Eosinophilic granulomatosis with polyangiitis (EGPA) και σοβαρό άσθμα

Φούκα Ευαγγελία
Πνευμονολόγος, PhD
Επιμελήτρια Πνευμονολογικής ΑΠΘ

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Conflicts of Interest

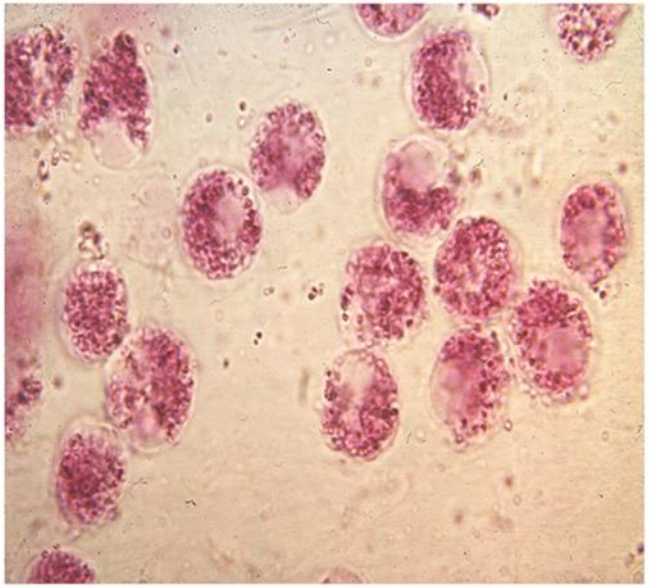
I have received travel Grants from ASTRA ZENECA, NOVARTIS, GSK, BOEHRINGER INGELHEIM, ELPEN, ROCHE, BAYER, MENARINI and PHARMATEN.

I have also received honorarium lecture fees from ASTRA ZENECA, ELPEN, CHIESI, BOEHRINGER INGELHEIM, ROCHE and GSK

Introduction

- Eosinophilia in pulmonary disorders can be detected as an increased percentage of the differential cell count on peripheral blood, induced sputum and BAL samples or as an eosinophilic infiltration seen on lung biopsy specimens

- Lung disease associated with marked peripheral blood or tissue eosinophilia is an unusual event and almost always points toward a diagnosis



Definitions

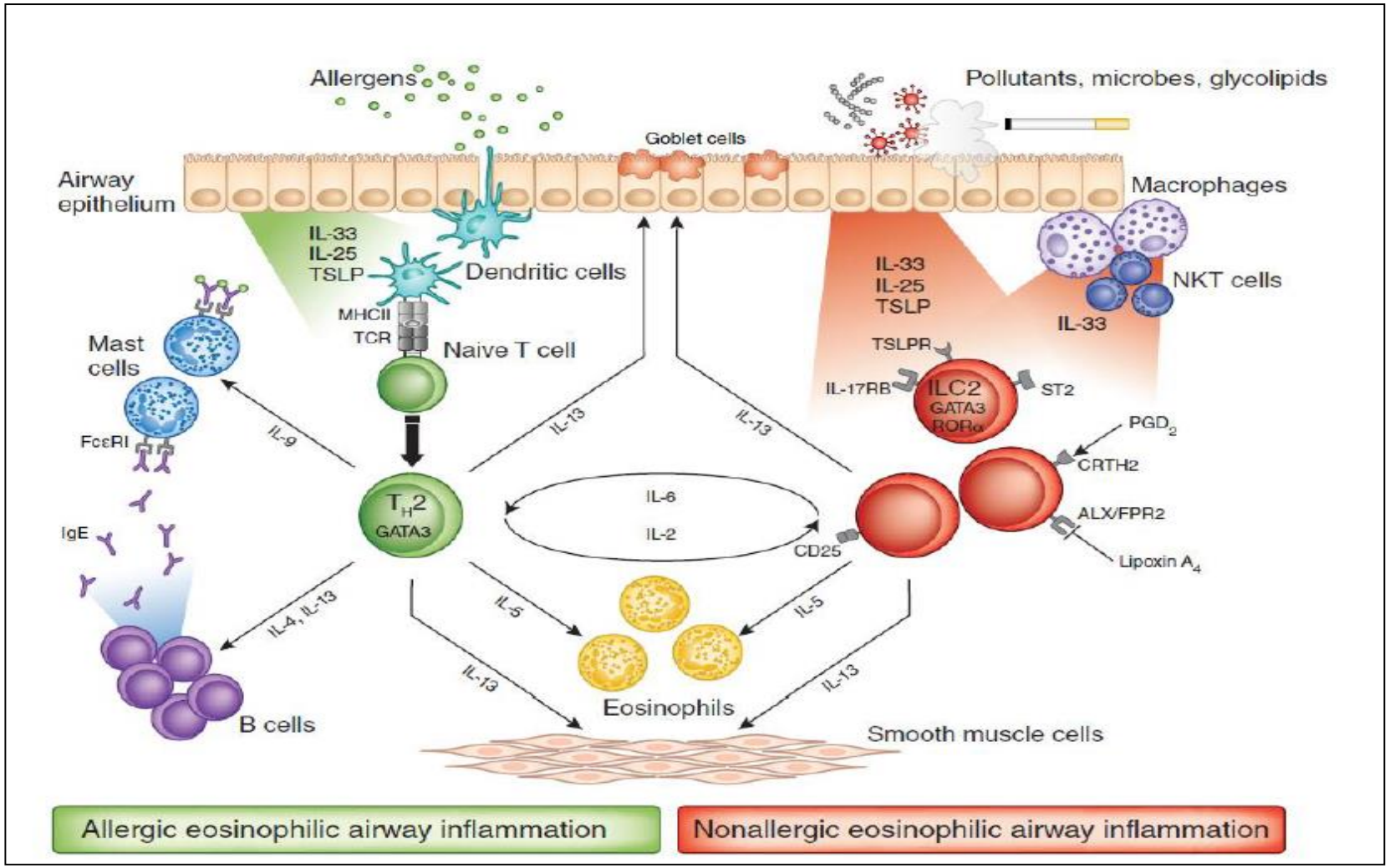
- **Blood Eosinophilia:** refers to an absolute eosinophil blood count **of ≥500 cells/µL**
  - The degree of eosinophilia can be categorized as
    - **Mild:** 500-1500 cells/µL
    - **Moderate:** 1500-5000 cells/µL
    - **Severe:** >5000 cells/µL

- **Hypereosinophilia:** defined as **moderate to severe eosinophilia (>1500 cells/µL)**
  - End-organ manifestations may be present, but not required

- **Alveolar eosinophilia:** defined by differential cell count of **at least 25% eosinophils at BAL** and **typically > 40%.**

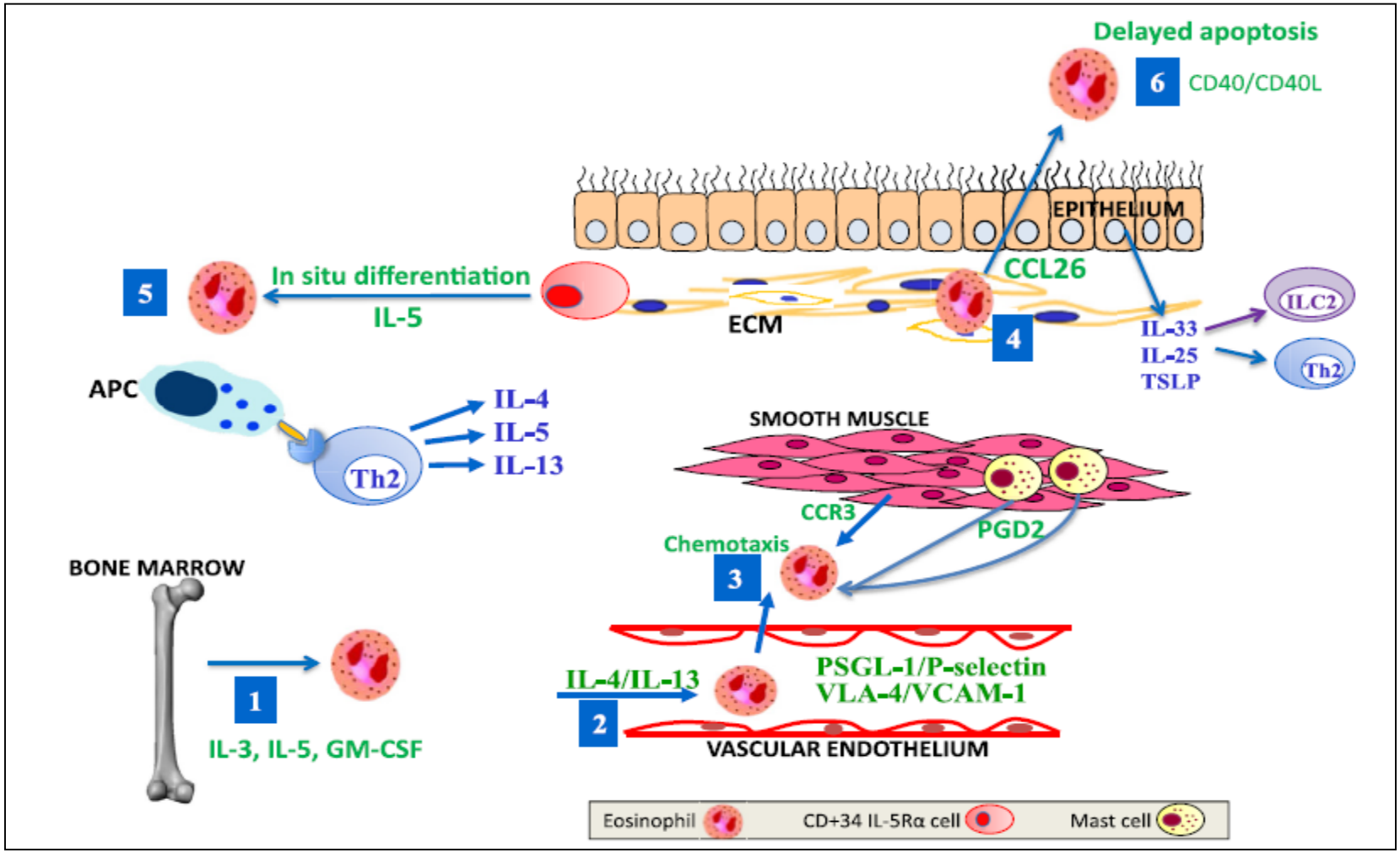
Roufosse S, J Allergy Clin Immunol. 2010;126:39-44

