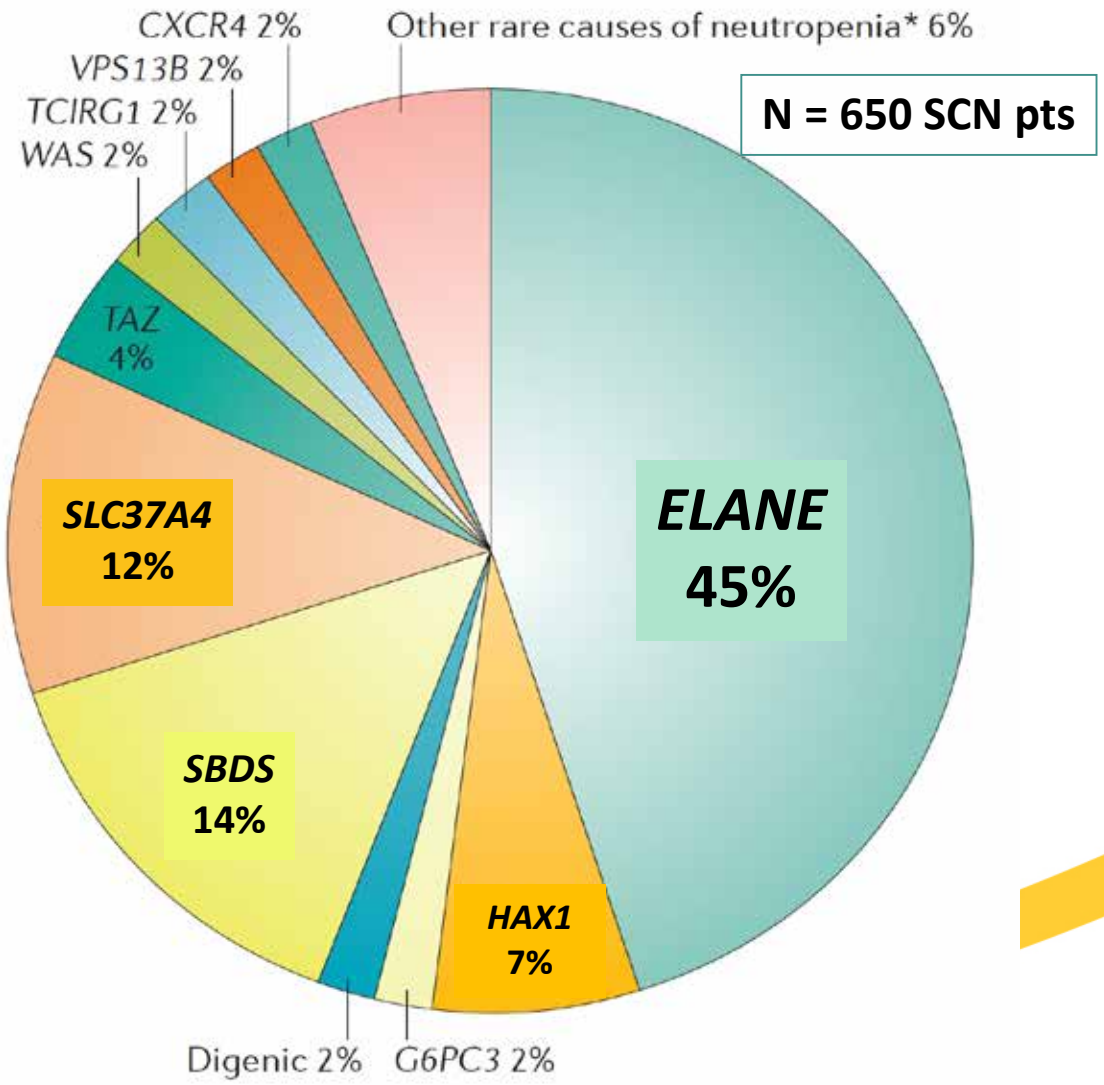
Autoimmune Neutropenia

- RA, SLE, Sjögren's; some drugs (PTU, rituximab)
- **Felty syndrome:** RA (usually severe), splenomegaly (90%) & neutropenia
  - Anti-G-CSF Ab (70%); ± ↑ oligoclonal CTLs (LGLs)
- **SLE-associated neutropenia (25-50% incidence)**
  - Anti-SSA/Ro; anti-SSB/La; TNF-related apoptosis
- **Therapy:** Glucocorticoids, methotrexate, cyclosporine, G-CSF* (low dose)

