EHA&EuroBloodNet Spotlight on Hypereosinophilic Syndrome

Practical Approach to the Patient with Persistent Unexplained Hypereosinophilia

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Learning objectives of the webinar

1. Ruling out common underlying causes of secondary hypereosinophilia
2. Knowing the relative frequency of different hypereosinophilic conditions
3. Navigating the diagnostic tools to identify HES variants and detect eosinophil-mediated damage
4. Understanding the difficult classification of patients with chronic eosinophilic pulmonary diease
5. Choosing among treatment options for HES, including eosinophil-targeted therapy
6. Knowing future research priorities with respect to targeted treatment

Conflicts of interest

Consultancy and/or speaker fees from GlaxoSmithKline, Astra Zeneca, Menarini, Merck.

Most common causes of Hypereosinophilia

- Allergic disorders
  - Atopy: ! Rarely causes HYPEReosinophilia (e.g. severe eosinophilic asthma)
  - Adverse drug reactions (e.g. DRESS)
- Parasitic infections
  - Helminthiasis mostly (e.g. Strongyloidiasis, Toxocarosis)
  - Ectoparasites (e.g. Scabies, Myiasis)
- Neoplasms - Cancer
  - Hematological malignancies (eosinophilia may be clonal or paraneoplastic)
  - Solid tumors (e.g. adenoC)

Diverse etiologies of (hyper)eosinophilia

Category	Examples (not inclusive)
Allergic disorders*	Asthma, atopic dermatitis
Drug hypersensitivity	Varied†
Infection	
Helminthic	Varied, including strongyloidiasis, [illegible] filariasis, schistosomiasis
Ectoparasite	Scabies, myiasis
Protozoan	Isosporiasis [illegible]
Fungal	Cocci[illegible] [illegible]onchopulmonary [illegible]plasmosis
Viral	
Neoplasms	[illegible]ia, lymphoma, adenocarcinoma
Immunolog[illegible]	
Im[illegible]	DOCK8 deficiency, Hyper-IgE syndrome, Omenn's syndrome
[illegible]e and idiopathic	Sarcoidosis, inflammatory bowel disease, IgG4 disease, and other connective tissue disorders
Miscellaneous	Radiation exposure, cholesterol emboli, hypoadrenalism, IL-2 therapy
Rare eosinophilic disorders	Idiopathic hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome), eosinophilic gastrointestinal disorders

'Wheezes, worms and weird diseases'

Klion AD. Blood 2015;126:1069–1077.

Definition of Hypereosinophilic Syndrome

Hypereosinophilia: Blood, Counts x 10^9/L Blood	
Hypereosinophilia	>1.5 recorded on ≥2 determinations with a minimum time interval of 2 weeks
Eosinophilia	0.5 - 1.5
Normal	0.05 – 0.5 (1% - 6% WBC)
Hypereosinophilia: Tissue	
The percentage of eosinophils >20% of all nucleated bone marrow cells AND/OR	
Pathologist is of the opinion that tissue eosinophil infiltration is excessive compared with the normal physiological range, compared with other inflammatory cells or both AND/OR	
A specific eosinophil granule protein stain demonstrates extensive extracellular deposition indicative of local eosinophil activation and degranulation even in the absence of local eosinophil infiltration	

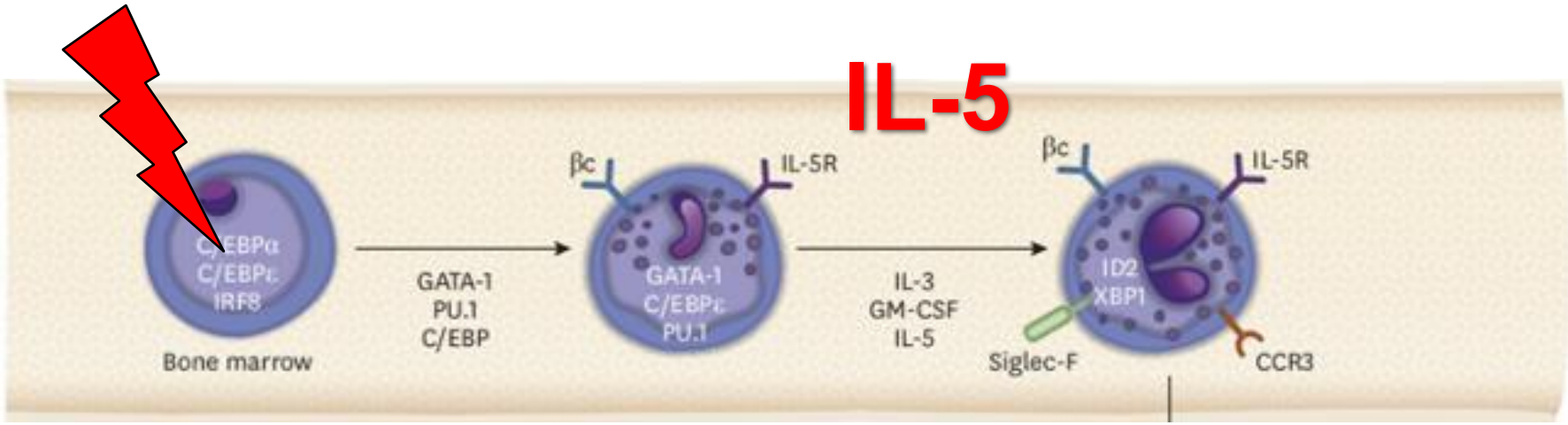
Hypereosinophilic syndrome(s)
Criteria for blood and tissue HE fulfilled AND
Organ damage and/or dysfunction attributable to tissue HE AND
Exclusion of other disorders or conditions as main reason for organ damage

Adapted from Valent et al. Allergy 2023 Jan;78(1):47-59

Pathogenesis of hypereosinophilia in HES

Somatic mutation driving clonal eosinophil expansion

Increased presence of eosinophilopoietic factors driving polyclonal eosinophil expansion



Familial hypereosinophilia: mapped to cytokine gene cluster 5q31-q33

UNKNOWN

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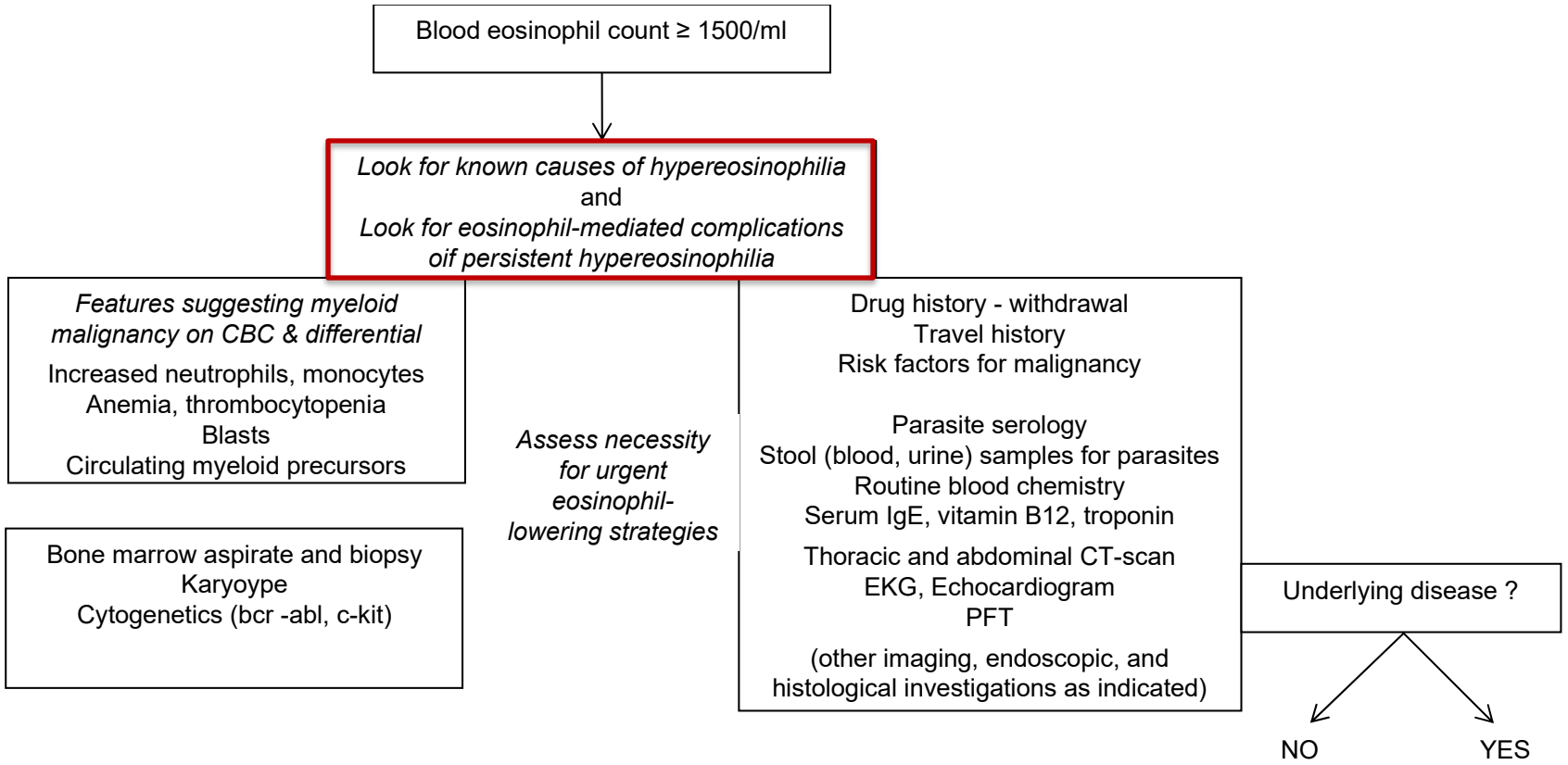
Work-up of hypereosinophilia



Roufosse F & Weller P. J Allergy Clin Immunol 2010;126(1):39. Khoury et al; Mayo Clin Proc 2023;98(7):1054.

Initial Work-Up of Hypereosinophilia

Thorough physical examination and detailed history including

- Drug exposure (including non-prescription), travel history and lifestyle associated with risk of exposure to helminthic parasites, risk factors and family history of cancer, evidence of primary immunodeficiency

Microscopic examination of blood/body fluids

- Testing for infections associated with HE: ova/larvae of helminthic parasites, fungal or other infectious cause as appropriate

Blood test/bone marrow exam[a]

- Complete blood count with differential, absolute eosinophil count, peripheral blood smear
- Serum tryptase, vitamin B12, IgE, IgG, IgM, IgG4
- ANCA (anti-PR3/anti-MPO testing by ELISA if ANCA detected)
- T-cell immunophenotyping by flow cytometry[b]
- Assessment for and quantification of blasts[b]
- Cytogenetic and molecular testing for *PDGFRA/B, FGFR1, JAK2* rearrangements or mutations associated with clonal eosinophilia, TCR gene rearrangement analysis by PCR/NGS[b]

Tests for end organ involvement/damage

- ECG, echocardiogram
- Blood tests; liver and muscle enzymes, kidney function, serum troponin I or T
- Chest x-ray/CT scan, abdominal ultrasound/CT scan
- Further imaging/endoscopy/histological examination/functional testing of target organs depending on clinical manifestations (see green box)
- Further testing for cancer: FDG-PET scan if neoplasia (solid or lymphoma) is suspected

Khoury et al; Mayo Clin Proc 2023;98(7):1054.

Work-up of hypereosinophilia

Blood eosinophil count ≥ 1500/ml

Look for known causes of hypereosinophilia
and
Look for eosinophil-mediated complications oif persistent hypereosinophilia

Features suggesting myeloid malignancy on CBC & differential

Increased neutrophils, monocytes
Anemia, thrombocytopenia
Blasts
Circulating myeloid precursors

Bone marrow aspirate and biopsy
Karyoype
Cytogenetics (bcr -abl, c-kit)

Assess necessity for urgent eosinophil-lowering strategies

Drug history - withdrawal
Travel history
Risk factors for malignancy

Parasite serology
Stool (blood, urine) samples for parasites
Routine blood chemistry
Serum IgE, vitamin B12, troponin

Thoracic and abdominal CT-scan
EKG, Echocardiogram
PFT

(other imaging, endoscopic, and histological investigations as indicated)

Additional means of investigating organ damage

To adapt to clinical situation (signs, symptoms, disease manifestations)

- Cardiac MRI, Holter monitor test
- Angiography, venous Doppler ultrasound
- Bronchoscopy with bronchoalveolar lavage, lung biopsies, pulmonary function tests
- Digestive endoscopy/colonoscopy, entero-MRI, small bowel transit
- Biopsy of affected tissue/organ(s)
- Brain MRI or CT with contrast, nerve conduction studies, electromyography, soft tissue MRI

Underlying disease ?