Two different pathways produce Type-2 cytokines and result in eosinophilia



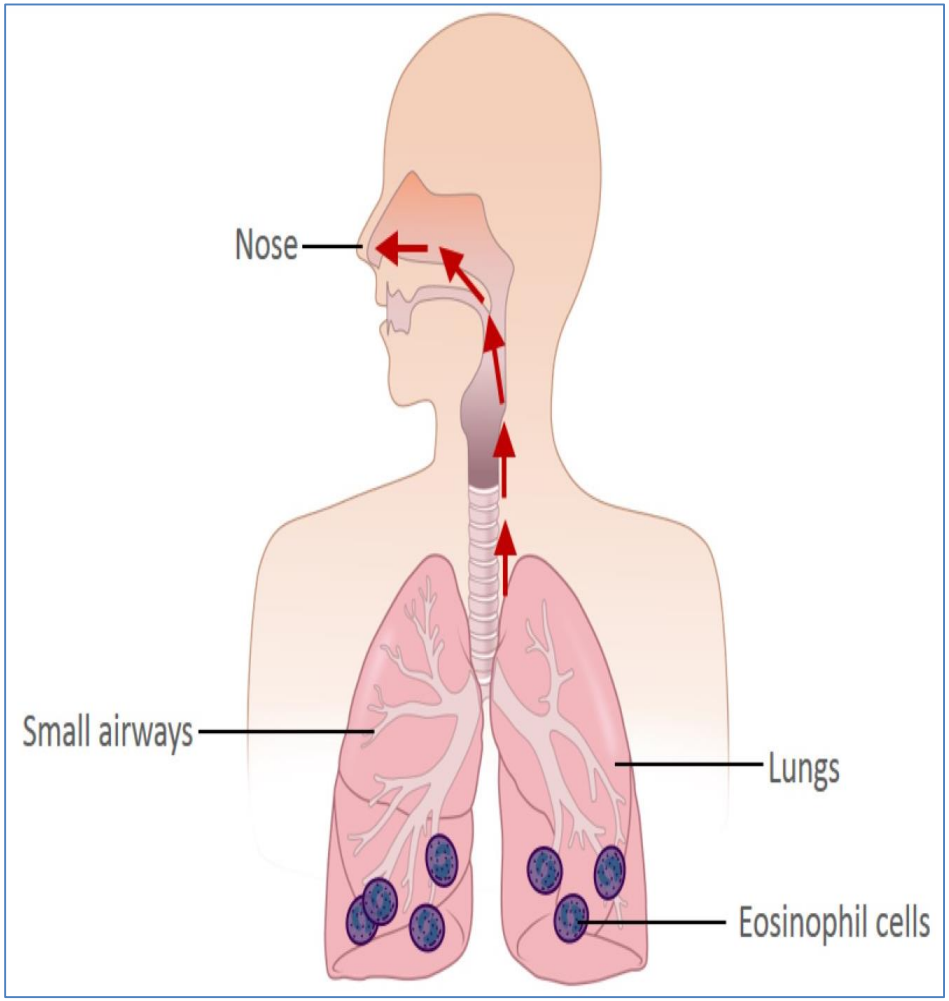
Brusselle GG, Nat Med 2013; 19: 977-9

Mechanisms of eosinophil migration into the lungs



Woolnough K, Immunol Allergy Clin North Am. 2015;35:477-92

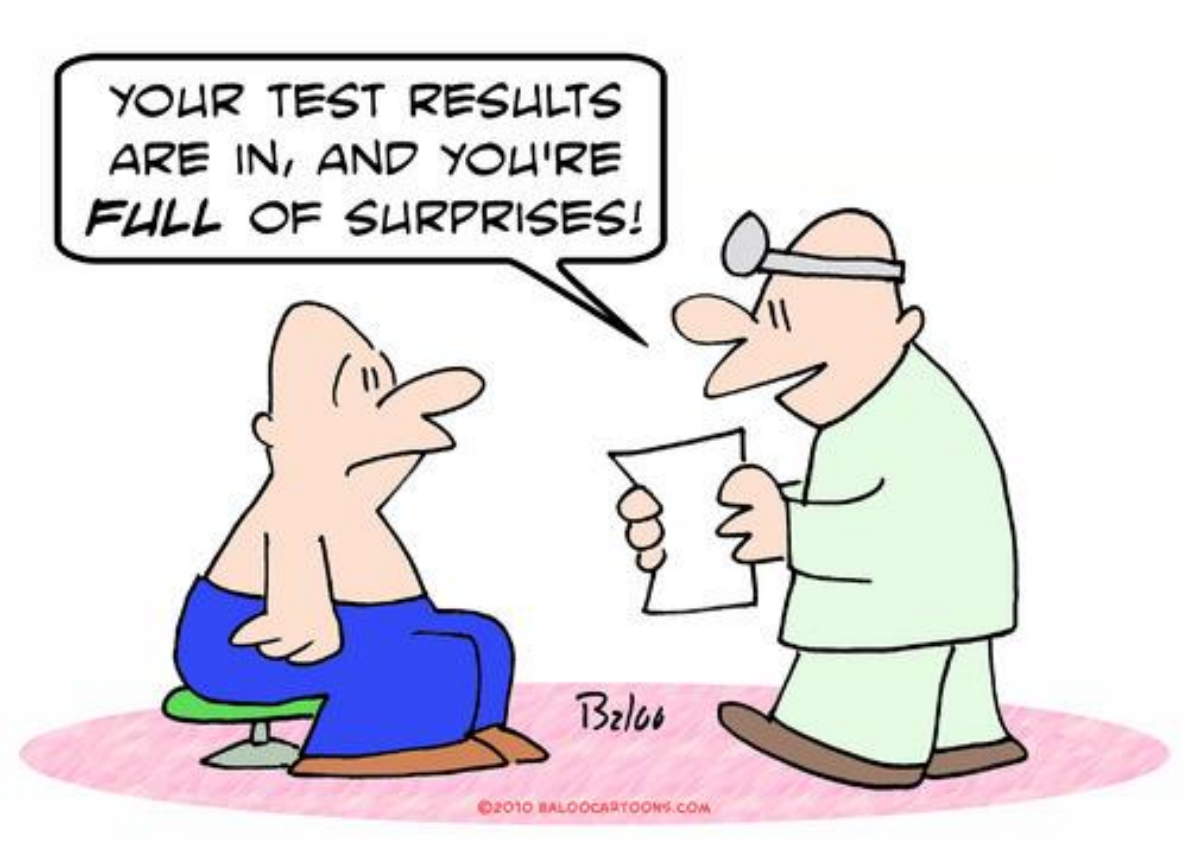
The severe asthma eosinophilic endotype



- Adult onset and equal distribution between sexes
- Lack of atopy
- **Sputum and peripheral blood eosinophilia**
- Chronis sinusitis with nasal polyposis
- Aspirin sensitivity
- Frequent, severe exacerbations
- Low FEV1 and persistent airflow limitation
- Air trapping and dynamic hyperinflation
- Good response to systemic CS

