GFEV GROUPE FRANÇAIS D'ÉTUDE DES VASCULARITES

Quels diagnostics devant une hyperéosinophilie et des manifestations systémiques ?

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Disclosures

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

Delayed Diagnosis of Systemic Eosinophilic Disorders

- Rare conditions
- Heterogeneous in their clinical and biological presentation
- Varied specialist referral because of multiplicity of target organs
- Diagnostic criteria confusing or non-existent
- Overlap between conditions associated with hypereosinophilia and/or vasculitis

Eosinophils contribute to pathogenesis of various diseases

Secondary hypereosinophilia

Eosinophils may be responsible for damage in addition to that caused by the underlying disease

- Parasitic infections (endomyocardial fibrosis)
- Adverse drug reactions : DRESS (eosinophilic myocarditis)
- Malignancies
  - Solid tumors (adenocarcinoma)
  - Haemopathies (T-cell lymphoma)

Eosinophil-related disorders

Eosinophils are 1 of several cells and mediators responsible for damage

- Pulmonary: severe eosinophilic asthma, eosinophilic granulomatos (EGPA), aller pulmonary as
- Cutaneous: a chronic spon bullous pemphigoid
- Digestive: eosinophilic oesophagitis, inflammatory bowel disease, etc.

Hypereosinophilic syndromes

Eosinophils are the predominant if not the only cell type responsible for the damage

od and/or sinophilia d with ediated organ damage and dysfunction

Eosinophilic Disorders

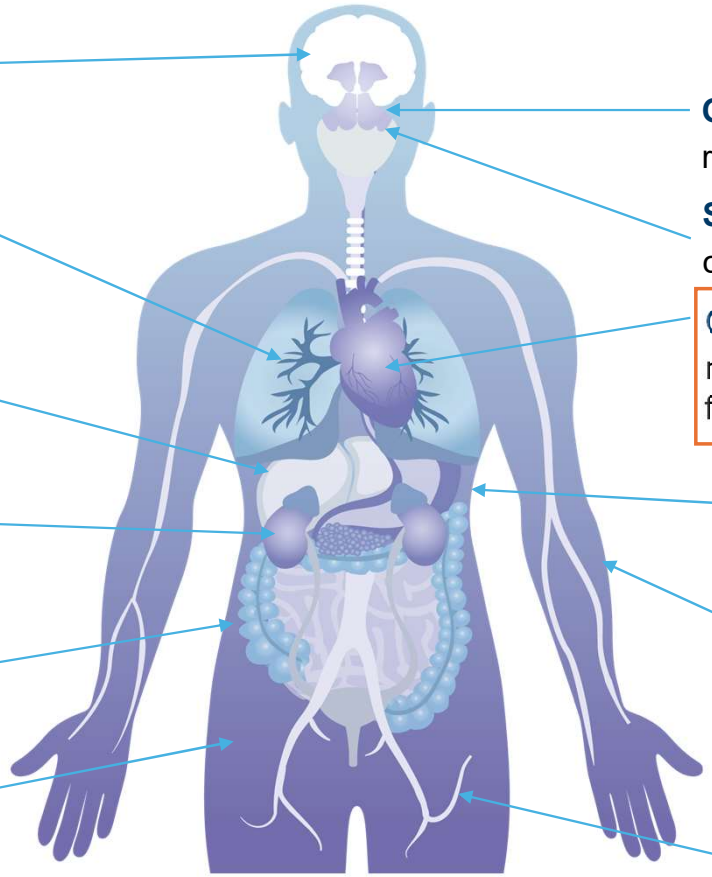
Hypereosinophilia and Hypereosinophilic Syndrome

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.

End-organ damage and clinical manifestations in HES



Neurological
embolic stroke, encephalitis, peripheral neuropathy

Pulmonary
asthma, eos. lung infiltrates, fibrosis, PAH vascular cuffing, pulmonary embolism

Hepatic
hepatitis, cholangitis

Renal/Urinary
interstitial nephritis, glomerulopathy, thrombotic microangiopathy, cystitis

Gastrointestinal
(gastro-)enteritis, colitis

Soft tissue / Rheumatological
angioedema, fasciitis, myositis, synovitis, arthritis

General
fatigue, myalgia, weight loss, fever

Ocular
retinal micro-emboli, choroidal inflammation

Sino-nasal cavities
chronic rhino-sinusitis, polyposis

Cardiac
myocarditis, intracavitary thrombus, subendocardial fibrosis, valve entrapment, pericarditis

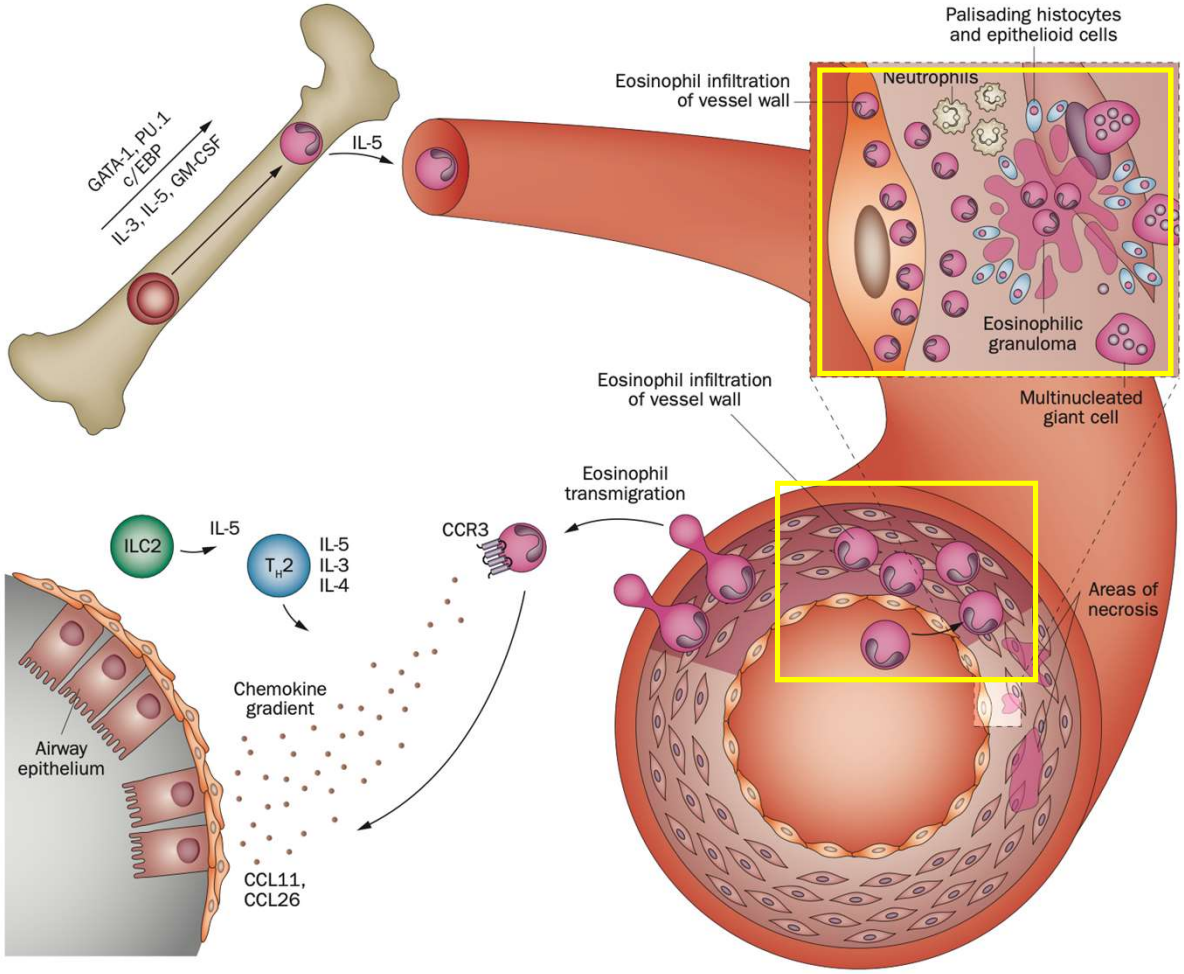
Hematological
splenomegaly, lymphadenopathy

Dermatologic
pruritis, eczema, dermatitis, urticaria, erythroderma, bullous lesions

Vascular
art/ven thrombosis, microvascular damage, Raynaud's
Vasculitis: digital necrosis, aneurysms, arterial dissection, …

Cogan & Roufosse. Expert Rev Hematol 2012;5:275. Roufosse F et al.

Eosinophils and vessel wall damage



- Direct cytotoxic effect on endothelial cells (granule proteins)
- Indirect cytotoxic effect through EPO-induced oxydation of bromide in presence of H2O2
- Expression of tissue factor by Eos, and induction on endothelial cells
- Eos inactivate endothelial cell-expressed thrombomodulin

Khoury et al. Nat Rev Rheumatol 2014; 10: 474–483. Roufosse F. Presse Médicale 2013; 42(5): 503-7.