  ***Beware** → Sx flare, leukocytoclastic vasculitis, ↑spleen

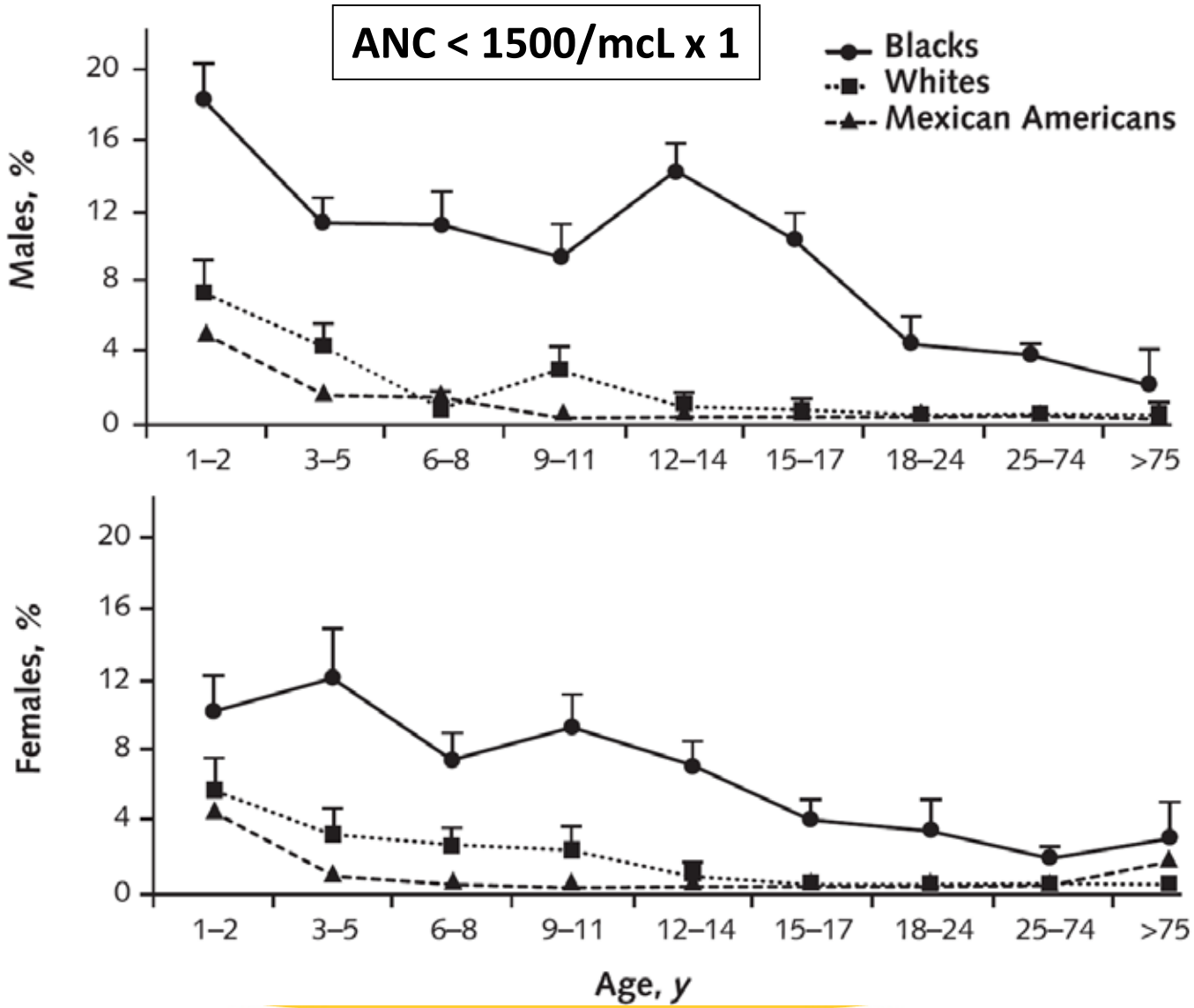
Congenital Neutropenia

- Severe congenital neutropenia (SCN)
- Cyclic neutropenia
- Multilineage disorders
  - Chediak-Higashi
  - Wiskott-Aldrich syndrome
  - Griscelli syndrome
- “Ethnic neutropenia”



Skokowa J et al. Nat Rev Dis Primers 2017;3:17032

Incidence of “Ethnic Neutropenia”



Hsieh MM et al.
Ann Intern Med
2007;146:486

Chronic Idiopathic Neutropenia

- **Dx of exclusion:** Chronic ANC < 500/mcL; **w/o 1° disorder/drug/infection**
- **Med age:** 25 yo (adult > child)
- **Prevalence:** 1.7%
- **Etiology:** Marrow suppressive T-cells/cytokines[1]
- **Treatment / Course: SCNIR Registry data[2,3]**
  - 54% w/o tx pre-entry to registry → most maintained on G-CSF
  - Med. G-CSF dose 1 mcg/kg/day
  - Infrequent ↓ plts, ↑ spleen, osteopenia (no MDS/AML)

- **Caucasian = 95%**
- **F:M = 2 : 1**
- **– "Remissions" = Rare**

[1] Exp Hematol 2008;36:293 [2]Am J Hematol 2003;72:82 [3]Dale D & Bolyard A. Curr Opin Hematol 2017;24:46

Clinical Case 2: Referral for Leukemia

- 28 yo Palestinian, 9 mo episodic abd pain (q4 wk); ED visits **w/ ↑ WBC**
- **Pain:** No triggers; acute; resolves in 12-36 hrs
- **ROS:** ± Fever; + sweats; 10 lb wt loss
- **PMH:** Orchitis
- **Meds:** Codeine, testosterone
- **FH:** Noncontributory (left Middle East 10 yrs ago)
- **PE:** Afebrile; nl BS, general tender, no organomegaly
- **Labs:** Hct 40%, **WBC 13,000/mcL**, **ANC 9,600/mcL;** plt ct 250,000/mcL; ESR 45; nl amylase / Cr; **U/A 3+ protein**
- **CT:** ± **Mesenteric LAD;** nl liver/spleen/kidneys

Non-Clonal Neutrophilia – Differential Dx

(Negative *BCR-ABL, JAK2 V617F, CALR, MPL, CSFR3*)

- **Secondary / Reactive / ↓ Sequestration**
  - Infection, inflammation (obesity, smoking)
  - Asplenia
  - Drugs (lithium, corticosteroids, G-CSF)
  - Tumor (G-CSF-secreting)
- **Constitutional:** Down syndrome w/leukemoid rxn's, transient MPD
- **Primary neutrophil disorders with 2^{o} neutrophilia**
  - Familial Mediterranean Fever: PMNs are auto-activated
  - Leukocyte adhesion deficiency: PMNs can't adhere/migrate
  - Chronic Granulomatous Disease: PMNs can't kill

Clinical Case 3: Eosinophilia

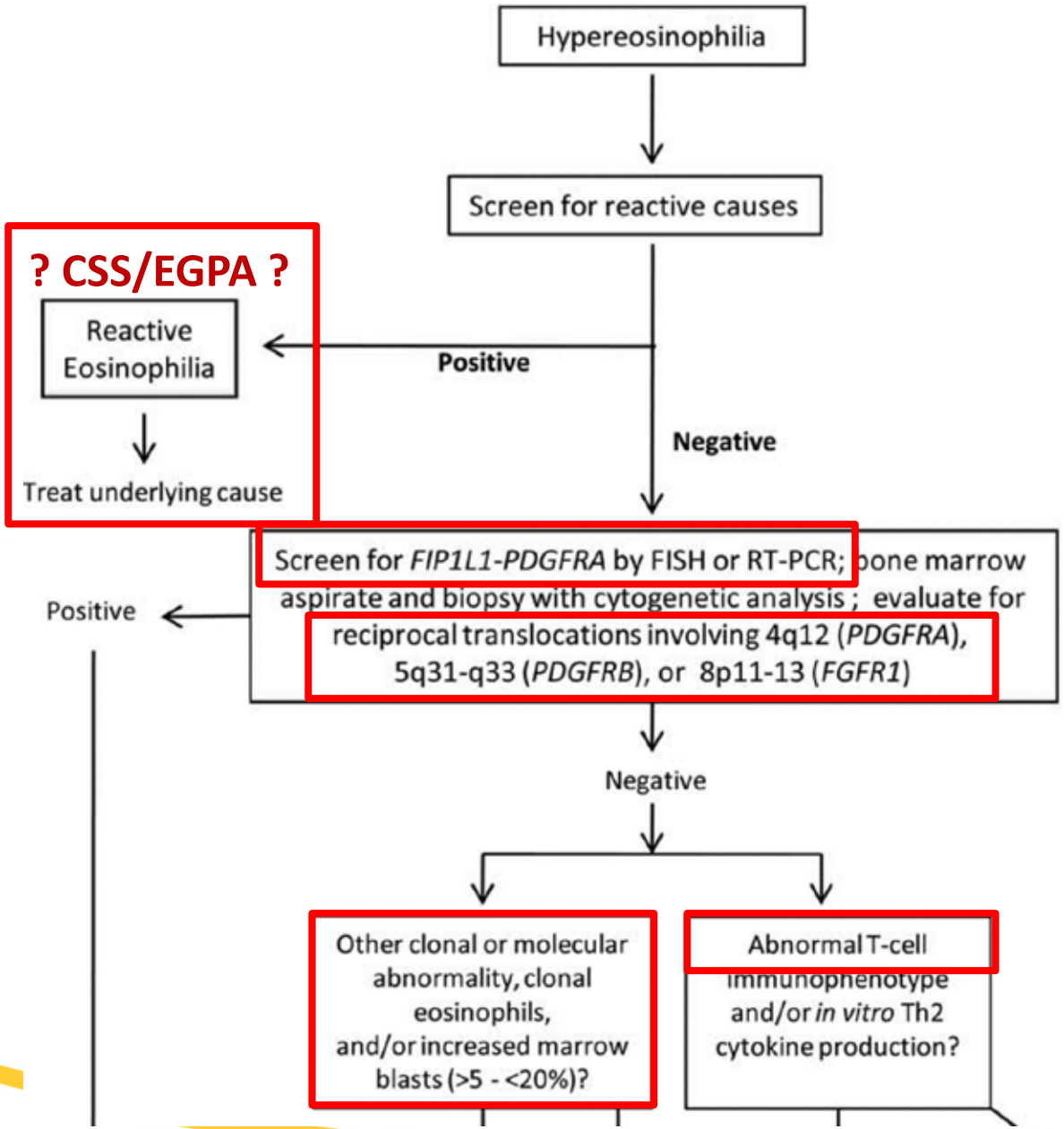
- 19 yo M admitted to outside hospital after cardiac arrest
- **PMH:** Aspergers / ADHD & asthma
- Admission Data from outside hospital
  - **Troponin 8.41**
  - **BNP 12,087**
  - Utox (+) for amphetamines (lisdexamfetamine)
  - **TTE – LVEF 15-20%,** severe concentric LVH & hypokineses, ballooning apex
  - IABP placed → transfer to UWMC