De Groot JC. ERJ Open Res. 2015 Sep 23;1(1)

Είναι όμως πάντα «άσθμα»;



Causes of eosinophilia linked to respiratory diseases

General diagnosis	Specific diagnosis
• **Primary respiratory disease**	• Severe asthma • Allergic fungal airway disease • Eosinophilic pneumonias (idiopathic) • COPD
• **Chronic infection with helminthic parasites**	• Strongyloides, schistosomiasis, filariasis
• **Drug allergy**	
• **Hypereosinophilic syndromes**	• **EGPA** • HES general • Myeloproliferative
• **Malignant disease**	• Lung cancer, lymphomas
• **Miscellaneous**	

Woolnough K, Immunol Allergy Clin N Am. 2015: 477-492

Eosinophilic granulomatosis with polyangiitis (Formely Churg-Strauss syndrome)

" In addition to asthma, there were fever and hypereosinophilia, and symptoms of cardiac failure, renal damage and peripheral neuropathy resulting from vascular embarrassment in various systems of organs"

Churg Strauss syndrome -1951

Dr. J Churg **Dr. L Strauss**

- Their publication was the first description of these patients, and data were analyzed from 13 patients – most from autopsy specimens
- Key findings included asthma, eosinophilia, granulomatous inflammation necrotizing systemic vasculitis and necrotizing glomerulonephritis
- In 2012, it was renamed EGPA

Churg J, Strauss L. Allergic granulomatosis, allergic angiitis and periarteritis nodosa. Am J Pathol 1951; 27:277-301.

Eosinophilic granulomatosis with polyangiitis (Formely Churg-Strauss syndrome)

- **Systemic, small vessel vasculitis** associated with **asthma, eosinophilia** (>1500 cells/µL or 10% of total WBC) and **ANCA antibodies** in 40% of cases
- Predominates in the 4^{th}-5^{th} decade, no gender predominance , familial cases have been reported
- Incidence: 0.5-6.8 cases / million inhabitants/ per year
- Prevelance: 2-38 / million inhabitants
- Can affect the vessels of any organ system, leading to a wide range of symptoms

Vaglio A, Allergy 2013; 68: 261–273

Pathogenesis

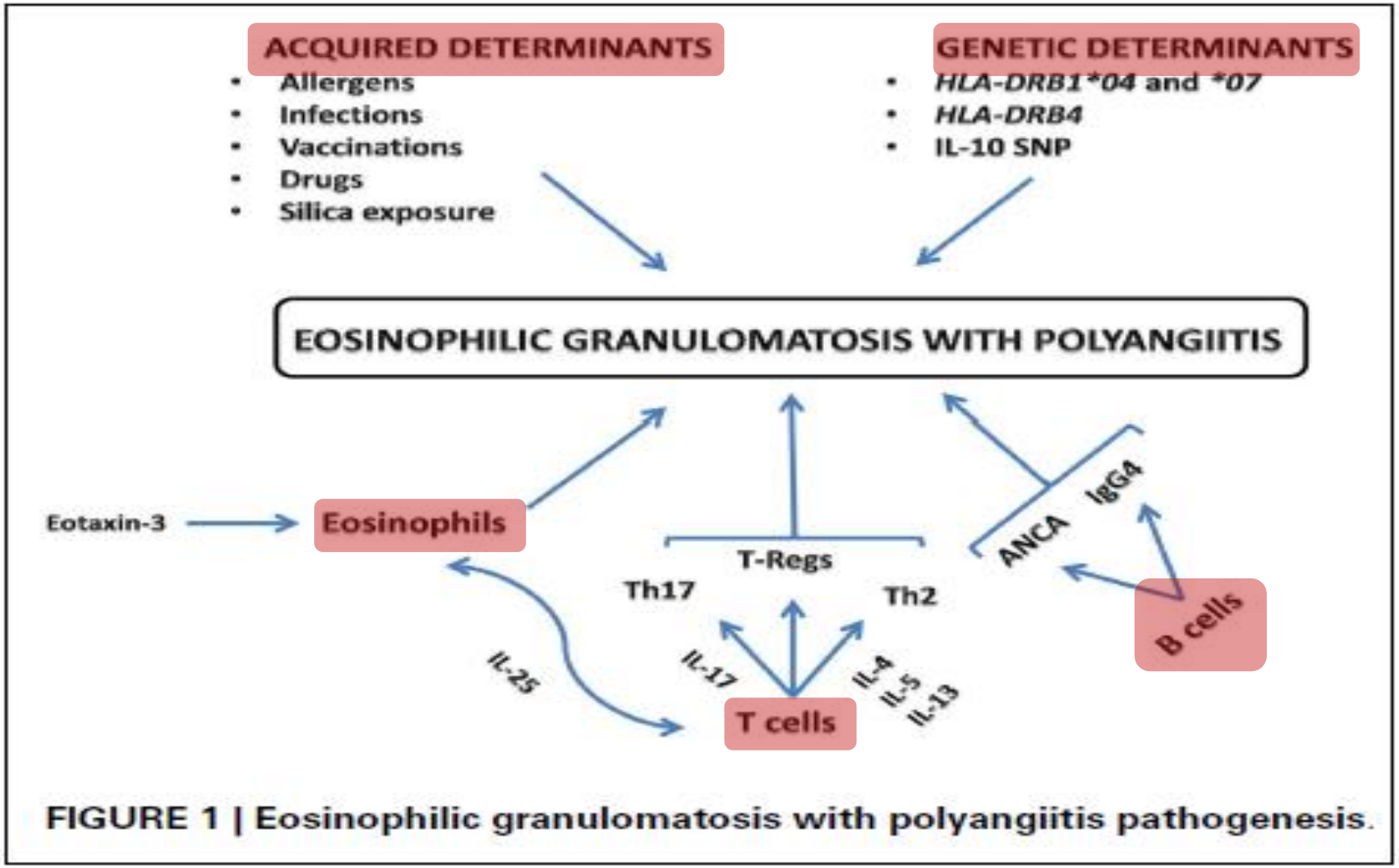


FIGURE 1 | Eosinophilic granulomatosis with polyangiitis pathogenesis.

Gioffredi A, Front Immunol. 2014;5:549

Clinical manifestations

The natural course of EGPA has been described to follow 3 phases:

- **Prodromic or allergic phase:** asthma, allergic rhinitis, sinusitis (2^{nd} or 3^{rd} decade of life)
- **Eosinophilic phase:** peripheral eosinophilia and eosinophilic organ infiltrations (lung, heart, gastrointenstinal system)
- **Vasculitic phase:** purpura, peripheral neuropathy, constitutional symptoms (fever, malaise, weight loss)