Hypereosinophilia and Hypereosinophilic Syndrome

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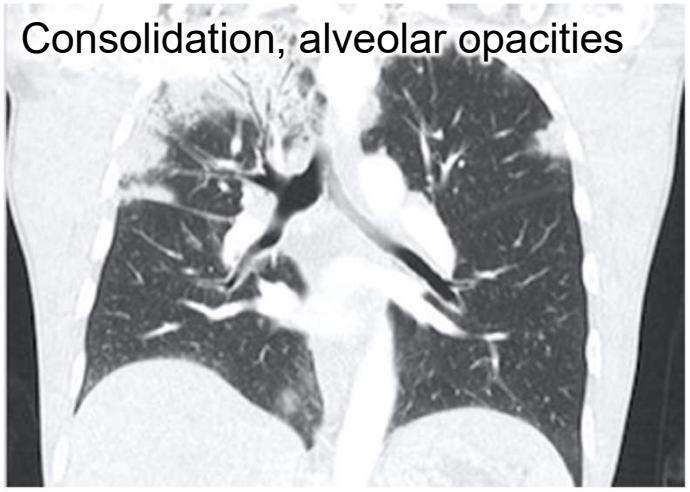
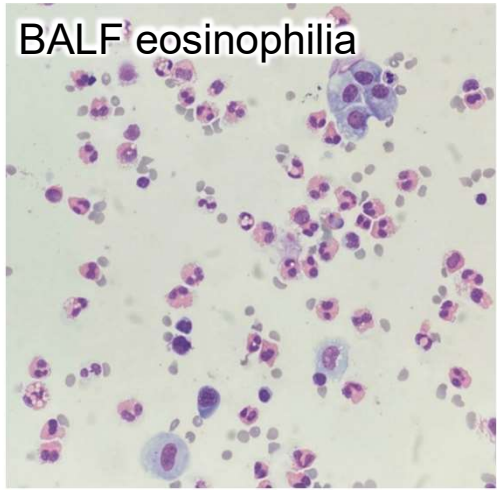
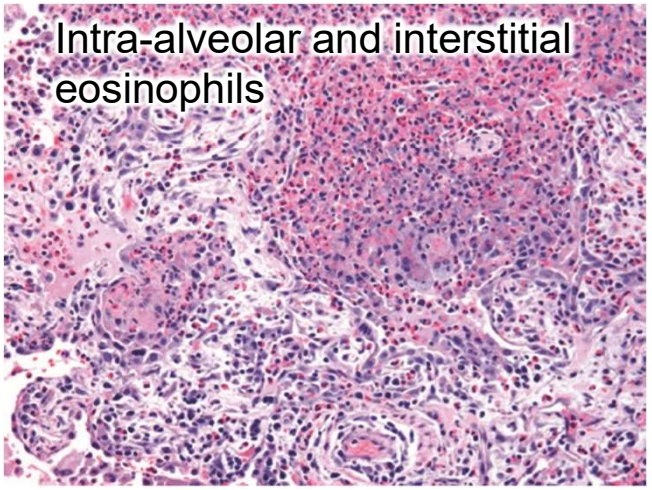
Hypereosinophilic syndrome(s)
Criteria for blood and tissue HE fulfilled AND
Organ damage and/or dysfunction attributable to tissue HE AND
Exclusion of other disorders or conditions as main reason for organ damage
Tissue/organ-restricted HES
Tissue HE but criteria for blood HE **not** fulfilled AND
Organ damage and/or dysfunction attributable to tissue HE AND
Exclusion of other disorders or conditions as major reason for organ damage

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

Idiopathic chronic eosinophilic pneumonia







Diagnostic criteria

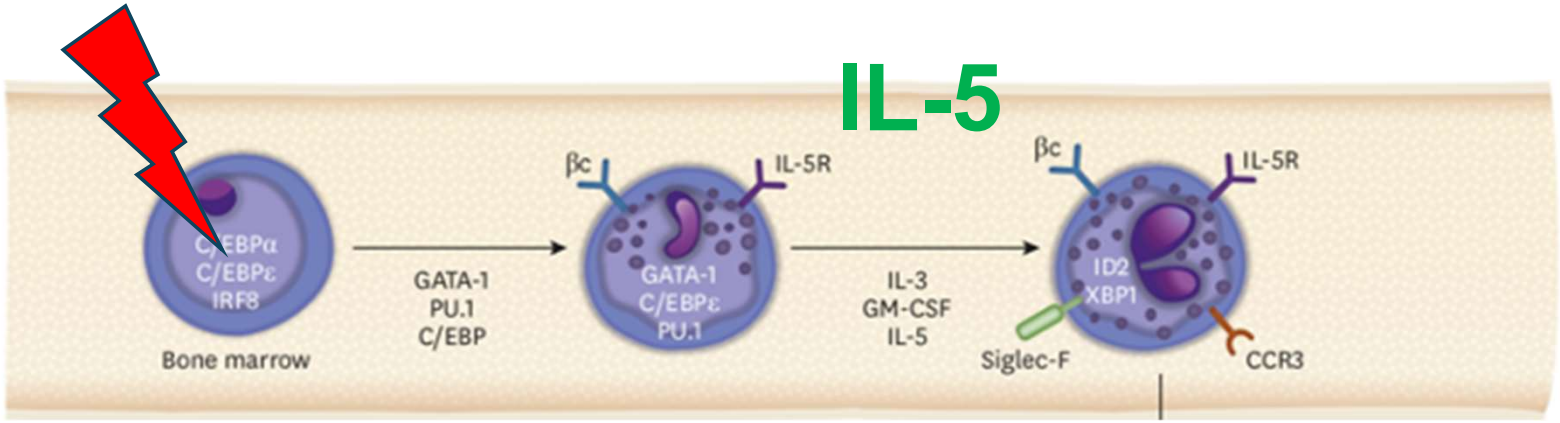
✓ Ongoing respiratory symptoms, usually > 2 weeks duration
✓ Blood eos > 1000/mm^3 and/or BALF eos > 25 (40)% and/or pulmonary eosinophilia
✓ Pulmonary infiltrates, usually with a peripheral predominance
✓ Exclusion of other known causes of eosinophilic lung disease

Crowe et al. Therapeutics and Clinical Risk Management 2019;15: 397. Suzuki et al. Allergology International 2019; 68: 413.

Pathogenesis of hypereosinophilia in HES

Somatic mutation driving clonal eosinophil expansion

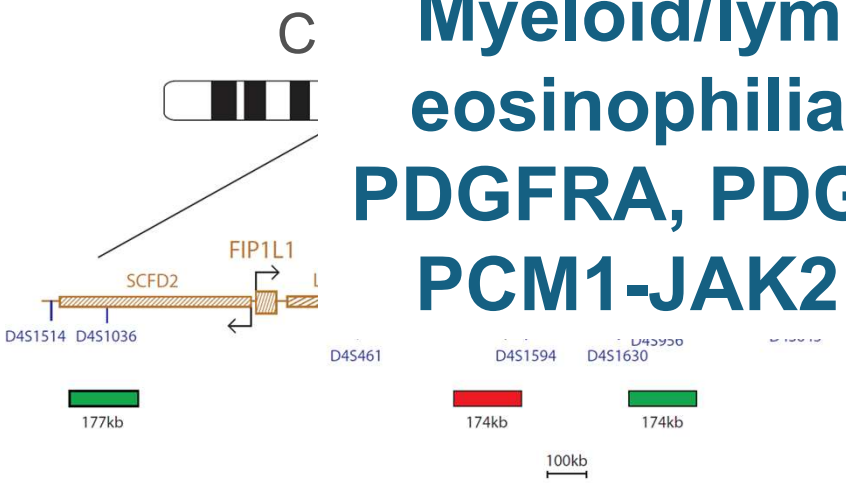
Increased presence of eosinophilopoietic factors driving polyclonal eosinophil expansion



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

UNKNOWN

HES variants: pathogenic classification



Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2 (revised WHO classif)

Autonomous TK activity
Clonal eosinophil expansion

Suspect in presence of:

- Male gender
- Elevated serum vitamin B12 and/or tryptase
- Enlarged spleen
- Corticosteroid resistance

DIAGNOSIS reached by :

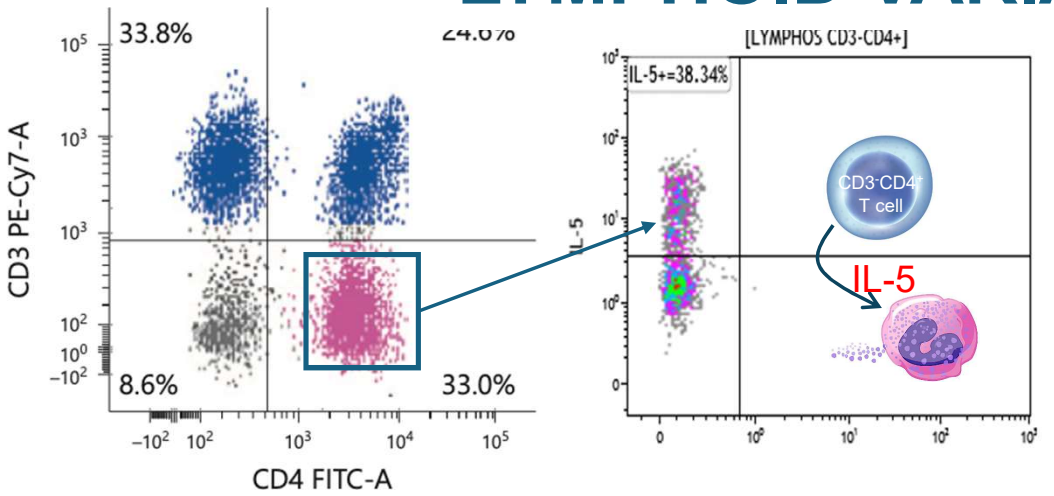
- PCR for the FIP1L1-PDGFRA fusion
- FISH for CHIC2 locus (deleted)

Cools et al. New Engl J Med 2003; 348(13):1201.

