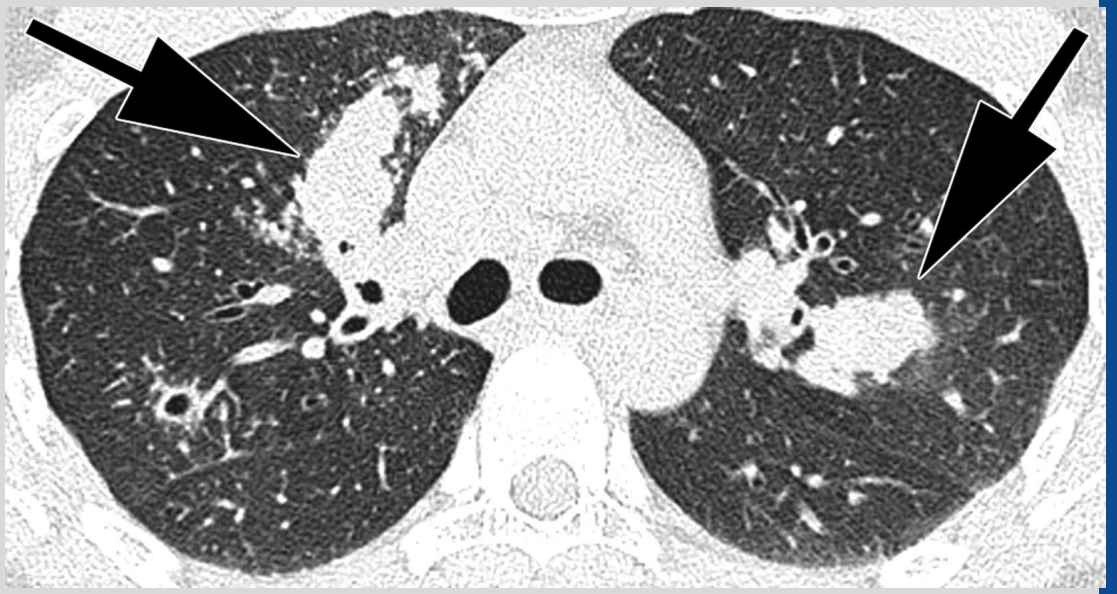

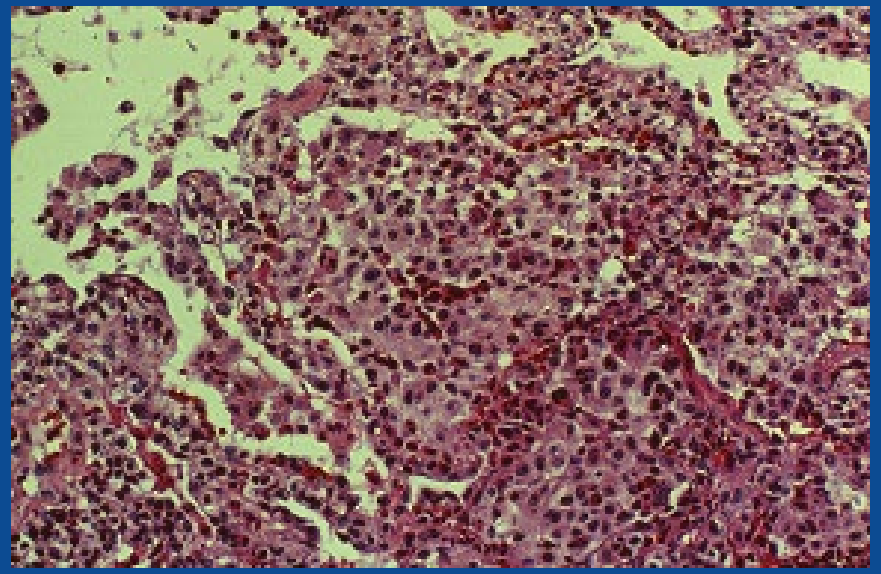

# Allergic Bronchopulmonary Aspergillosis and Eosinophilic Lung Disease


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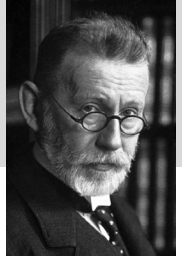
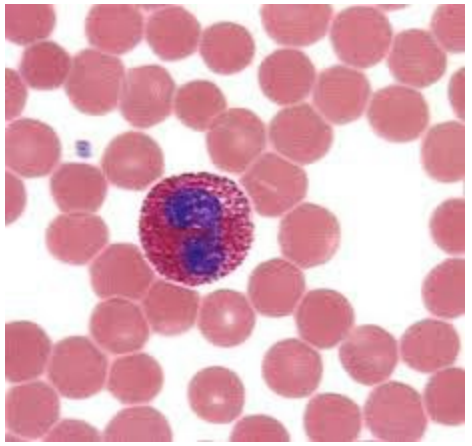


**Paul Erlich**
**1854-1915**

# Eosinophils



- Bone marrow-derived granulocytes
- Arise from myeloid progenitor shared with basophils
- Major distribution in tissues (gut, visceral fat, generally not respiratory)
- Production in marrow increases selectively in helminth infections, allergic disease, certain tumors
