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Asthma mimics: Recognizing Eosinophilic bronchitis, EGPA, and hypereosinophilic syndrome

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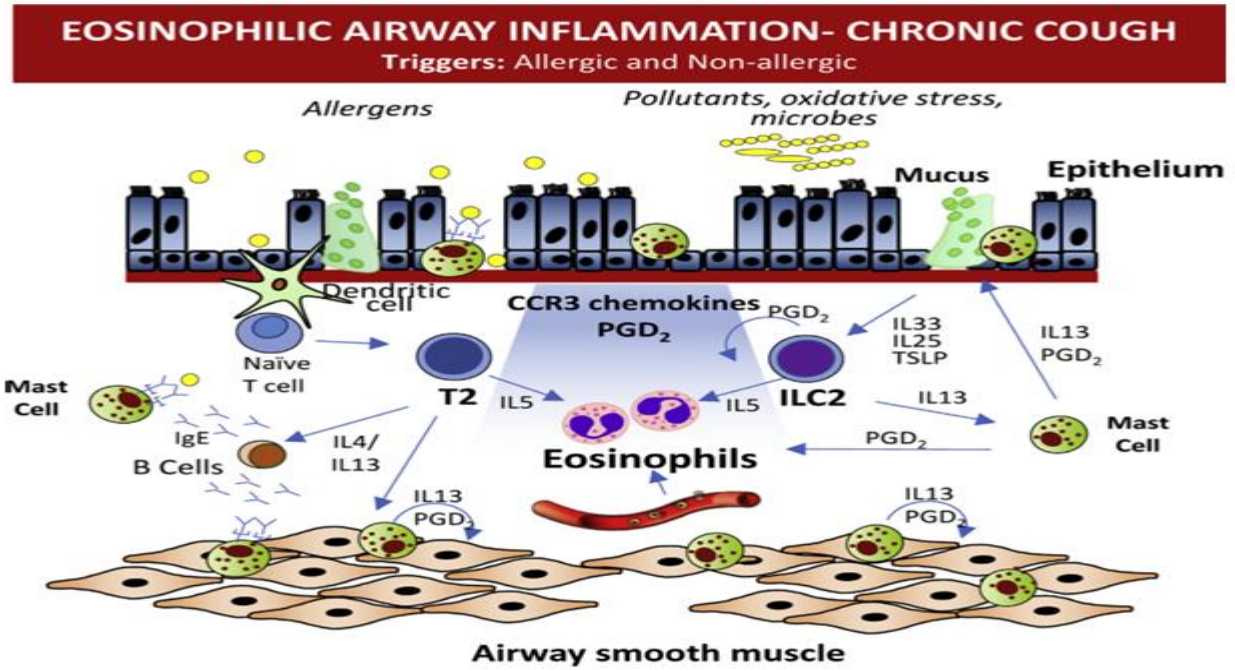
Index

- Increased eosinophil with respiratory symptoms
  - DDx asthma (cough variant asthma)
- Eosinophilic bronchitis (EB)
- Eosinophilic Granulomatosis with Polyangiitis (EGPA)
- Hypereosinophilic syndrome (HES)

Chronic cough and increased airway eosinophil

- Eosinophilic airway inflammation in chronic cough (>8 weeks)
  - Prevalence: 30-50%
  - Asthma vs cough variant asthma vs EB (eosinophilic bronchitis)



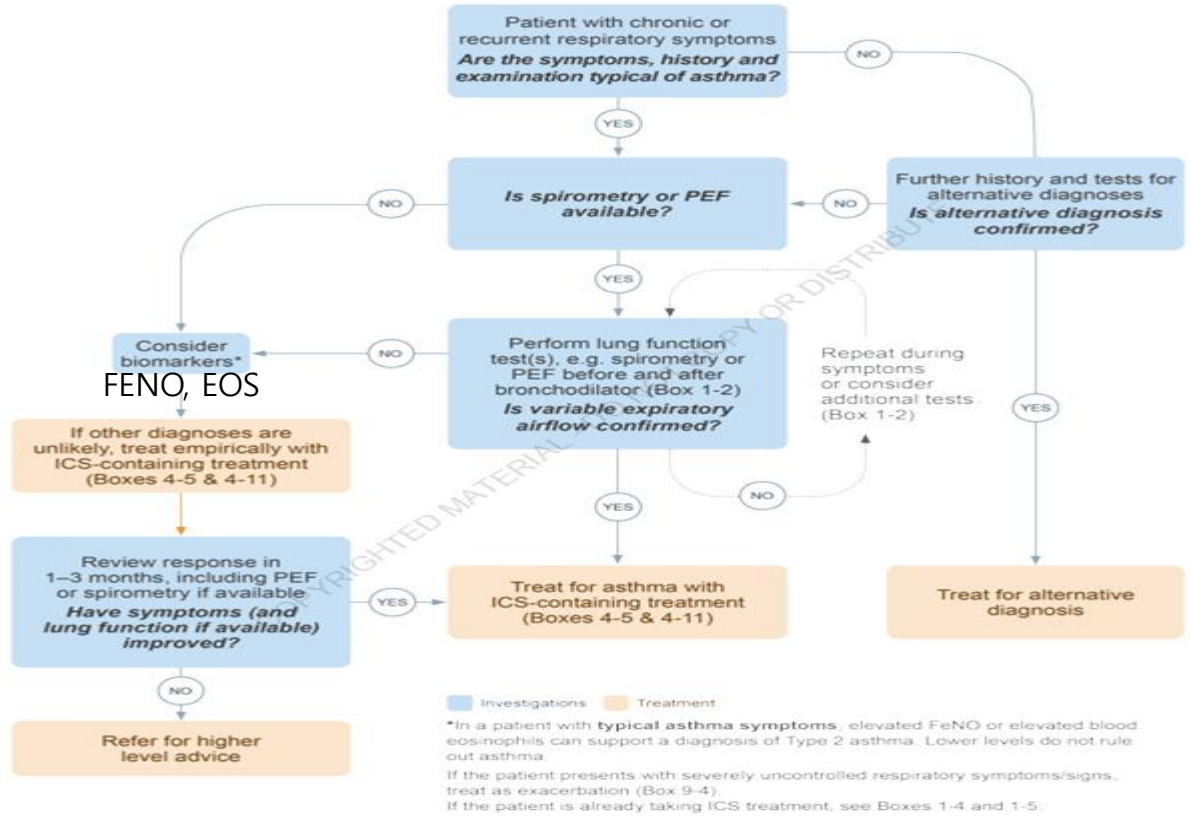
J Allergy Clin Immunol Pract. 2019;7(6):1740-1747.

Asthma

- Definition

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and vary in intensity, together with variable expiratory airflow.

- Diagnosis



FENO, EOS

GINA 2026

Asthma diagnosis

1. HISTORY OF TYPICAL VARIABLE RESPIRATORY SYMPTOMS	
Symptoms may include:	*Symptoms or features that support the diagnosis of asthma*
Wheeze, shortness of breath, chest tightness, cough (Descriptors may vary by region and by age)	• Symptoms occur variably over time and vary in intensity • Symptoms are often worse at night or on waking • Symptoms are often triggered by exercise, laughter, allergens, cold air • Symptoms worsen after stopping exercise (very distinctive) • Symptoms often appear or worsen with viral infections

2. CONFIRMED VARIABLE EXPIRATORY AIRFLOW	
Feature	*Considerations, definitions, criteria*
Excessive variability in expiratory lung function (one or more of the following):	The greater the variations, or the more occasions excess variation is seen, the more confidently the diagnosis of asthma can be made. If spirometry is not possible, PEF† may be used, but it is less reliable.
Positive bronchodilator (BD) responsiveness (reversibility) test with spirometry (or PEF†) When possible, test during symptoms or in the morning	Measure change 10–15 minutes after 200–400 mcg salbutamol (albuterol) or equivalent, compared with pre-BD readings. Positive test more likely if BD withheld before test: SABA ≥4 hours, long-acting bronchodilators 24–48 hours (see below). *Adults*: increase from baseline in FEV_1 or FVC of ≥12% and ≥200 mL, with greater confidence if the increase is ≥15% and ≥400 mL; or increase in PEF† ≥20% if spirometry is not available (see p.32 for more information about these criteria) *Children*: increase from baseline in FEV_1 of ≥12% predicted (or in PEF† of ≥15%)
Excessive variability in twice-daily PEF over 2 weeks*	*Adults*: average daily diurnal PEF variability >10%* *Children*: average daily diurnal PEF variability >13%*
Increase in lung function after 4 weeks of ICS-containing treatment	*Adults*: increase from baseline in FEV_1 by ≥12% and ≥200 mL (or PEF† by ≥20%) after 4 weeks of daily ICS-containing treatment *Children*: increase from baseline in FEV_1 of ≥12% predicted (or in PEF† of ≥15%)
Positive bronchial provocation test	*Adults*: Fall from baseline in FEV_1 of ≥20% with standard doses of methacholine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge, or >10% and >200 mL with standardized exercise challenge *Children*: fall from baseline in FEV_1 of ≥20% with standard doses of methacholine, or >12% predicted (or fall in PEF† >15%) with standardized exercise challenge If FEV_1 decreases from baseline during a challenge test, check that FEV_1/FVC ratio has also decreased, since incomplete inhalation, e.g., due to inducible laryngeal obstruction or poor effort, can result in a false reduction in FEV_1.
Excessive variation in lung function between visits (good specificity but poor sensitivity)	*Adults*: variation in FEV_1 of ≥12% and ≥200 mL (or in PEF† of ≥20%) between visits *Children*: variation of ≥12% in FEV_1 (or ≥15% in PEF†) between visits

GINA 2026

Cough variant asthma

- Respiratory symptom: only cough
- Evidence of airflow limitation maybe absent except during bronchial provocation
- Diagnosis (ACCP, 2006)
- Diagnosis (China, 2022)
  - Cough> 8 weeks
  - Positive bronchial challenge or BDR positive
  - Cough improved with anti-asthmatic therapy
- Prevalence in chronic cough: 10-40%
  - In Korea, with EB: 25-50% or 16% (CVA)

RECOMMENDATION

2. In a patient suspected of having CVA but in whom physical examination and spirometry findings are nondiagnostic, MIC testing should be performed to confirm the presence of asthma. However, a diagnosis of CVA is established only after the resolution of cough with specific antiasthmatic therapy. If MIC testing cannot be performed, empiric therapy should

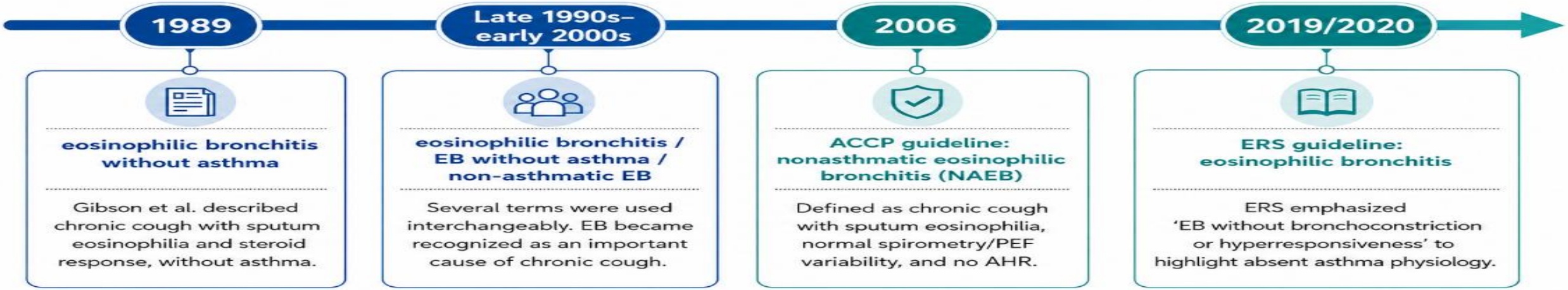
Asia Pac Allergy. 2016;6(4):198-206

Front Med (Lausanne). 2022;8:807385.

Chest. 2006;129(1 Suppl):75S-79S.

Eosinophilic bronchitis (EB)

- Definition
  - Characterized by chronic cough with eosinophilic airway inflammation in the absence of variable airflow limitation and airway hyperresponsiveness
  - ERS guideline on chronic cough: The third form of asthmatic cough is eosinophilic bronchitis without bronchoconstriction or hyperresponsiveness.
- Terminology
  - EB without asthma, non-asthmatic EB (NAEB), EB without bronchoconstriction or hyperresponsiveness

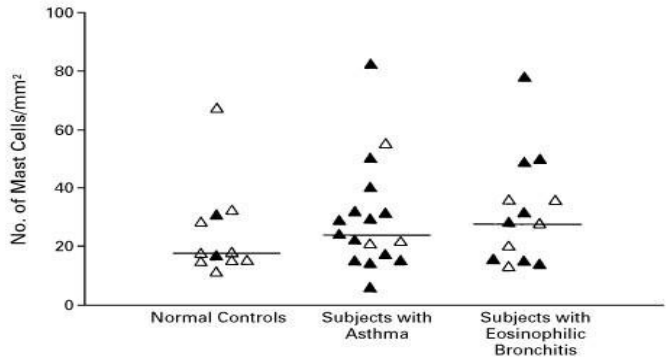


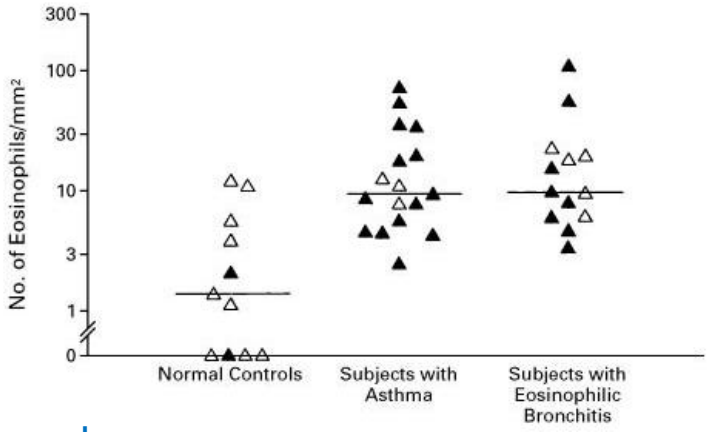
EB diagnosis

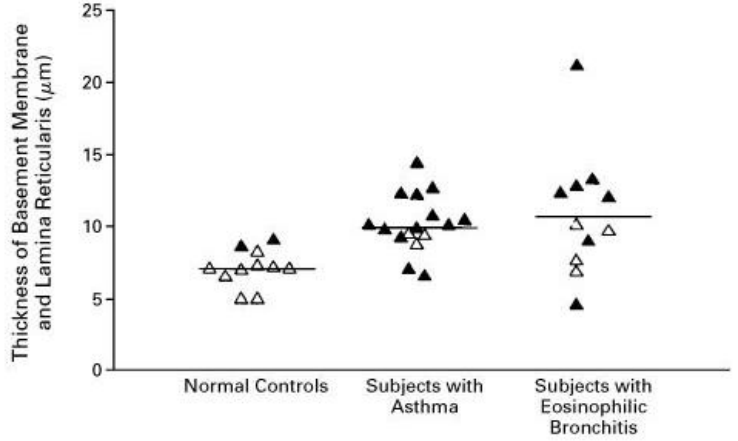
- Diagnosis (ACCP diagnostic criteria of NAEB)
  - Chronic cough with no symptoms or objective evidence of variable airflow obstruction, normal airway hyperresponsiveness, and sputum eosinophilia (>3%)

Chest. 2006;129(1 Suppl):116S-121S.