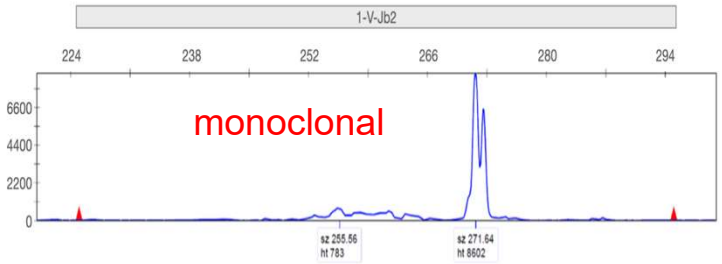
HES variants: pathogenic classification

Lymphocyte phenotypi

LYMPHOID VARIANT HES



TCR gene rearrangement pattern (PCR)



Suspect in presence of:

- Predominant cutaneous manifestations
- Serum hypergglobulinemia (IgG, IgM)
- Angioedema, fasciitis, tenosynovitis

DIAGNOSIS reached by :

- Lymphocyte (T cell) phenotyping
- PCR/NGS for TCR gene rearrangement pattern
- Serum TARC (CCL17) measurement

Cogan et al. New Engl J Med 1994; 330(8):535.

HES variants: pathogenic classification

Myeloid variant HES

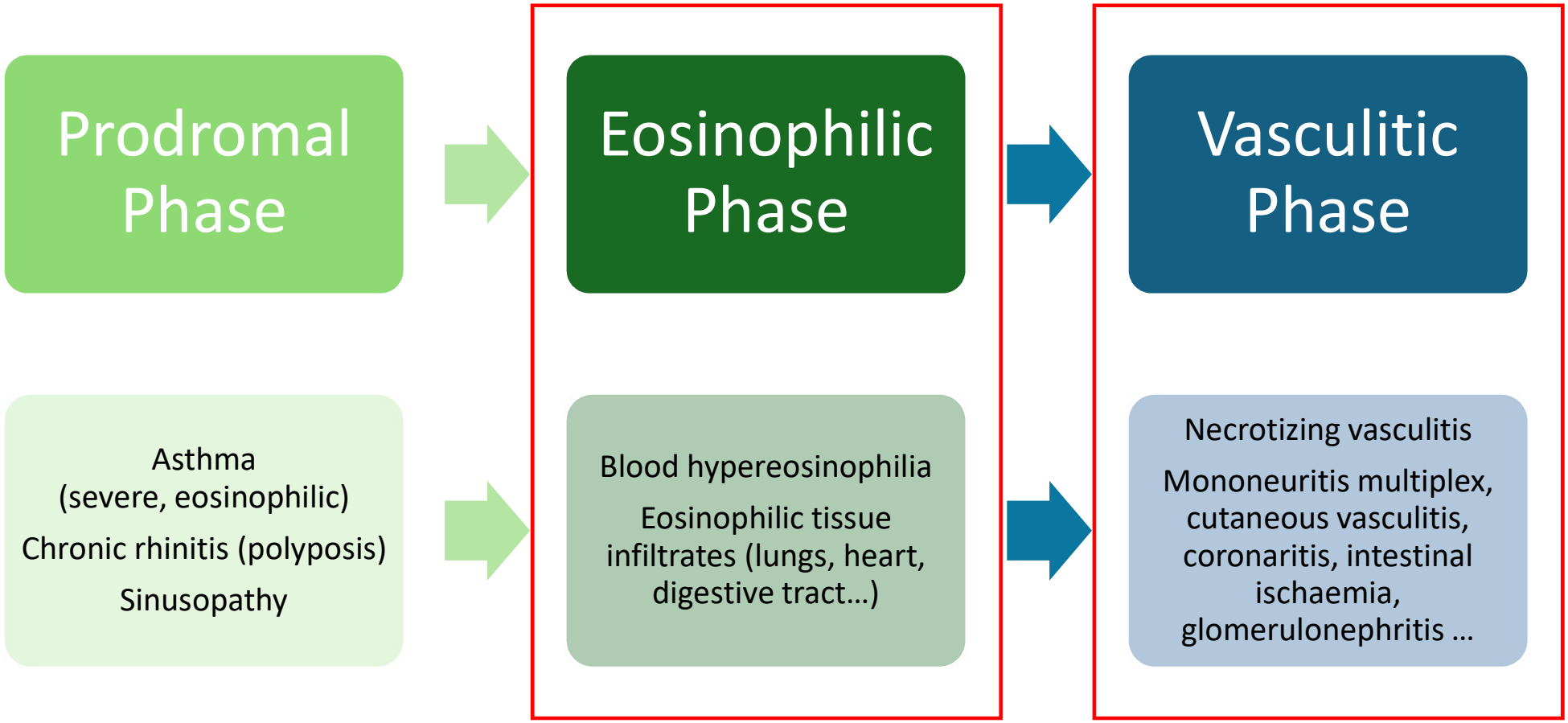
FIP1L1-PDGFRA
Other cytogenetic rearr (PDGFRA/B, FGFR1, …), mutations (JAK2 …)
Constellation of myeloproliferative features

Idiopathic HES (~70%)

Lymphoid variant HES

Clonal CD3-CD4+ T cells
Other phenotypic abN (CD3+TCRa/b+CD4-CD8-, CD3+CD4+CD7- …)
Constellation of type 2 inflammation markers

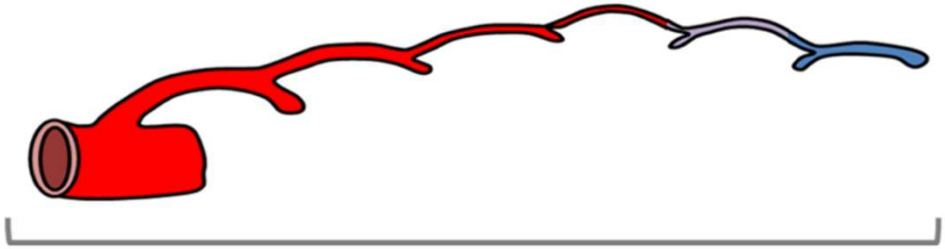
Eosinophilic granulomatosis with polyangiitis



Adapted from a slide kindly provided by Pr. A. Froidure.

Eosinophilic vasculitis (EoV)

- Case series (n=10) and literature review (n=107)
- Patients with Bx-proven eosinophilic vasculitis or strong clinical surrogates, without asthma or ANCA
- Authors excluded patients with myeloid or lymphoid HES variants
- 2 major sub-groups :



Idiopathic EoV (or idiopathic HES-associated vasculitis) (n=76)
Involved vessels can be small -(83%), medium- (22%) and/or large-sized (22%) (variable vessel vasculitis)

Single-organ EoV (n=41)
Isolated coronary (n=29), temporal (n=8), cerebral EoV (n=4)

Lefevre et al. J Allergy Clin Immunol In Pract 2020 ;8(4):1329-1340.

Eosinophilic vasculitis : Diagnostic criteria

All four of the following criteria must be met:

1. **At least one of the following histopathologic or clinical features of vasculitis**

a. Any organ manifestation associated with biopsy-proven necrotizing vasculitis and predominant eosinophilic infiltration in the vessel wall (and/or marked deposition of eosinophil granule proteins), and/or

b. Any organ manifestation associated with biopsy-proven perivascular eosinophilic infiltrates, and leukocytoclastic capillaritis, and/or eosinophilic infiltration in the vessel wall (and/or marked deposition of eosinophil granule proteins), and/or

c. Any case of blood hypereosinophilia >1.5 G/L associated with a clinical manifestation consistent with the involvement of vasculitis, such as palpable purpura, myocardial infarction caused by proven coronaritis, cerebral vasculitis, mononeuritis simplex, digital necrosis, etc…

2. **The absence of other disorders or conditions causing eosinophil-induced organ damage and secondary vasculitis (i.e underlying inflammatory, infectious, neoplastic or drug-induced disorders)**

3. **The absence of ANCAs**

4. **No persistent/active asthma on diagnosis** (and no history of persistent unexplained cough, dyspnea, wheezing, etc..).

Coronary arteritis, temporal arteritis and cerebral arteritis may be considered as *idiopathic single-organ EoV* when there is no other organ involvement (*e.g.* coronary EoV, temporal EoV, etc..). The term *EoV* may be suitable for all other situations, even when the disease appears to be restricted to a single organ or vascular territory.

Lefevre et al. J Allergy Clin Immunol In Pract 2020 ;8(4):1329-1340.

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY

CLASSIFICATION CRITERIA FOR **EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS**

Idiopathic EoV

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- These classification criteria should be applied to classify a patient as having eosinophilic granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria