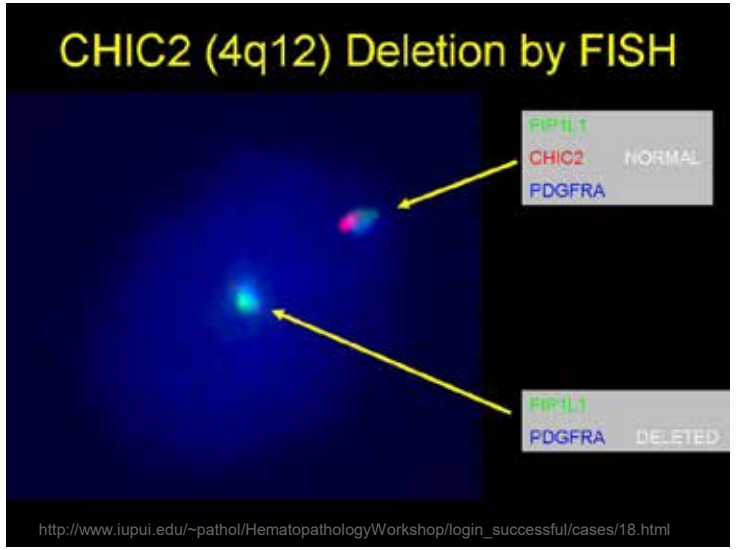
Clinical Case 3: Laboratory Data

	Day 1	Day 2	Day 3	1 Mo PTA
WBC	14.70	17.65	18.74	25
Hg	11.3	15.8	16.4	
HCT	31	43	46	
PLT	116	171	236	
% Neutrophils	36	43	42	
% Lymph	14	8	8	
% Monocytes	6	10	8	
% Eosinophils	44	38	40	69
%Basophils	0	1	1	
Abs. Eos	6.4	6.65	7.53	17.3

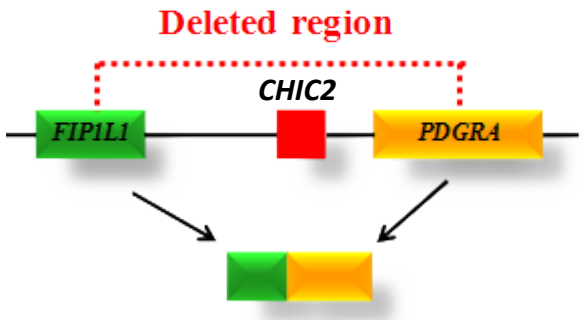
Hypereosinophilia

- **Eosinophil ct > 1,500/mcL for > 1 month, on ≥ 2 occasions**
  - **Or** > 1,500/mcL & life-threatening organ dysfunction
  - **Or** > 20% BM eos; extensive tissue eos + degranulation
- **Idiopathic Hypereosinophilic Syndrome (HES)**
  - Hypereosinophilia & evidence of end-organ involvement
  - Lack of evidence for other causes of hypereosinophilia
    - Neoplasm (MPN; LPD; carcinoma)
    - Drugs
    - Parasite (strongyloides, hookworm, scabies, filaria)
    - Addisons
    - Allergy (asthma, atopic dermatitis)
    - Collagen vascular disease (CSS/EGPA, IBD, sarcoidosis)
    - Other (chronic TB, HIV, cocciodiomycosis)