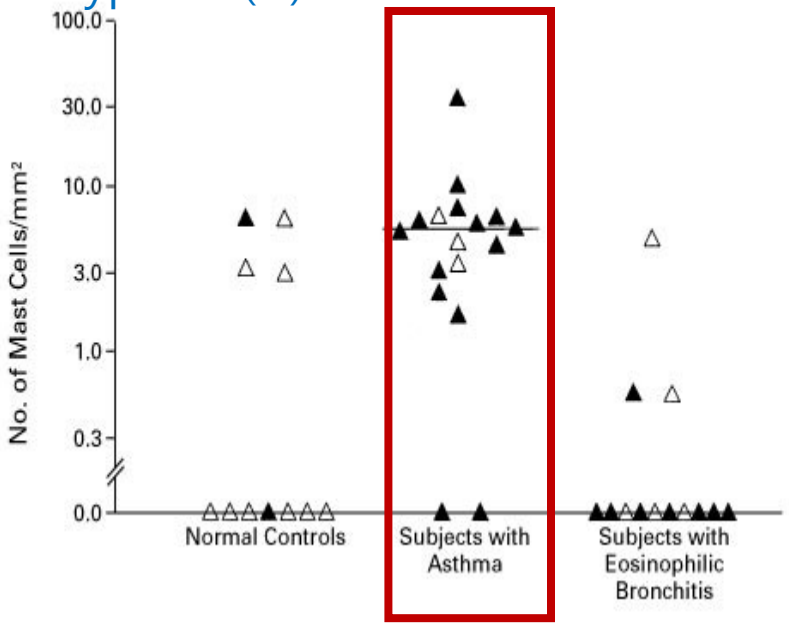
Why EB no airway hyperresponsiveness?





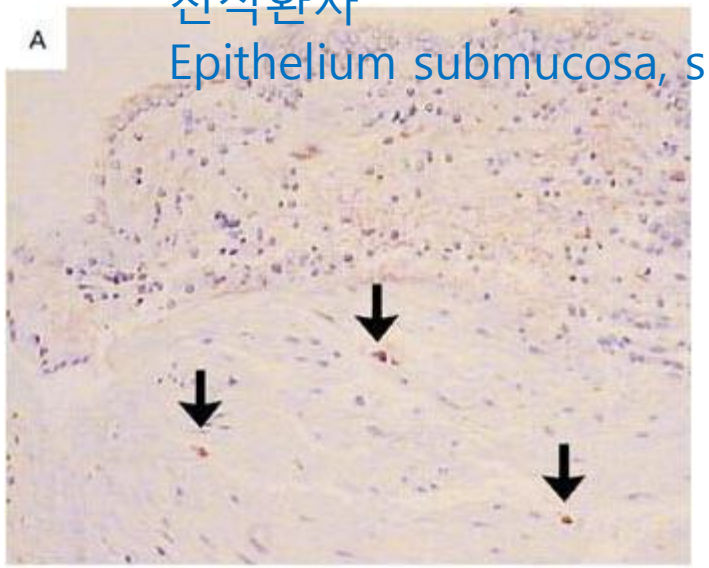


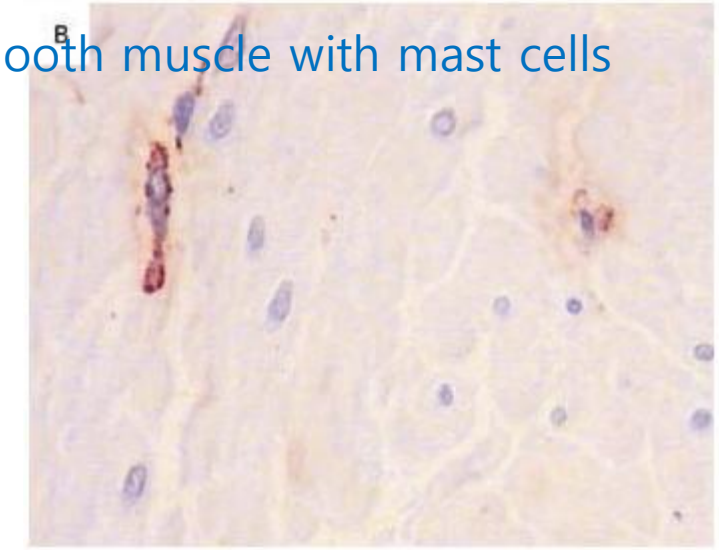
Tryptase (+) mast cell in smooth muscle



천식환자

Epithelium submucosa, smooth muscle with mast cells





N Engl J Med. 2002;346:1699–1705.

EB vs cough-variant asthma

구분	EB	CVA / Asthma
Symptom	chronic cough	cough-only 가능, 특히 CVA
Sputum eosinophilia	있음	있음
Steroid response	있음	있음
AHR	없음	있음
Variable airflow obstruction	없음	classic asthma에서는 있음, CVA는 없거나 미약
Pathophysiology	Eosinophilic airway inflammation ->enhanced cough reflex sensitivity	mast cell infiltration airway smooth muscle bundles

Asthma vs CVA vs EB

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TABLE I. Summary of typical symptoms, investigations for common conditions associated with chronic cough

Condition	Typical symptoms	Investigations
Asthma	Episodic cough, wheeze, and dyspnea	Spirometry with reversibility, bronchial provocation tests, and FeNO
Cough variant asthma	Predominantly cough only	Spirometry with reversibility, bronchial provocation tests, and FeNO
NAEB	Mainly dry, occasionally productive cough. Minimal wheeze	No evidence of reversibility, or airway hyper-responsiveness. Sputum cytology, FeNO, and endobronchial biopsy

J Allergy Clin Immunol. 2023;152(3):622-632

EB treatment

- Initial
  - ICS (first line), LTRA (second line->controversial) CHEST 2020 guideline
  - In Korea, LTRA is not recommended to improve cough
  - Duration: chronic cough에서 2-4 weeks, >2months (China)
- Follow up
  - If not controlled, ICS dose up, oral corticosteroid, add LTRA
- Avoid
  - SABA use, bronchodilator use, biologics

8. Eosinophilic bronchitis (EB)

1) Recommendation

– In EB, ICS is recommended to improve cough (evidence, expert opinion; recommendation, strong).

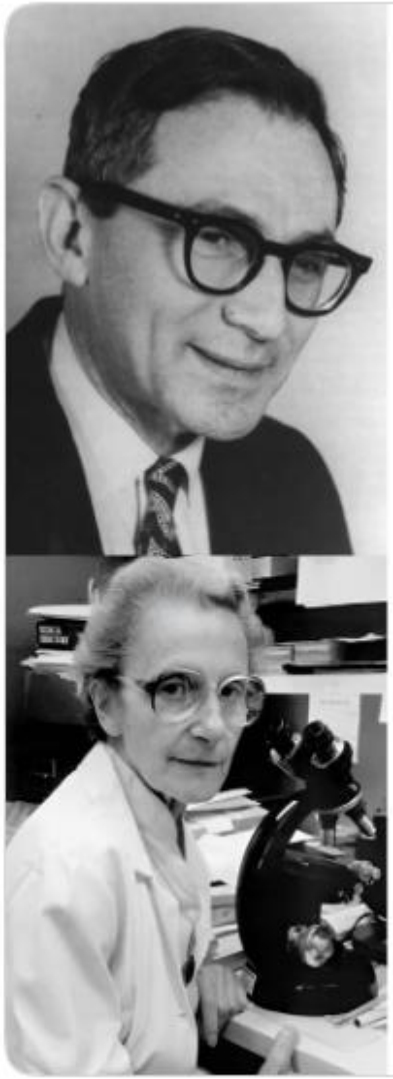
– In EB, LTRA is not recommended to improve cough (evidence, expert opinion; recommendation, strong).

Ther Adv Respir Dis. 2019 Jan-Dec

Joo H, et al. Revised Korean Cough Guidelines, 2020. *Tuberc Respir Dis*. 2021.

Chest. 2020;158(1):68-96 *J Investig Allergol Clin Immunol*. 2024;34(5):282-292.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)



ALLERGIC GRANULOMATOSIS, ALLERGIC ANGIITIS, AND PERIARTERITIS NODOSA *

JACOB CHURG, M.D., and LOTTE STRAUSS, M.D.
(From the Laboratories, Division of Pathology, the Mount Sinai Hospital, New York 29, N.Y.)

During the past 25 years a relation between allergic states and vascular lesions of the type seen in periarteritis nodosa has been firmly established by study of human disease and by experimental evidence. Gruber [1] suggested that periarteritis nodosa is a hyperergic vascular response to infection. Cohen, Kline, and Young [2] postulated a causal relationship between allergy, as exemplified by severe asthma, and periarteritis nodosa developing in its course. Wilson and Alexander,[3] on reviewing the literature, found association of these two diseases in 18 per cent of 300 cases of periarteritis nodosa. Cases of this type have been studied also by Rackemann and Greene,[4] who described the clinical syndrome in some detail, and by Harkavy,[5] who interpreted this syndrome as an expression of vascular allergy. Rich [6,7] and other authors [8] found vascular lesions in patients who developed reactions to foreign serum or drugs (sulfonamides, iodine, dilantin), which Rich believed to be identical with those of periarteritis nodosa. Rich and Gregory [9] were able to reproduce these lesions experimentally in animals.

While most of the authors concerned themselves with pathologic changes in the vascular system, there are a number of reports in the literature indicating that, in addition, widely dispersed extravascular lesions may occur in connective tissue (Rössle,[10] Bergstrand,[11] Rich,[12] Smith [13]). Such lesions are characterized by inflammatory exudate rich in eosinophilic leukocytes, by necrosis of the exudate, and by severe alteration of collagen with granulomatous (epithelioid and giant cell) reaction.

The present report deals with cases of severe asthma which presented the clinical syndrome described by Rackemann and Greene,[4] and by Harkavy,[5] and which, on pathologic examination, exhibited the granulomatous extravascular lesions noted above, as well as necrotizing, inflammatory, and granulomatous vascular changes.

Most of our material is derived from cases autopsied in the Department of Pathology of the Mount Sinai Hospital, New York City. Of 23 patients in whom death was accompanied, or preceded, by severe asthma (status asthmaticus), 9 showed a strikingly uniform clinical

* Read by title at the Forty-sixth Annual Meeting of The American Association of Pathologists and Bacteriologists, Boston, April 15 and 16, 1949.
Received for publication, June 16, 1950.

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Churg-Strauss syndrome (CSS) from 1951~2012

Am J Pathol. 1951;27:277–301

Arthritis Rheum. 2013;65:1–11

Published in final edited form as:
Clin Exp Nephrol. 2013 October ; 17(5): 603–606. doi:10.1007/s10157-013-0869-6.

Overview of the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

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Small vessel vasculitis (SVV)

SVV is divided into antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and immune complex SVV [2]. This categorization was not in CHCC 1994 and reflects a greater level of confidence that ANCA are of pathogenic significance in AAV [4].

AAV is necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels, associated with MPO-ANCA or PR3-ANCA [2]. A prefix should be added to indicate ANCA reactivity, e.g. PR3-ANCA, MPO-ANCA, ANCA-negative. This is important because mounting evidence indicates that the ANCA specificity identifies distinct categories of disease [5,6]. AAV is subdivided into microscopic polyangiitis (MPA), granulomatosis with polyangiitis (Wegener's) (GPA), and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) [2]. The eponyms Wegener's granulomatosis and Churg-Strauss syndrome were replaced with the more descriptive terms GPA and EGPA respectively. The change to GPA was influenced by a decision that had already been made by several relevant medical societies [7].