CLINICAL CRITERIA

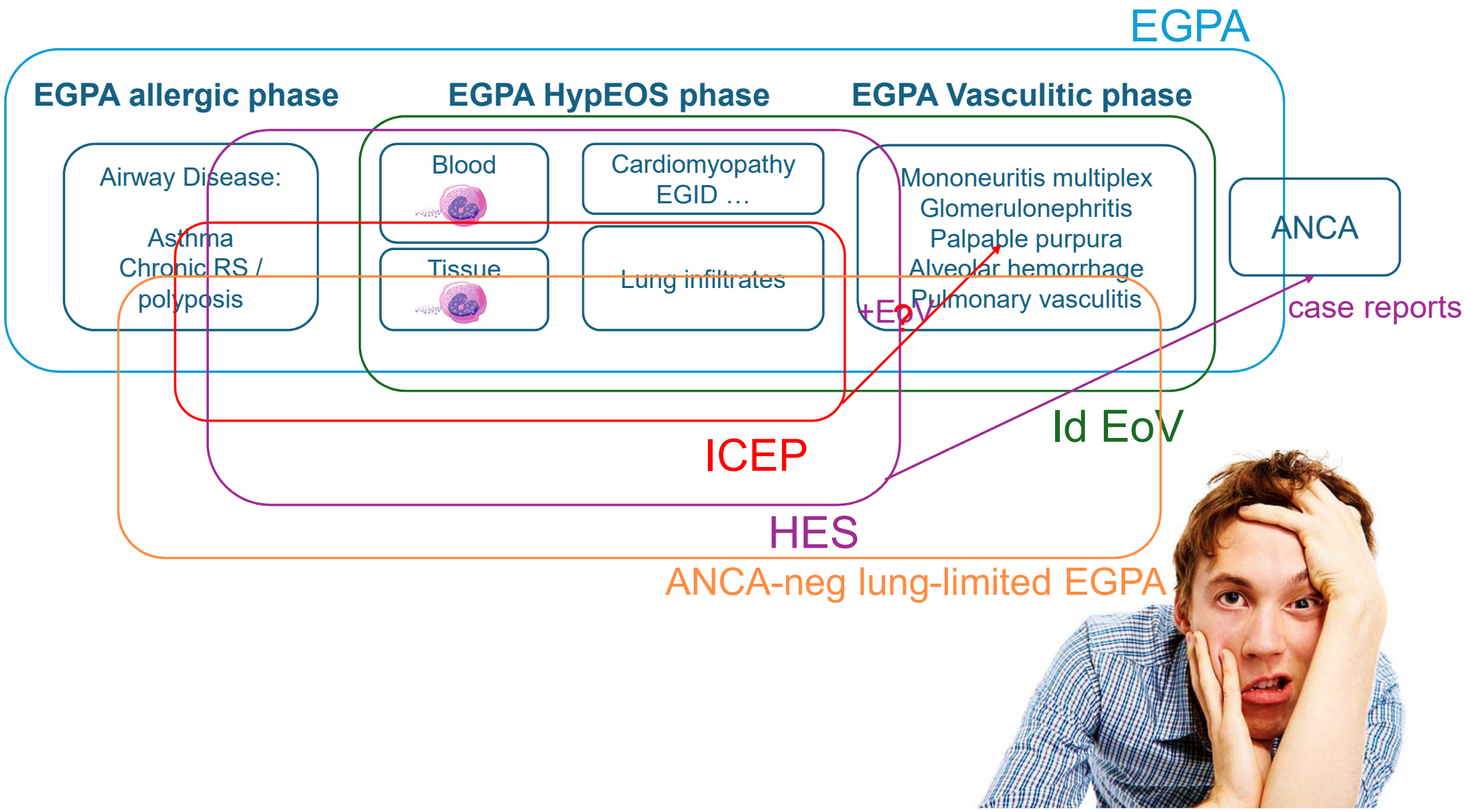
~~Obstructive airway disease~~	+3
Nasal polyps	+3
Mononeuritis multiplex	+1

LABORATORY AND BIOPSY CRITERIA

Blood eosinophil count ≥ 1 x10^9/liter	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
~~Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies~~	-3
Hematuria	-1

7

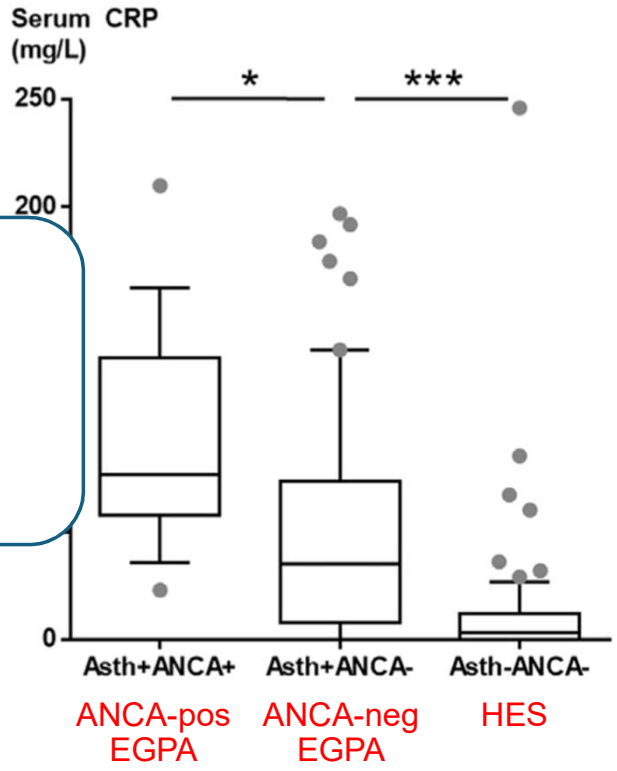
Sum the scores for 7 items, if present. A score of ≥ 6 is needed for classification of EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS.


EGPA
EGPA allergic phase
EGPA HypEOS phase
EGPA Vasculitic phase
Airway Disease:
Asthma
Chronic RS / polyposis
Blood
Tissue
Cardiomyopathy
EGID …
Lung infiltrates
Mononeuritis multiplex
Glomerulonephritis
Palpable purpura
Alveolar hemorrhage
Pulmonary vasculitis
+EoV?
ANCA
case reports
ICEP
Id EoV
HES
ANCA-neg lung-limited EGPA

What about disease-specific biomarkers?

Biomarker	Description	Associated with disease activity in EGPA?	Associated with eosinophil count?	Differs between patients with EGPA and healthy individuals?	Differs between patients with EGPA and other diseases?	Key reference(s)
Peripheral blood biomarkers						
ECP	Eosinophil granule protein	Yes	Yes	ND	ND	90
CCL17	Chemokine	Yes	Yes	Yes	No (HES)	57,89
CCL11 (eotaxin)	Chemokine	No	No	No	No (asthma, HES, SVV)	87
CCL24 (eotaxin 2)	Chemokine	No				
CCL26 (eotaxin 3)	Chemokine	Yes				
sIL-2R	Cytokine receptor	Yes				
IL-5	Cytokine	No				
IL-8	Chemokine	ND				
IL-25	Cytokine	Yes				
IgE	Immunoglobulin	Yes				
IgG4	Immunoglobulin	Yes	ND			
T-cell stimulation						
IL-4	T_H2-type cytokine	ND	Yes	Yes	Yes (SVV)	70
IL-13	T_H2-type cytokine	ND	No	Yes	Yes (SVV)	70
Tissue biomarkers						
Eosinophil count	Sputum	Yes	ND	ND	Yes (asthma)	84
Sputum ECP	Eosinophil granule protein	Yes	ND	ND	Yes (asthma)	84
Exhaled 12-HETE	Arachidonic acid metabolite	No	No	Yes	Yes (asthma, HES)	93

NOTHING really amazing so far



Khoury et al. Nat Rev Rheumatol 2014; 10: 474–483.
Leurs et al. J Allergy Clin Immunol Pract. 2019 Apr;7(4):1347-1351.

Case study

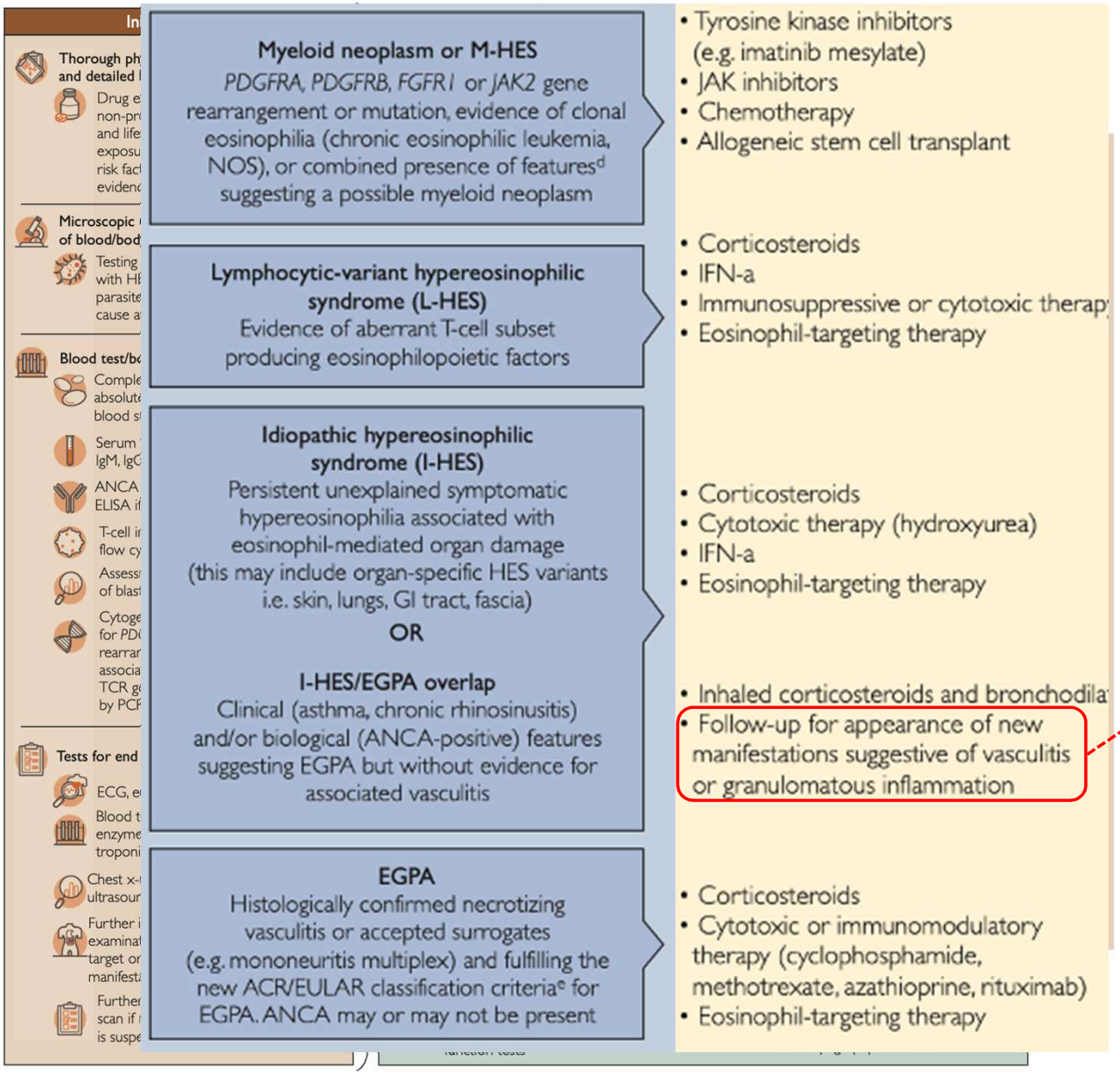
- Asthma during adolescence > resolved
- 30y: sinusitis > 35y: invalidating, numerous courses ABT
- 40y:
  - Bx
  - AE
- 41y:
  - AE
  - Ch
  - Sinu
  - EBUS with LN Bx: numerous eosinophils, fibrosis, and granulomatous inflammation