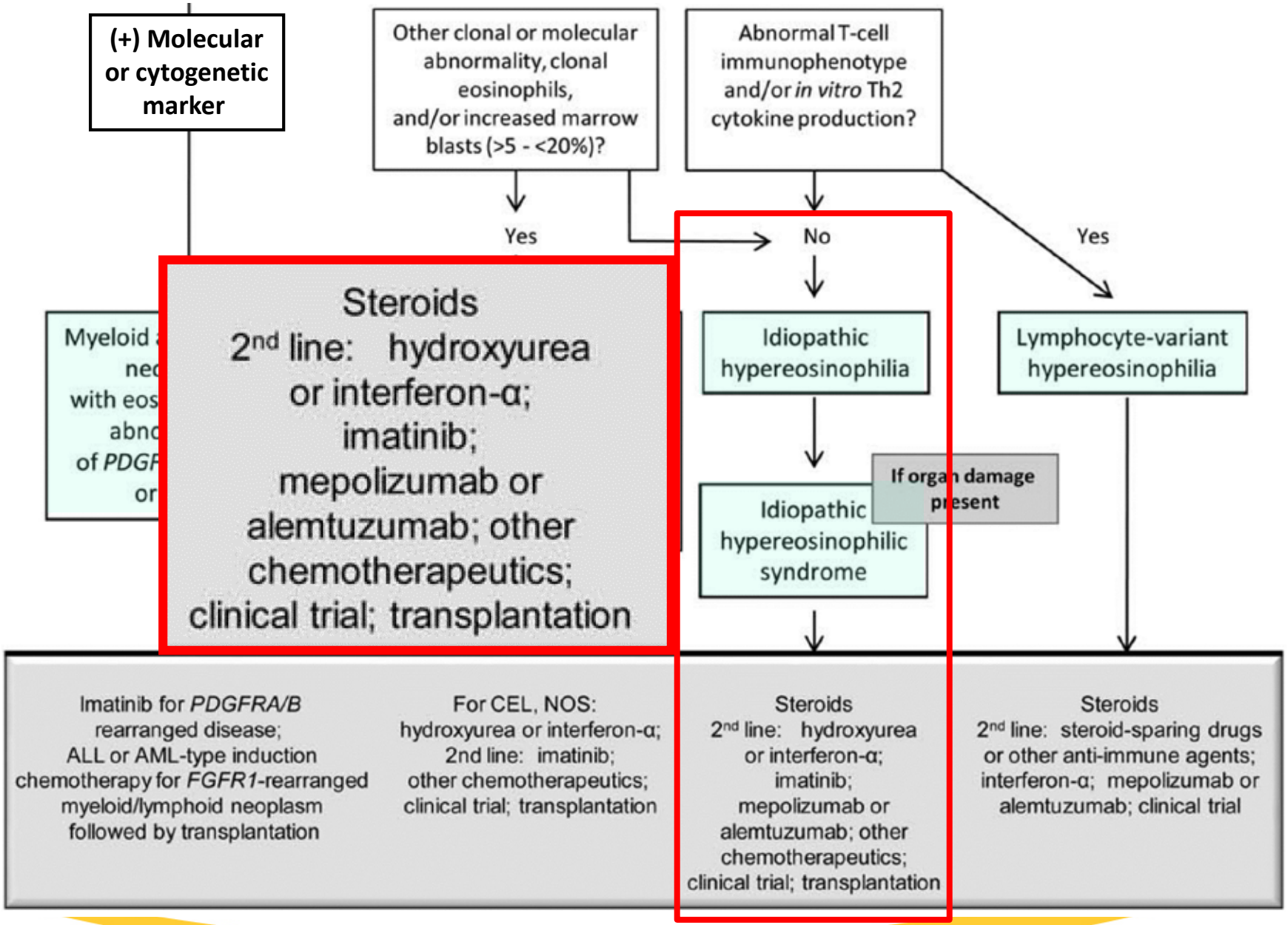




***FIP1L1-PDGRA* fusion gene**



Gotlib J. Am J Hematol 2014;89:326



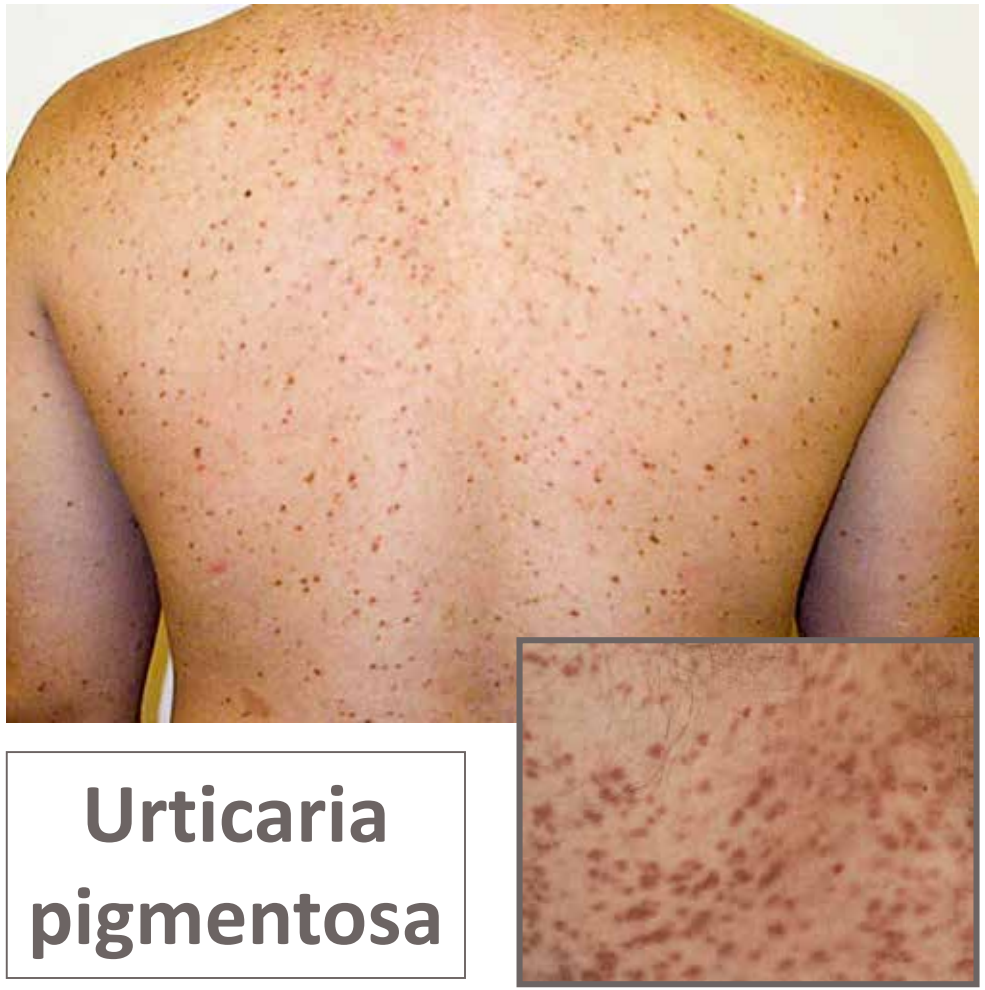
Gotlib J. Am J Hematol 2014;89:326

Clinical Case 4: Mast Cell Disease

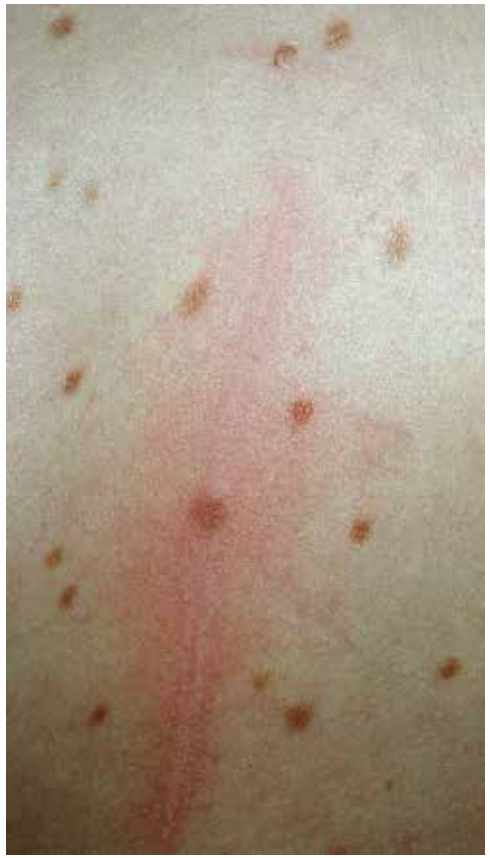
- 57 yo man, 6 mos episodic abd pain, nausea, diarrhea
- **Provocative features:** ? Stress & spicy food ?
- **Pain:** Gradual onset, cramping → nausea, diarrhea; resolves w/in 5d
- **Additional:** Occasional episodes flushing, presyncope, hives/pruritis
- **PMH:** Gastric ulcer 1 yr ago; urticaria x 3yr
- **Meds:** Omeprazole
- **PE**: Pigmented macules, (+) dermatographism
- **Labs:** Hct 45%, WBC 5600/mcL, plt ct 195,000/mcL; normal LFTs; normal amylase & VIP; **Tryptase 30 ng/mL (nl < 11.5 ng/mL)**