EGPA from 2012

EGPA definition and diagnosis

- Definition (CHCC 2012)

Phase 1: Prodromal	Phase 2: Eosinophilic	Phase 3: Vasculitic
Adult-onset Asthma, Chronic Rhinosinusitis, Nasal Polyps. Can last for years.	Blood/Tissue Hypereosinophilia. Migratory lung infiltrates, Eosinophilic gastroenteritis.	**Necrotizing Vasculitis. Mononeuritis Multiplex, Purpura, Myocarditis (Critical).**

- Diagnosis (classification criteria)
  - 2022 ACR/EULAR criteria (score ≥6)
  - Asthma, increased eosinophil, vasculitis manifestations, ANCA/ biopsy findings
  - Mimic disease exclusion

"EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update." *Annals of the rheumatic diseases* 83.1 (2024): 30-47
Arthritis Rheum. 2013;65:1–11

EGPA classification criteria

- Asthma, increased EOS, nasal polyps->의심
- MPO (P-ANCA) positive rate (30-40%)

Table 1. Demographic and disease features of cases of EGPA and comparators*

	EGPA (n = 226)	Comparators (n = 887)†	*P*
Age, mean ± SD years	52.9 ± 14.4	56.2 ± 17.6	0.009
Sex, no. (%) female	113 (50.0)	445 (50.2)	1.000
Maximum serum creatinine, mean ± SD			<0.001
μmoles/liter	85.0 ± 53.6	205.90 ± 237.0	
mg/dl	0.96 ± 0.6	2.33 ± 2.7	
cANCA positive, no. (%)	17 (7.5)	251 (28.3)	<0.001
pANCA positive, no. (%)	83 (36.7)	289 (32.6)	0.271
Anti–PR3-ANCA positive, no. (%)	7 (3.1)	264 (29.8)	<0.001
Anti–MPO-ANCA positive, no. (%)	98 (43.4)	323 (36.4)	0.065
Maximum eosinophil count ≥1 × 10^9/liter, no. (%)	208 (92.0)	53 (6.0)	<0.001

CLINICAL CRITERIA

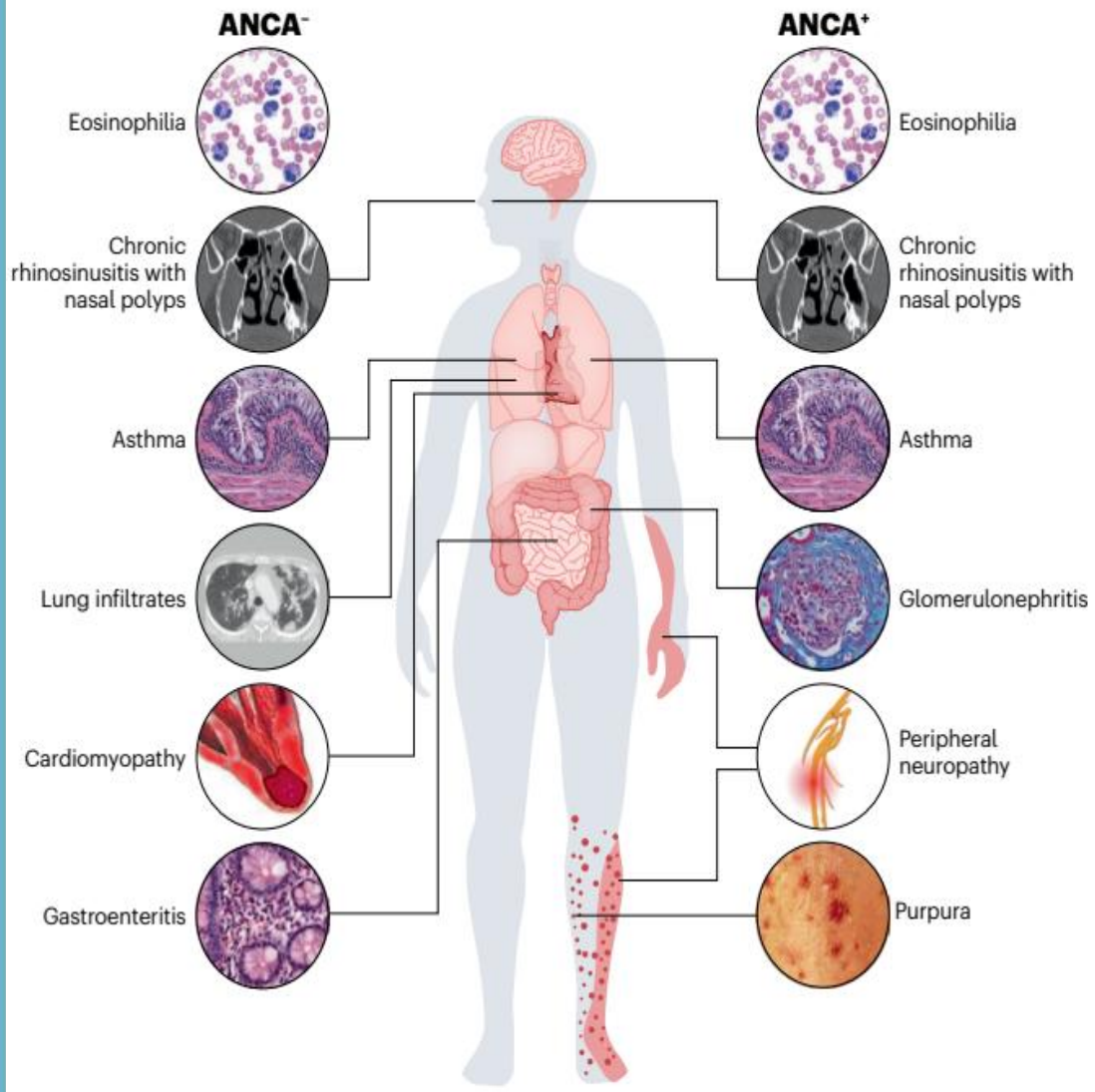
Obstructive airway disease	+3
Nasal polyps	+3
Mononeuritis multiplex	+1

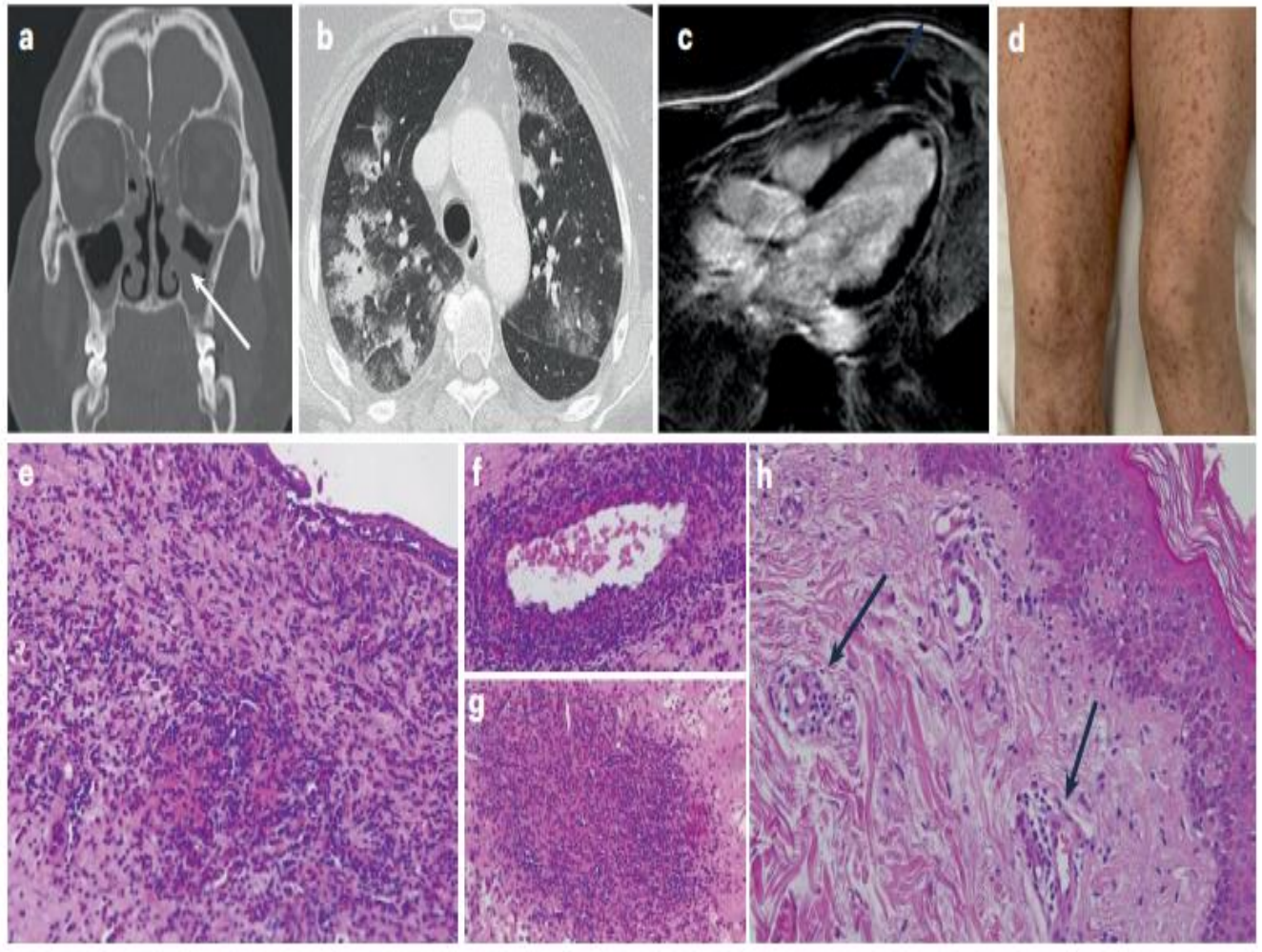
LABORATORY AND BIOPSY CRITERIA

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

"EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update." *Annals of the rheumatic diseases* 83.1 (2024): 30-47

EGPA work-up


ANCA⁻
ANCA⁺
Eosinophilia
Chronic rhinosinusitis with nasal polyps
Asthma
Lung infiltrates
Cardiomyopathy
Gastroenteritis
Eosinophilia
Chronic rhinosinusitis with nasal polyps
Asthma
Glomerulonephritis
Peripheral neuropathy
Purpura


a
b
c
d
e
f
g
h

EGPA diagnostic work-up

Investigations to be performed in all patients

Baseline investigations	Screening/diagnostic aims
Routine laboratory investigations	
Routine serum chemistries	General/haematological assessment
Complete blood count with differential diagnosis	
Urinalysis, 24-h proteinuria or urinary protein-to-creatinine ratio	Kidney involvement screening
Sputum culture (where available)	Infectious disease screening
D-dimer, Troponin, BNP	Cardiac involvement screening
Faecal occult blood	Intestinal involvement screening
C-reactive protein	Disease activity assessment
LDH, tryptase, vitamin B12	Screening for myeloproliferative forms
Immunological and/or allergic tests ANCA, IgG, IgA, IgM, IgE, IgG4	EGPA-related immune parameters
Infectious tests • Stool cultures for parasites (e.g. *Strongyloides stercoralis*) • HIV serology	Screening for parasitic and viral infections
Haematological tests • Blood smear (dysplastic eosinophils or blasts) • FIP1L1 fusion proteins	Screening for haematologic forms of hypereosinophillia
Imaging studies and other procedures	
Chest radiograph and/or HRCT	Lung involvement screening
Pulmonary function tests	
ENT consultation (with nasal endoscopy)	ENT involvement screening
Echocardiography	Cardiac involvement screening
Abdominal ultrasonography	General assessment, screening for hepato-splenomegaly (haematological hypereosinophillia)

Investigations to be performed in selected cases

Indications	Procedure(s)
Peripheral neuropathy	EMG–ENG (sural nerve biopsy)
Renal function impairment, urinary abnormalities*	Kidney biopsy
GI symptoms and/or bleeding	Endoscopy
ENT abnormalities (e.g. polyps, sino-nasal obstruction symptoms, hearing loss)	• Audiometry • Sinus CT scan • FESS
Lung infiltrates/pleural effusions	BAL, pleural puncture, lung biopsy
Clinical signs of allergic bronchopulmonary aspergillosis	*Aspergillus*-specific IgE and/or IgG sputum (or BAL) cultures for *Aspergillus* spp.
Purpura	Skin biopsy
Clinical or echocardiogram signs of cardiomyopathy	Cardiac MRI (endomyocardial biopsy)
Vascular events and/or high CV risk	Arterial and venous Doppler ultrasonography
CNS manifestations	Brain and/or spinal cord MRI (CSF analysis)
Miscellaneous/haematological	• T cell immunophenotyping • Bone marrow biopsy

Nat Rev Rheumatol. 2023;19:378–393

EGPA w/u ->must exclude mimics

- Hypereosinophilic syndrome, HES
- Eosinophilic pneumonia
- ABPA
- Parasitic infection: Strongyloides, Toxocara 등
- Drug-induced eosinophilia / DRESS
- Hematologic malignancy
- IgG4-related disease
- GPA/MPA/PAN/ other vasculitis

Nat Rev Rheumatol. 2023;19:378–393

EGPA severity (five factor score FFS)

- FFS

Renal insufficiency	Serum creatinine >1.58 mg/dL	+1
Proteinuria	>1 g/day	+1
Cardiomyopathy	있음	+1
Gastrointestinal involvement	있음	+1
CNS involvement	있음	+1