  Treatment: high-dose GC > 4 wks later, AEC still at 5.2 10^9/L
- Referred to a hematologist for BM Bx > FIP1L1/PDGFRA

Even in presence of clinical presentations that are strongly suggestive of (ANCA-negative) EGPA (i.e. asthma, sino-nasal disease, lung infiltrates, vasculitis/granulomatous inflammation, systemic symptoms), investigation for underlying myeloid or lymphocyte-driven disease is recommended

Khoury et al. Mayo Clin Proc 2023; 98(7): 1054-1070.

From work-up and investigation of hypereosinophilia to diagnosis of HES and EGPA



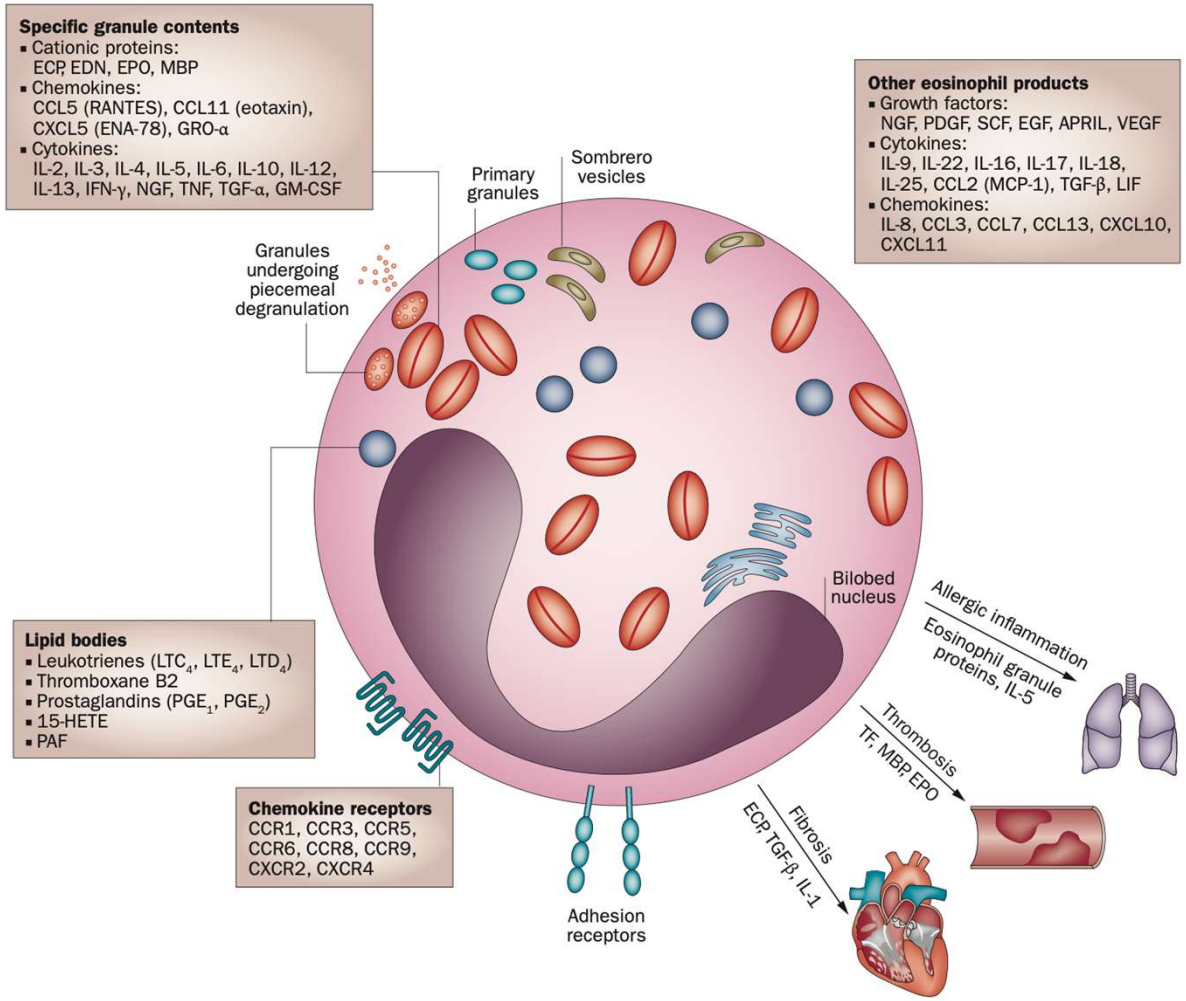
Therapeutic strategy

unclear

What to do with the biologic that may have been initiated?

Khoury et al. Mayo Clin Proc 2023; 98(7): 1054-1070.

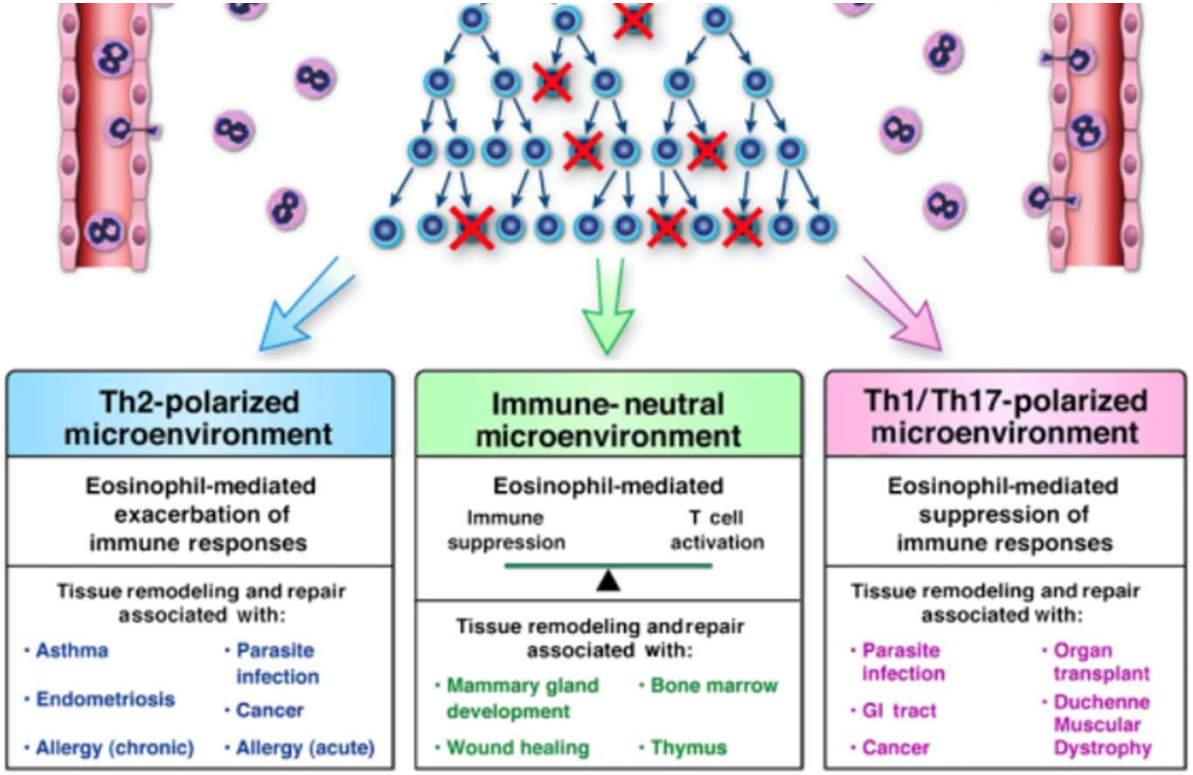
Eosinophils as mediators of damage



Khoury et al. Nat Rev Rheumatol 2014; 10: 474–483.