24º urine Histamine/Creatinine: 2100 nmol/g (nl < 386 nm/g)

Clinical Case 4: Skin Manifestations



Urticaria pigmentosa



Darier's Sign

https://healthjade.com/urticaria-pigmentosa/ https://www.healthline.com/health/urticaria-pigmentosa

Cutaneous Mast Cell Disease

- **Urticaria pigmentosa**
  - Maculopapular rash, Darier's sign, ± histamine-type sx's
  - **Skin Biopsy:** Nl mast cells, Kit+ (CD117), (-) *c-kit* mutations
  - **In Childhood:** Usually resolves spontaneously after puberty
  - **In Adults:** R/O systemic mastocytosis and associated clonal non-mast cell disease (marrow/blood studies)
  - Indolent course, good prognosis if no progression
- **Mediators:** Histamine; tryptase; TGF-b; IL's; proteases

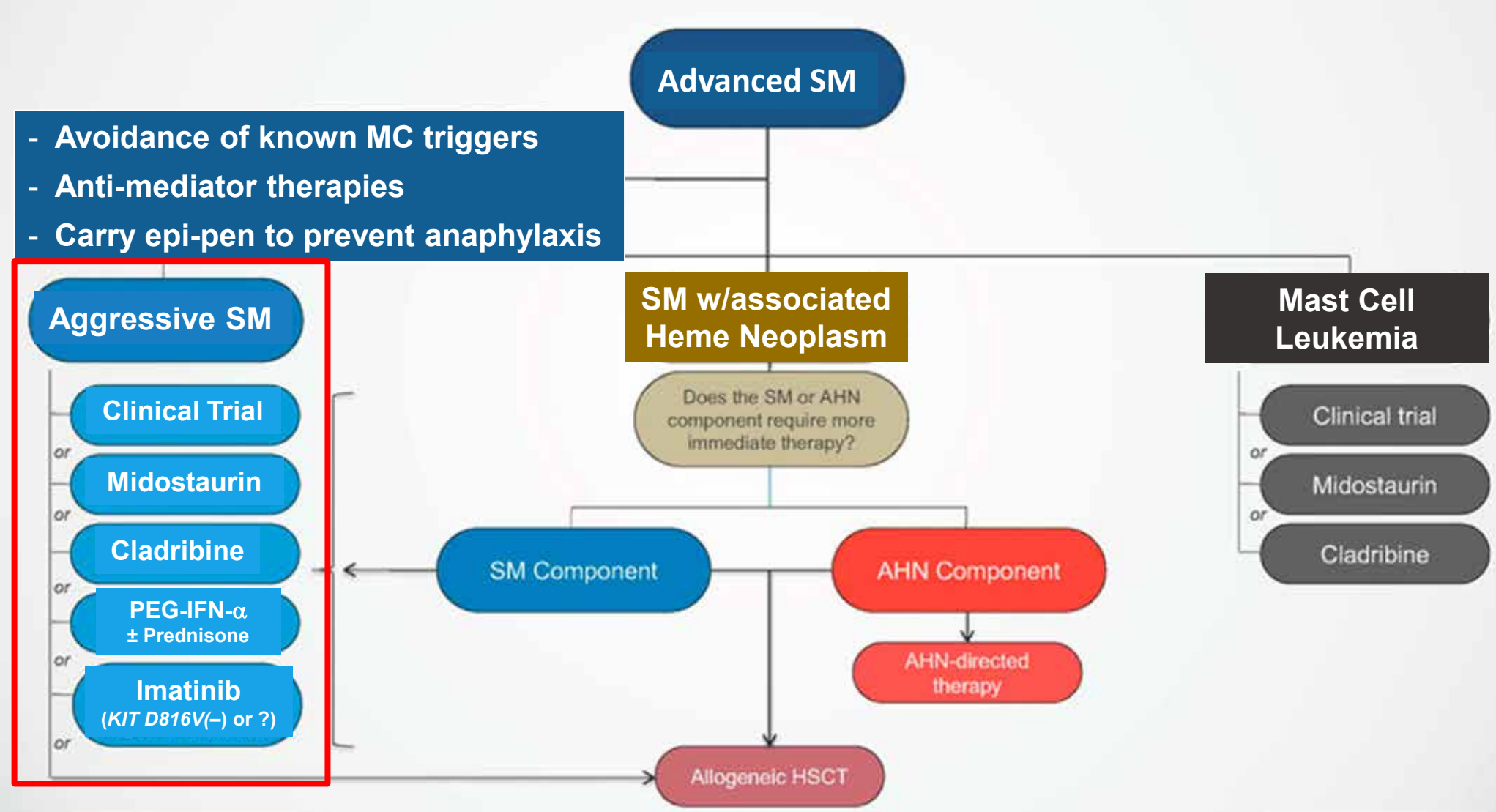
Systemic Mastocytosis (SM): WHO 2016

- **Major Criteria**
  - Multifocal, dense mast cell infiltrates (> 15 aggregating, atypical spindle cells) in marrow or extracutaneous tissue
- **Minor Criteria**
  - BM/organ infiltrates with > 25% atypical/spindle mast cells
  - *c-kit* point mutation (D816V >> others) in marrow/tissue
  - Kit+ (CD117) mast cells that co-express CD2 and/or CD25
  - Serum tryptase > 20 ng/mL