- Likely involved in elimination/containment of certain helminths; potential important in brown fat maintenance and metabolic homeostasis
- Signature of allergic inflammation; frequently found in fibrotic/remodeling tissues, tumors

# Eosinophil effector systems and functions

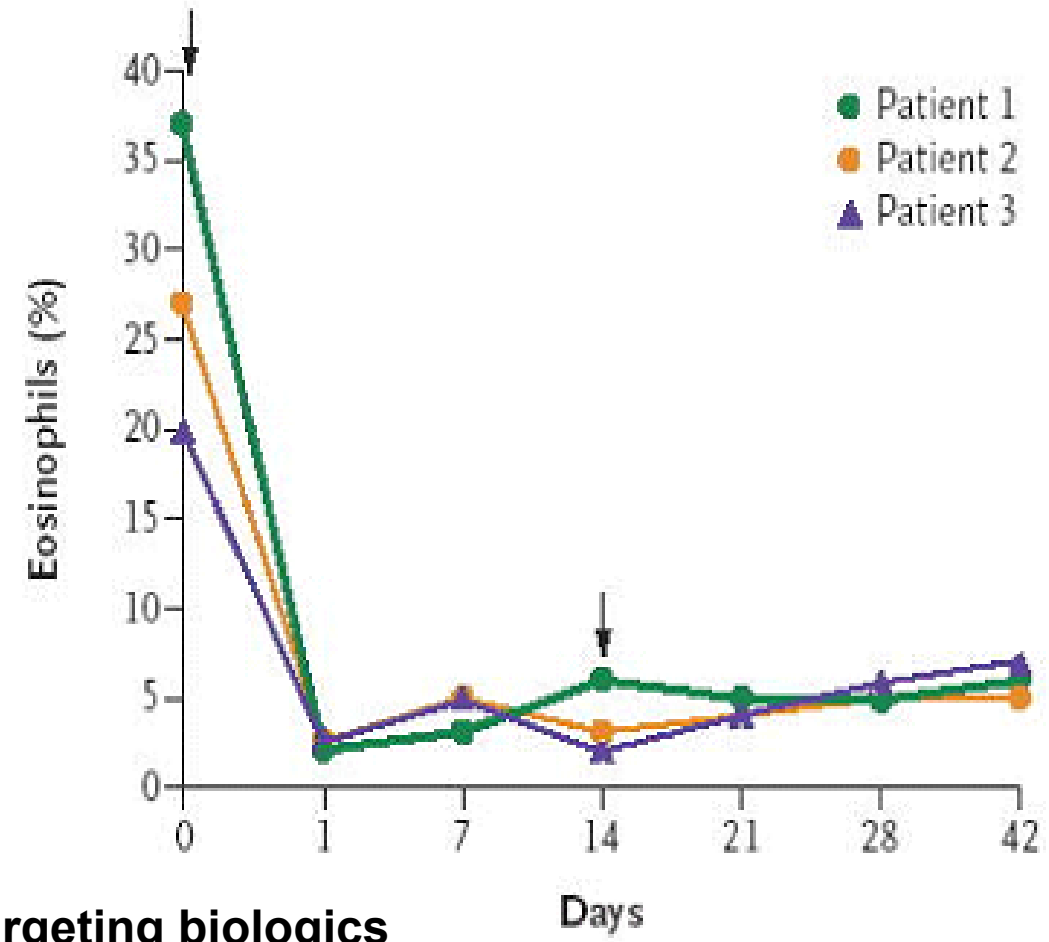
- Cationic granule proteins (MBP, ECP, EPX, EPO, CLC)- neurotoxic, epithelial damage, helminthicidal
- Cytokines (IL-4 (in mice), TGFβ)- proinflammatory, pro-fibrotic
- Lipid mediators; 5-LO (leukotrienes), 15-LO (15-HETE and products), COX ($PGD_2$)- bronchoconstriction, vascular leak, effector cell recruitment