NO

YES

1. Treat as indicated
2. Add corticosteroids if rapid eosinophil lowering is warranted

Follow-up : ensure eosinophils normalized

Evaluate for HES

NO

YES

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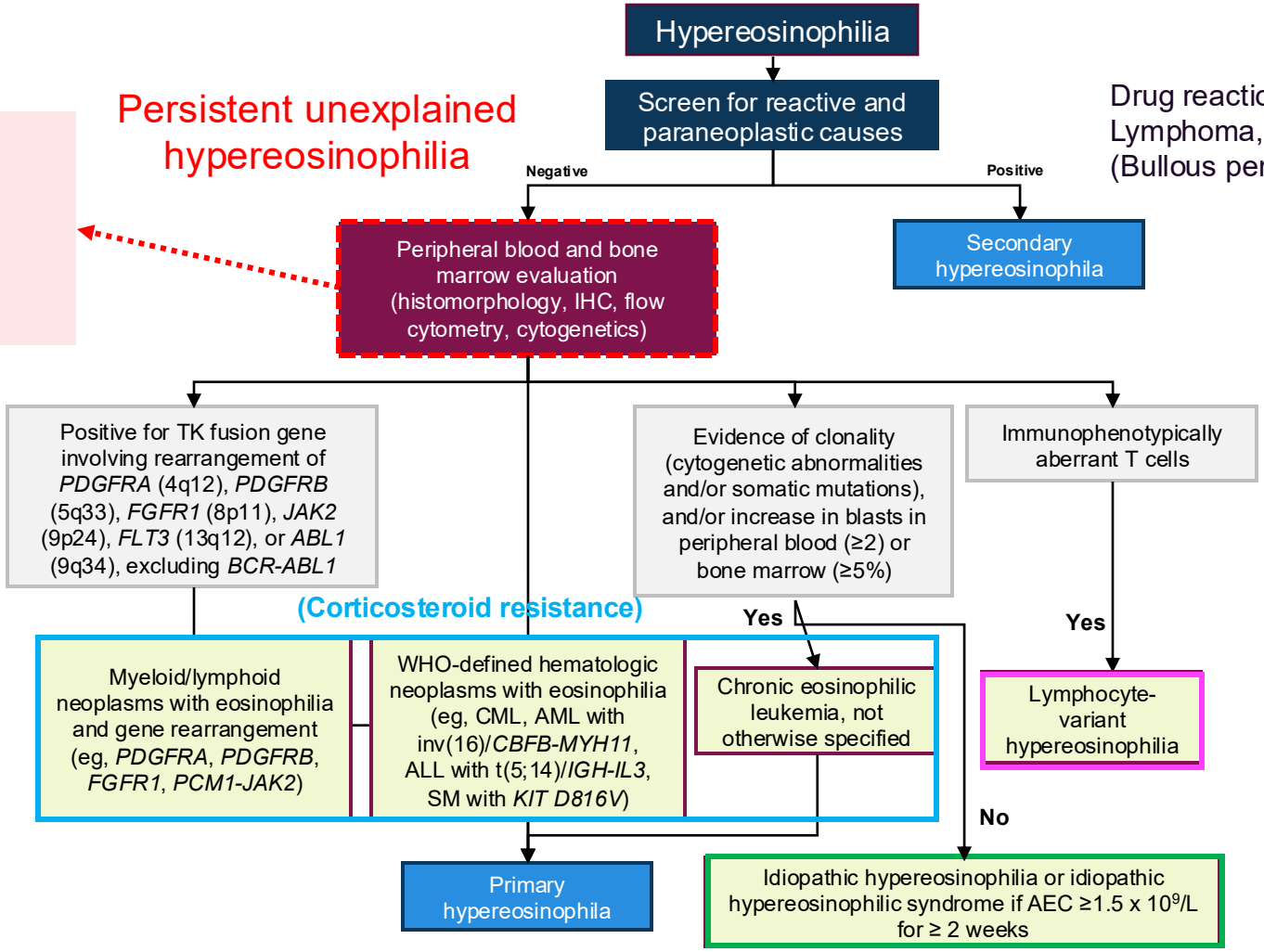
Roufosse F & Weller P. J Allergy Clin Immunol 2010;126(1):39. Khoury et al; Mayo Clin Proc 2023;98(7):1054.

Assessment for hypereosinophilic syndrome variants

PCR for FIP1L1-PDGFRA fusion
FISH for CHIC deletion
Other cytogenetic assessments
T-cell phenotyping
TCR gene rearrangement pattern
Serum tryptase, TARC

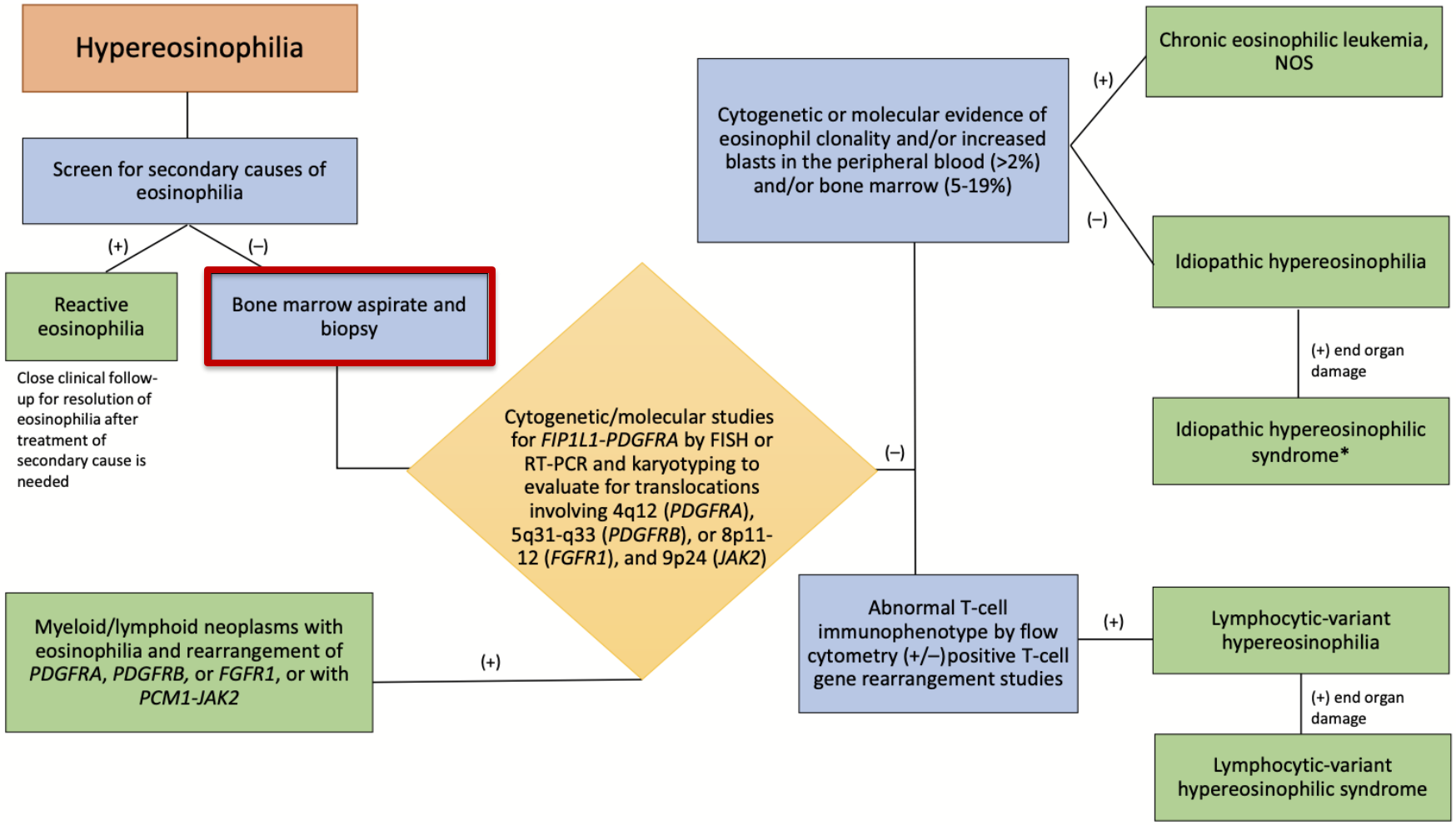
Persistent unexplained hypereosinophilia

Drug reaction, Parasitic infection, PID, Lymphoma, Cancer,
(Bullous pemphigoid, Ulcerative colitis…)



Adapted from Mattis DM, et al. Am J Clin Pathol. 2020;154(3).

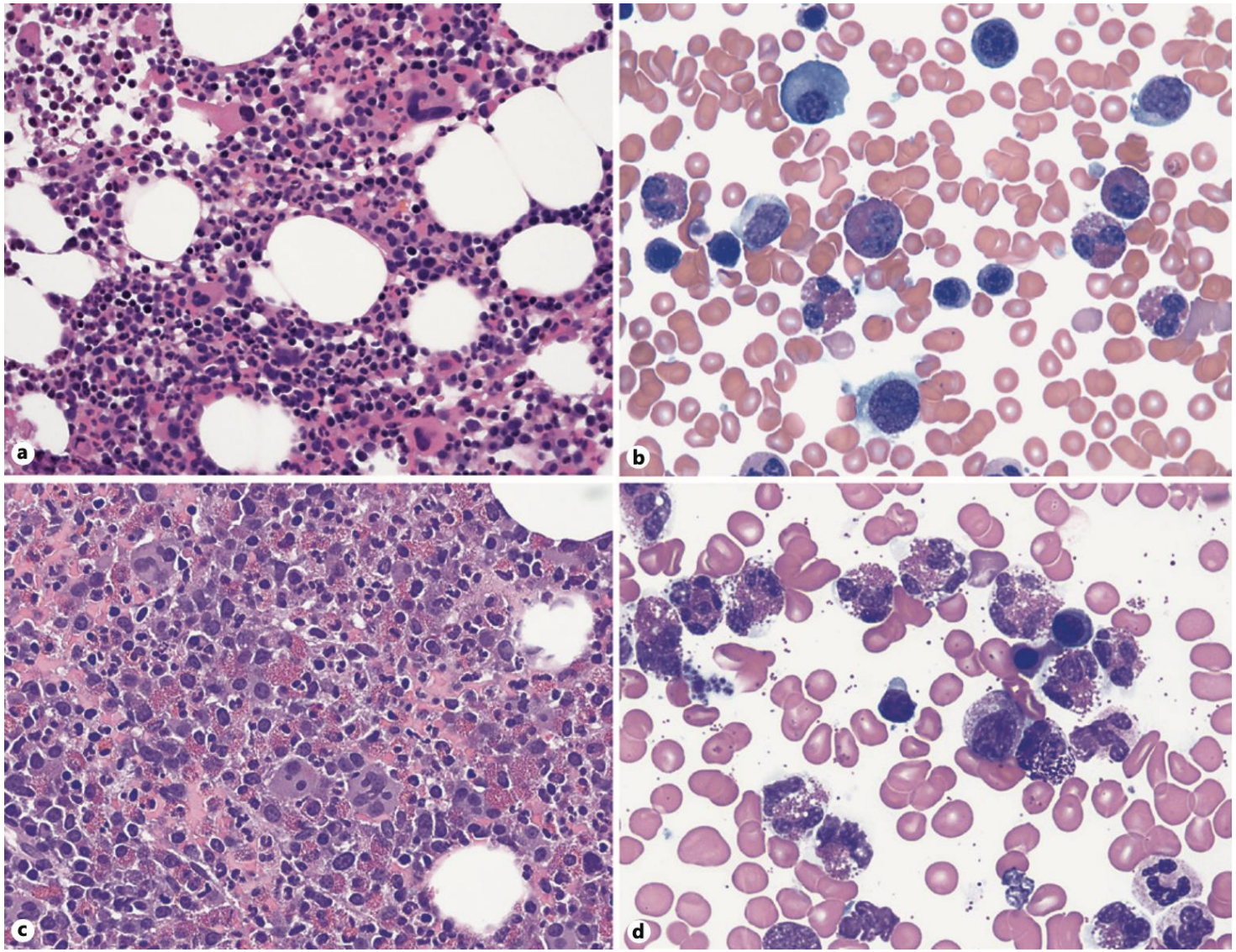
Assessment for HES variants: pathobiologist's viewpoint