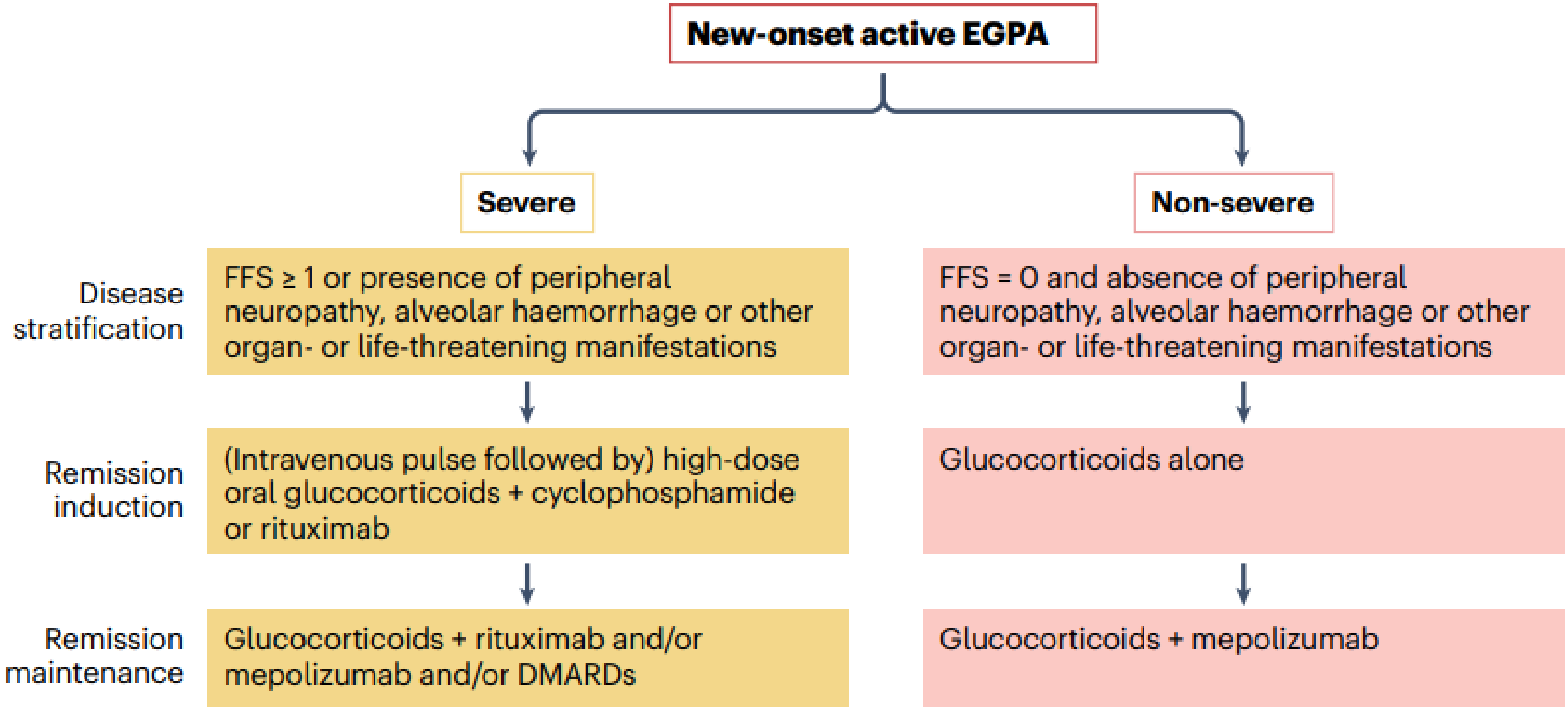
Table 2 Examples of organ/life-threatening and not organ/life-threatening manifestations in patients with AAV

Examples of potentially organ/life-threatening manifestations*	Examples of manifestations that are not ultimately organ/life-threatening*
Glomerulonephritis	Nasal and paranasal disease without bony involvement (erosion) or cartilage collapse or olfactory dysfunction or deafness
Pulmonary haemorrhage	Skin involvement without ulceration
Meningeal involvement	Myositis (skeletal muscle only)
Central nervous system involvement	Non-cavitating pulmonary nodules
Retro-orbital disease	Episcleritis
Cardiac involvement	
Mesenteric involvement	
Mononeuritis multiplex	

*These are just examples of typical disease manifestations and many other manifestations of AAV exist. Assessment of severity in the individual patient may differ (eg, scleritis can become organ threatening under certain circumstances).
AAV, antineutrophil cytoplasmic antibody-associated vasculitis.

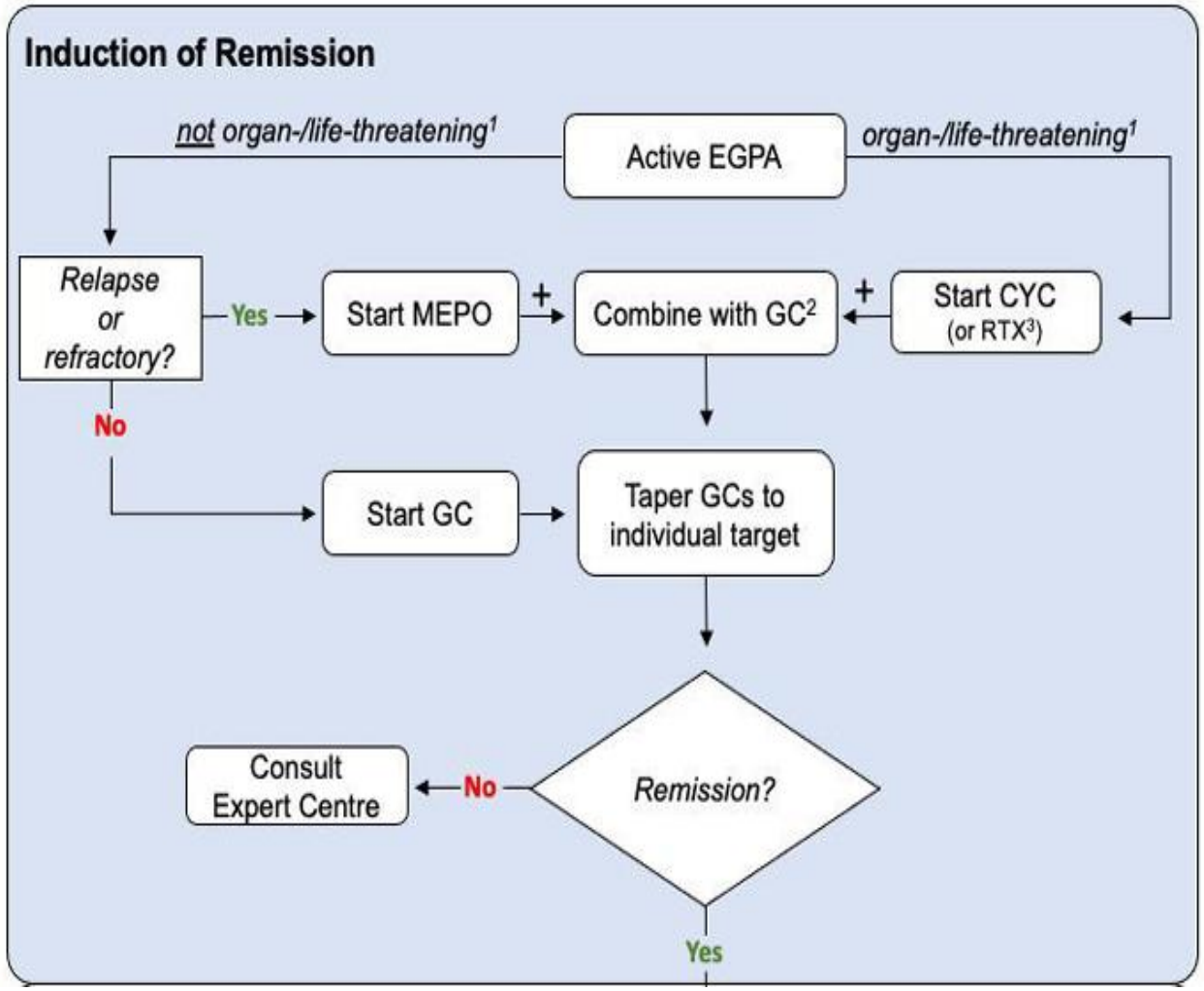
"EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update." *Annals of the rheumatic diseases* 83.1 (2024): 30-47

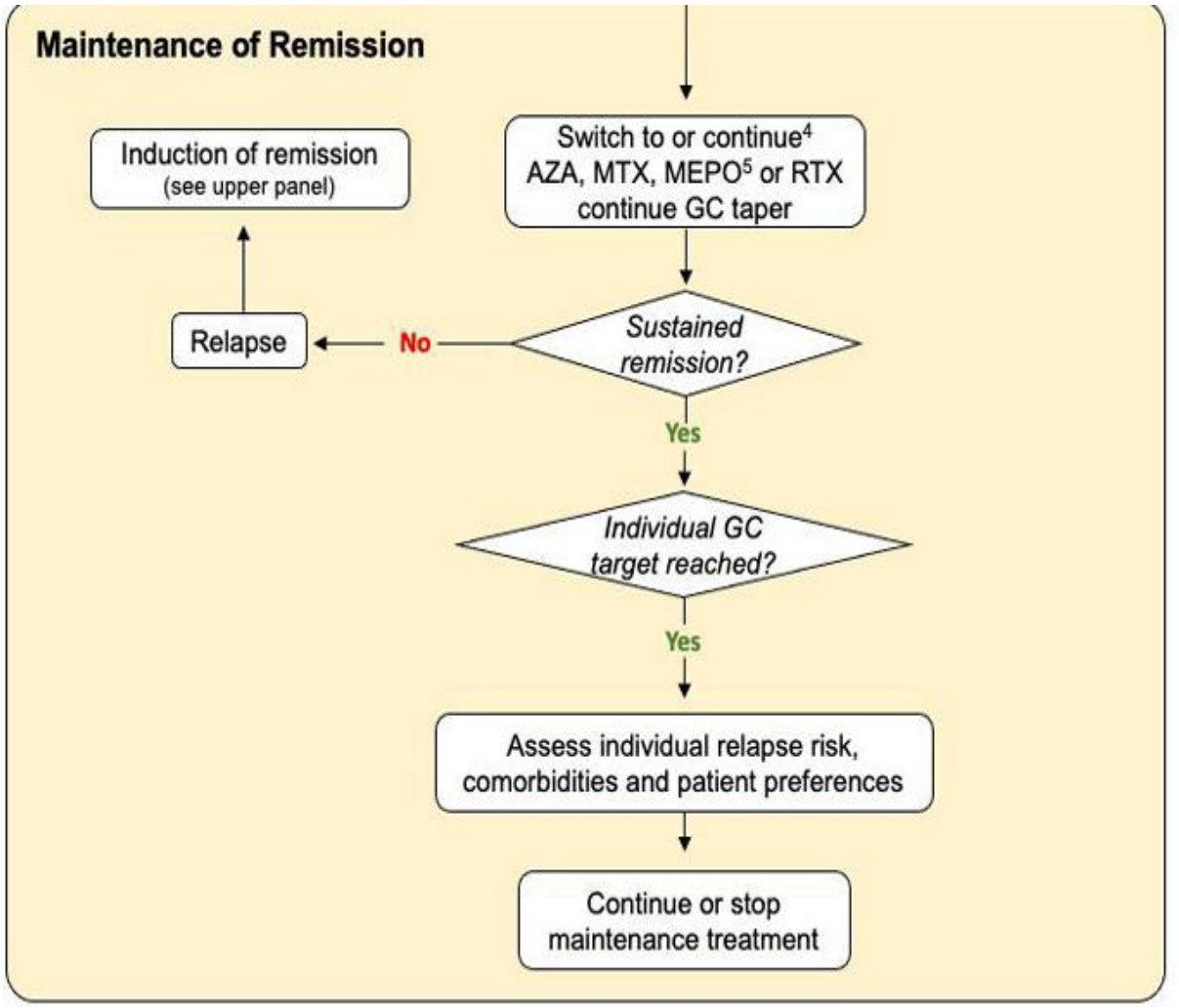
EGPA treatment according to severity



Nat Rev Rheumatol. 2023;19:378–393

EGPA treatment according to severity (EURLA)