# Eosinophil development

- Regulated by eosinophilopoietic cytokines (IL-3, GM-CSF, IL-5*); produced mainly by T cells
- Receptors composed of ligand-specific α subunits and a shared β subunit (eosinophils, but not neutrophils or monocytes, express IL-5Rα)
- Overlapping functions, but different cellular targets (IL-3, GM-CSF act on multiple lineages; only IL-5 is selective for eosinophils)
- All three sustain survival, augment effector functions
- IL-5 is an eosinophil-selective terminal differentiation factor and a mobilization factor from marrow
- Eosinophil migration to tissues requires cooperation between IL-5 plus CCR3-binding chemokines (eotaxins 1, 2, and 3; MCP3, RANTES)

*Clutterbunk et al., Blood 1989

# Sustained reduction in blood eosinophil counts in patients with hypereosinophilic syndrome (HES) in response to anti-IL-5 (mepolizumab)




**Multiple IL-5 targeting biologics**

- Anti-IL-5: Mepolizumab, Reslizumab, Depemokimab (ultra-long-acting)
- Anti-IL-5Rα: Benralizumab

**Plotz SG, NEJM 2003**

# Eosinophil-associated disease processes

- Helminth infection
- Hypersensitivity reactions (e.g., DRESS)
- Tumors (lymphomas, esp. Hodgkin's and cutaneous T cell lymphoma)
- Organ-specific diseases (eosinophilic lung disease, GI disease, fasciitis, myositis, cellulitis)
- Systemic mastocytosis (15% have eosinophilia)
- Hypereosinophilic syndrome(s)

# Eosinophilic lung diseases

**Asthma-associated**

- Allergic bronchopulmonary aspergillosis (ABPA)
- Chronic eosinophilic pneumonia (CEP)
- Eosinophilic granulomatosis and polyangiitis (EGPA, formerly Churg-Strauss syndrome)

**Non-asthma-associated**

- Acute eosinophilic pneumonia (AEP)
- Simple pulmonary eosinophilia (Loeffler's)
- Tropical eosinophilia (filariasis)

*Note: pulmonary eosinophilia may occur as a secondary finding in numerous systemic autoimmune, infectious and malignant diseases

# Illustrative case 1

## 17-year-old male with type 1 diabetes, nut allergy and longstanding mild asthma (albuterol only) presents for evaluation of worsening asthma control

- 6-month history of worsening symptoms; wheeze, dyspnea, productive cough (brown sputum, occasional blood tinge)
- Prompt improvement with oral steroids but rapid recrudescence with cessation
- Denies travel, fevers, night sweats, weight loss
- Meds: Insulin, albuterol PRN (use of 1 cannister/month)

# Illustrative case 1

**Exam**:

- Alert, oriented, NAD
- Vital signs unremarkable, Sa02 96%
- Boggy, edematous turbinates, no polyps