"Indolent SM": Low-level MC; no marrow/tissue dz

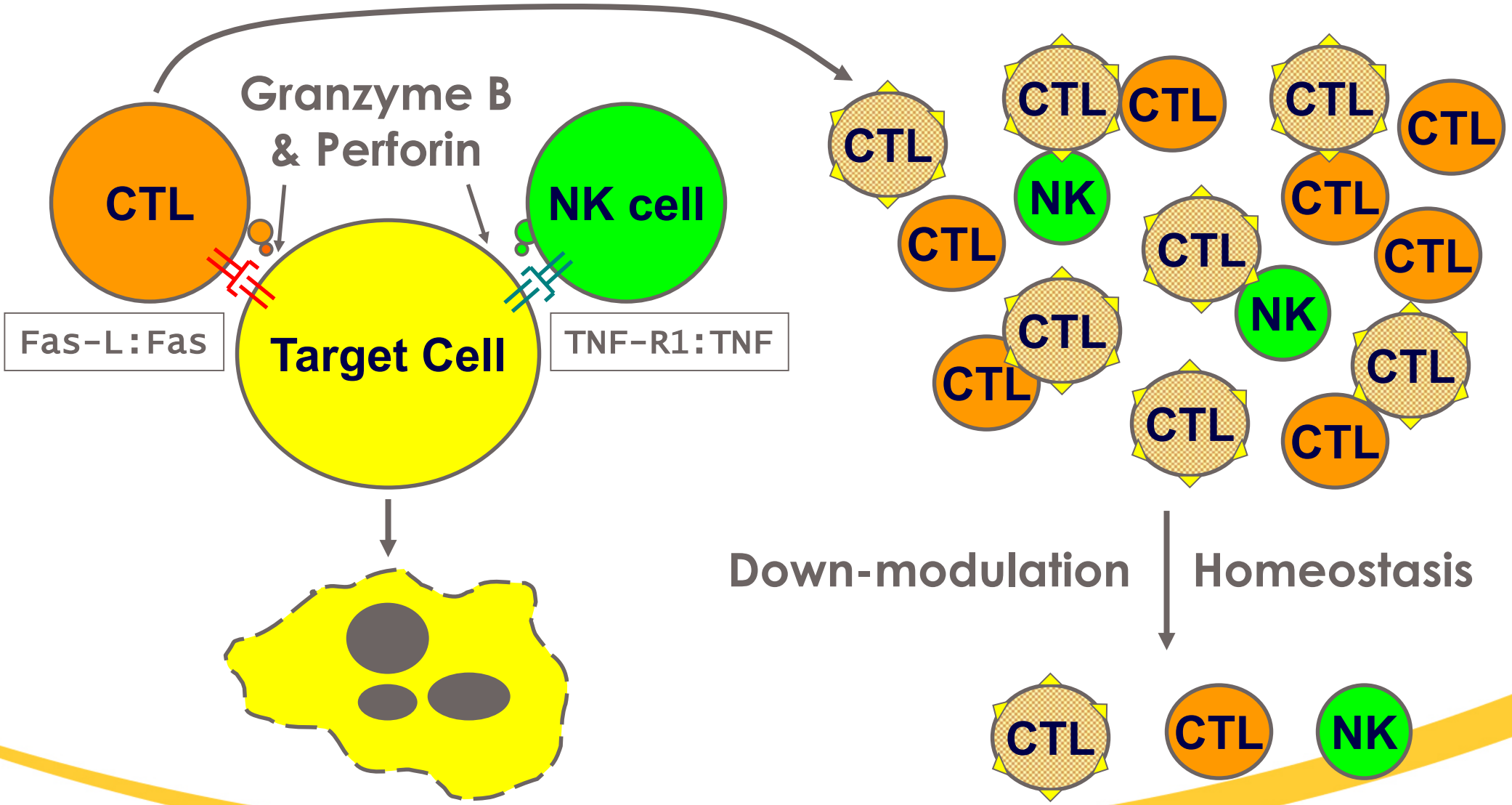
*Diagnosis requires: 1 major & 1 minor or 3 minor criteria

Advanced SM: Subtypes & Treatment

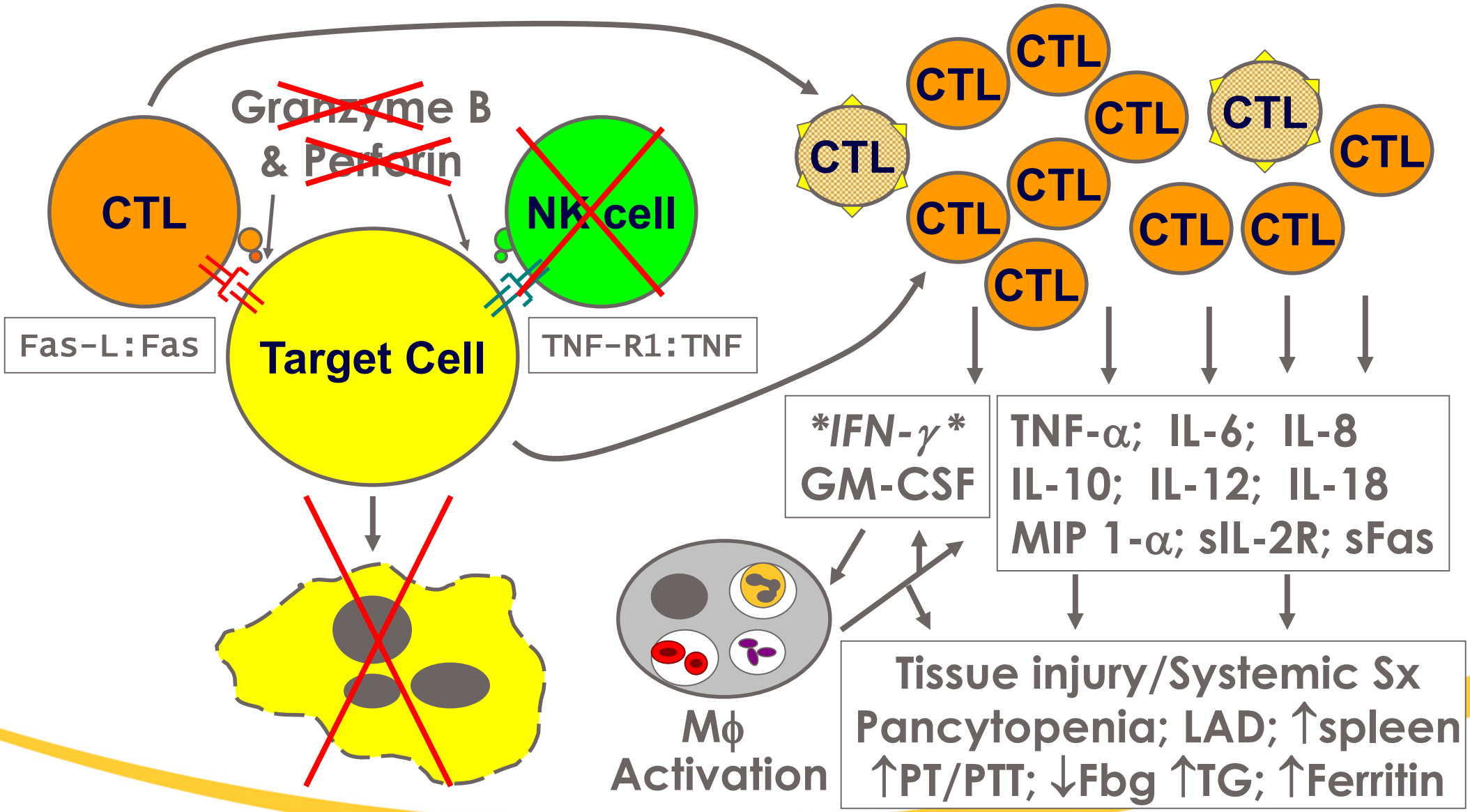


Adapted from: Gotib J. Hematology Am Soc Hematol Educ Program. 2018 Nov 30;2018(1):**132:1769**

CTL & NK Cytotoxicity: “Kiss of Death”



Hemophagocytic Lymphohistiocytosis (HLH)



Familial HLH: Inherited NK Cell Defects

- **Primary HLH associated with lymphocyte cytotoxic defects**
  - **FHL2 - *PRF1*** (perforin; pore-forming) (50% cases)
  - **FHL3 - *UNC 13D*** (cytolytic granule secretion) (30%)
  - **FHL4 - *STX11*** (intracellular vesicle transport)
  - **FHL5 – *STXBP2*** (syntaxin binding protein; membrane fusion)
  - – X-linked lymphoproliferative synd. 1 (***SHD21A***)
  - – FHL1 9q21.3 locus 6
  - – Griscelli syndrome 2 (***RAB27A***)
  - – Chediak-Higashi syndrome (***LYST***)