Pagnoux C, Curr Opin Reumatol. 2007; 19:25-32

Clinical phenotypes

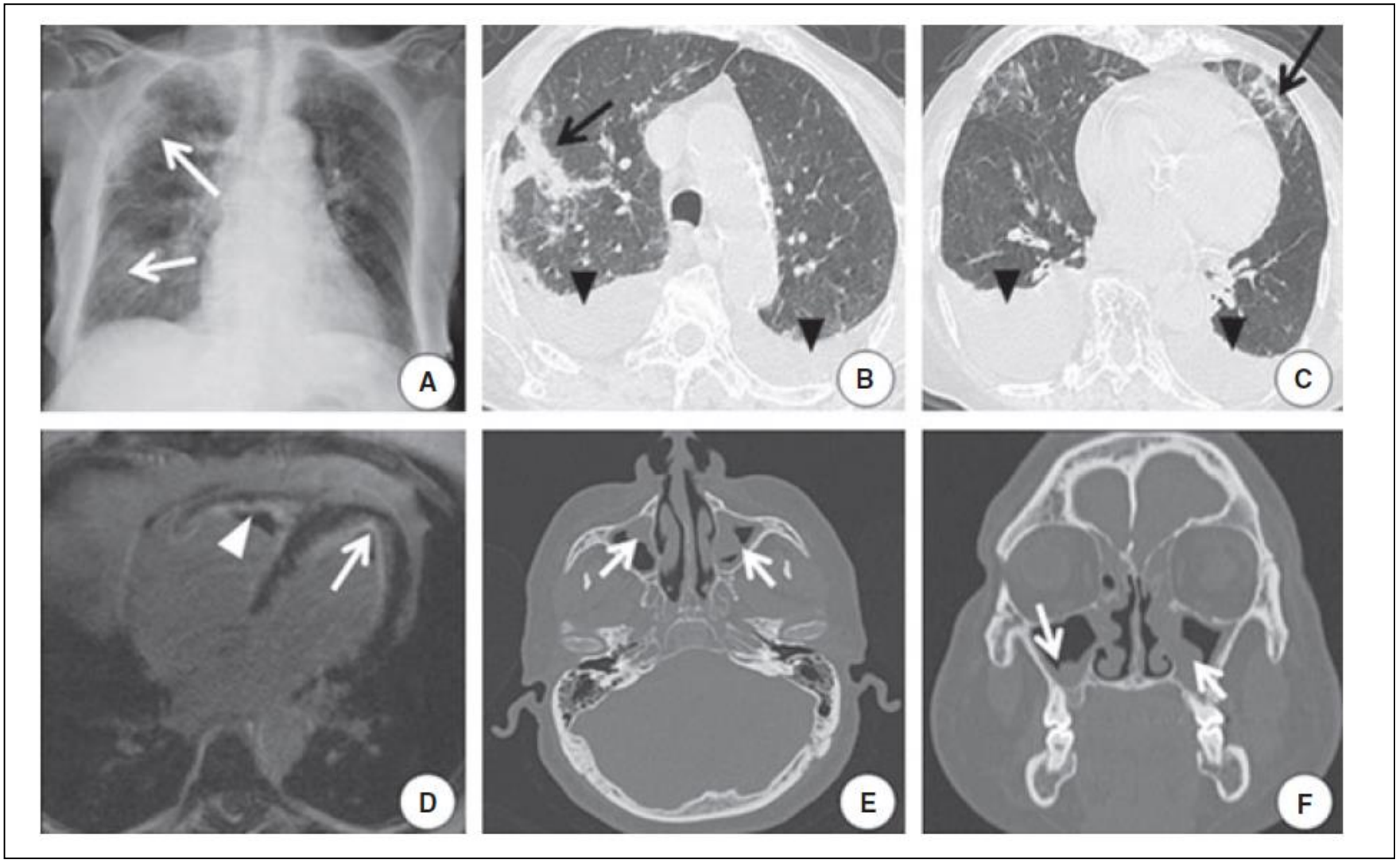
Table 2 Major organ manifestations and ANCA status in three published series of patients with EGPA (Churg–Strauss).

	Sablé-Fourtassou et al. (60)			Sinico et al. (54)			Healy et al. (65)		
	ANCA+ (n = 43) (%)	ANCA− (n = 69) (%)	P-value	ANCA+ (n = 35) (%)	ANCA− (n = 58) (%)	P-value	MPO-ANCA+ (n = 15) (%)	ANCA− (n = 55) (%)	P-value
Asthma	100	100	ns	97	95	ns	100	100	ns
Sinusitis	76	53	0.01	77	78	ns	60	64	ns
Lung involvement, *all kinds*	56	71	ns	34	60	0.02	40	76	<0.01
Alveolar hemorrhage	7	7	ns	20	0	0.001	na	na	na
Heart involvement	12	49	<0.001	6	22	<0.01	0	38	<0.01
Gastrointestinal involvement	42	26	ns	20	22	ns	0	14	0.03
Skin involvement, *all kinds*	53	51	ns	60	48	ns	67	62	ns
Purpura	39	20	0.03	26	7	0.02	53	40	ns
Peripheral neuropathy, *all kinds*	84	65	0.03	71	60	ns	73	42	0.02
Mononeuritis multiplex	na	na	na	51	24	0.01	na	na	na
CNS involvement	13	7	ns	17	12	ns	20	13	ns
Renal involvement, *all kinds*	35	4	<0.001	51	12	<0.001	33	16	ns
RPGN/biopsy-proven GN	19	0	<0.001	29	5	<0.01	na	na	na
Vasculitis on biopsy	79	39	<0.001	76	32	<0.001	81	61	ns

ANCA, anti-neutrophil cytoplasmic antibodies; MPO-ANCA, myeloperoxidase-ANCA; CNS, central nervous system; RPGN, rapidly progressive glomerulonephritis; GN, glomerulonephritis; ns, not significant; na, not available; EGPA, eosinophilic granulomatosis with polyangiitis.

Vaglio A, Allergy 2013; 68: 261–273

Imaging

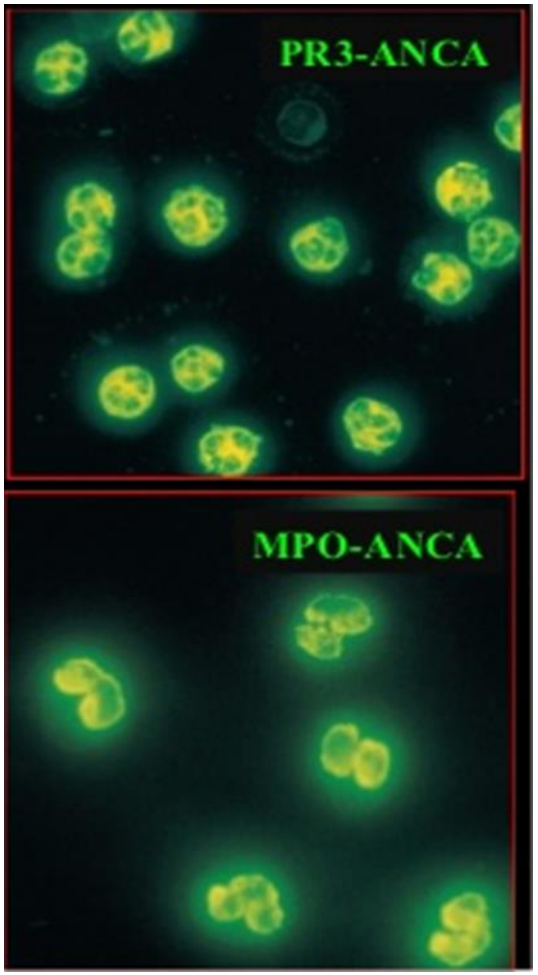


Vaglio A, Allergy 2013; 68: 261–273

Laboratory findings

- Peripheral blood eosinophilia:
  -5000-9000 cells/µL (> 1500 cells/µL or > 10%)
- ↑ CRP and ESR, microscopic or gross hematuria, proteinuria
- ↑ total serum IgE
- ↑ ANCA in 40% (p-ANCA (MPO) in 75%)
  - titer does not correlate with disease activity
- ↑ serum IgG4 (in 75%)
- ↑ serum eotaxin-3

- at a cut-off level of 80 pg/ml: sens 87.5% and spec 98.6%



Vaglio A, Ann Rheum Dis. 2012;71:390-3, Sinico RA, Arthritis Rheum. 2005;52:2926-35, Zwerina J, Rheumatology. 2011;50: 1823-27

BAL findings

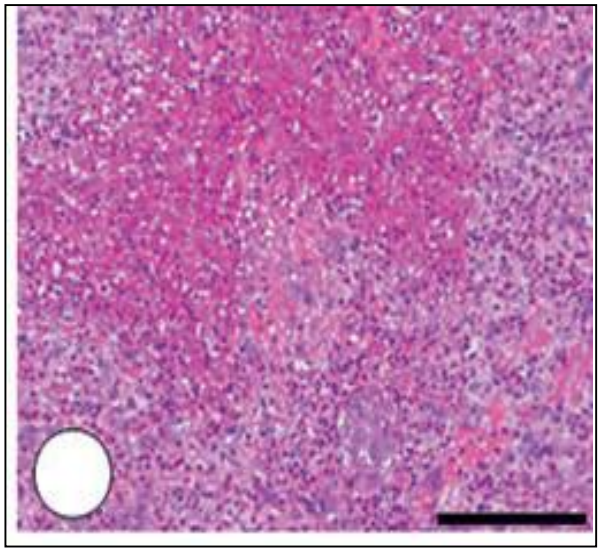
TABLE 5 Bronchoalveolar lavage findings in patients with eosinophilic granulomatosis with polyangiitis

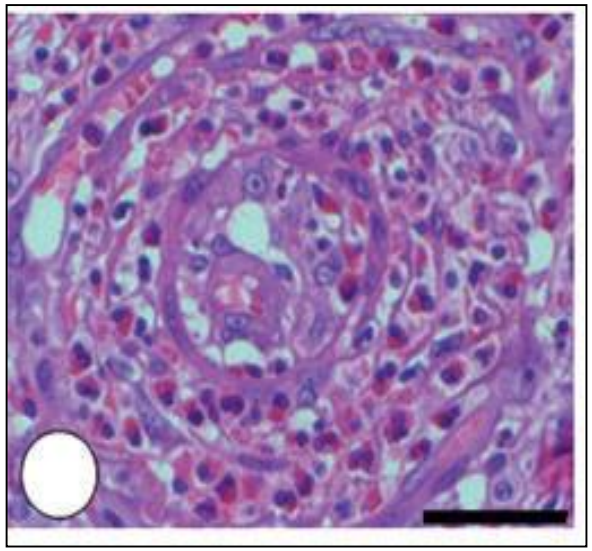
Subjects n	92
Blood eosinophils at the time of BAL $\times 10^9$ L^{-1}	3.8±5.2
Patients receiving oral corticosteroids	22 (24%)
Total number of leukocytes in BAL mm^{-3}	296±496
Differential cell count	
Macrophages %	46±31
Eosinophils %	33±29
Neutrophils %	15±24
Lymphocytes %	8±10
Mast cells %	0
Alveolar haemorrhage	
Macroscopic bloody fluid	0
Siderophages >20% or GOLDE score >100	2±9