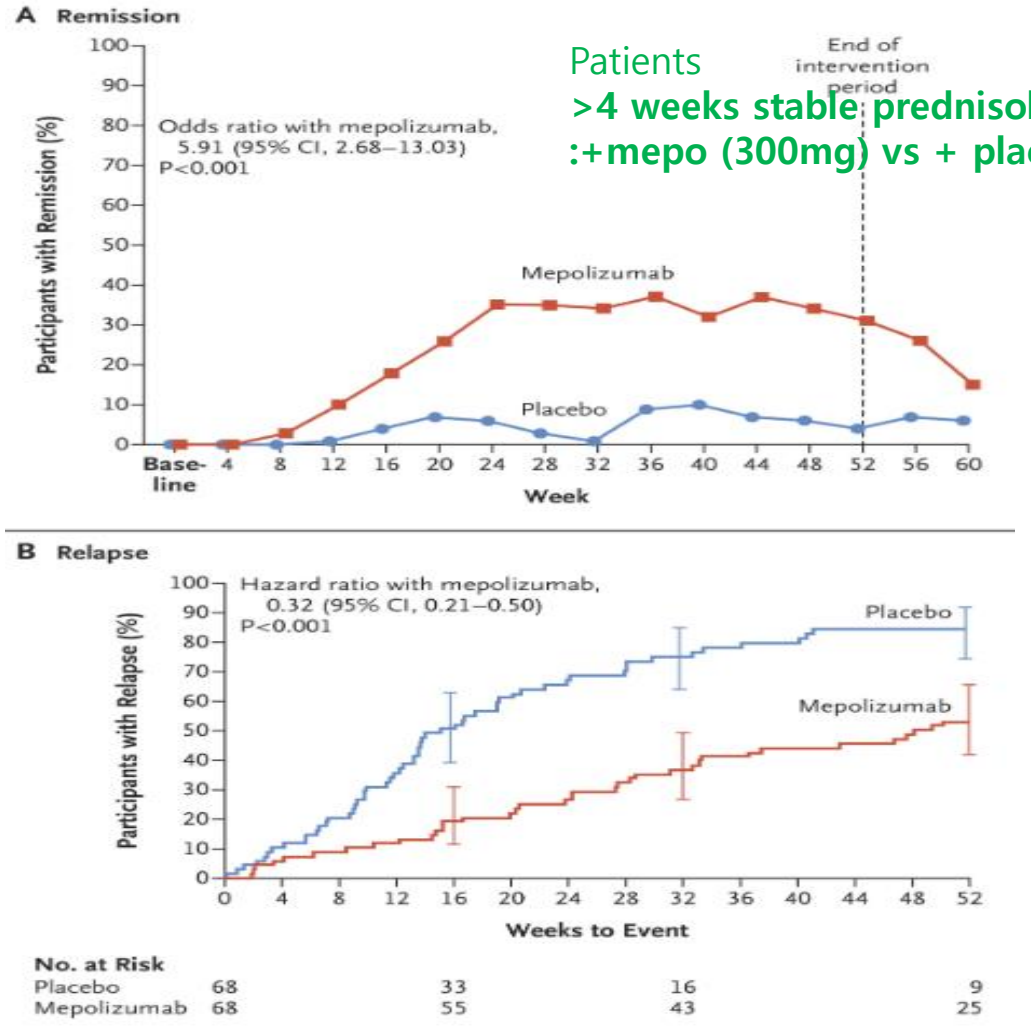




EGPA (non severe) treatment

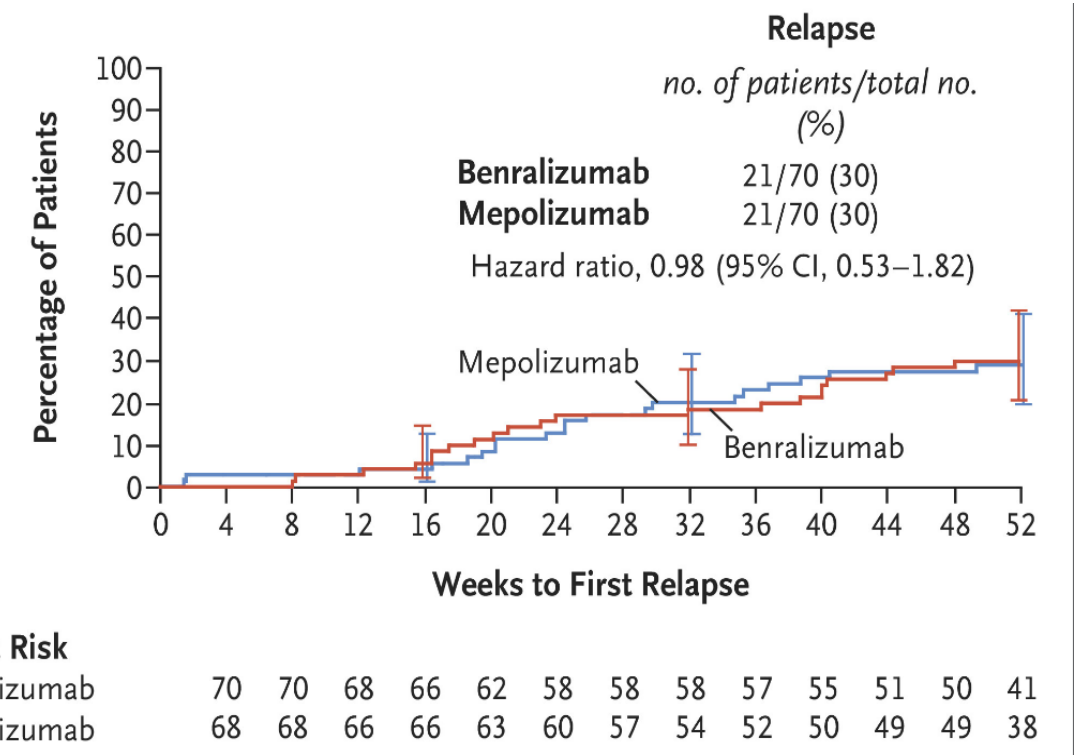
- MIRRA trial (2017)

Patients
>4 weeks stable prednisolone
:+mepo (300mg) vs + placebo



- MANDARA trial (mepolizumab vs benralizumab)

Patients
Replasing or refractory with steroid (7.5-50mg)
Benralizumab (30mg) vs mepolizumab (300mg)
SQ 4 weeks



N. Engl. J. Med. 376, 1921–1932 (2017) N Engl J Med 2024;390:911-921

Benralizumab in EGPA

2025 BSR Management recommendations for AAV

British Society for Rheumatology

Striving to improve care for people living with AAV

(1) Management of GPA and MPA

- All people with active (newly diagnosed or relapsed) GPA/MPA should be considered as having potentially life or organ-threatening disease
- Treatment should follow 2 paradigms: Remission induction and remission maintenance
- CYC or RTX are recommended for induction remission. RTX is preferred in those with active relapsing disease
- Reduced dose GC tapering regimens are recommended.
- Avacopan should be considered in active disease to reduce GC-related morbidity
- Adjunctive plasmapheresis should be considered in cases of severe kidney involvement but NOT pulmonary haemorrhage alone

(2) Management of SGS and ENT disease associated with GPA

- Both subglottic stenosis and sino-nasal disease are challenging disease manifestations that require expert management by an ENT ± specialist with expertise in vasculitis
- The term 'limited GPA' may underestimate disease burden; terms such as 'ENT-localised GPA' or 'sino-nasal GPA' are preferred
- Systemic therapy with CYC or RTX can provide early disease control, delay need for recurrent dilatations in SGS, and limit morbidity in ENT disease
- Care is required to identify potential sino-nasal disease mimics, including recognition of cocaine-associated vasculitis conditions

- AAV = ANCA-associated vasculitis
- Anti-IL-5/5R = anti-interleukin 5/5 receptor
- CYC = cyclophosphamide
- EGPA = eosinophilic granulomatosis with polyangiitis
- ENT = ear, nose and throat
- GC = glucocorticoid
- GPA = granulomatosis with polyangiitis
- MDT = multidisciplinary team
- MPA = microscopic polyangiitis
- RTX = rituximab
- SGS = subglottic stenosis

(3) Management of EGPA

- EGPA should be considered in anyone with asthma, rhinosinusitis and an eosinophil count $\geq 1 \times 10^9$/L
- Treatment should follow 2 paradigms: Remission induction and remission maintenance
- Anti-IL-5/5R biologics are recommended (if available) in non-life and non-organ-threatening disease to reduce glucocorticoid-related morbidity
- Life-threatening disease should be treated with CYC or RTX, if there is intolerance or contraindication to CYC

(4) AAV Service specification

- Specialist vasculitis review within 7 days for people with new suspected AAV is associated with fewer serious infections, hospital admissions and reduced mortality
- Nurse-led components of care, specialist vasculitis MDT meetings and cohorted clinics are associated with improved health outcomes

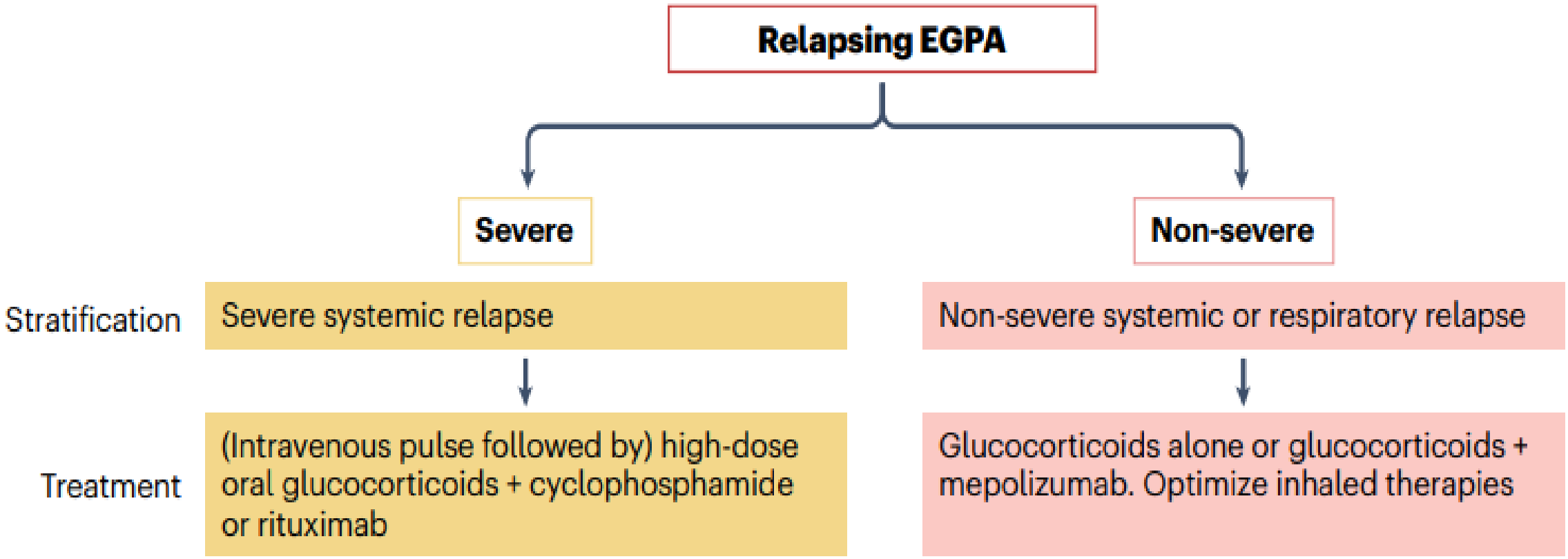
(5) Patient education and support

- All adults, children and young people with AAV (and their families and carers) should receive ongoing, tailored information and education about AAV
- People with AAV should be empowered to collaborate in shared decision making with their healthcare team to reach a joint decision about their care

Scan the QR code for the full guideline
or visit rheumatology.org.uk/guidelines

Rheumatology. 2025;64(8):4470–4494

EGPA if relapsing



EGPA vs severe eosinophilic asthma

	Severe eosinophilic asthma	EGPA favor
기본 개념	Severe asthma phenotype with Type 2/eosinophilic inflammation	Asthma + eosinophilia + eosinophilic granulomatous inflammation/vasculitis
Eosinophil count	보통 ≥150/μL 또는 ≥300/μL가 T2/eosinophilic asthma biomarker로 사용됨	2022 ACR/EULAR EGPA classification에서 maximum eosinophil count ≥1.0 × 10^9/L = ≥1,000/μL가 +5점 핵심 항목
Asthma 양상	Long-standing severe asthma, frequent exacerbation, OCS-dependent	Adult-onset asthma 또는 기존 asthma의 급격한 악화, OCS taper 중 systemic symptom이 드러날 수 있음
ENT disease	Allergic rhinitis, CRS, nasal polyp 동반 가능	Refractory chronic rhinosinusitis, recurrent nasal polyps가 흔하고 nasal polyps가 +3점
Lung imaging	정상, air trapping, mucus plugging, bronchial wall thickening 정도	Migratory/transient pulmonary infiltrates, eosinophilic pneumonia pattern, consolidation/GGO
Systemic symptoms	보통 asthma-related dyspnea/wheeze 중심	Involve된 organ에 따라서 다름 피부 침범: Palpable purpura, nodules, urticaria-like vasculitic lesions 신경: Mononeuritis multiplex, asymmetric motor/sensory neuropathy Cardiac: Myocarditis, cardiomyopathy, heart failure, pericarditis Renal: proteinuria, GN 가능
ANCA	보통 음성	약 30–40% 양성, 대부분 MPO-ANCA/p-ANCA
Biopsy	airway eosinophilic inflammation 정도	Extravascular eosinophils, eosinophil-rich inflammation, necrotizing vasculitis, granulomatous inflammation

Hypereosinophilic Syndrome (HES)

- Definition
  - heterogeneous group of conditions that is defined at its core by hypereosinophilia (HE) (AEC>1.5×10^9/L) and organ damage directly attributable to the HE
    - HE tissue infiltration, release of eosinophil-derived mediators, and cytotoxic protein ->organ damage
- Diagnosis
  - Persistent HE: AEC ≥1.5×10^9/L at least 4 weeks (allergy-> time interval 2 weeks)
  - Eosinophil mediated organ damage
  - Primary/secondary(reactive)/idiopathic (WHO classification) vs ICOG-EO classification

Allergy. 2023 Jan;78(1):47-59.

HE and HES definition

Name/term	Abbreviation	Definition and criteria
Hypereosinophilia	HE	≥1.5 eosinophils $\times 10^9$/L peripheral blood on two examinations (interval ≥2 weeks).[a] Tissue HE may or may not be detected.
Tissue hypereosinophilia	Tissue HE	One or more of the following applies: a) the percentage of eosinophils in bone marrow section exceeds 20% of all nucleated cells, and/or b) a pathologist is of the opinion that tissue infiltration by eosinophils is extensive and/or c) marked deposition of eosinophil granule proteins is found (in the absence or presence of tissue infiltration by eosinophils)
Hypereosinophilic syndrome	HES	a) criteria for blood HE fulfilled and: b) organ damage and/or dysfunction attributable to tissue HE[b] and: c) exclusion of other disorders or condition as major reason for organ damage
Tissue-restricted HES[c] (organ-restricted HES)		a) tissue HE but criteria for blood HE not fulfilled and: b) organ damage and/or dysfunction attributable to tissue HE[b] and: c) exclusion of other disorders or conditions as major reason for organ damage

Allergy. 2023 Jan;78(1):47-59.