- **Abnormal Inflammasome/Inflammation**
  - ***– BIRC4***
  - ***– NLRC4***
  - ***– HMOX1***
  - ***– SLC7A7***

- **Immune Deficiencies with <u>sporadic</u> HLH**
  - – Lymphoproliferative syndrome I ***(ITK)***
  - – CD27 deficiency (***CD27***)
  - – Hermansky-Pudlak syndrome ***(AP3BI)***
  - – X-SCID ***(IL2RG)***
  - – XMEN syndrome (**MAGT1**)
  - – Others

*Emile JF et al. Blood 2016;127:2672-81 (Classification of Histiocytoses)

Acquired/2º HLH: Impaired NK/CTL Activity

Consider with pancytopenia, "sepsis syndrome" &/or MODS*

- **Infection-associated:** Virus (EBV, CMV, HIV), bacteria, parasite, fungal
- **Malignancy-associated:** B- or T-cell NHL, HL, NK, myeloid, solid tumor
- **Immune Deficiencies:** Post-transplant, post-chemoimmunotherapy
- **Iatrogenic immune activation:** Cytokine release syndrome
- **Sporadic:** 15% associated with hypomorphic allele for fHLH

****Mortality = 40 – 60%****

Macrophage Activation Syndrome (MAS-HLH) – Rheumatic disorders

- SLE, vasculitis, ***systemic-onset juvenile idiopathic arthritis, *adult onset Still disease** (*consider screen for hypomorphic alleles for fHLH); others

Emile JF et al. Blood 2016;127:2672-81 (Classification of Histiocytoses)

*Ravelli A et al. Ann Rheum Dis 2016;75:481

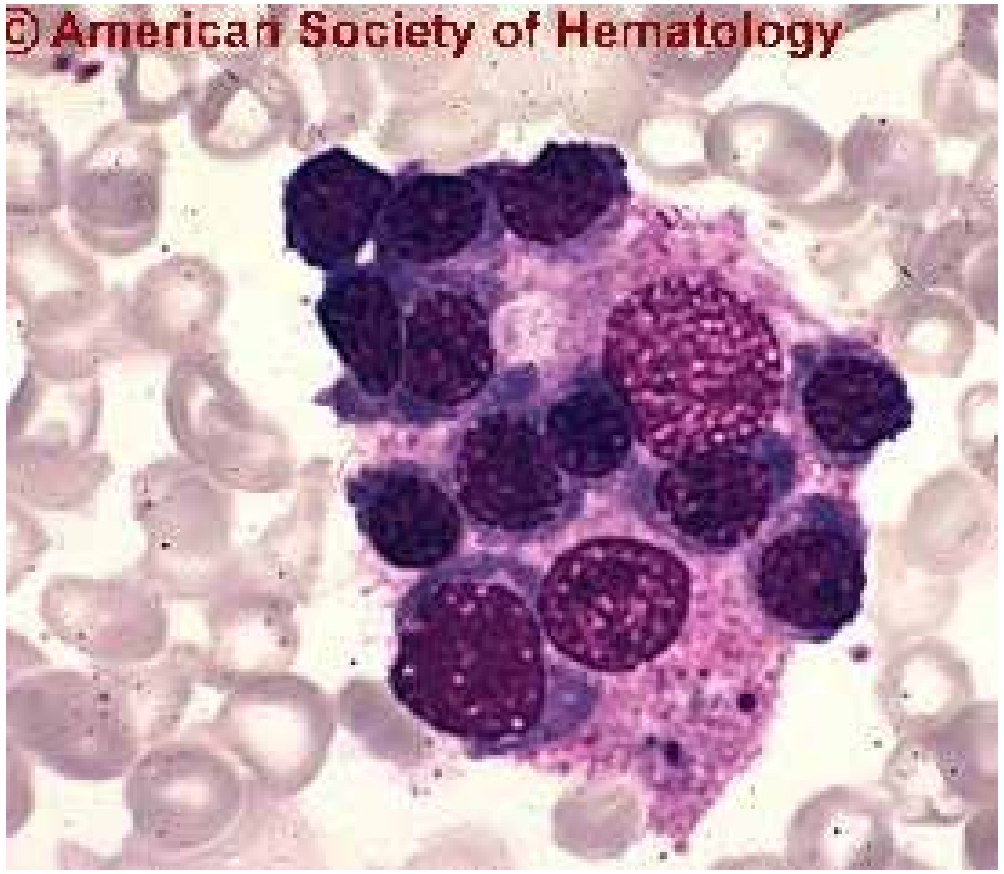
HLH: Clinical Dx Criteria (need ≥5)
[Macrophage Activation Syndrome (MAS)]

1. **Fever ≥7 days** (92-100% in adults w/HLH)
2. **Splenomegaly** (26-100%)
3. **Cytopenias ≥2 cell lines**
   – Hgb <9 gm/dL (59-94%) – Plt <100,000/mcL (86-96%) – PMN <1,000/mcL (25-100%)
4. **Ferritin ≥ 500 mg/L** (85-100%; low specificity in adults except > 10,000[1])
5. **Triglycerides >265 mg/dL** (30-89%) **or Fbg <150 mg/dL** (38-62%)
6. **Hemophagocytosis** in BM; LN; CSF (52-100%) (***poor sensitivity/specificity***)
7. **Low/absent NK activity** (36%; ↑ Sens/Spec w/perforin & CD107a flow assay[2])
8. **Soluble CD25 (sIL-2Rα) >2400 U/mL** (77-100%)

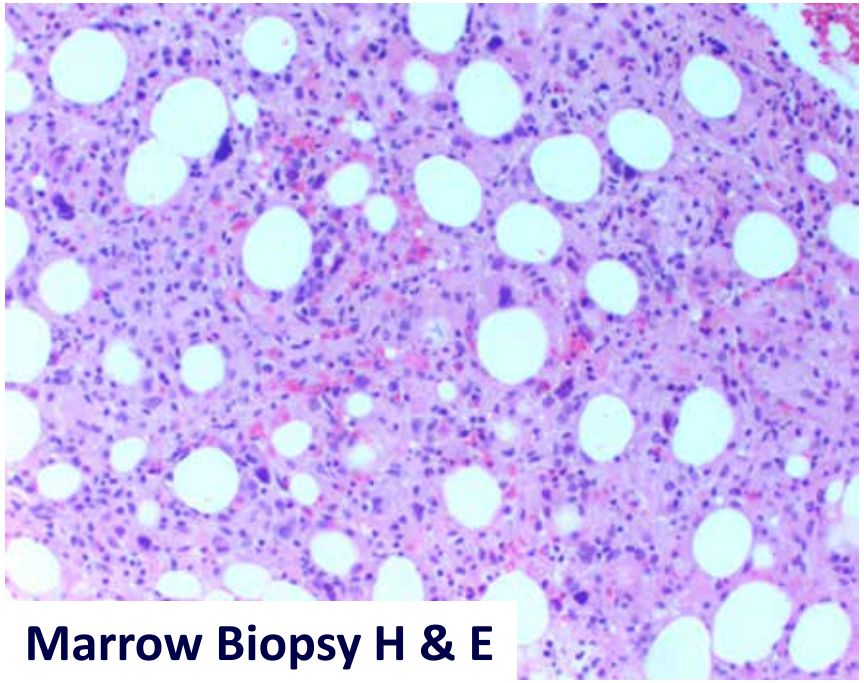
HScore for reactive HLH*
http://saintantoine.aphp.fr/score/
*Fardet L et al. Arthritis Rheumatol 2014;66:2613