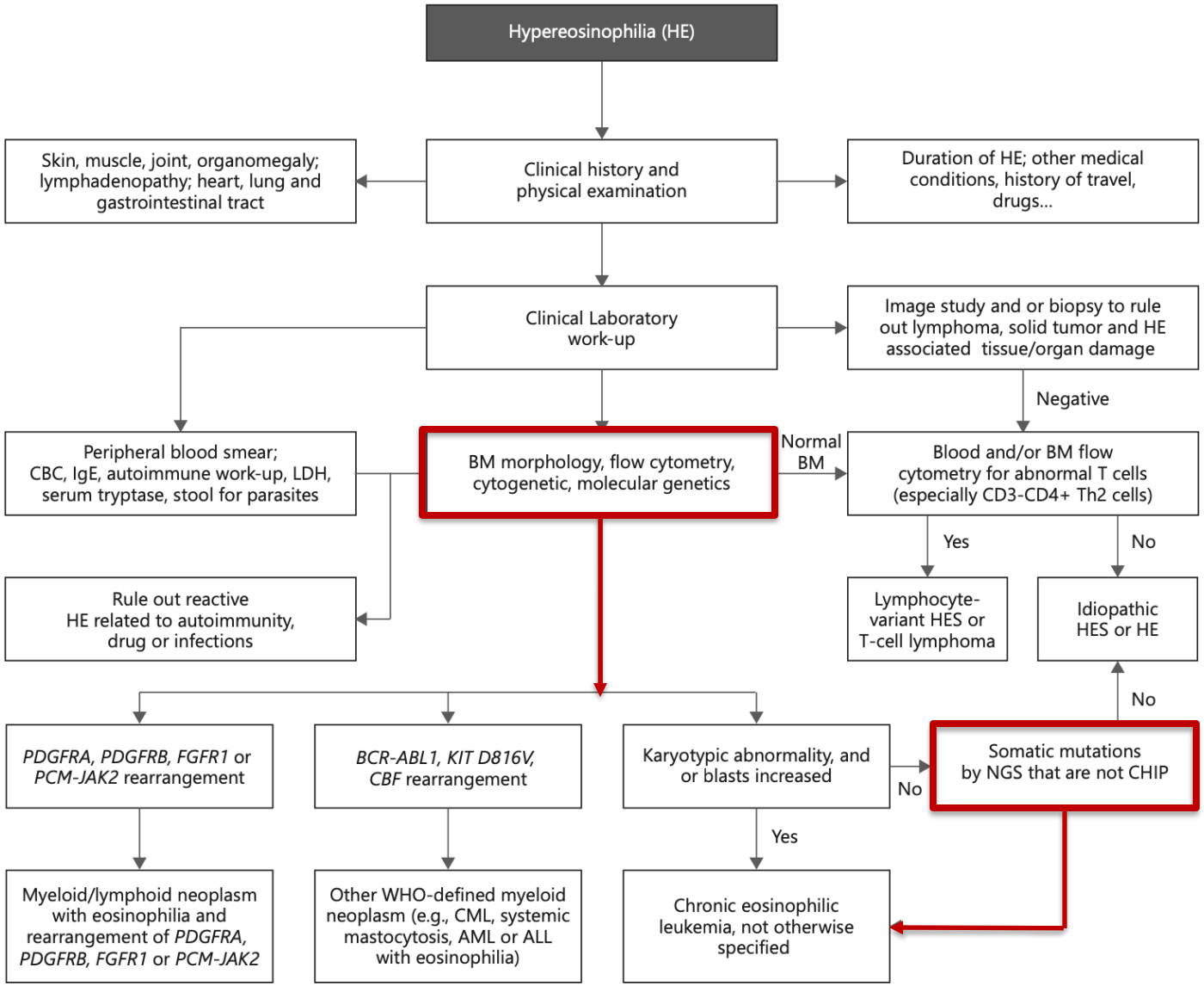
Larsen R & Savage N. Int J Lab Hem 2019;41:153.

Bone marrow in the assessment of hypereosinophilia

- Marked blood HE (> 5 G/L)
- Organomegaly
- Perturbed CBC
- Increased serum vit B12, tryptase
- Other features suggesting perturbations of myeloid lineage
- Abnormal T cell phenotype and/or clonal TCR gene rearrangement



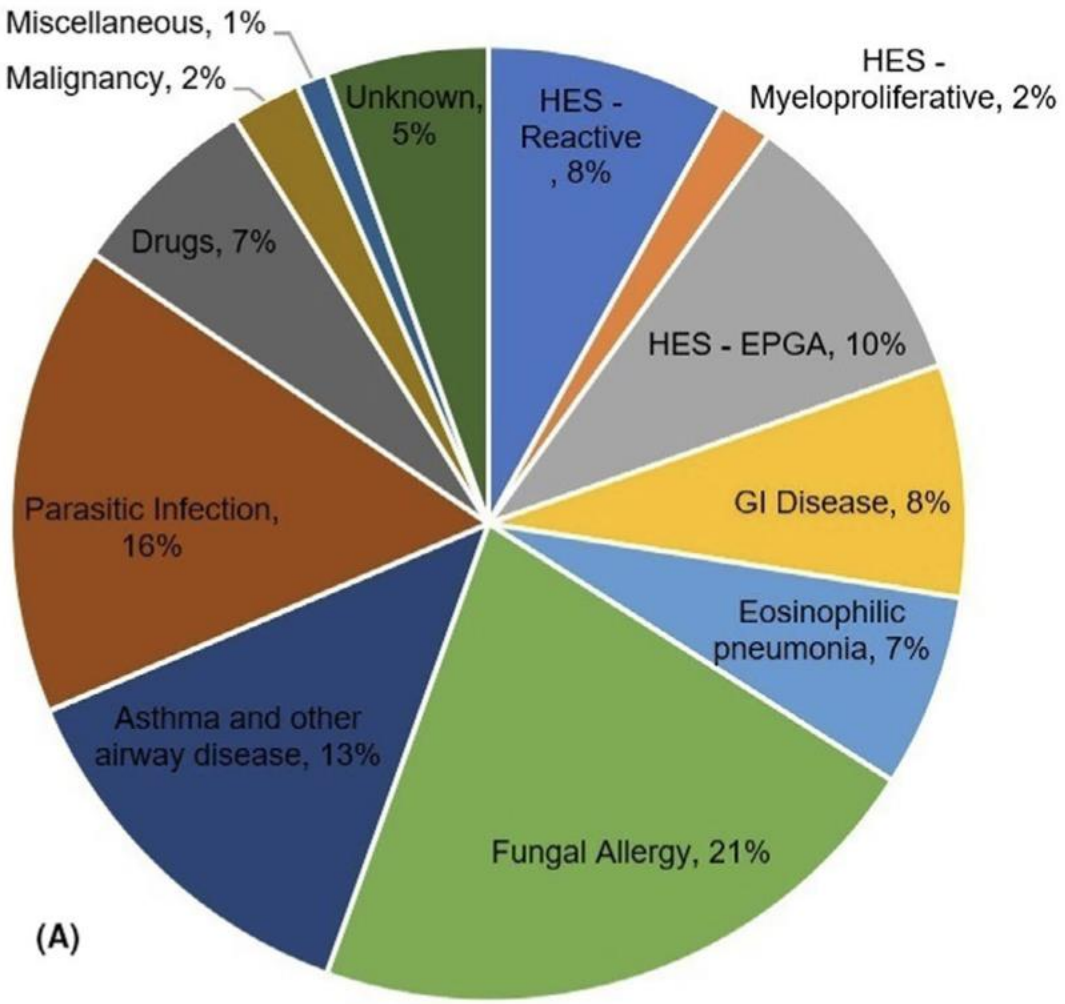
Wang S. Pathobiology 2019; 86(1):39.



Wang S. Pathobiology 2019; 86(1):39.

Relative distribution of causes of Hypereosinophilia

Secondary care center, pulmonary physicians, Leicester, UK: referrals for blood eosinophilia > 1G/L (2003-2019)



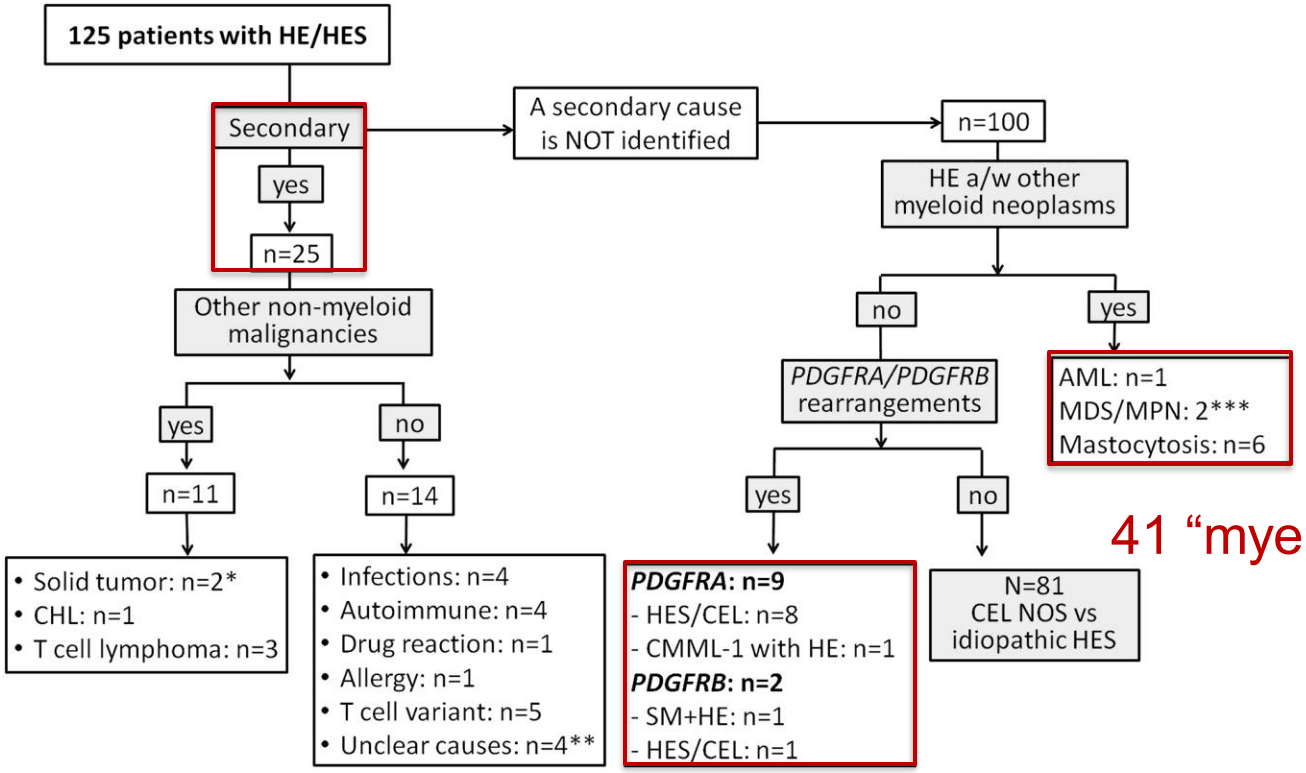
382 patients

Wardlaw A et al. Clin Exp Allergy 2021;51:902.