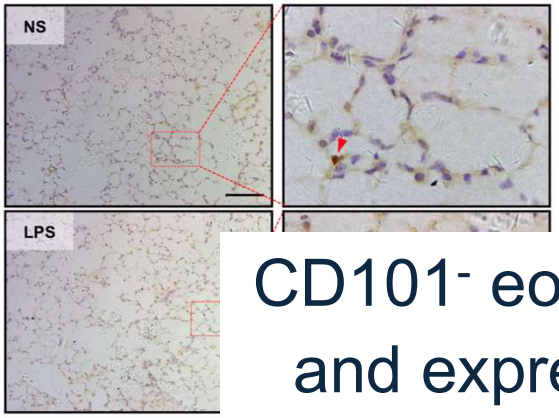
Eosinophils as homeostatic cells: LIAR hypothesis

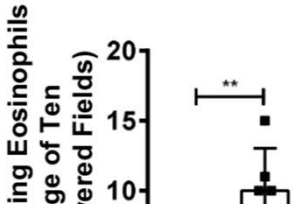
Local Immunity And/or Remodelling/Repair



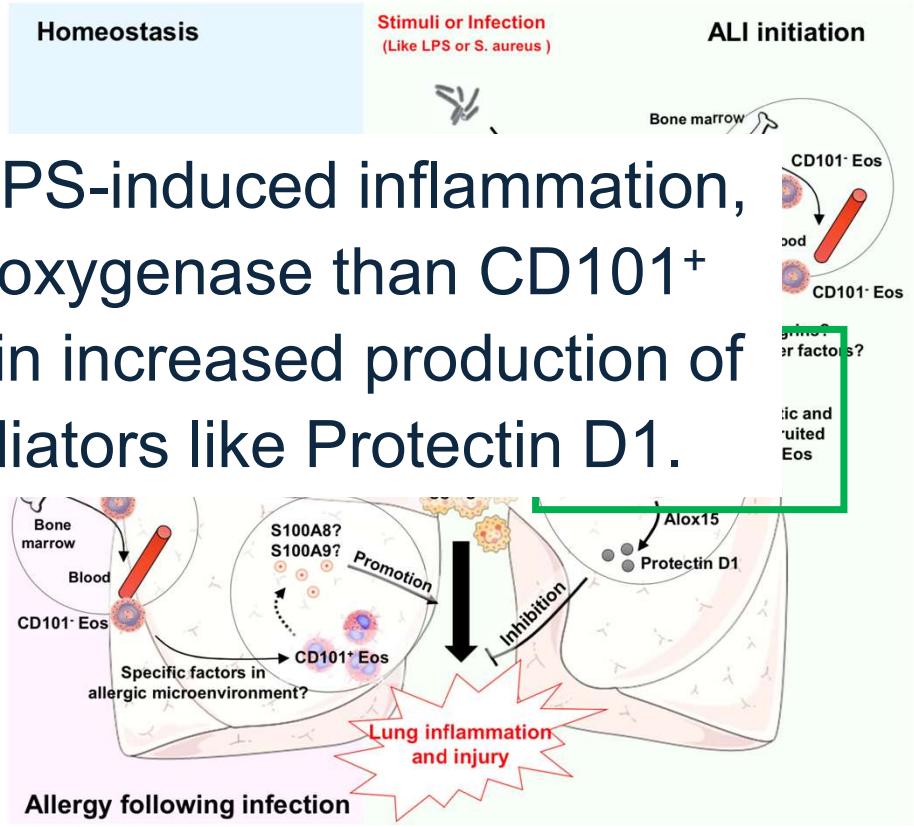
Lee et al. Clinic Exper Allergy 2010; 40: 563.

Acute Lung Injury: Eosinophils inhibit type 1 inflammation

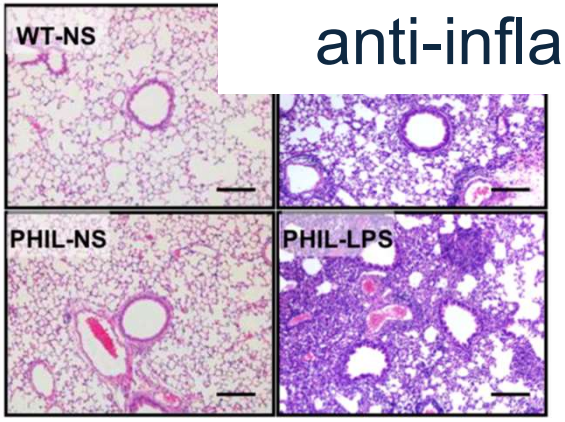




Endotoxin-induced ALI model



CD101^{-} eosinophils reduce LPS-induced inflammation, and express more 12,15-lipoxygenase than CD101^{+} eosinophils. This may result in increased production of anti-inflammatory lipid mediators like Protectin D1.

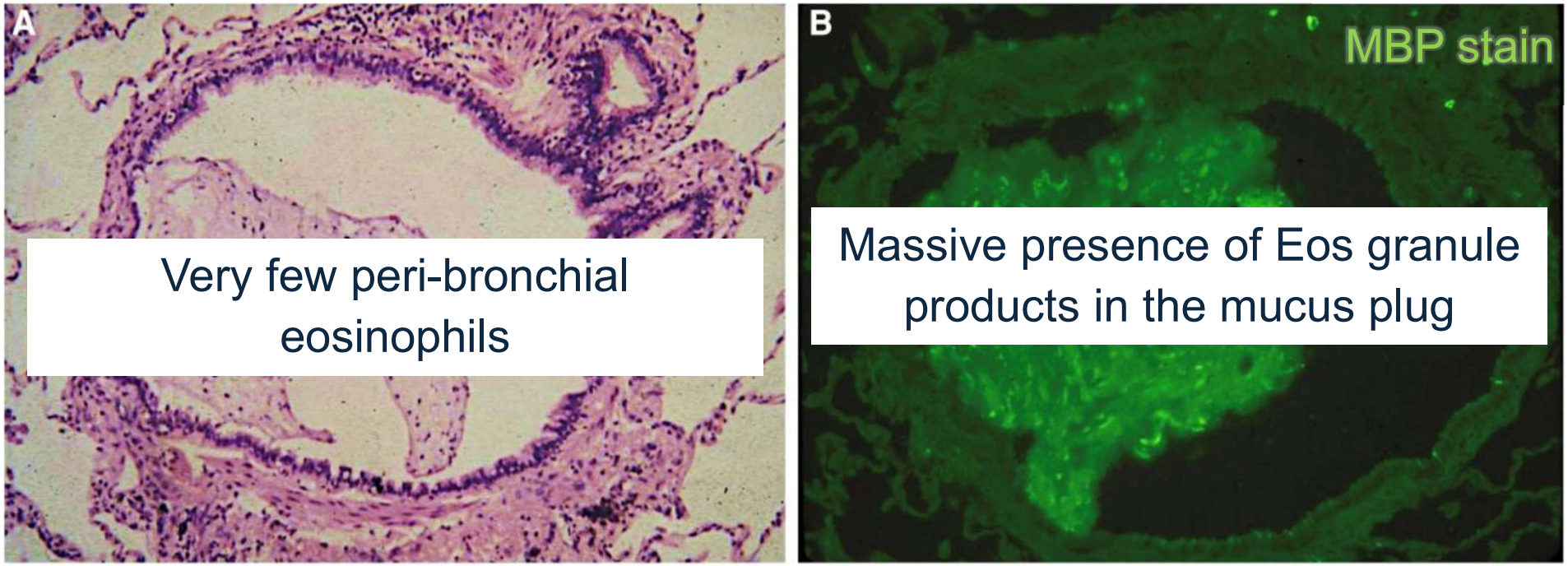


EOS KO mice

Chen Zhu et al. Eur Respir J 2020; Nov 5;56(5):1902354.

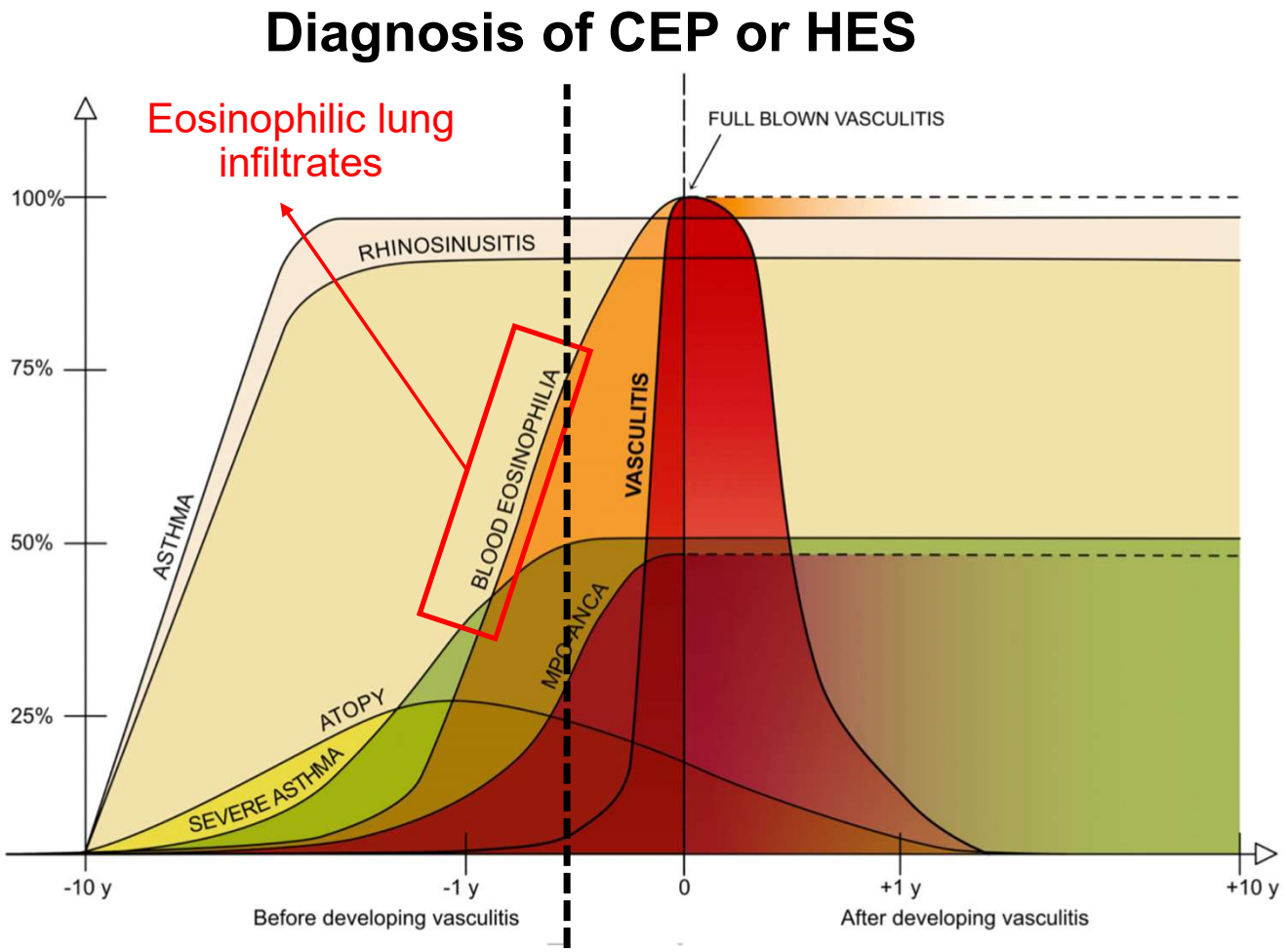
Eosinophils … as invisible trouble-makers