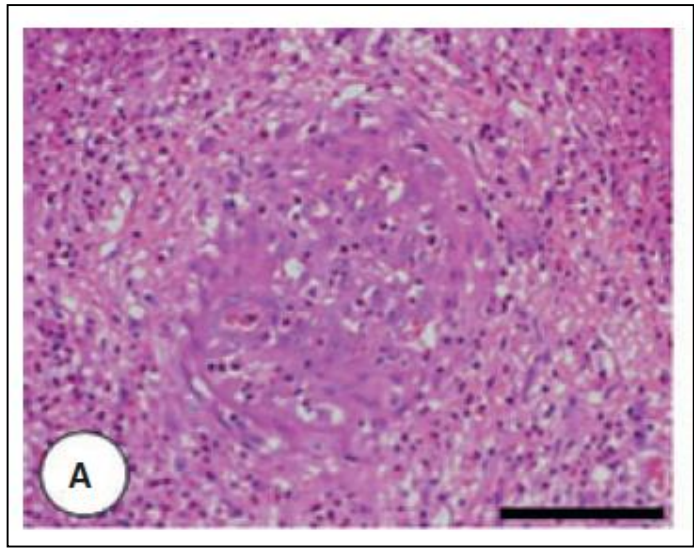
Data are presented as mean±SD or n (%), unless otherwise stated. BAL: bronchoalveolar lavage.

Cottin V, Eur Respir J. 2016;48:1429-1441

Biopsy is the Gold Standard for EGPA diagnosis







- The key histological features of EGPA are **tissue eosinophilia**, necrotizing vasculitis, and extravascular eosinophilic granulomas.

- **Vasculitis** is characterized by **fibrinoid necrosis** and **eosinophilic vessel wall infiltration**.

- **Granulomas** may involve the arteries, but the more EGPA-specific lesion is the **extravascular granuloma**, which consists of a core of **necrotic eosinophilic material** surrounded by **palisading lymphocytes** and **epithelioid and multinucleated giant cells**

Vaglio A, Allergy 2013; 68: 261–273

Diagnostic criteria

Lanham diagnostic criteria (1984)[a]	American College of Rheumatology classification criteria (1990)[b]	Revised International Chapel Hill consensus conference nomenclature of vasculitides (2012)
Asthma Blood eosinophilia >1500/mm^3 or >10% of total WBC Evidence of vasculitis involving two or more organs	Asthma Eosinophilia (>10% of total WBC) Neuropathy Pulmonary infiltrates non-fixed Paranasal sinus abnormalities Extravascular eosinophils	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessel, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.

b: presence of ≥ 4 criteria yields a sensitivity of 85% and a specificity of 99.7% for EGPA

Vaglio A, Allergy 2013; 68: 261–273

EGPA diagnosis may be difficult

- in patients with asthma, blood eosinophilia, (-) ANCA and mild extrathoracic manifestations
- when a single extrarespiratory manifestation attributable to the systemic disease is present ("forme fruste" of EGPA)
- in subjects receiving corticosteroid treatment

“Working diagnosis” for EGPA

1. Asthma
2. Peripheral blood eosinophilia greater than 1500/mm^3 and/or alveolar eosinophilia greater than 25%
3. Extrapulmonary clinical manifestations of disease (other than rhinosinusitis), with at least 1 of the following:
   a. Systemic manifestation typical of the disease: mononeuritis multiplex; or cardiomyopathy confidently attributed to the eosinophilic disorder; or palpable purpura;
   b. Any extrapulmonary manifestation with histopathological evidence of vasculitis as demonstrated especially by skin, muscle, or nerve biopsy;
   c. Any extrapulmonary manifestation with evidence of antineutrophil cytoplasmic antibodies with antimyeloperoxidase or antiproteinase 3 specificity.

Cottin V, Clin Chest Med 2016

Differential diagnosis

- Asthma
- Allergic rhinitis
- Parasitic infections
- Hypersensitivity reactions
- Hypereosinophilic syndrome (HES)
- Allergic fungal airway disease
- Acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- Other vasculitis (GPA, MPA)
- IgG4-RD
- Systemic mastocytosis

Proposed diagnostic algorithm

Peripheral eosinophilia
± presence of pulmonary eosinophilia (induced sputum / BAL)

Asthma	Persistant consolidation	Multiorgan involvement	Travel exposure to helminths /parasites	Peripheral Lymphadenopathy/ Opportunistic Infection/ weight loss
Total IgE, specific IgE to *A.fumingatus, Peniccilium, Candida, Malessezia*, CT scan	Drugs, food and toxins exposure	ANCA, Cardiac MRI, biopsy of involved tissue FIP1L1-PDGFRα mutation, drug history	Serology & stool examination	CT of abdomen and pelvis, lymph node biopsy, peripheral blood lymphocyte subsets and clonality, bone marrow evaluation (cryptogenic and molecular testing) serum immunoglobulins and immunoglobulin isotypes, other immune deficiencies
AFAD, severe asthma	**ICEP**	**EGPA, CEL, DRESS, HES**		

Treatment

Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management

EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

Remission-induction therapy according to prognostic score:

- Patients with lower scores are considered to have a better prognosis, as measured by the 5-year mortality rate

The five factors score (FFS)

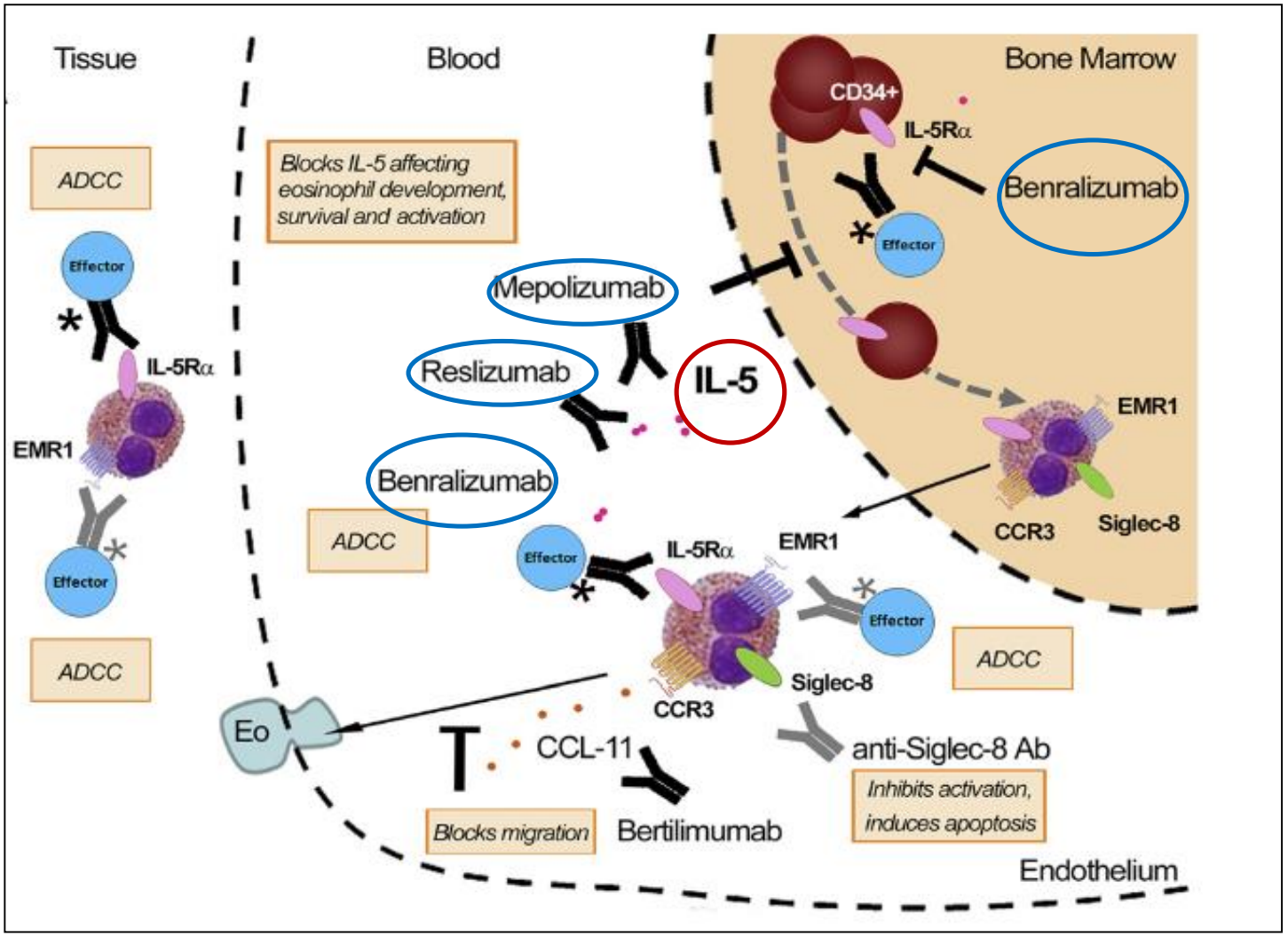
- Age > 65 years
- Cardiac insufficiency
- Gastrointestinal involvement
- Renal insufficiency
- Absence of ENT manifestations