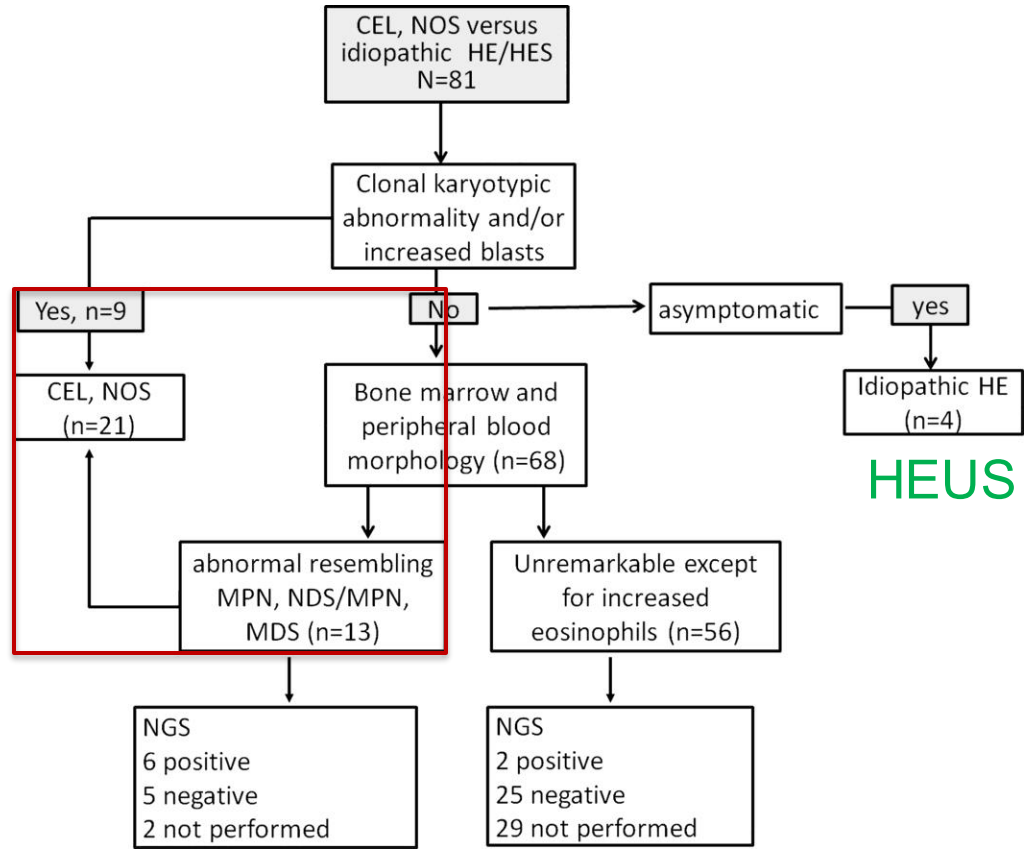
Relative distribution of causes of Hypereosinophilia

Tertiary cancer center, hemato-pathology department, USA: referrals for hypereosinophilia (2003-2016)

125 patients



41 "myeloid"



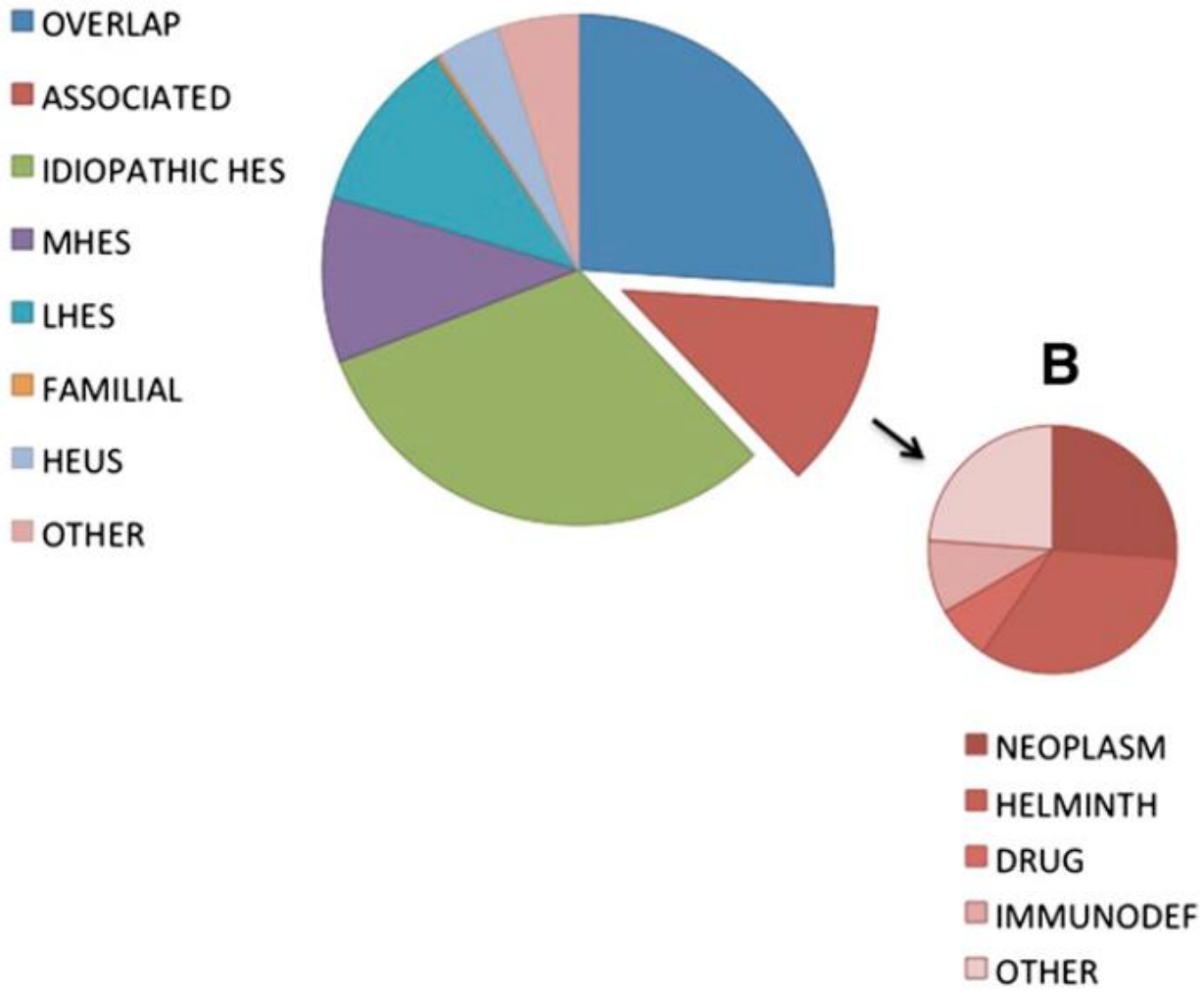
HEUS

*solid tumor: 1 head and neck squamous cell carcinoma, and 1 lung squamous cell carcinoma
** Asyptomatic and resolved spontaenously
*** One patient with mastocytosis and MDS/MPN

Hu et al, Am J Hematol 2018; 93(11):1337.

Relative distribution of causes of Hypereosinophilia

Tertiary referral center, NIH, USA: Patients sent for evaluation of "unexplained" hypereosinophilia



302 patients

Klion A. Blood 2015;126(9):1069.

Differential Diagnosis of Pulmonary Infiltrates With Eosinophilia

- Eosinophilic granulomatosis with polyangiitis
  - Other vasculitides
    - Granulomatosis with polyangiitis
    - Microscopic polyangiitis
- Hypereosinophilic syndromes
  - Overlap
  - Myeloid
  - Lymphoid-variant
  - Idiopathic
- Aspirin-exacerbated respiratory disease
- Chronic eosinophilic pneumonia
- Acute eosinophilic pneumonia
- Eosinophilic bronchitis
- Allergic bronchopulmonary aspergillosis
- Infectious causes of pulmonary eosinophilia
  - Helminthic infections
  - Non-helminthic infections
    - Ectoparasites
    - Fungal infections
- Drug-induced pulmonary eosinophilic syndromes

Adapted from Rosenberg C & Khoury P. Chest 2021; 159(2):507.

Chronic eosinophilic pulmonary conditions

	AEP	CEP	EGPA	HES
Incidence	9.1/100,000 per person-year	0.23–7/100,000 per person-years	0.9 to 2 per million person-years	0.03 to 0.042/100,000 per person-years
			In asthmatics, 35 to 67 per million person-years	
Demographics	Smokers (age 20–40 y); M > F	Nonsmokers; age 30 to 40 y; F > M; asthma	Age >50 y; asthma	Myeloproliferative HES: age 20 to 50 y, M> F
Presentation	Respiratory and constitutional symptoms to acute respiratory failure	Respiratory and constitutional symptoms	Respiratory and constitutional symptoms	Respiratory and constitutional symptoms
	Over several days	Over months to year; slow and progressive	Over months to years	Over months to years
Extrapulmonary involvement	None	None. Atopy/allergic rhinitis/sinusitis symptoms common	Allergic rhinitis/sinusitis with nasal polyposis; atopic disease; cardiac, GI, renal, nervous system, skin, or joint disease	Sinuses, cardiac skin, GI, nervous system, uterine. Less commonly hepatic, pancreatic, ocular, synovial and renal disease
Imaging	X-ray: alveolar and/or interstitial infiltrates and Kerley B lines	X-ray: "photographic negative pulmonary edema"	X-ray: fleeting lung infiltrates	X-ray: fleeting lung infiltrates
	HRCT: bilateral diffuse GGO and/or air-space consolidations, septal thickening, and bilateral small pleural effusions	HRCT: patchy, bilateral, migratory dense consolidations and/or GGO	HRCT: CEP features. Heterogeneous and migratory bilateral consolidations or GGO; nodules; cavities; airways thickening; pleural effusions	HRCT: CEP features. Heterogeneous and migratory bilateral consolidations or GGO; nodules; cavities; airways thickening; pleural effusions
Pathology	Rarely required. Eosinophils filling the alveolar spaces in a background of interstitial pneumonia	Rarely required, eosinophilic and lymphocytic interstitial and alveolar infiltrates	Eosinophilic bronchitis/pneumonia, necrotizing granulomatous inflammation, and granulomas vasculitis	Eosinophilic bronchitis/pneumonia
Prognosis	Good. Rare recurrence	Good; but risk of recurrence	5-year mortality, FFS = 0 is 9%, FFS = 1 is 21%, FFS = 2 is 40%; worse if cardiac involvement	Worse with cardiac disease or neoplastic HES; lymphoid variant HES has better prognosis
Differential diagnosis	CHF, ARDS, pneumonia; acute hypersensitivity pneumonitis, acute organizing pneumonia	EGPA, ABPA, drug toxicity, parasitic infection, COP	GPA, MPA, eosinophilic asthma, HES, CEP, ABPA, DRESS	EGPA, HE, CEP, DRESS, parasitic infection (e.g., filaria), malignancies (e.g., CML)