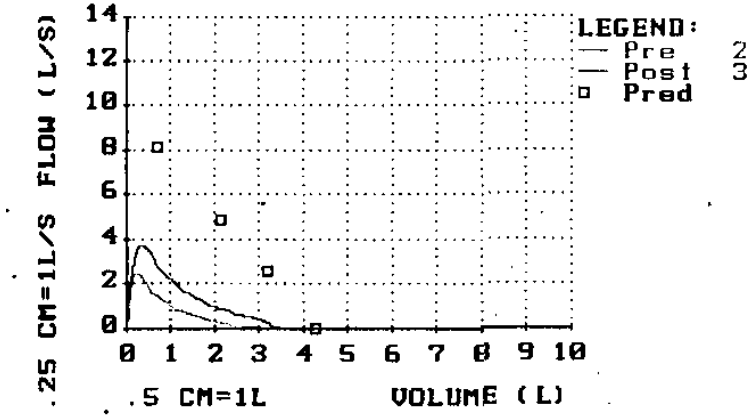
- Diffuse wheezing, fair air entry

- No clubbing

# Illustrative case 1

**Labs**:

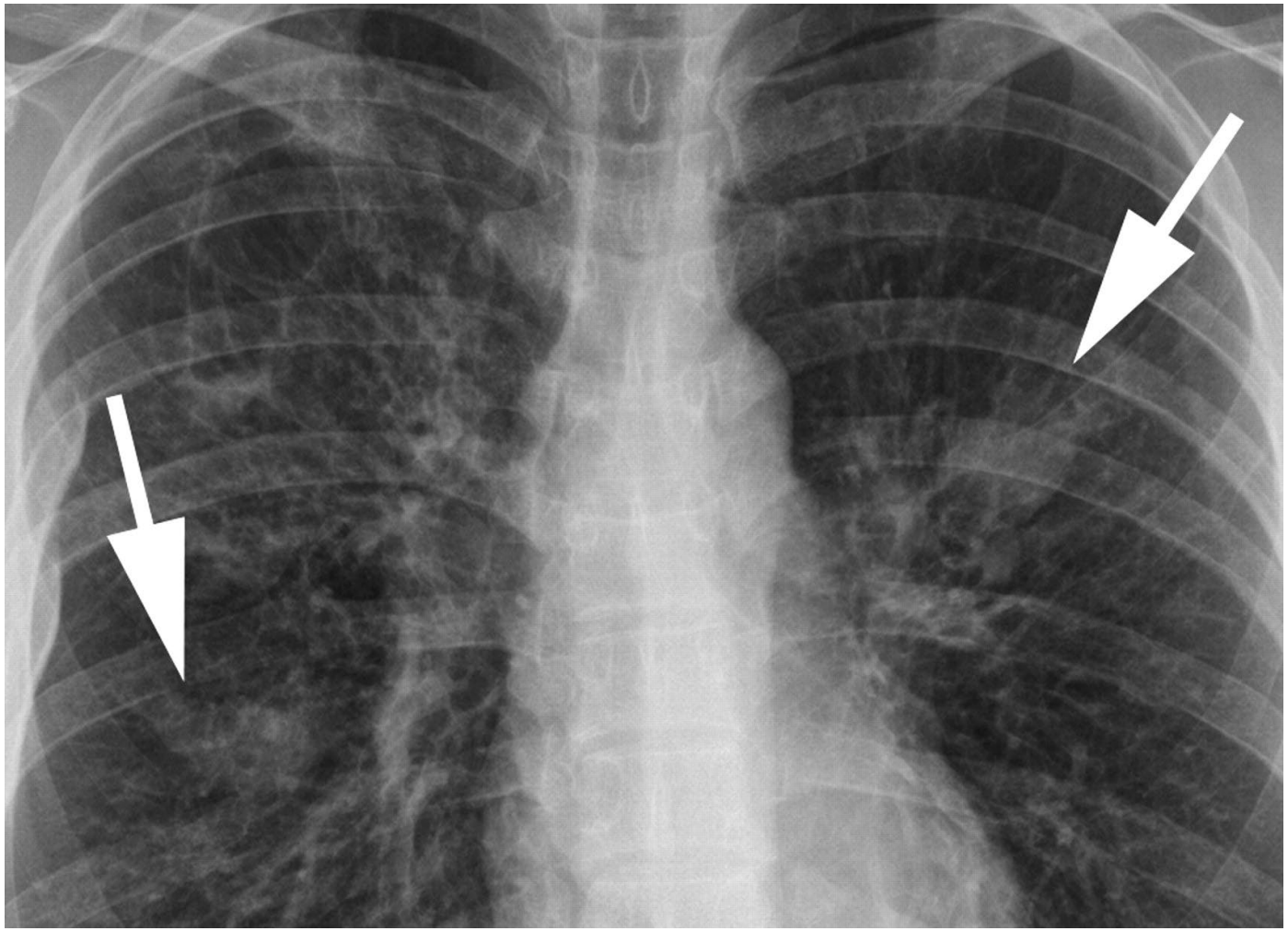
- CBC: Hct 45.7, WBC 6,270 (15% eos, TEC 940)
- IgE: 36,700
- Aspergillus SPT; 22 mm wheal, 45 mm flare
- A. fumigatus precipitins; positive
- *CFTR* mutations; none