HES classification

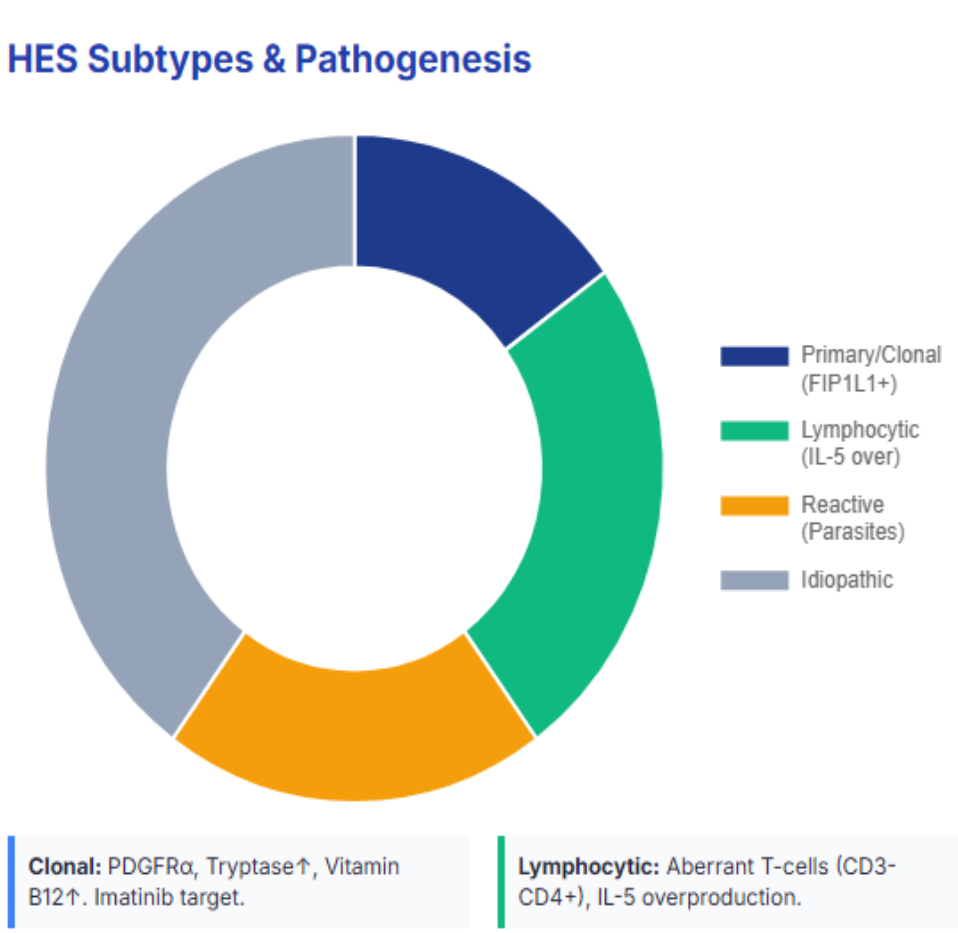
Myeloid/neoplastic FIP1L1–PDGFRA, PDGFRB, FGFR1, JAK2 등

Lymphocytic variant aberrant/clonal T-cell → IL-5 overproduction

Idiopathic HES 원인 미확인

organ-restricted Tissue HE+ organ damage but no peripheral eosinophilia

Reactive/secondary parasite, drug, autoimmune, malignancy



HE classification (ICOG-EO)

- International Cooperative Working Group on Eosinophil Disorders(ICOG-EO)

Variant of HE	Abbreviation	Features
Hereditary (familial) HE	HE_{FA}	Familial clustering, often evidence of a hereditary immunodeficiency (inborn errors of immunity with eosinophilia), no evidence of a reactive or neoplastic underlying disease, and no signs or symptoms indicative of HES
HE of unknown significance	HE_{US}	No known underlying etiology of HE, no positive family history, no evidence of a reactive or neoplastic condition or disorder underlying HE, and no signs or symptoms indicative of HES
Secondary (reactive) HE	HE_{R}	Underlying reactive condition or disease that explains HE, no evidence for a clonal bone marrow disease that explains HE[a]; and no signs or symptoms indicative of HES
Clonal (neoplastic) HE	HE_{N}	Underlying stem cell, myeloid, or eosinophil neoplasm inducing HE[a]; no signs/symptoms indicative of HES

Idiopathic

Secondary(reactive)

Primary

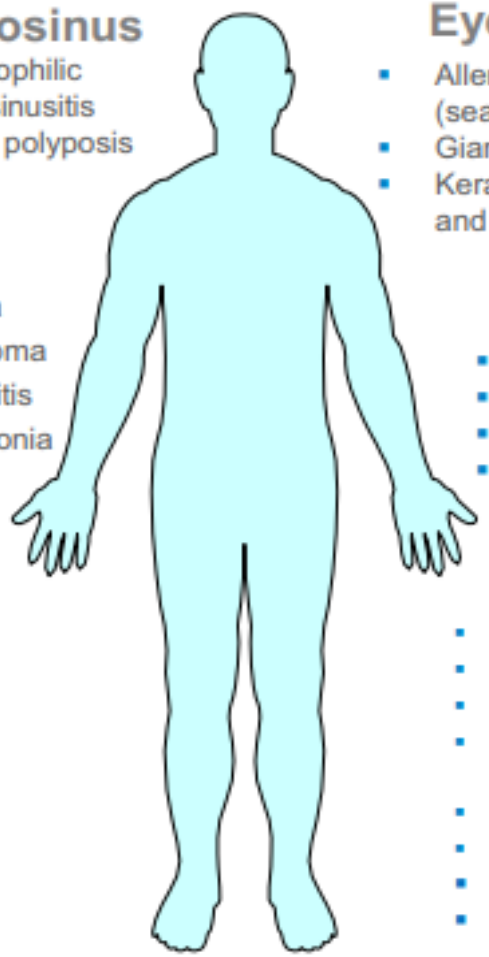
Allergy. 2023 Jan;78(1):47-59.

HES classification (ICOG-EO)

Variant	Typical features
Familial HES (HES_{FA})	Familial clustering, very rare, IEI-EO excluded[a], typical end organ damage attributable to HE, no evidence of a reactive or neoplastic condition/disorder underlying HE
Idiopathic HES (HES_I)	No underlying cause of HE, no evidence of a reactive or neoplastic condition/disorder underlying HE; and: end organ damage attributable to HE.
Primary (neoplastic) HES (HES_N)	Underlying stem cell, myeloid, or eosinophil neoplasm classified according to WHO criteria[b], and end organ damage attributable to HE. Eosinophils are neoplastic (clonal) cells; in many patients, rearranged/fusion variants of *PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *STAT5*, *FLT3*, *ABL1* or other driver genes, are found.
Secondary (reactive) HES (HES_R)	Underlying condition/disease where eosinophils are considered non-clonal cells, and HE is considered to be cytokine-driven (HES_R); and end organ damage attributable to HE.
Special variants of HES_R:[c]	
a. Lymphoid variant of HES (L-HES)	Abnormal clonal T cells are often detected, and HES-related organ damage is found
b. Defined syndromes	
Episodic angioedema and eosinophilia (Gleich Syndrome)	Abnormal clonal T cells are often detected, angioedema, increased polyclonal IgM.
Eosinophilic granulomatosis with polyangiitis (eGPA) = Churg–Strauss syndrome	Polyangiitis, necrotizing angiitis, asthma, lung infiltrates; in a subset of patients, ANCA are detected (ANCA+ form of eGPA)
Eosinophilia myalgia syndrome (EMS)	Myalgia, muscle weakness, cramping, skin rash, dyspnea, fatigue.
IgG4-related disease (IgG4-RD)	Elevated serum IgG4 levels, HE, and HES-like organ damages are found in about 30% of cases

Allergy. 2023 Jan;78(1):47-59.

HES tissue damage



Nasosinus

- Eosinophilic rhinosinusitis
- Nasal polyposis

Eye

- Allergic conjunctivitis (seasonal and perennial)
- Giant papillary conjunctivitis
- Keratoconjunctivitis (atopic and vernal)

Skin

- Atopic dermatitis
- Urticarial dermatitis
- Chronic contact dermatitis
- Pemphigoid
- Ectoparasites
- Eosinophilic folliculitis
- Eosinophilic cellulitis (Wells syndrome
- Eosinophilic dermatosis of hematologic malignancy
- T-cell lymphoma
- Eosinophilic ulcer of the oral mucosa

Lung

- Eosinophilic asthma
- Eosinophilic granuloma
- Eosinophilic bronchitis
- Eosinophilic pneumonia
- Simple pulmonary eosinophilia
- Eosinophil pleuritis
- Occupational lung syndromes
- Allergic bronchopulmonary aspergillosis
- Tropical pulmonary eosinophilia

Connective Tissue

- Eosinophilic myositis
- Eosinophilic synovitis
- Eosinophilic arthritis
- Eosinophilic fasciitis

Systemic

- Eosinophilic granulomatosis with polyangiitis (EGPA)
- Eosinophilic leukemia
- IgG4-related disease
- Eosinophilia myalgia syndrome
- Episodic angioedema with eosinophilia (Gleich syndrome)
- Acute transplant graft rejections
- Drug reactions
- Hematologic malignancy
- Inborn errors of immunity with eosinophilia

GI Tract

- Eosinophilic esophagitis
- Eosinophilic gastritis
- Eosinophilic enteritis
- Eosinophil gastrointestinal disorder (EGID)
- Eosinophilic cholecystitis
- Eosinophilic colitis
- Eosinophilic pancreatitis
- Eosinophilic hepatitis

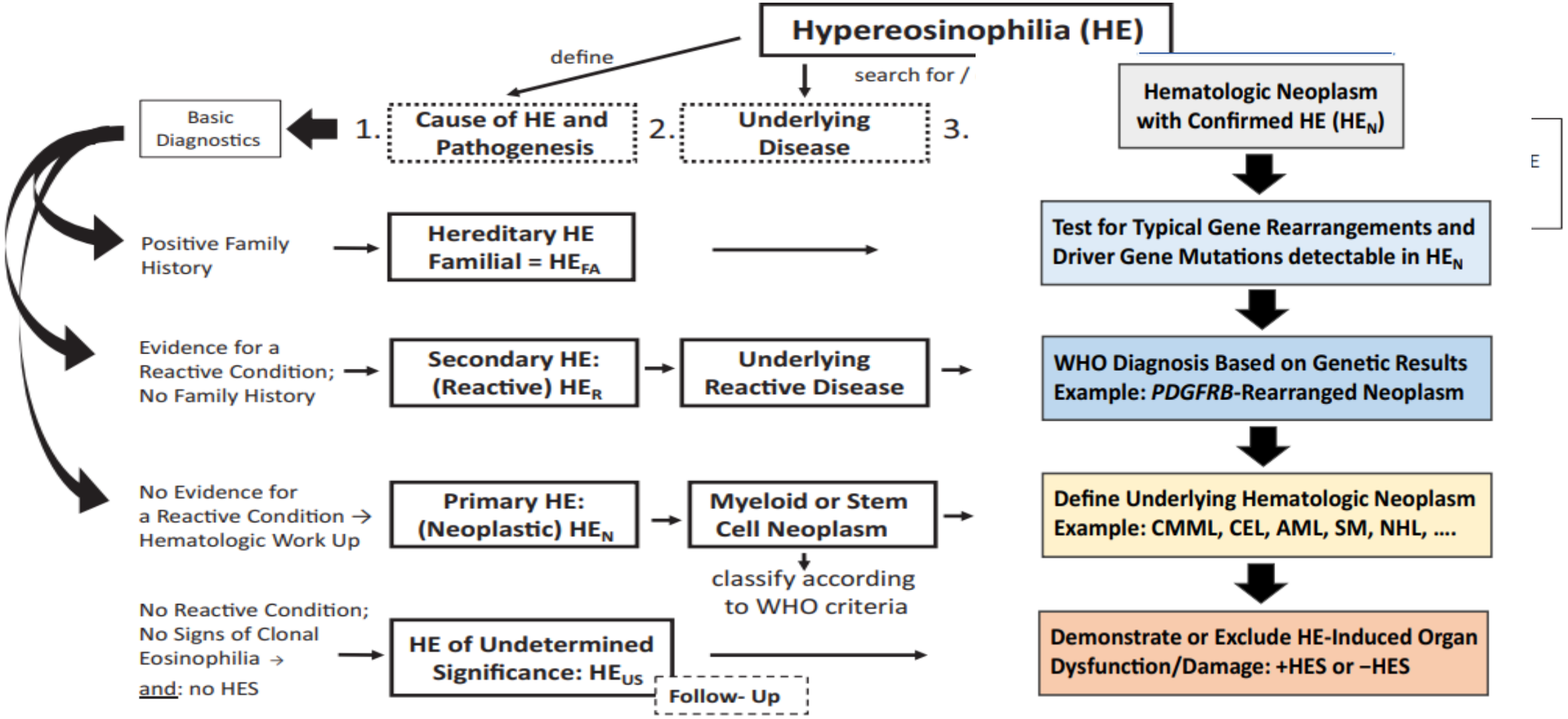
Other

- Eosinophilic ascites
- Eosinophilic myocarditis
- Eosinophilic coronary periarteritis
- Eosinophilic nephritis
- Eosinophilic cystitis
- Eosinophilic prostatitis
- Eosinophilic endometritis and myometritis (uterus)
- Eosinophilic mastitis