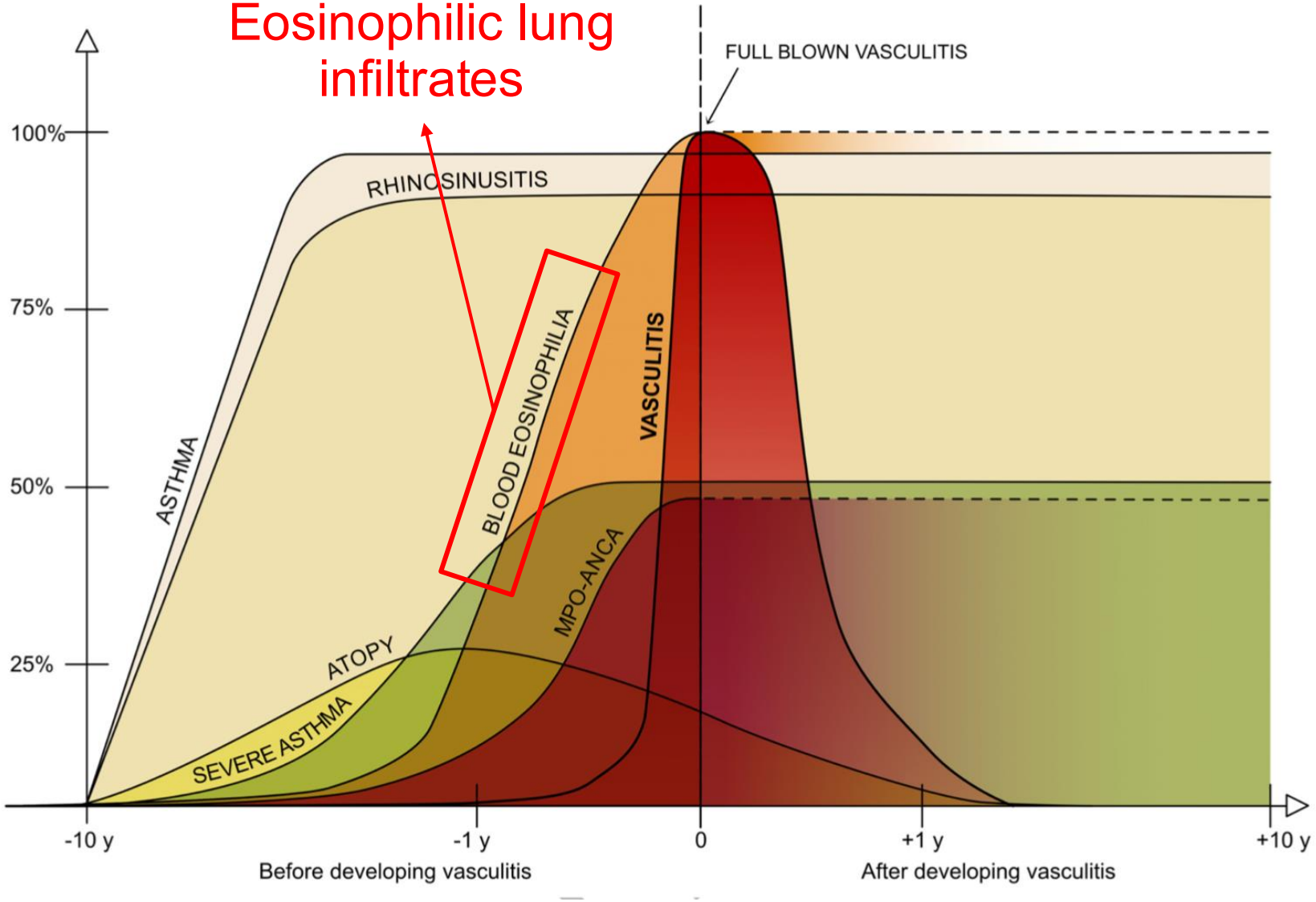
Atopy
Sinusitis

Infiltrates
- GGO
- consolidation

Eos in BALF

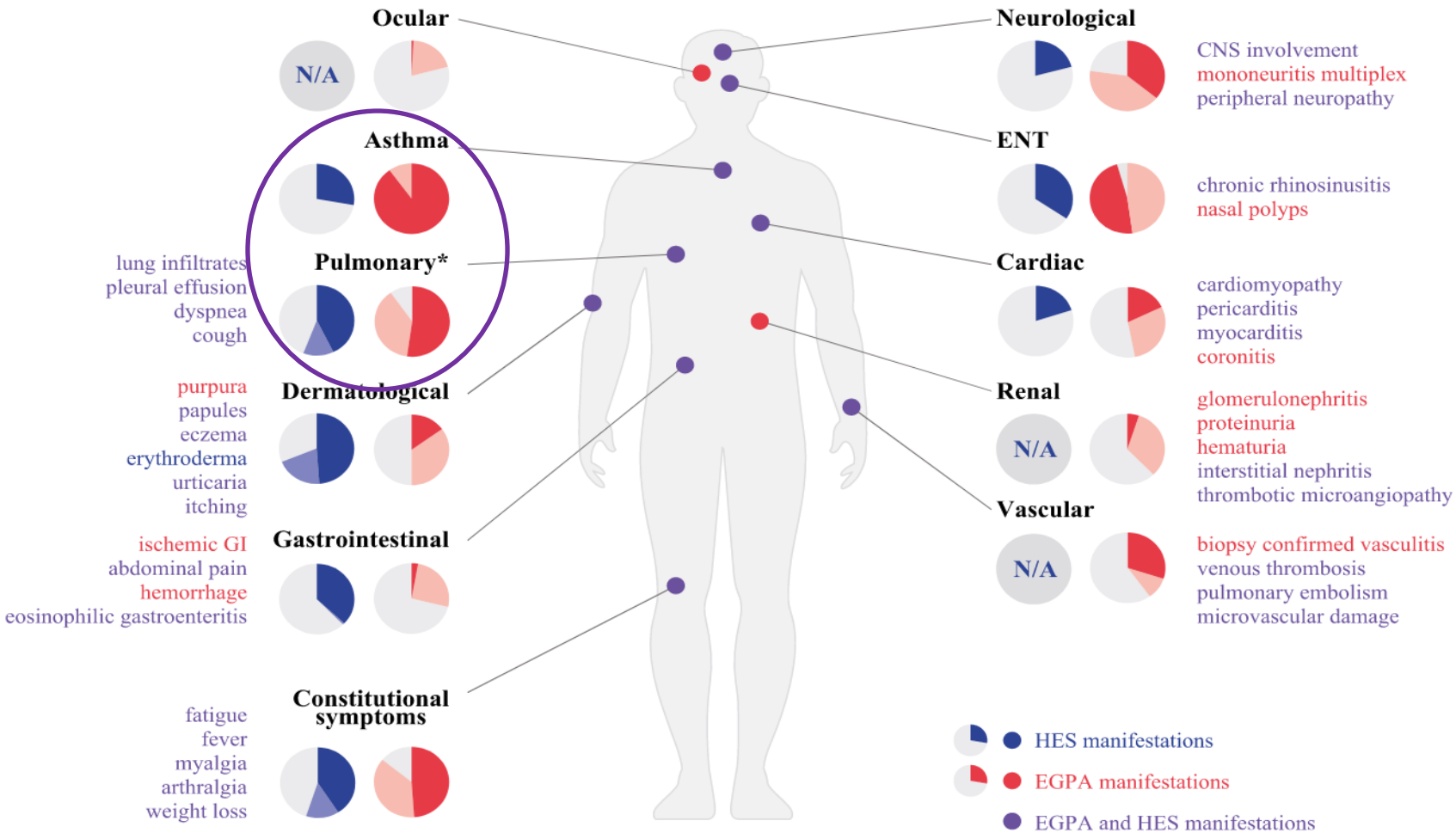
Sergew A & Fernandez-Perez E. Semin Respir Crit Care Med 2016;37:441.

EGPA clinical course: overlap with HES



Chronic eosinophilic pulmonary conditions: OVERLAP !!

HES - EGPA



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Wechsler M et al. J Allergy Clin Immunol 2023 Jun;151(6):1415.

EGPA: the MIRRA clinical trial criteria for diagnosis

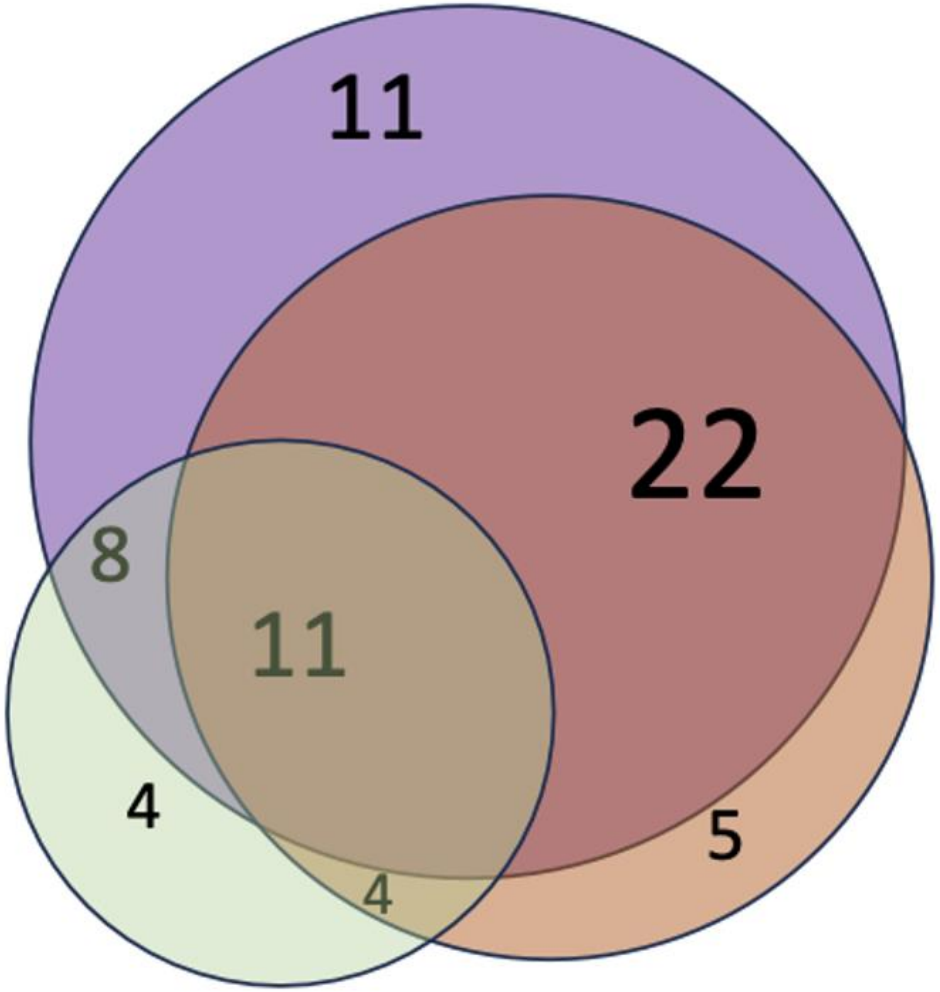
- Current or past history of asthma
- Blood eosinophil count >10 % of WBC or absolute count of >1000 cells/µl

And at least 2 of the following:

- Histopathological evidence for eosinophilic vasculitis, perivascular eosinophilic infiltration or eosinophil-rich granulomatous inflammation
- Neuropathy
- Pulmonary infiltrates
- Sinonasal pathological findings
- Cardiomyopathy
- Glomerulonephritis
- Alveolar haemorrhage
- Palpable purpura
- Anti-neutrophil cytoplasmic antibodies (ANCA)

Wechsler M et al. N Engl J Med. 2017; 376(20):1921

Chronic eosinophilic pulmonary conditions: OVERLAP !!



HES

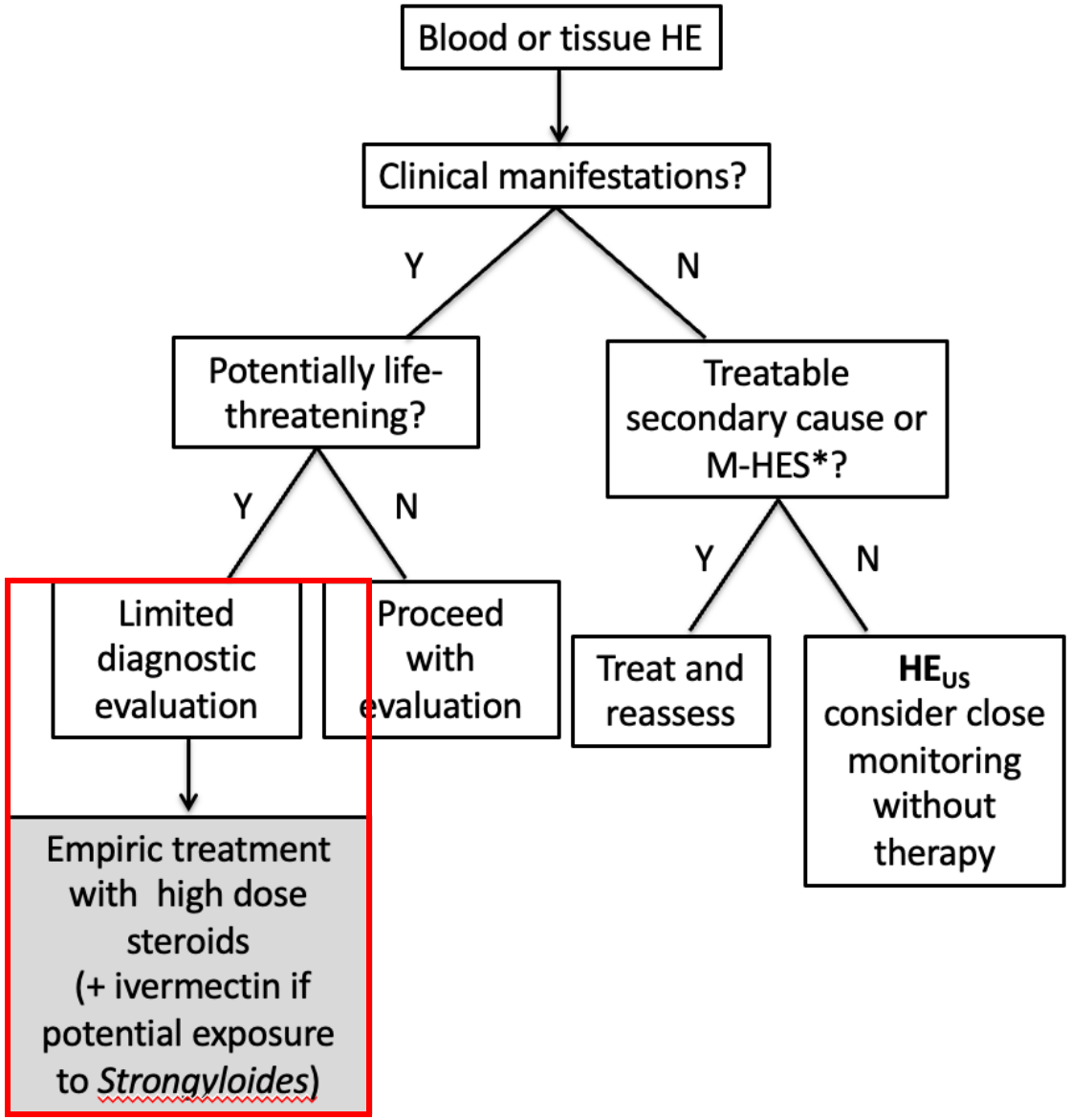
CEP

EGPA

MIRRA criteria

Adapted from Bier N et al. Master thesis (unpublished data), May 2024.