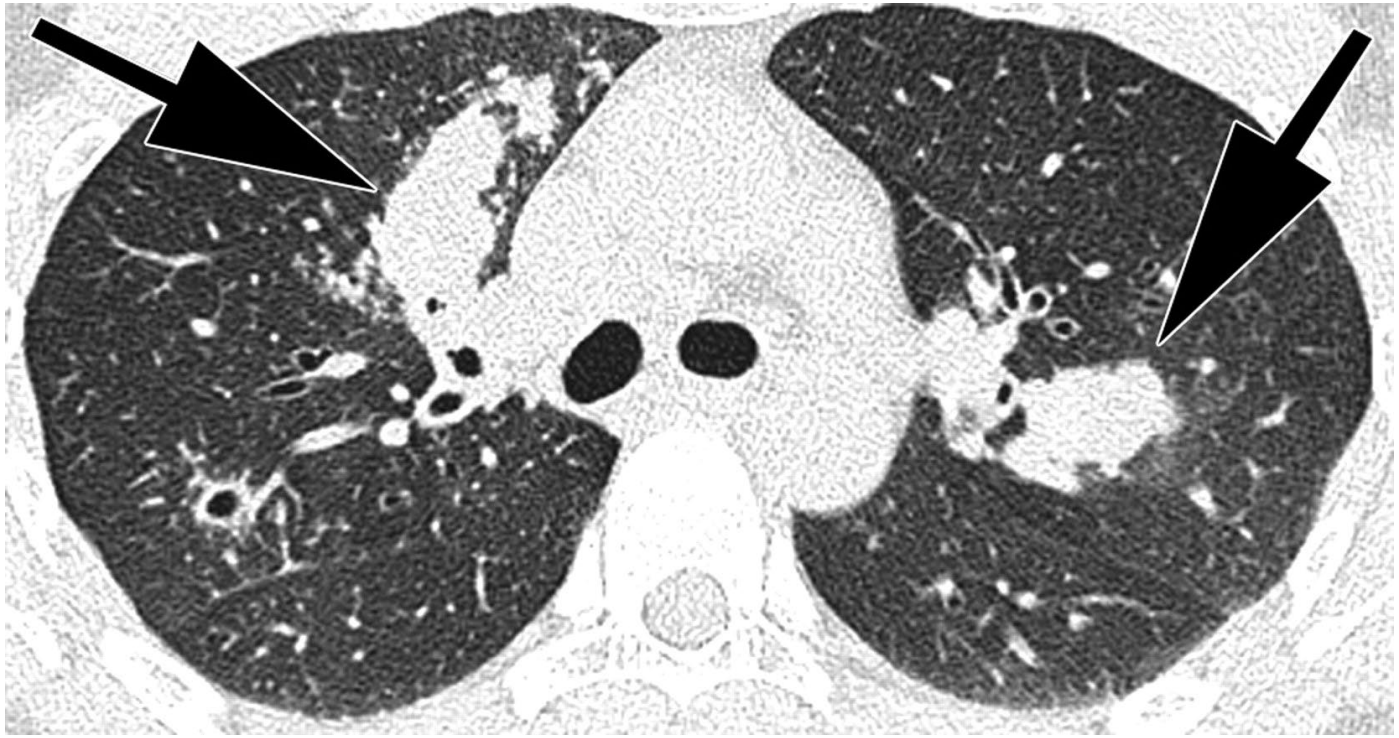

FVC = 3.22 L (74% of pred)
FEV1 = 1.36 L (33% of pred)