[1] Rubin TS et al. Blood 2017;129:2993 [2]Nikiforow S & Berliner N et al. Hematology Am Soc Hematol Educ Program 2015;183-89

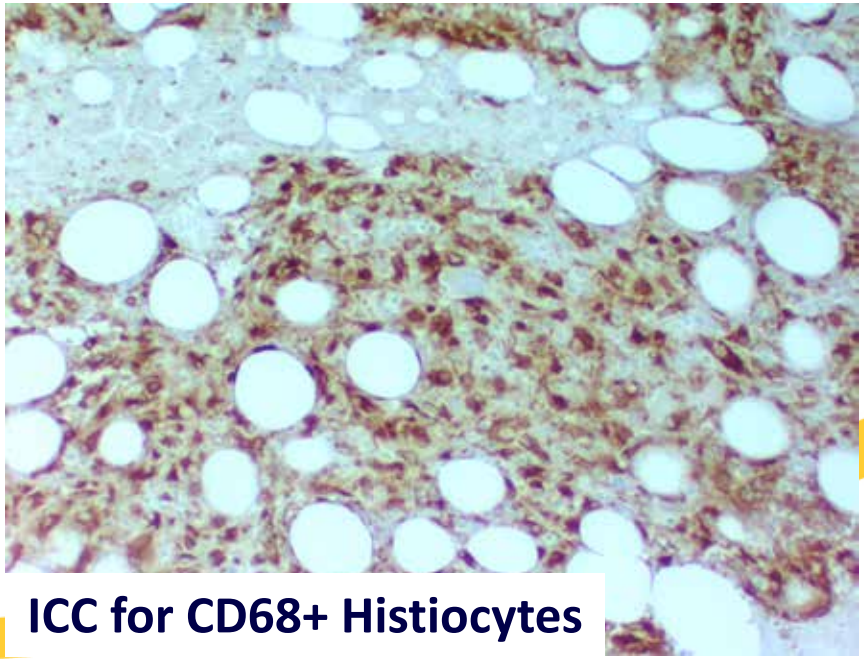
HLH: Marrow Findings



Cytophagic Histiocyte (aspirate)

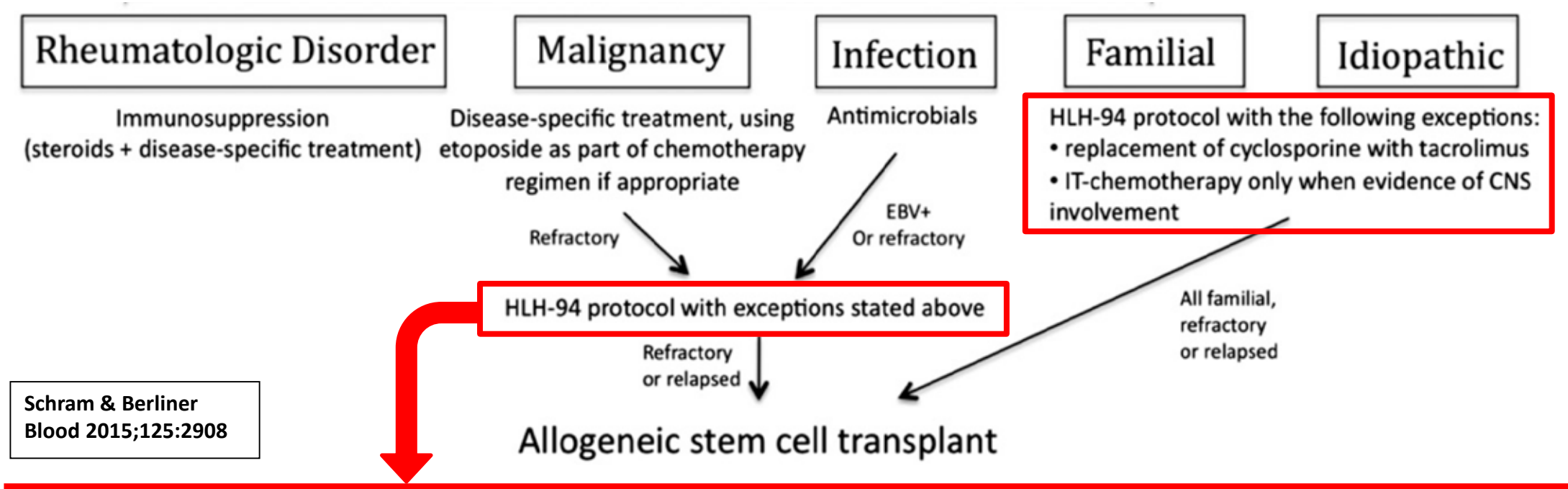


Marrow Biopsy H & E



ICC for CD68+ Histiocytes

HLH: Treatment Algorithm



Schram & Berliner
Blood 2015;125:2908

HLH-94 protocol

Dexamethasone + VP-16 + CSA [or tacrolimus] + IT chemo

Secondary

± Dexa/VP-16, IVIg, ATG, CSA, Alemtuzumab

MAS/Adult-Onset Still's

Hi-dose steroids, ± CSA [tacrolimus], Anakinra, Cytoxan, IVIg, plasma exchange

Primary/Familial HLH Therapy: Anti-IFNγ

- **Emapalumab-Izsg (Gamifant®)**
  - IFNγ blocking antibody (given with dexamethasone)
  - FDA approved for primary HLH
  - Refractory, recurrent or progressive or with intolerance to conventional HLH therapy
- **Clinical trial of 34 pediatric patients (median age 1 yo)***
  - Suspected or confirmed primary HLH - refractory, recurrent or progressive or intolerant of conventional therapy
  - **65% response; 70% able to proceed to BMT**
  - Common side effects: Infections, hypertension, infusion-related reactions, low potassium & fever

*Locatelli F, et al. NEJM 2020;382:1811-22

Summary

- Important to recognize the causes & management of acquired neutropenias & possible 1º congenital disorders
- Reactive hypereosinophilia & mastocytosis may be pathological; targeted treatment is available for clonal disorders
- HLH & MAS represent 1º & acquired disorders driven by CTL/NK dysregulation & cytokine storm → multisystem complications; early Dx is critical; Tx: Underlying trigger & aggressive immunosuppression (HLH-94) as needed

Questions

Thank You