Management of severe/acute presentations of HES



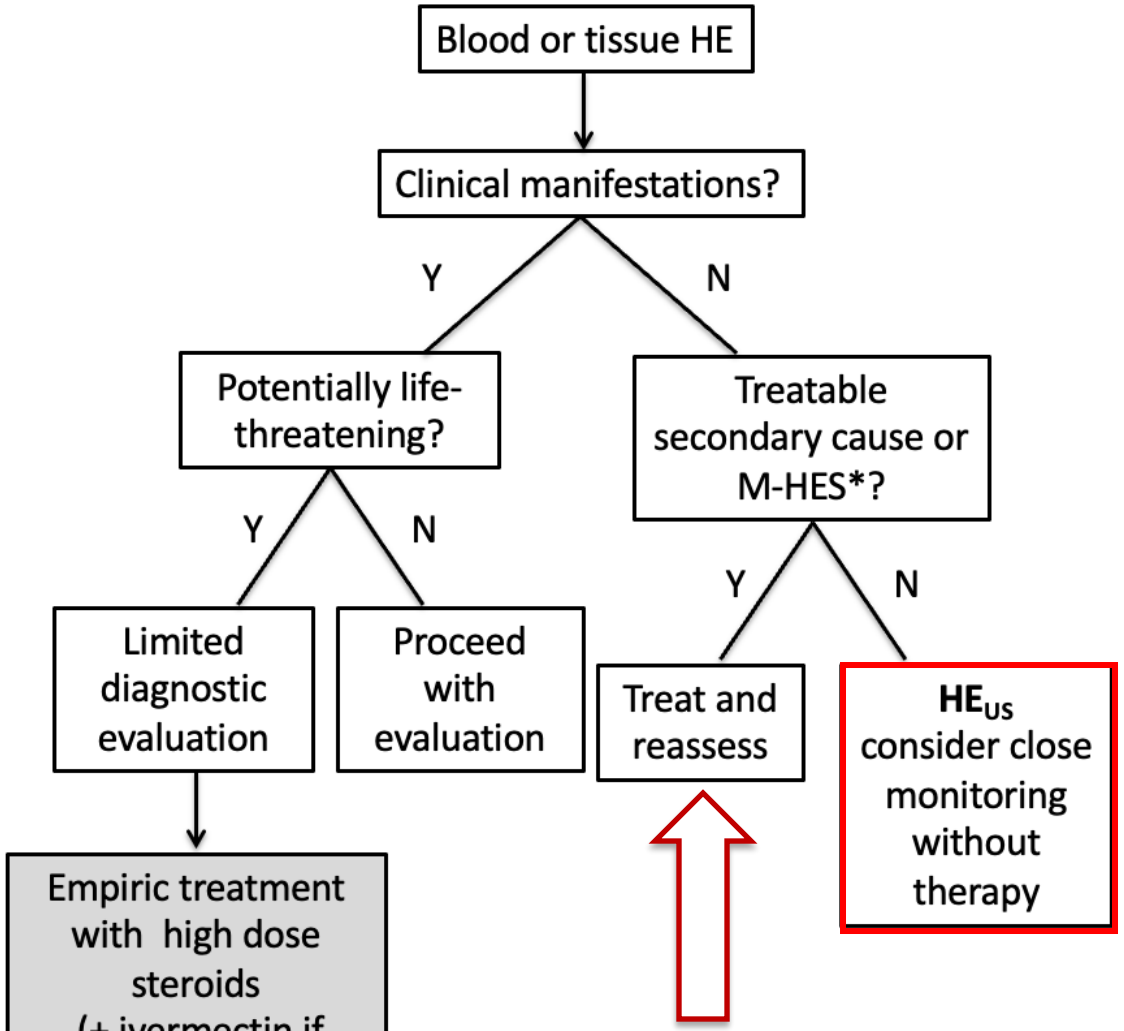
*HES with a genetic abnormality known to cause clonal eosinophilia or idiopathic HES with ≥4 of the following features:

- dysplastic eosinophils,
- serum B12 >1000 pg/mL,
- serum tryptase >12 ng/mL,
- anemia and/or thrombocytopenia,
- splenomegaly,
- bone marrow cellularity >80%,
- myelofibrosis,
- spindle-shaped mast cells >25%,

or strong clinical suspicion of a myeloproliferative disorder

Klion A. Blood 2015;126(9):1069.

Management of asymptomatic hypereosinophilia



Klion A. Blood 2015;126(9):1069.

Classical treatment options according to disease variant

HES VARIANT	HES VARIANT subset	First line treatment	Second line treatment *
Myeloid HES	FIP1L1-PDGFRA+ HES	Imatinib mesylate 100 mg/d PDN 1 mg/kg first days	Other TKI: dasatinib, nilotinib, sorafenib Specialist referral; ASCT
	Myeloid/lymphoid neoplasm with eosinophilia and PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2 rearrangement	Hematologist referral for targeted treatment and/or inclusion in clinical trial	
	Chronic eosinophilic leukemia, NOS		
	Suspected M-HES	Corticosteroid (may be refractory)	Hydroxyurea Imatinib mes 400-800 mg/d (Peg-) IFN-alpha JAK inhibitors [MMF, CPA, AZA, MTX]
Lymphoid HES	CD3-CD4+ L-HES	Corticosteroid: Systemic and topic if applicable (skin lesions, bronchial and/or digestive involvement)	(Peg-) IFN-alpha JAK inhibitors Alemtuzumab [CSA, MMF, CPA, AZA, MTX]
	Suspected L-HES		
Idiopathic HES			Hydroxyurea (Peg-) IFN-alpha Imatinib mes 400-800 mg/d Alemtuzumab [CSA, MMF, CPA, AZA, MTX]

Interferon-alpha

Hydroxyurea

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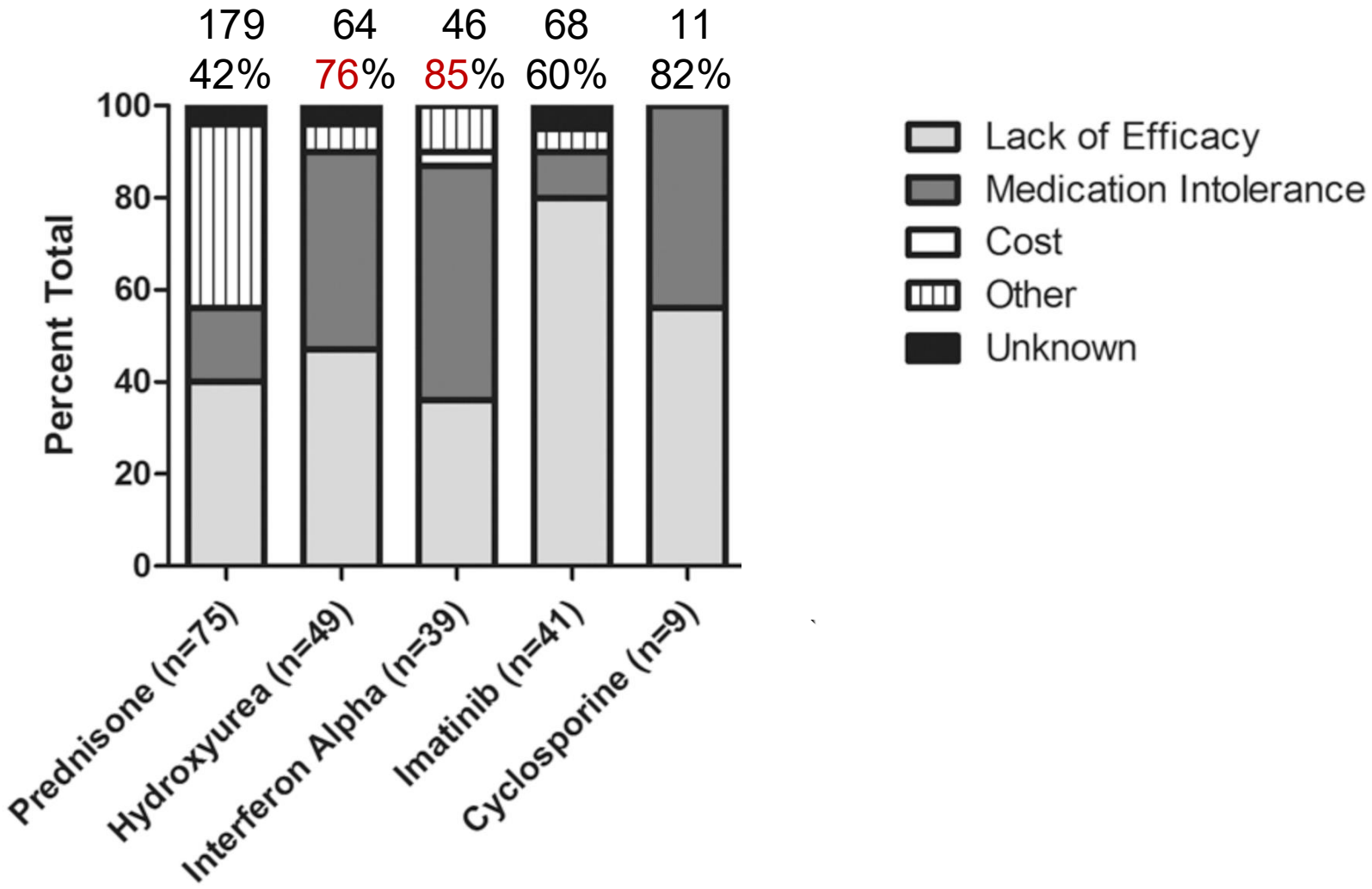
Taton et al, ERS Monograph: Eosinophilic Lung Diseases. EDU-0302-2020.R1