The true extent of eosinophil involvement in disease is unrecognized: the secret life of dead eosinophils



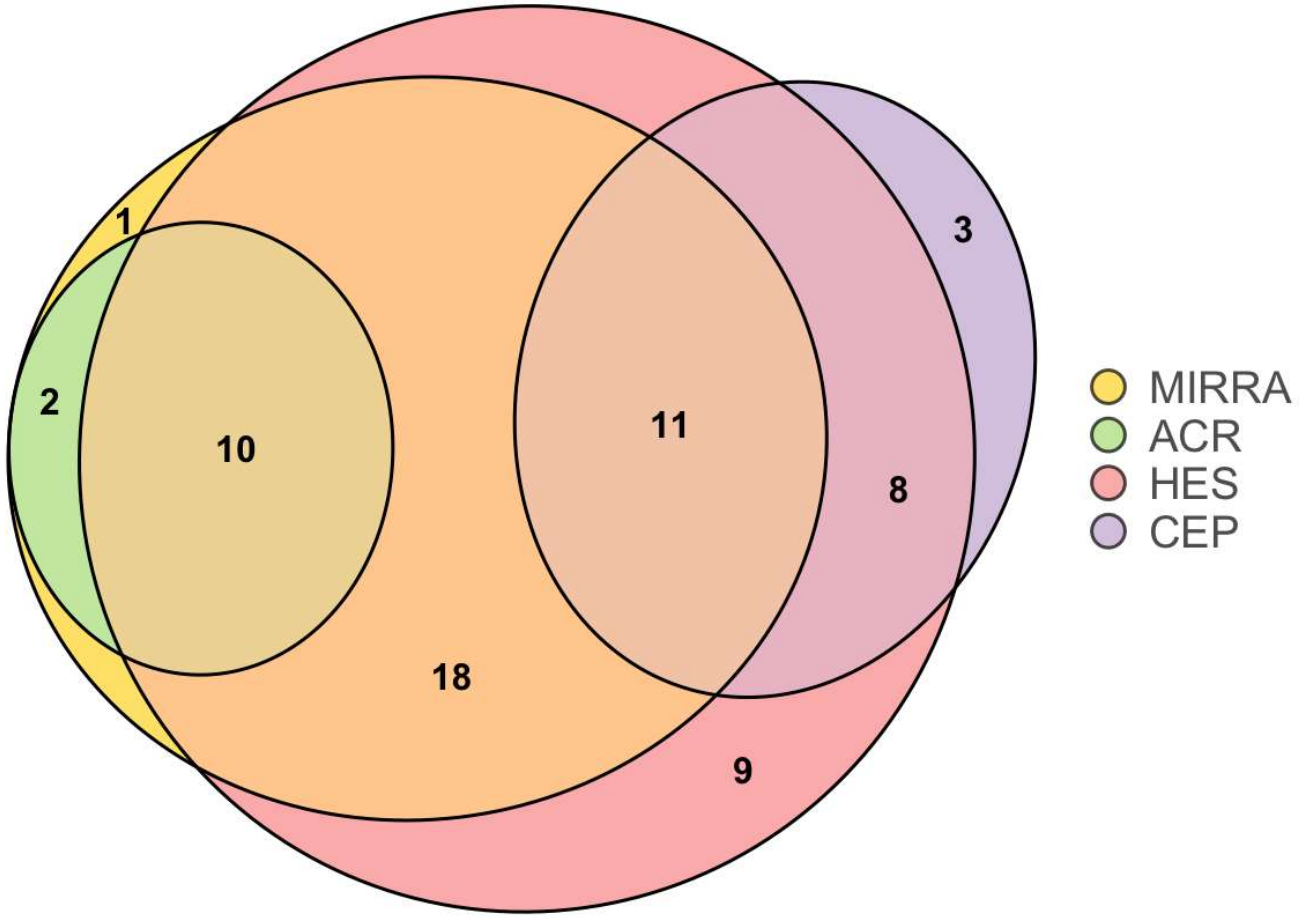
Leiferman K. & Gleich G. J Leuk Biol 2024; 116 (2): 271-287.

EGPA clinical course: overlap with HES and CEP



GC treatment ➡ GC-sparing treatment … … ???

OVERLAP : Eosinophilic pulmonary conditions



Unpublished; abstract submitted to International Eosinophil Society congress; Montpellier July 2025

Paradoxically, the delay in diagnosis may increase

- Heightened awareness of hypereosinophilia and its consequences
- More prompt assessment and implementation of eosinophil-lowering treatment
  - Glucocorticoids
  - Eosinophil-tageted treatment (anti-IL-5, anti-IL-5R)
- Prudence during GC-tapering and follow-up!!
  - Regular assessment in the clinic
  - Education of patients and first-line physicians about clinical manifestations related to vasculitis

In conclusion

- Besides text-book cases where a patient endures the full spectrum of disease before receiving medical attention (i.e. MPO-ANCA, vasculitis, asthma, polyposis, hypereosinophilia), differential diagnosis between EGPA, HES, ICEP, and EoV is challenging...
- And sometimes just plain impossible because the definitions/classifications/nomenclature truly do overlap
- Although it is strongly recommended to biopsy as much as possible in hopes of detecting vasculitis and eosinophilic granuloma to reach a diagnosis of EGPA, it is well-known that results are often disappointing
- What really counts is targeting the appropriate mediators and cells with treatment, to reverse damage, and prevent further emergence of complications
- Targeting eosinophils is proving to be a valid approach for all these conditions, but whether concomitant therapy directed against other disease mechanisms is warranted in specific patient sub-groups remains elusive
- Clinicians must remain wary of emergence of vasculitic / ischemic complications in patients initially presenting with asthma, and blood and tissue hypereosinophilia

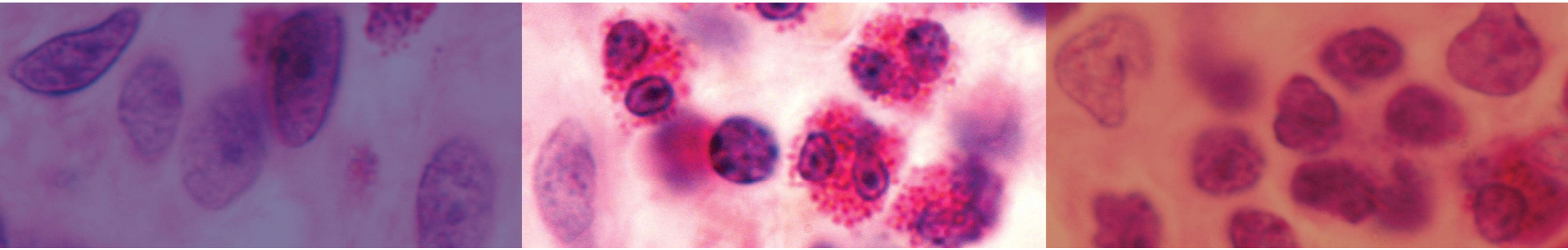
THANK YOU FOR YOUR ATTENTION

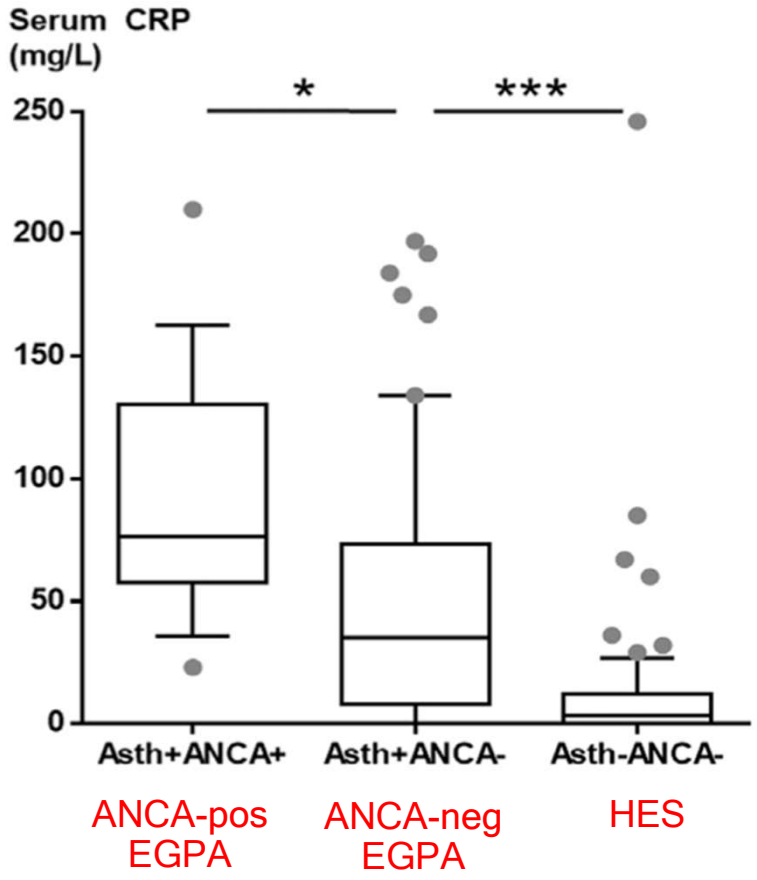
13th Biennial Congress of the International Eosinophil Society