Groh M, Eur J Intern Med. 2015;26:545-53
Yates M, Ann Rheum Dis 2016;0:1–12

- **FFS=0 : only GCS** (1mg/kg/day, max 75mg/day, for 2-4 weeks, then tapered to 7.5-10mg/day by 3-5 months) **[A]**
- **FFS≥1: GCS** (initial methylprednisolone bolus of 7.5-15mg/kg/day for 3-5 days) **+ CYC** (0.6-0.7 g/m2 i.v. at days 1, 15 and 30, then every 3 weeks) **[B]**
- Rapidly progressive glomerulonephritis, peripheral neuropathy or alveolar hemorrhage: **PLEX [C]**
- ANCA (+) with renal involvement or refractory disease: **RTX [C]**
  - **2nd or 3rd line Tx** (selected patients): **IVIg or INF-α [C]**
- **Remission maintenance** (according to BVAS score): **± AZA** (2mg/Kg/day for up to 18 months) **or MTX [C]**

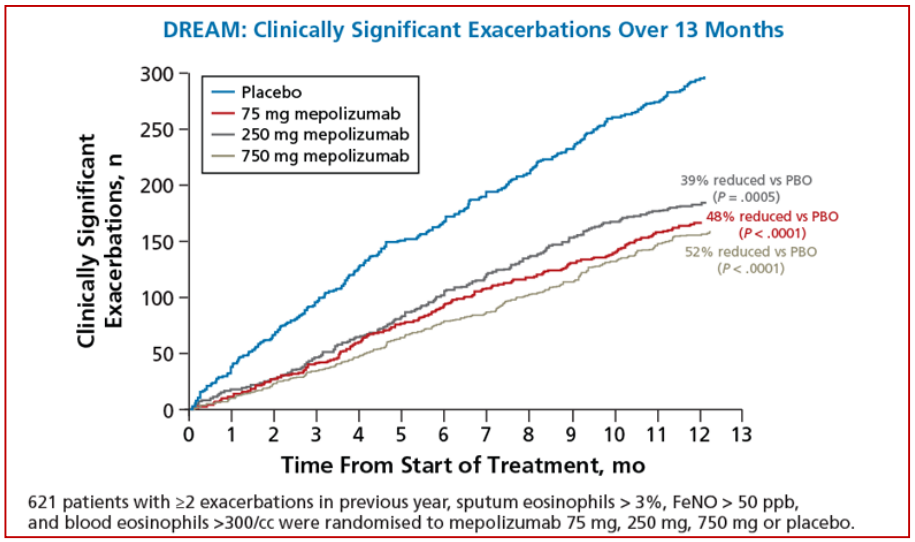
Yates M, Ann Rheum Dis 2016;0:1–12

IL-5 is an ideal target for the treatment of refractory eosinophilic asthma

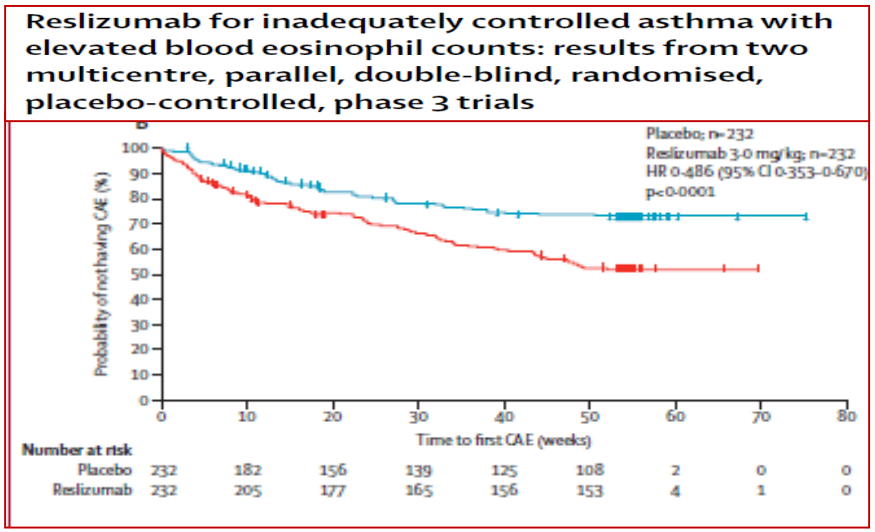


Legrand, J Allergy Clin Immunol Pract 2015

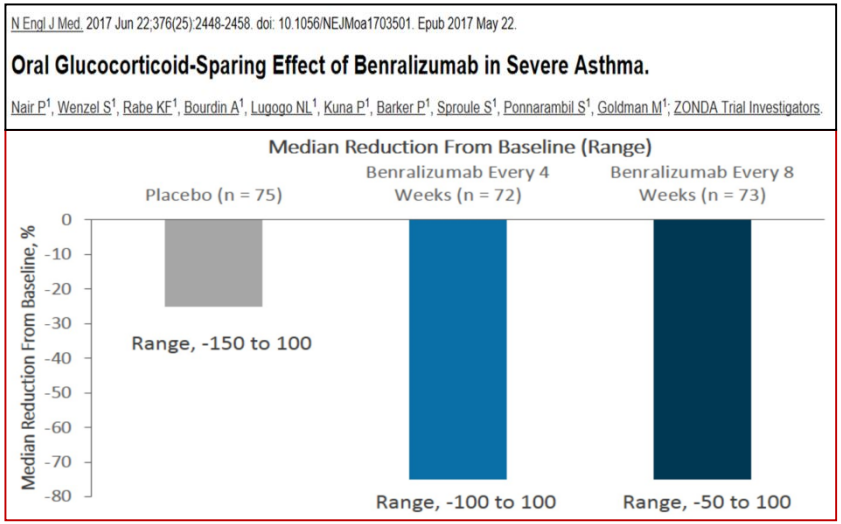
Anti-IL5 therapies decrease exacerbations and help to reduce OCS dose in patients with severe asthma and elevated blood eosinophils



Pavord Lancet 2012;380:651-59



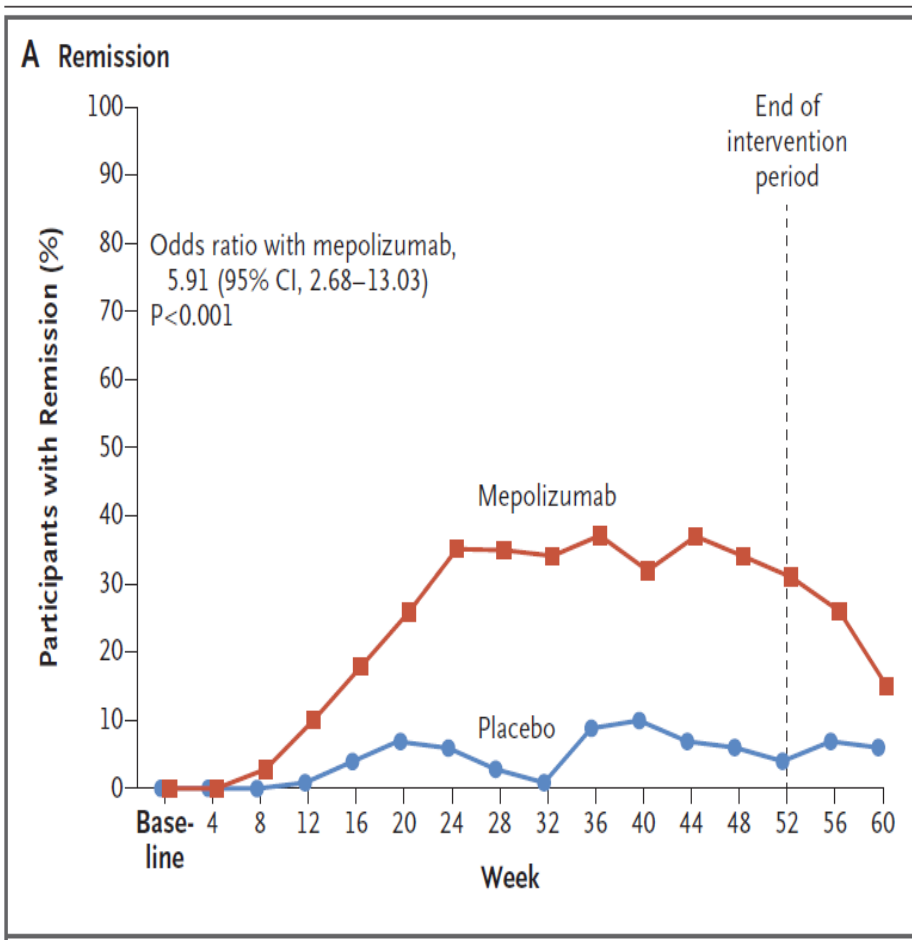
Castro, Lancet Respir Med. 2015; 3:355-66