Interruption of classical treatment options



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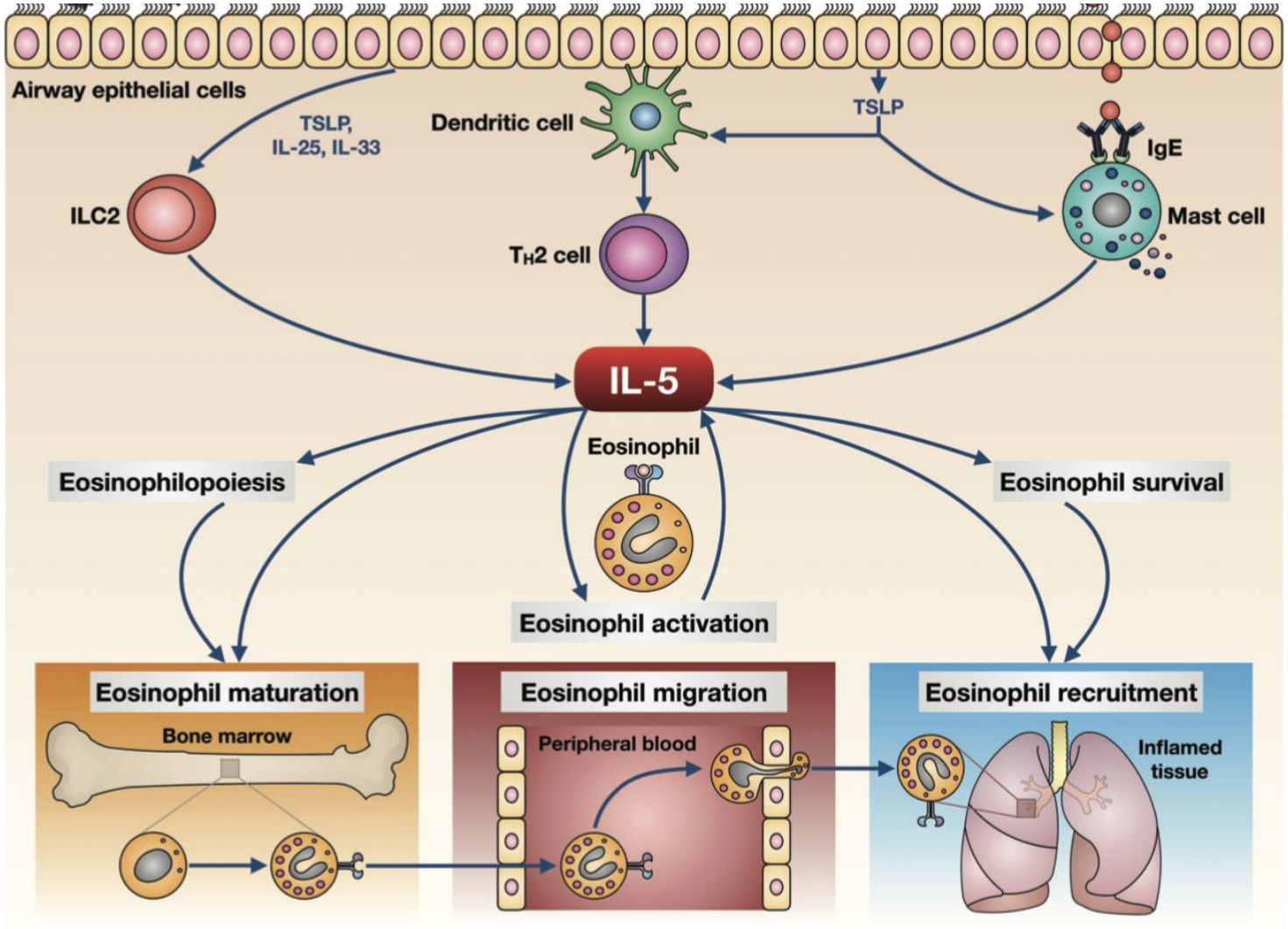
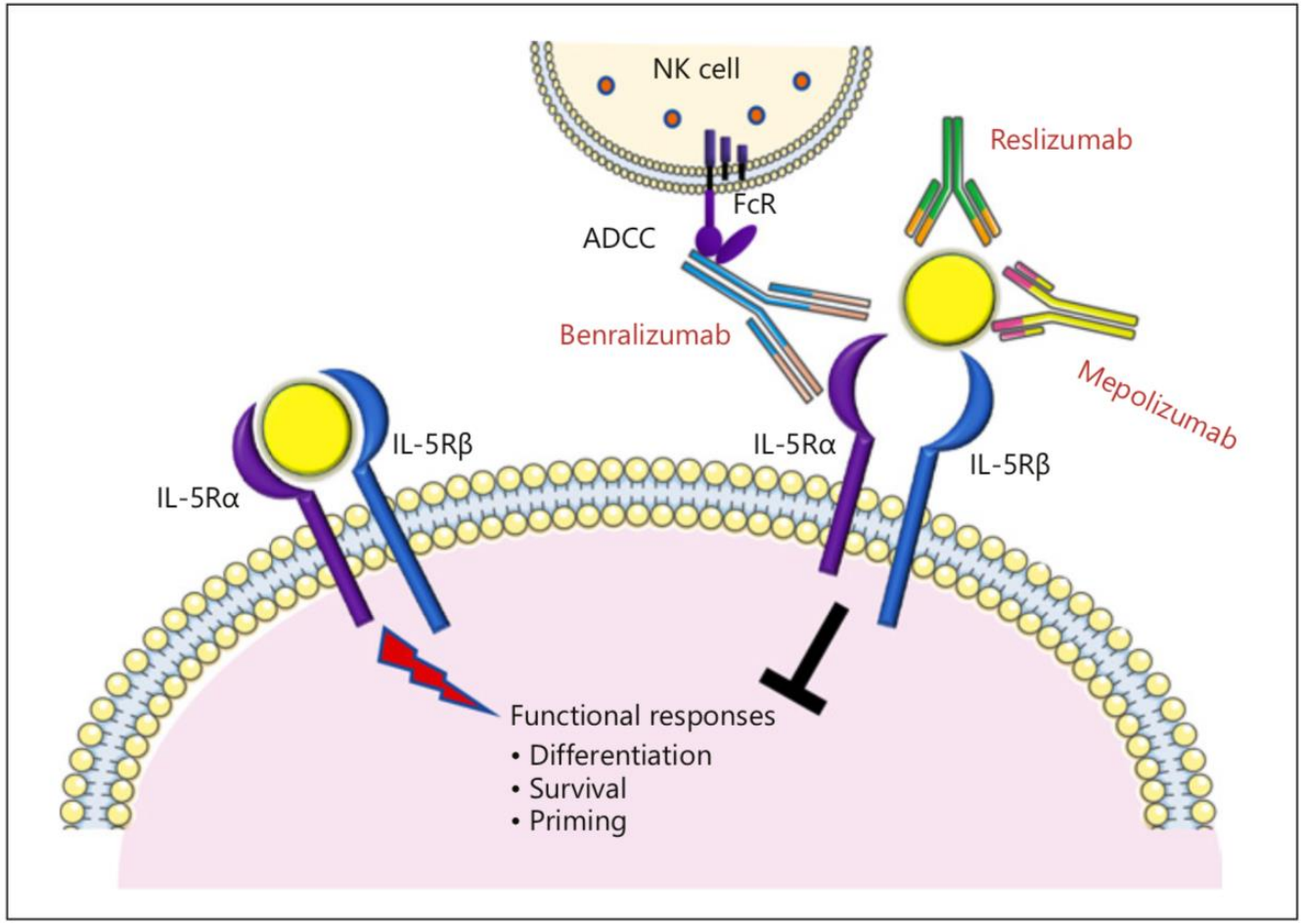
Ogbogu et al. J Allergy Clin Immunol 2009;124(6):1319.

Critical role of IL-5 in eosinophil biology



Pellaia et al. Front Physiol 2019; 10: 1514.

IL-5 (R) as therapeutic targets in eosinophilic disorders



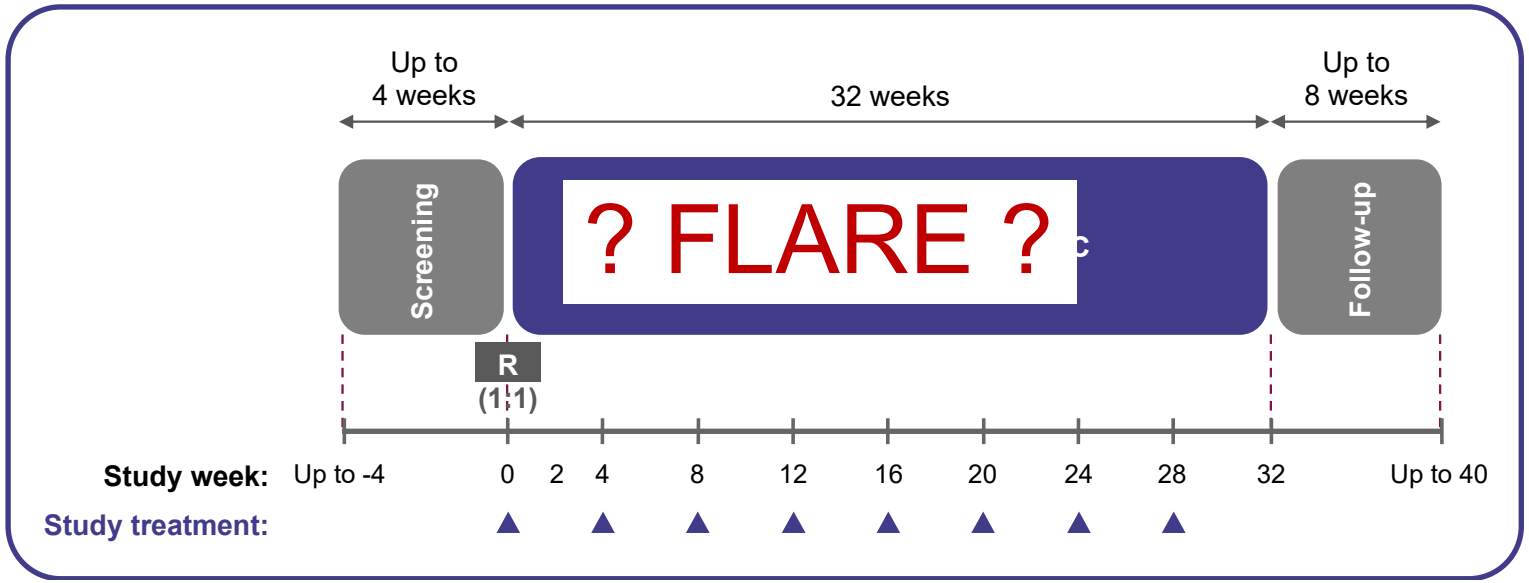
Simon et al. Int Arch Allergy Immunol 2020;181:11–23

200622 RCT: Mepolizumab 300 mg for HES

- ≥12 years of age
- Uncontrolled HES
- **Active Disease**
  ≥1000 cells/μL at screening
- **Diagnosis of *FIP1L1-PDGFRA*-negative HES***
  ≥6 months previously
- **Receiving a stable dose of HES therapy†**
  ≥4 weeks before the baseline visit

Randomized

Double blind



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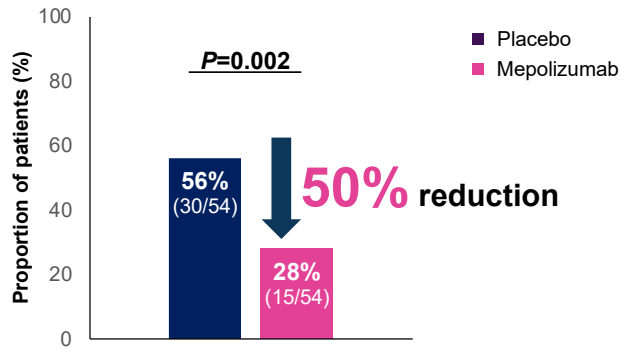
Roufosse F. et al, J Allergy Clin Immunol 2020;146:1397.

200622 RCT: Mepolizumab 300 mg for HES

PATIENTS

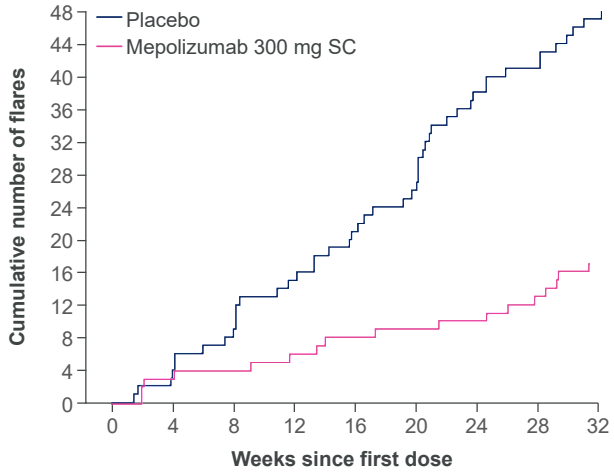
Proportion of patients who experienced a flare or withdrew* during the study period