Pathogenesis of organ damage

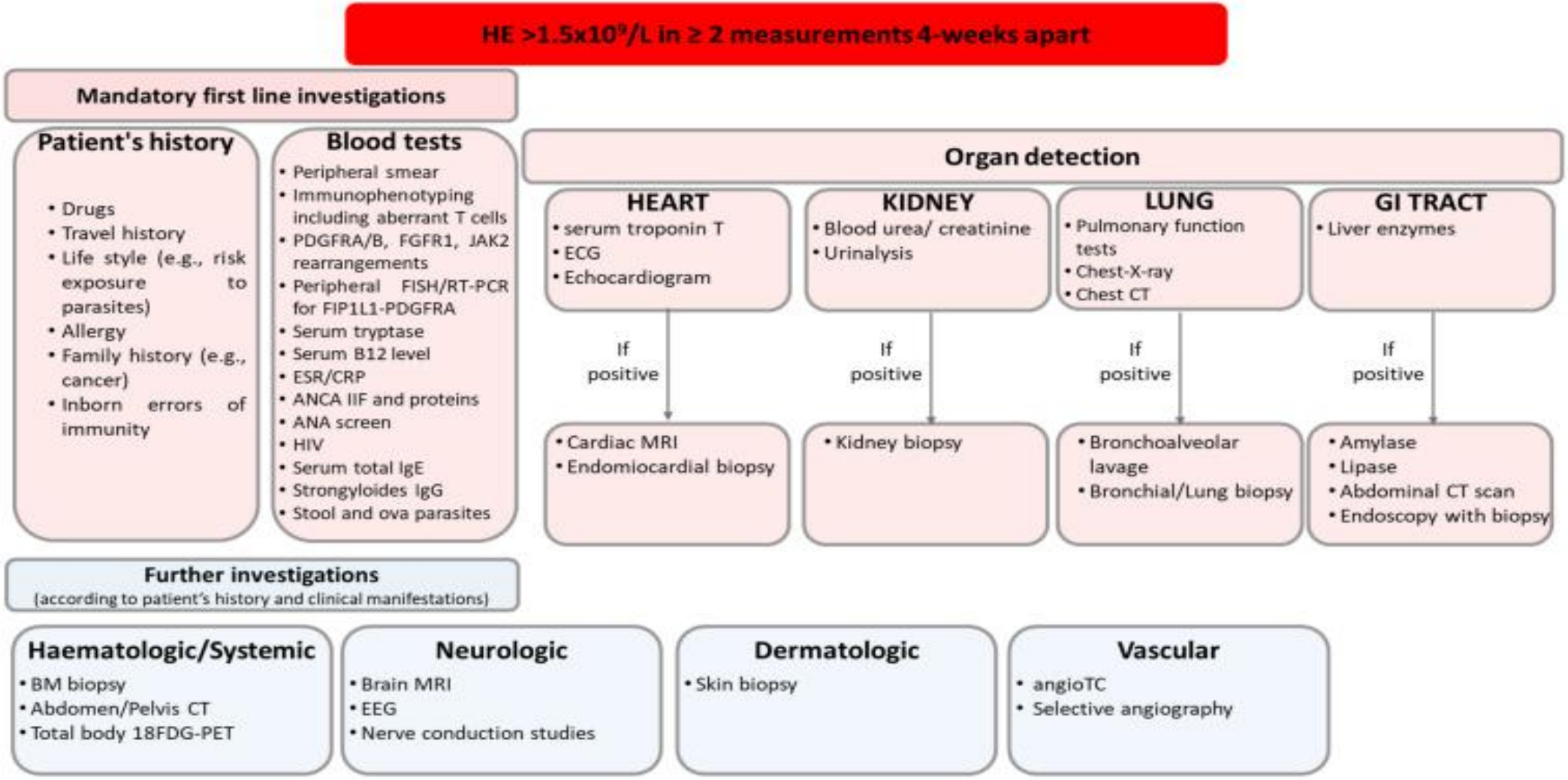
- Blood EOS->Tissue EOS
  - CCR3-eotaxin axis, adhesion molecule, endothelial activation->survival signal (IL-5)
- Tissue EOS degranulation and cytotoxicity
  - Activated EOS degranulation in tissue: major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin, eosinophil peroxidase
- Thrombosis
  - Eosinophil granule protein, EPO product-> endothelial injury, platelet activation, coagulation activation (JAMA Network Open 2021 cohort, 24%: thrombotic event)
- Fibrosis

HES diagnosis



Allergy. 2023 Jan;78(1):47-59.

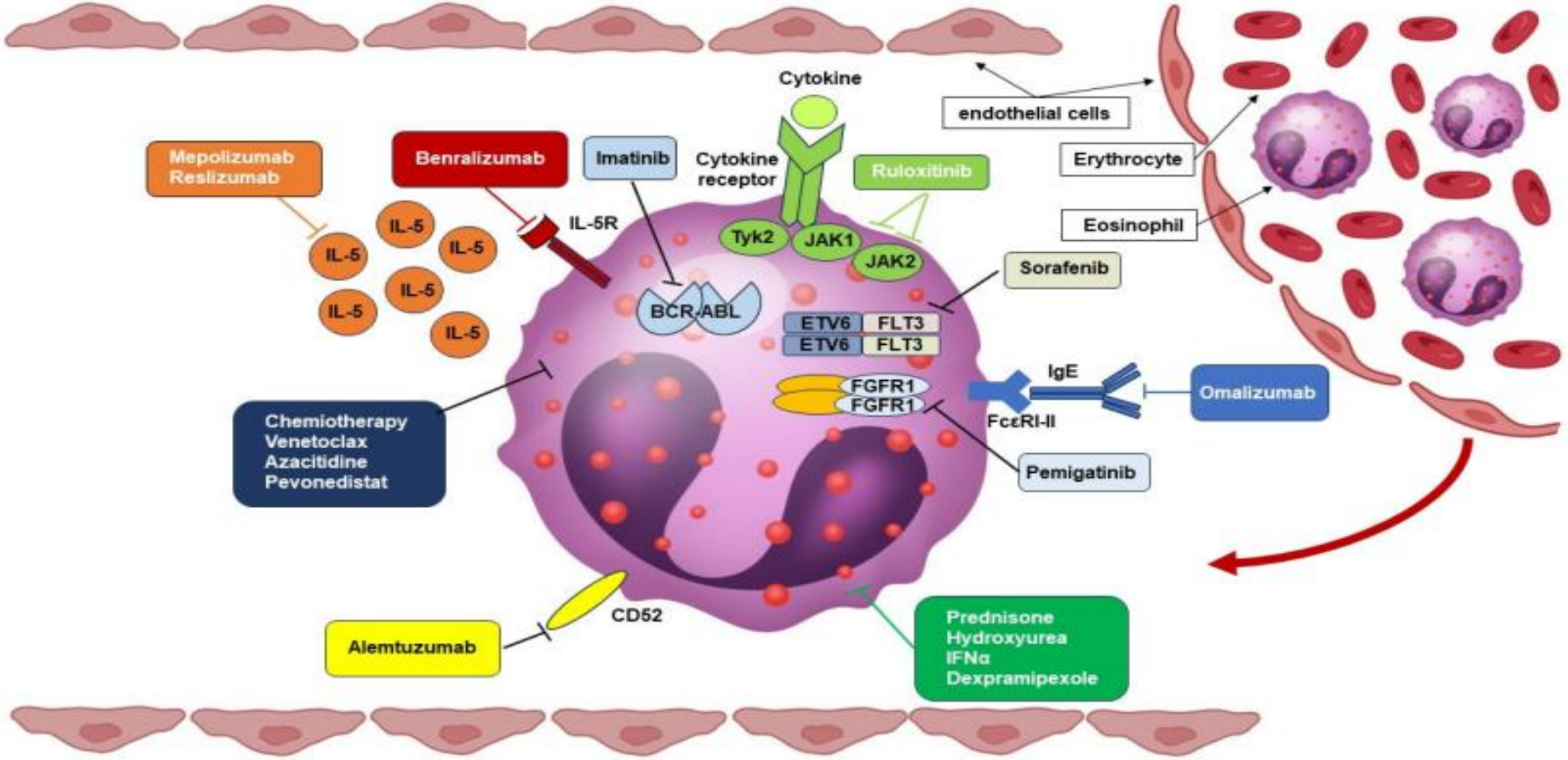
HES work up


HE >1.5x10⁹/L in ≥ 2 measurements 4-weeks apart
Mandatory first line investigations
Patient's history
• Drugs
• Travel history
• Life style (e.g., risk exposure to parasites)
• Allergy
• Family history (e.g., cancer)
• Inborn errors of immunity
Blood tests
• Peripheral smear
• Immunophenotyping including aberrant T cells
• PDGFRA/B, FGFR1, JAK2 rearrangements
• Peripheral FISH/RT-PCR for FIP1L1-PDGFRA
• Serum tryptase
• Serum B12 level
• ESR/CRP
• ANCA IIF and proteins
• ANA screen
• HIV
• Serum total IgE
• Strongyloides IgG
• Stool and ova parasites
Organ detection
HEART
• serum troponin T
• ECG
• Echocardiogram
KIDNEY
• Blood urea/ creatinine
• Urinalysis
LUNG
• Pulmonary function tests
• Chest-X-ray
• Chest CT
GI TRACT
• Liver enzymes
If positive
If positive
If positive
If positive
• Cardiac MRI
• Endomiocardial biopsy
• Kidney biopsy
• Bronchoalveolar lavage
• Bronchial/Lung biopsy
• Amylase
• Lipase
• Abdominal CT scan
• Endoscopy with biopsy
Further investigations
(according to patient's history and clinical manifestations)
Haematologic/Systemic
• BM biopsy
• Abdomen/Pelvis CT
• Total body 18FDG-PET
Neurologic
• Brain MRI
• EEG
• Nerve conduction studies
Dermatologic
• Skin biopsy
Vascular
• angioTC
• Selective angiography

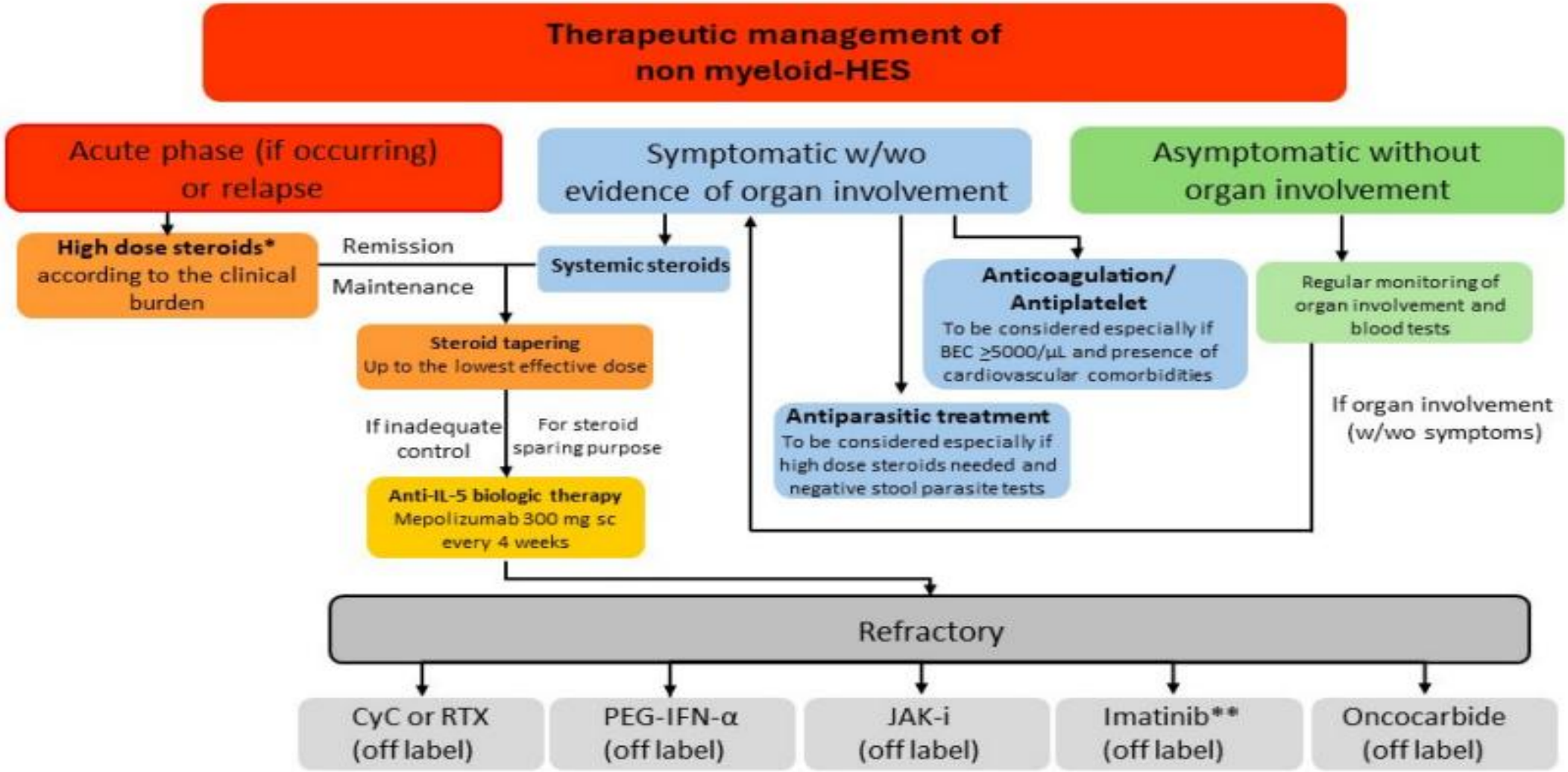
HES therapeutic option

Drug	Mechanism of Action	Dose	Target Neoplasm
		Corticosteroids	
Prednisone	Slow and prevent end-organ damage	1 mg/kg daily	HES
		Cytotoxic agents	
Hydroxyurea	Inhibit DNA synthesis	500–1000 mg/daily	HES (+ corticosteroids); Steroid non-responders.
IFNα	Inhibit cell growth and induct apoptosis	Initiation: 1 million units tiw * Escalation: 3–4 million units tiw *	HES (+ corticosteroids); HES & CEL, NOS refractory to other therapies; Lymphocyte-variant hypereosinophilia.
		Targeted therapies	
TKIs Imatinib	Inhibit both TGFb and PDGF-R pathway	100–400 mg/daily	*PDGFRα* rearranged; *PDGRFβ* rearranged; Alternate *PDGRFβ* fusions; Selected cases HES and CEL, NOS.
Ruxolitinib	Inhibit dysregulated JAK/STAT signalling pathway	20 mg PO BID	Eosinophilic leukemia with the *PCM1-JAK2* fusion [t(8;9)(p22;p24)].
Sorafenib	Inhibit several kinases involved in both tumour cell proliferation and angiogenesis	400 mg/twice daily	*FIP1L1-PDGFRα* rearranged pts with T674I mutation; FLT3-rearranged cases.
		Monoclonal antibodies	
Anti-IL-5 Mepolizumab	Inhibit binding of IL-5 to the α chain of the IL-5R	100–300 mg every 4 weeks	Eosinophilic asthma and eosinophilic granulomatosis with polyangiitis.
Reslizumab	Inhibit the proliferation of eosinophils by binding to the α chain of the IL-5R	1 mg/kg	Eosinophilic asthma and eosinophilic esophagitis.
Anti-IL-5R Benralizumab	Inhibit hetero-oligomerization of α and β subunits of IL-5R	30 mg by subcutaneous injection every 4 weeks	Severe asthma.
Anti-IgE Omalizumab	Inhibit release of cytokines such as IL-4, IL-5, and IL-13; block unbound IgE.	dose/frequency calculated bases on weight per serum IgE	Eosinophilic disorders, in particular asthma/nasal polyps
Anti-CD52 Alemtuzumab	Mediate the lysis of CD52+ cells	5–30 mg 1 to 3 times weekly	Refractory HES pts.