7-11 July 2025

International Eosinophil Society
IES

MONTPELLIER *France*



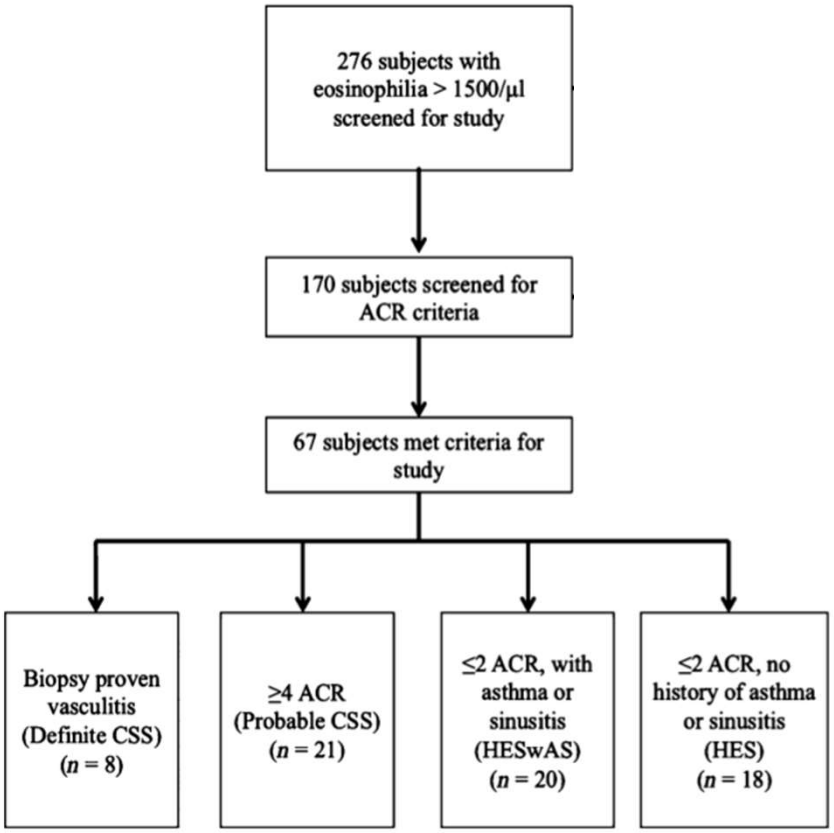


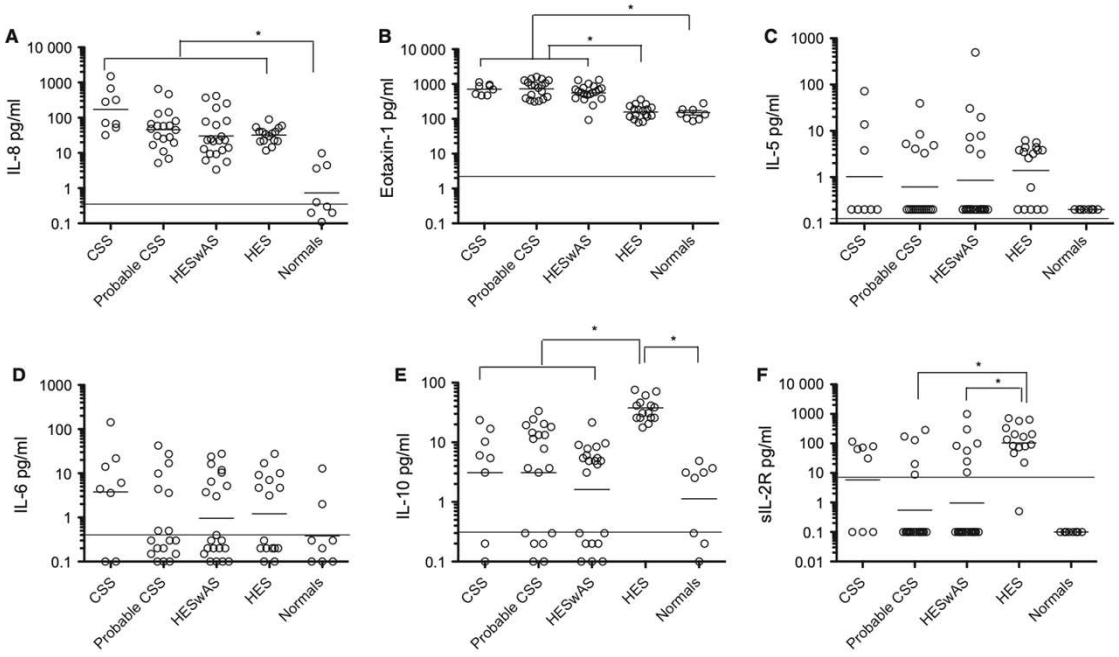
C-Reactive protein as a diagnostic tool in differential diagnosis of hypereosinophilic syndrome and antineutrophil cytoplasmic antibody–negative eosinophilic granulomatosis with polyangiitis

we considered Asth−ANCA− patients to be our reference set for HES diagnosis. Conversely, MPO/ANCAs being the strongest biomarker for EGPA, Asth+ANCA+ patients were chosen as the reference set for EGPA diagnosis.

Leurs et al. J Allergy Clin Immunol Pract. 2019 Apr;7(4):1347-1351

Questionable approach to studies seeking differences





Serum biomarkers are similar in Churg–Strauss syndrome and hypereosinophilic syndrome

Khoury et al. Allergy 2012;67(9):1149-56.

Questionable approach to studies seeking differences

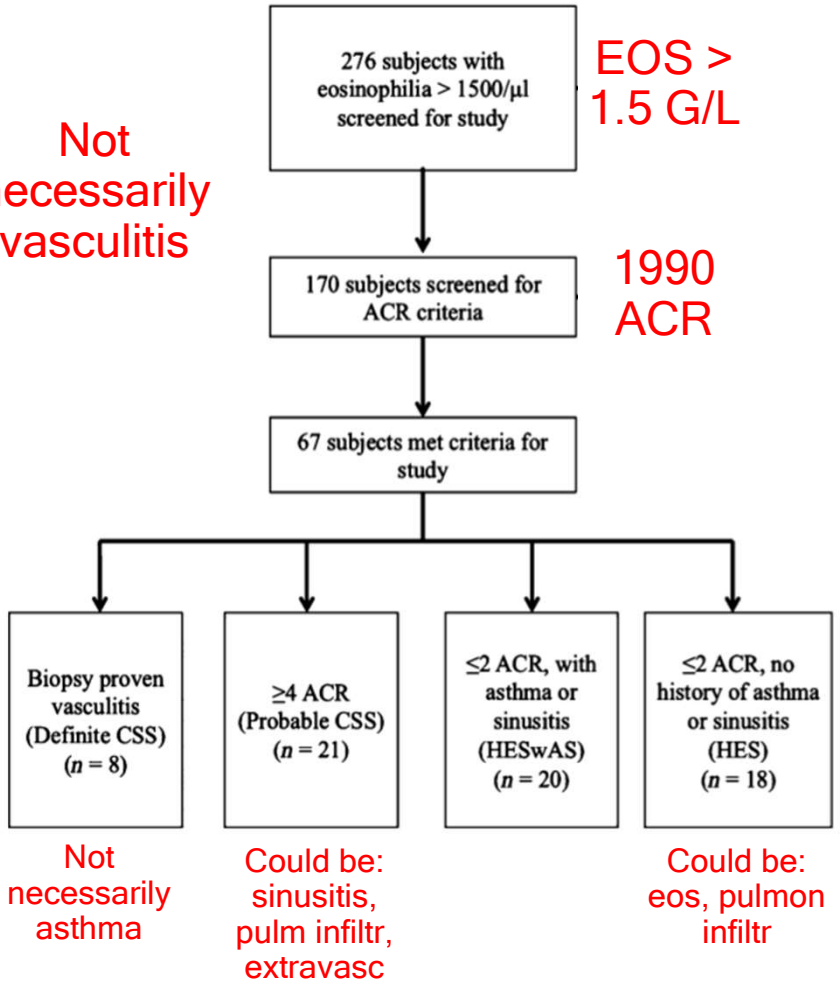


Table 2. 1990 criteria for the classification of Churg-Strauss syndrome (traditional format), their sensitivity and specificity versus other defined vasculitis syndromes*

Criterion	No. of CSS patients (n = 20)	Sensitivity (%)	No. of control patients (n = 787)	Specificity (%)
Asthma	19	100	782	96.3
Eosinophilia >10%	20	95	708	96.6
Neuropathy, mono or poly	20	75	781	79.8
Pulmonary infiltrates, non-fixed	20	40	736	92.4
Paranasal sinus abnormality	14	85.7	366	79.3
Extravascular eosinophils	16	81.3	385	84.4

* For classification purposes, a patient shall be said to have Churg-Strauss syndrome (CSS) if at least 4 of these 6 criteria are positive. The presence of any 4 or more of the 6 criteria yields a sensitivity of 85% and a specificity of 99.7%. (See Table 3 for criteria definitions.)

Some of these patients were treated at the time biomarkers were assessed

Khoury et al. Allergy 2012;67(9):1149-56.