Odds ratio (95% CI) mepolizumab versus placebo: 0.28 (0.12, 0.64); *P*=0.003

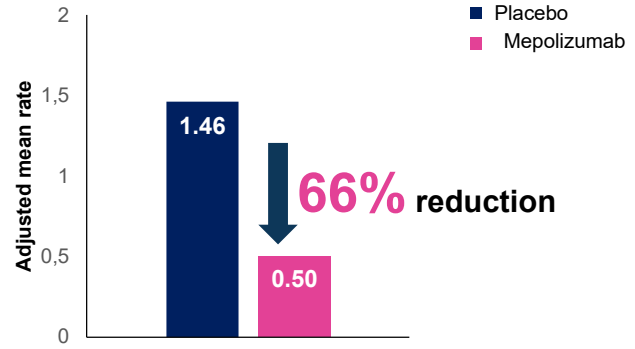
FLARES

Cumulative number of flares during the study period



FLARES

Annualized rate of flares



Rate ratio (95% CI) mepolizumab versus placebo: 0.34 (0.19, 0.63); *P*<0.001

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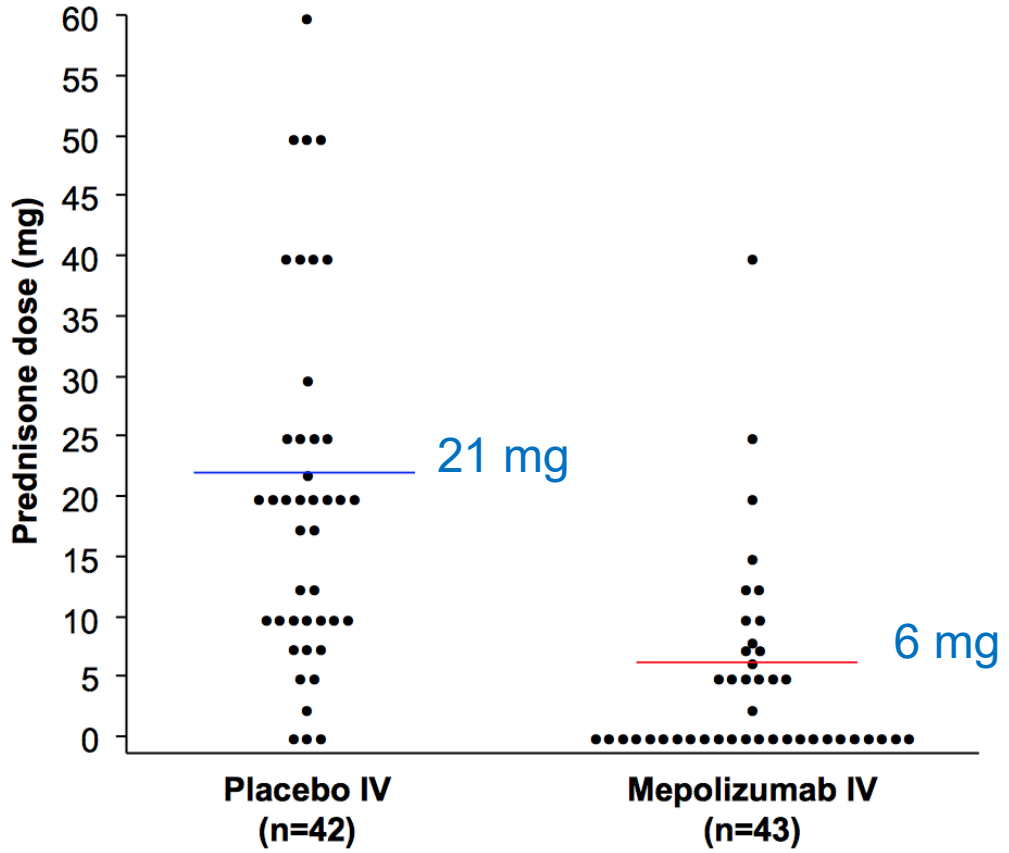
Roufosse F. et al, J Allergy Clin Immunol 2020;146:1397.

OCS - sparing with anti-IL-5

Mepolizumab 750 mg IV

Prednisone dose at end of study



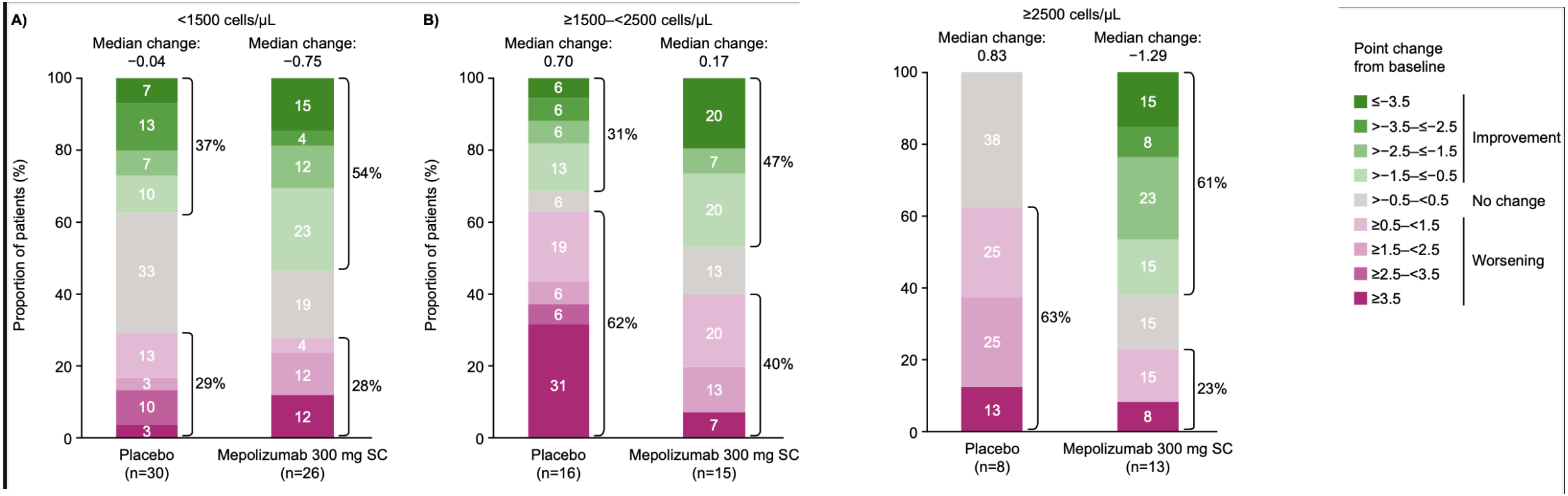
Rothenberg et al, New Engl J Med 2008; 358(12): 1215.

200622: Impact of Mepolizumab on Fatigue

< 1500 EOS

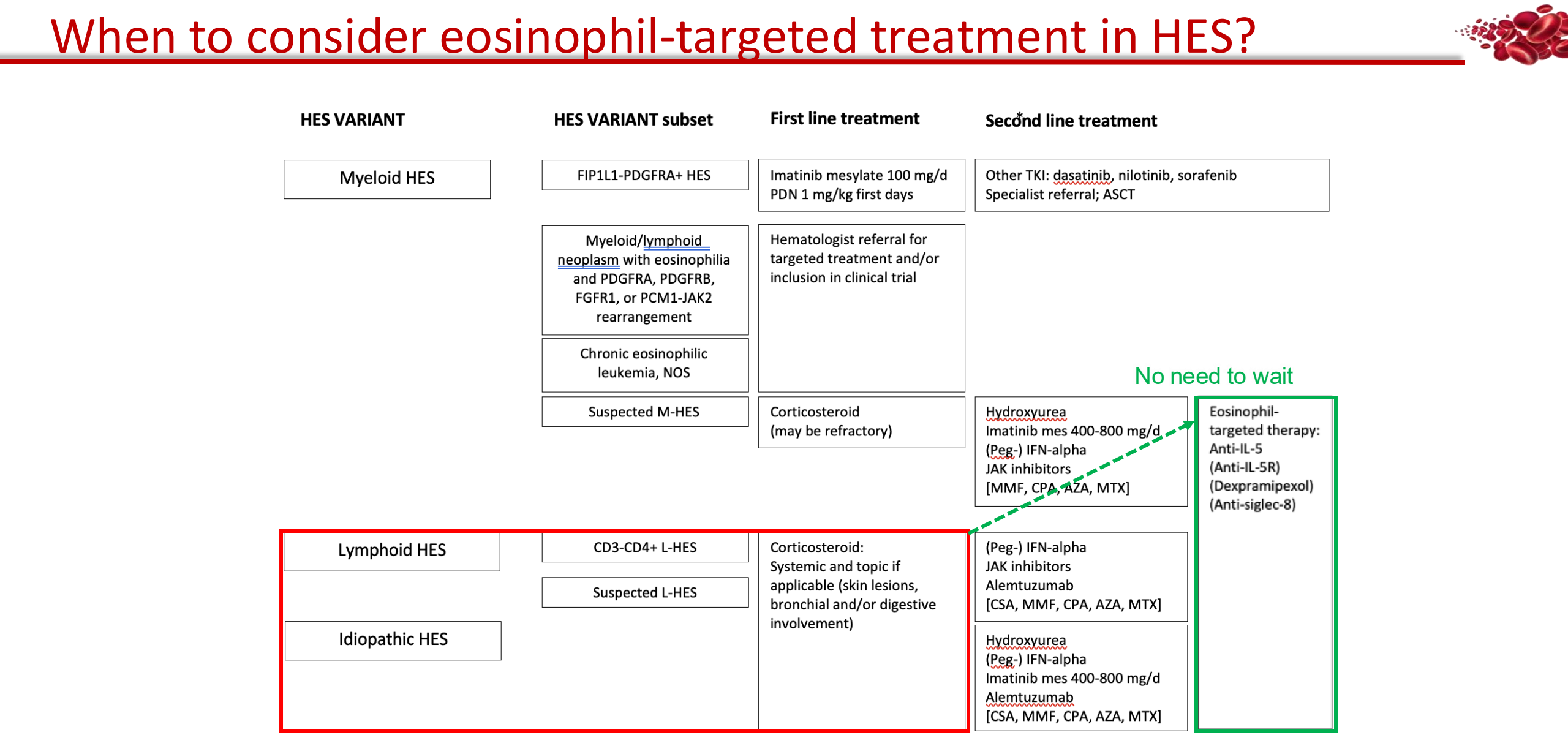
1500-2499 EOS

≥ 2500 EOS



Rothenberg et al, JACI In Practice 2022; 10(9):2367.

When to consider eosinophil-targeted treatment in HES?



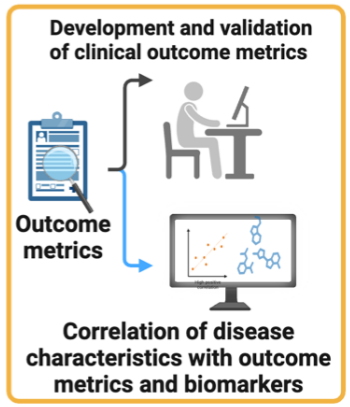
Taton et al, ERS Monograph: Eosinophilic Lung Diseases. EDU-0302-2020.R1

Treating HES: open questions and unmet needs

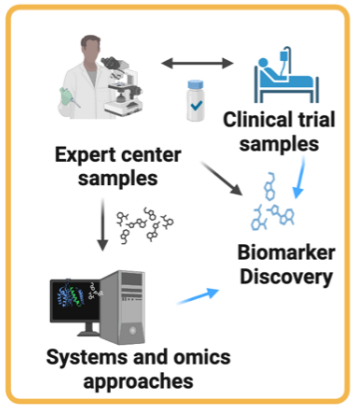
1 Outcomes

Development and monitoring of outcomes in EADs:

- Development and validation of clinical outcome measures
- Assessing outcomes based on disease subtypes, disease activity and severity
- Differentiation between modifiable disease activity and permanent damage



2 Biomarkers



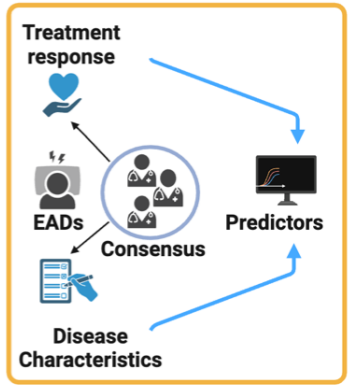
Important issues for blood and tissue biomarker discovery:

- Standardization and harmonization of sample collection and storage in expert centers and from clinical trials
- Assay standardization
- Search for biomarkers of disease severity and progression
- Systems biology and "omics" approaches

3 Predictors

Development of predictors for EADs:

- Consensus criteria for treatment response
- Predictors of response or non-response to different biologics
- Use of existing or available laboratory parameters or disease characteristics to develop predictors



4 Safety

Safety considerations of biologic use:

- Longer term studies
- Benefit:risk in pregnant individuals
- Effects of eosinophil depletion on homeostatic functions of eosinophils
- Infectious complications
- Risk for malignancies
- Risk for eosinophilia with certain biologics
- Use of dual biologics

Khoury P et al. J Leukoc Biol. 2024 Mar 8:qiae051.

Take home messages

- Patients with asymptomatic uncomplicated and idiopathic HE do not require treatment; regular follow-up for complications of HE!!
- Patients with hypereosinophilia and symptoms require thorough investigations for both the etiology and possible consequences of hypereosinophilia
- Even when you think it is HES… look twice!! It may be secondary hypereosinophilia
- HES is a set of rare chronic inflammatory systemic disorders generally requiring long-term treatment
- Clonal eosinophilic disorders must be investigated (expert referral) as they mandate treatment targeting molecular disease mechanisms (when possible)
- Otherwise, for all other disease forms, CS are a cornerstone for initial treatment
- Most classical second-line agents (e.g. hydroxyurea, interferon-alpha) are poorly tolerated and/or lack efficacy
- Many HES patients may benefit from eosinophil-targeted therapy
- Early introduction of eosinophil-targeting agents will reduce the morbidity associated with long-term use of CS and other immunosuppressive/cytotoxic agents
- Anti-IL-5 Abs do not target the primum movens of type 2 inflammation; treatment is suspensive, not curative.

THANK YOU FOR YOUR ATTENTION

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European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

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