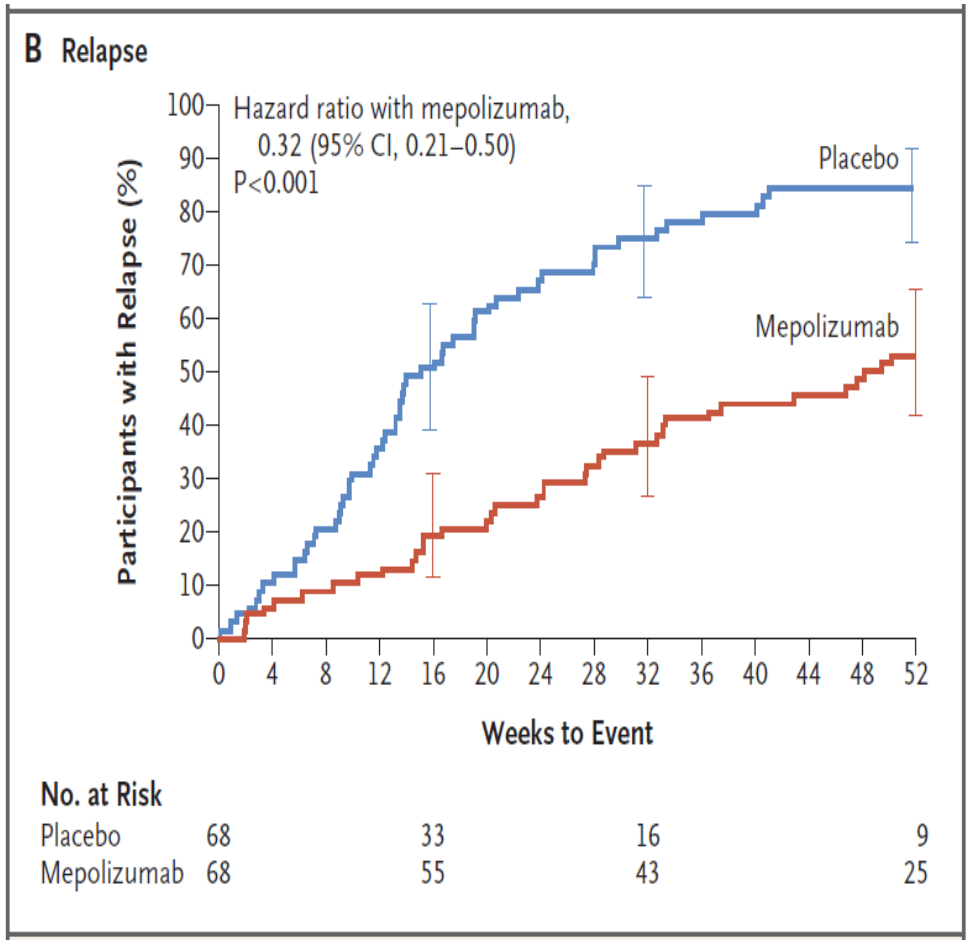


Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

- 136 patients with relapsing or refractory EGPA on stable prednisolone or prednisone dose
- Mepolizumab 300 mg or placebo sbc every 4 weeks, plus standard care, for 52 weeks.
- **PEPs:** accrued weeks of remission over a 52-week period and the proportion of participants in remission at both weeks 36 and 48
- **SEPs:** time to first relapse and the average daily GCS dose during weeks 48 through 52

Wechsler ME, NEJM. 2017; 376: 1921-32





- Mepolizumab led to significantly more weeks of remission than PBO (28% vs. 3%, P<0.001) and a higher % of participants in remission at both weeks 36 and 48 (32% vs. 3%, P<0.001)

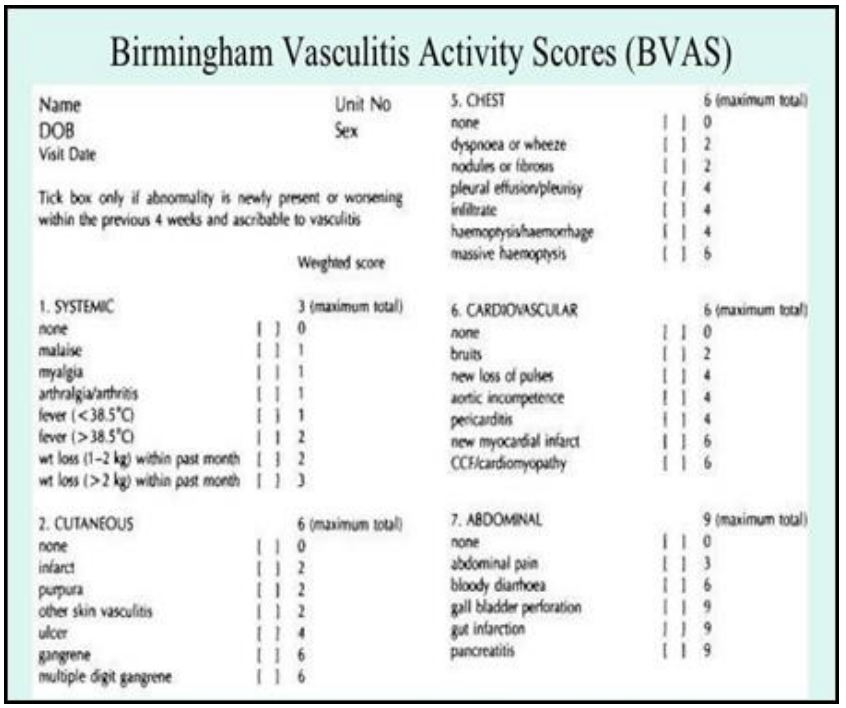
Wechsler ME, NEJM. 2017; 376: 1921-32

Ongoing Clinical Studies in EGPA

The REOVAS study (NCT02807103)
▪ 118 patients assigned to different arms based on prognostic scores
▪ Patients with favourable FFS: rituximab vs. placebo plus corticosteroid standard therapy
▪ Patients with severe organ involvement: rituximab vs. cyclophosphamide
▪ PEP: complete remission at 6 months as defined by the BVAS = 0 and prednisone doses < 7.5 mg/day
The MAINRITSEG study (NCT03164473)
▪ maintenance treatment with rituximab (500 mg every 6 months for 18 months) vs. azathioprine 2 mg/kg/day
The RITE study (NCT02947945)
▪ Evaluation of the efficacy and safety of reslizumab for EGPA
The BITE study (NCT03010436)
▪ Evaluation of the efficacy and safety of benralizumab in EGPA

Refractory disease is defined by EULAR as

- Unchanged or increased disease activity after 4 weeks of treatment with standard therapy in acute EGPA, or
- Lack of response, defined as <50% reduction in the disease activity score (BVAS Score), after 6 weeks of treatment, or
- Chronic, persistent disease defined as presence of at least 1 major or 3 minor items on the disease activity score after >12 weeks of treatment



Birmingham Vasculitis Activity Scores (BVAS)

Name Unit No
DOB Sex
Visit Date

Tick box only if abnormality is newly present or worsening within the previous 4 weeks and ascribable to vasculitis

Weighted score

1. SYSTEMIC	3 (maximum total)
none	0
malaise	1
myalgia	1
arthralgia/arthritis	1
fever (<38.5°C)	1
fever (>38.5°C)	2
wt loss (1–2 kg) within past month	2
wt loss (>2 kg) within past month	3

2. CUTANEOUS	6 (maximum total)
none	0
infarct	2
purpura	2
other skin vasculitis	2
ulcer	4
gangrene	6
multiple digit gangrene	6

5. CHEST	6 (maximum total)
none	0
dyspnoea or wheeze	2
nodules or fibrosis	2
pleural effusion/pleurisy	4
infiltrate	4
haemoptysis/haemorrhage	4
massive haemoptysis	6

6. CARDIOVASCULAR	6 (maximum total)
none	0
bruits	2
new loss of pulses	4
aortic incompetence	4
pericarditis	4
new myocardial infarct	6
CCF/cardiomyopathy	6

7. ABDOMINAL	9 (maximum total)
none	0
abdominal pain	3
bloody diarrhoea	6
gall bladder perforation	9
gut infarction	9
pancreatitis	9

Hellmich B, Ann Rheum Dis. 2007;66:605–17.