HES therapeutic option



HES treatment of non myeloid



HES treatment (primary 제외)

- Stepwise
  - First line steroid (1mg/kg/day or pulse 1g)
  - Steroid sparing agents: hydroxyurea or interferon-a

Table 4. Currently available and investigational biologic agents used in HES

Drug	Target	Indication	Status	Clinical trial
Mepolizumab	Anti–IL-5	iHES and L-HES	Approved (FDA, EMA)	NCT02836496
Benralizumab	Anti–IL-5Rα	PDGFRA-negative, refractory HES	Off-label / Under investigation	NATRON: NCT04191304
Depemokimab	Anti–IL-5 (long-acting)	HES with residual tissue symptoms	Phase III	DESTINY: NCT05334368
Dupilumab	Anti–IL-4Rα	HES with uncontrolled tissue symptoms	Investigational	NCT06477653

HES, hypereosinophilic syndrome; IL, interleukin.

Curr Opin Allergy Clin Immunol. 2025 Aug 1;25(4):258-268.

HES treatment-biologics (mepolizumab)

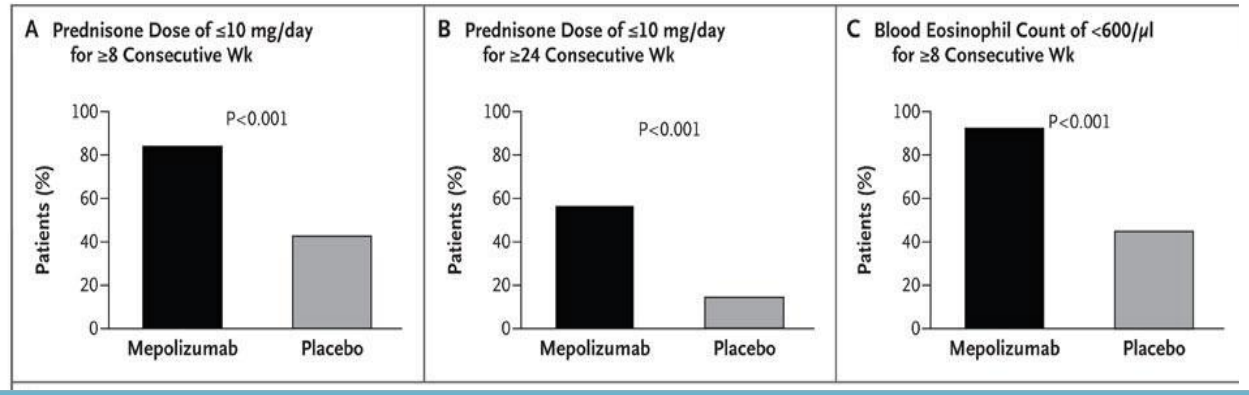
Patients:18-85 yr, HES, *FIP1L1–PDGFRA* fusion gene (-),

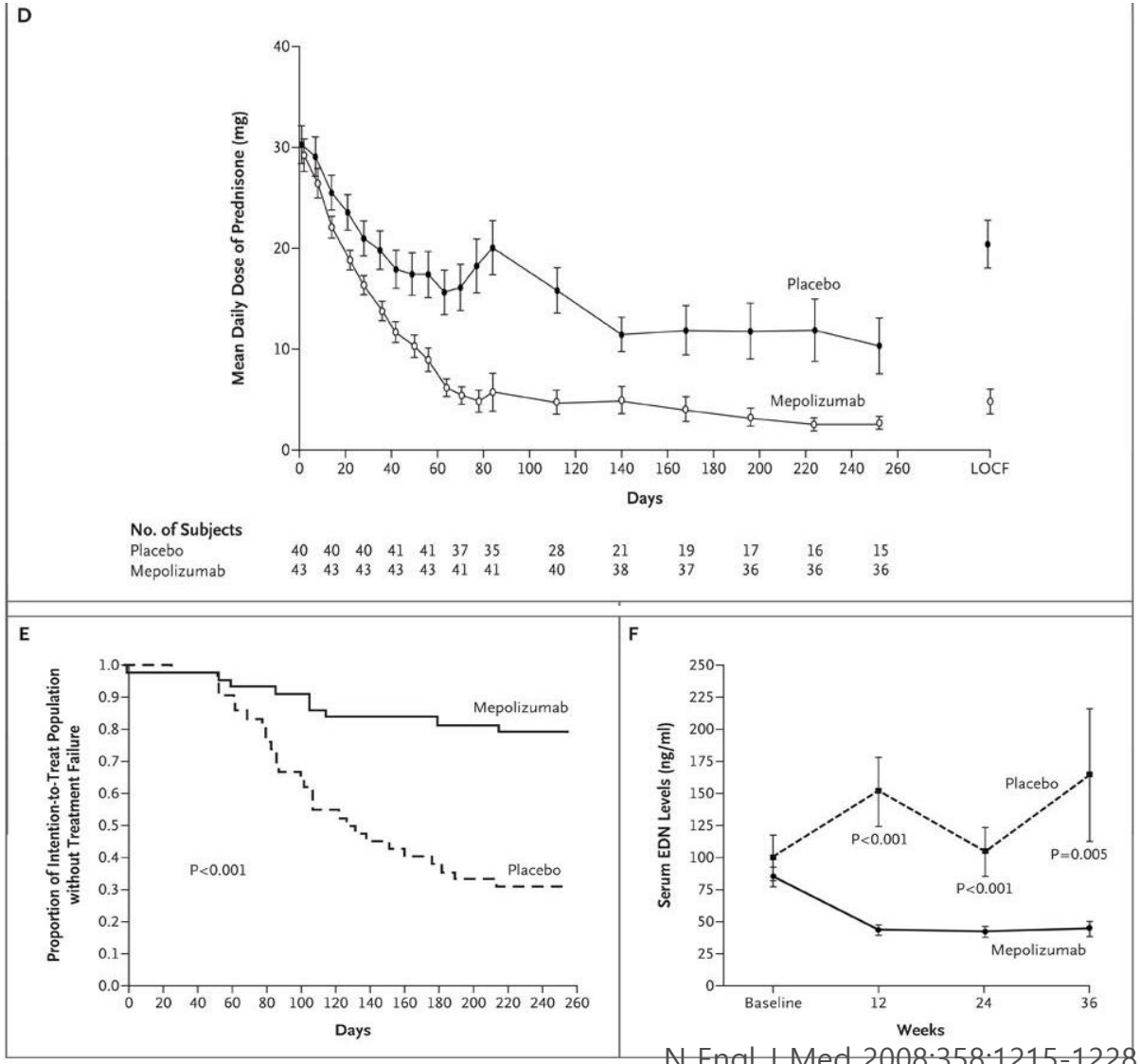
Stabilized with use of PD (20-60mg)

Study design : RCT double blind multicenter US

Intervention: mepolizumab (750mg IV) vs placebo

300mg SC (4w) FDA approved (2020)





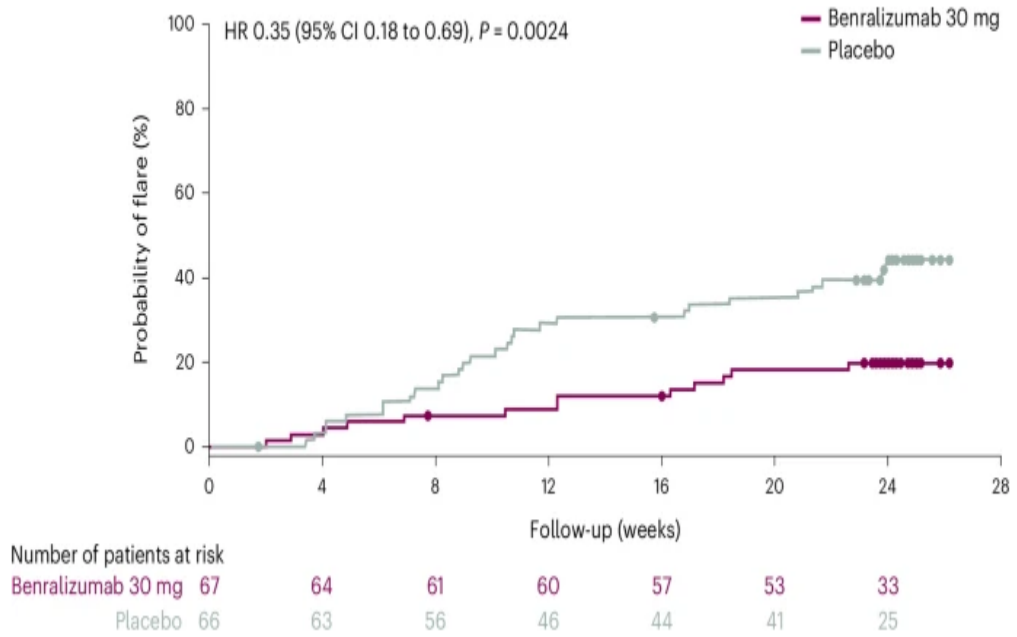
N Engl J Med 2008;358:1215-1228

HES treatment-biologics (Benralizumab)

- NATRON trial
  - Patients(n=134): FIP1L1::PDGFRA(-), stable HES therapy for >4w or Hx of ≥2 HES flares
  - Study design: double blinded RCT
  - Primary endpoint: time to first HES flare
  - Intervention: 30mg q4wks vs placebo

30mg SC (4w) FDA approved (2026.5.13)

Fig. 2: Time to first HES flare (primary endpoint).



Nat Med **32**, 2017–2025 (2026).

HES vs severe eosinophilic asthma vs EGPA

	Severe eosinophilic asthma	EGPA	HES
개념	Type 2/eosinophilic airway disease	Asthma + eosinophilia + **systemic small-vessel vasculitis**	Persistent hypereosinophilia with **eosinophil-mediated organ damage**
Eosinophil count	보통 **≥150–300/μL**부터 T2-high marker로 사용; severe eosinophilic asthma biologic 기준은 보통 ≥150 또는 ≥300/μL	흔히 높음. 2022 ACR/EULAR classification에서는 **≥1.0 × 10^9/L, 즉 ≥1000/μL**가 +5점	전형적으로 **≥1.5 × 10^9/L, 즉 ≥1500/μL**의 hypereosinophilia (twice, duration 2-4wks)
Pathophysiology	IL-4/IL-5/IL-13-driven airway inflammation	Eosinophilic inflammation + ANCA-associated vasulitis	Eosinophil expansion + tissue homing + activation/degranulation → organ injury (thrombosis, fibrosis)
Asthma	(+)	(+)	(+/-)
Sinonasal disease	allergic rhinitis, CRS 동반 가능	CRS, nasal polyp 흔함	있을 수 있으나 disease-defining feature는 아님
Vasculitis	없음	mononeuritis multiplex, purpura, GN, etc	원칙적으로 없음
ANCA	보통 음성/관련 없음	약 30–40%에서 MPO-ANCA/p-ANCA 양성; 양성이면 vasculitic phenotype 많음	대개 음성. 양성이면 EGPA/AAV 감별 필요
Organ damage	주로 bronchial wall/remodeling, exacerbation	Lung, skin, nerve, kidney, heart, GI 등 systemic	Heart, skin, lung, GI, nerve, thrombotic complication 등 다양
폐 침범	가변적 airflow obstruction, AHR	Asthma + transient infiltrates, eosinophilic pneumonia-like lesion 가능	Pulmonary infiltrates 가능하지만 없을 수 있음
Bone marrow / clonal work-up	불필요	비전형적이면 필요	FIP1L1–PDGFRA, PDGFRB, FGFR1, JAK2, KIT, T-cell clonality 등 평가
진단의 핵심	"천식" 진단 + eosinophilic/T2 marker	Asthma/eosinophilia에 **vasculitis 또는 vasculitic organ involvement**가 붙음	다른 원인 배제 후 **persistent HE + eosinophil-related organ damage**
치료 방향	ICS/LABA ± LAMA, biologics: anti-IL-5/5R, anti-IL-4R, anti-IgE, anti-TSLP	Systemic steroid ± immunosuppressant; severe disease는 rituximab/cyclophosphamide; non severe-mepolizumab/benralizumab	원인별 치료: steroid, imatinib for PDGFRA/B, anti-IL-5/IL-5R biologics, cytoreduction 등

Take home messages

1. FeNO/BEC는 asthma를 진단, 확진이 아니라 type 2 감별을 위한 biomarker
2. EB: chronic cough + sputum eosinophilia + no AHR/variable obstruction
   - ICS
3. EGPA: adult-onset asthma/CRSwNP + eosinophilia + vasculitis evidence
   - Steroid with immunosuppressive agent (FFS≥1) or anti-IL-5/IL-5Rα
4. HES: AEC ≥1.5×10^9/L 또는 organ damage → primary/secondary/idiopathic (HES_{FA}, HES_N, HES_R, and HES_I)
   - Non myeloid HES: Steroid (first line)->stabilization->anti-IL-5/IL-5Rα agent