Prognosis

- Χωρίς θεραπεία, η 5ετής επιβίωση δεν ξεπερνά το 25%
- Υπό θεραπεία, τα ποσοστά επιβίωσης σε 5 και 8 έτη φθάνουν το 97% και 92% αντίστοιχα
- Προγνωστικούς παράγοντες υποτροπής αποτελούν τα θετικά ANCA και οι η προσβολή οργάνων όπως η καρδιά και τα περιφερικά νεύρα, ενώ η θεραπεία με ανοσοκατασταλτικά συμβάλλει στη θνητότητα από τη νόσο (λοιμώξεις, κακοήθειες)
- Συχνότερες αιτίες θανάτου:
  - Καρδιακή ανεπάρκεια, έμφραγμα του μυοκαρδίου ή και τα δύο
  - Νεφρική ανεπάρκεια
  - Εγκεφαλική αιμορραγία
  - Αιμορραγία από το ΓΕΣ
  - Status asthmaticus

Greco A, Autoimmun Rev. 2015 ; 14:341-8

The eosinophilic phenotype of asthma

- Refers to **airway eosinophilia**
- No consensus on definition - relative instability
  - **> 3% Eos** in induced sputum?
- High risk of severe attacks, including episodes requiring ventilation
- Responds generally well to anti-inflammatory treatment with steroids

Haldar, JACI 2007
Haldar, AJRCCM 2008
Berry, Thorax 2007

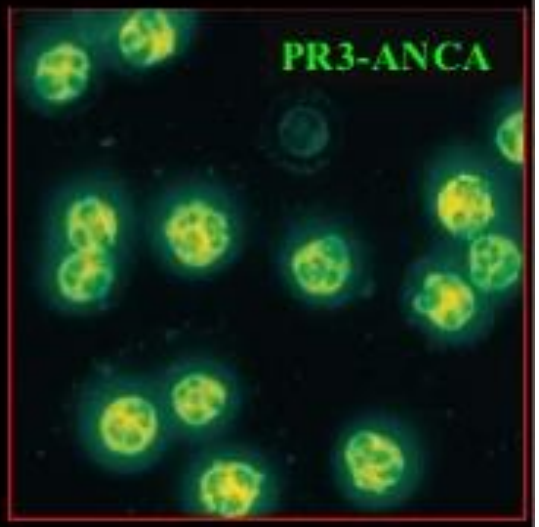
Approach to the patient with asthma and peripheral eosinophilia

- **Acutely ill patient or extremely high eosinophil count**
  - Hospitalization for urgent evaluation of the cause of eosinophilia and prompt initiation of therapy
- **Outpatient with signs of organ involvement**
  - Referral to a physician experienced in evaluating eosinophilic disorders and /or hospital admission
- **Incidental finding – no signs of organ involvement**
  - Periodic monitoring for the development of organ involvement at 6 month intervals

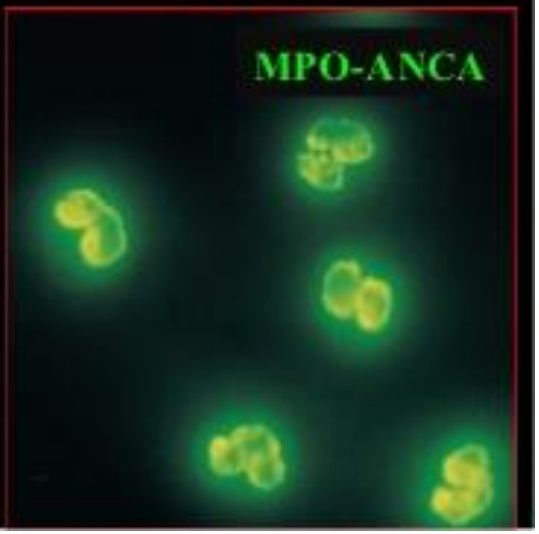
ANCA

- ANCAs are directed against antigens that reside within the primary granules of neutrophils and monocytes.

Two types of ANCA are relevant to vasculitis

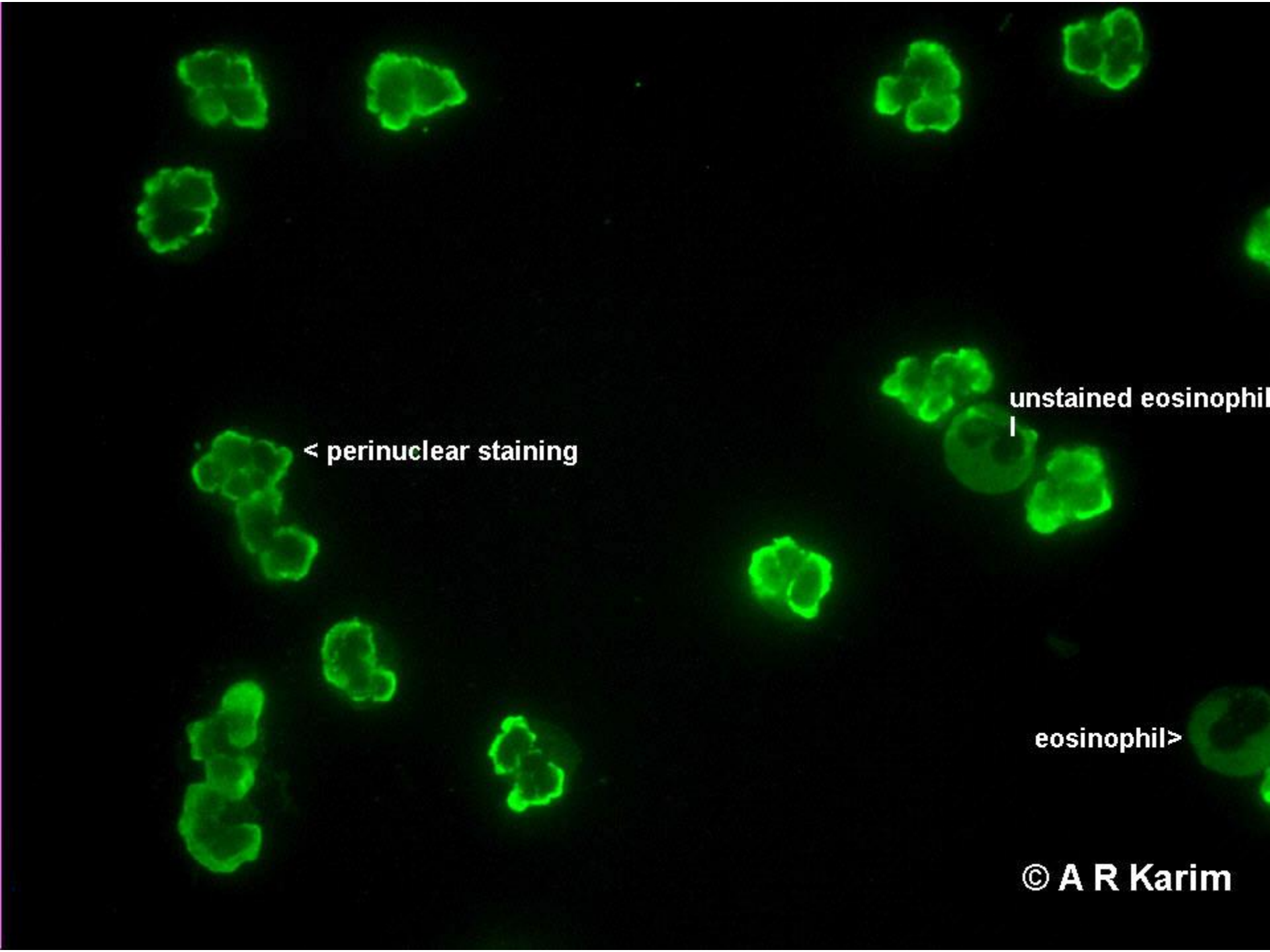


♠ Proteinase 3 (PR3) PR3-ANCA



♠ Myeloperoxidase (MPO) MPO-ANCA.

- Staining on ethanol
- ANCA titres are generally measured using ELISA and indirect immunofluorescence


< perinuclear staining
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eosinophil>
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