Increases of 9 and 46% after albuterol

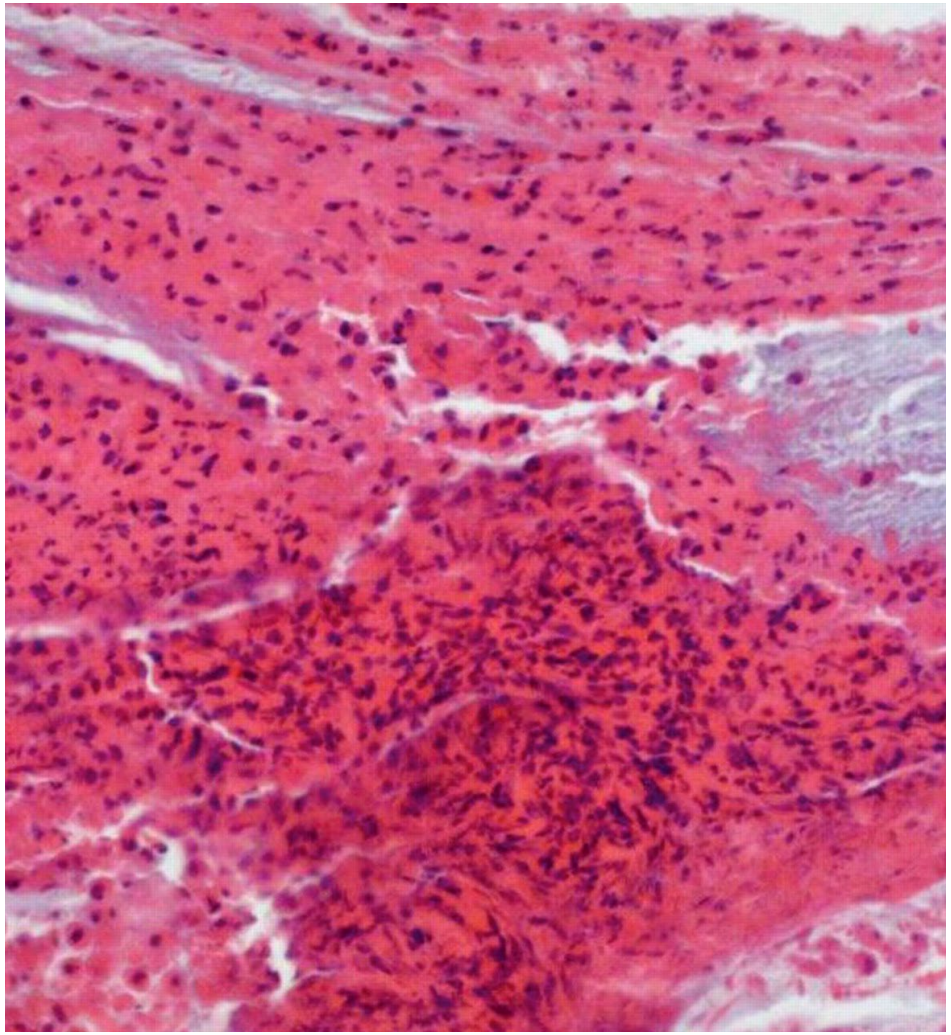
# CXR-Case 1



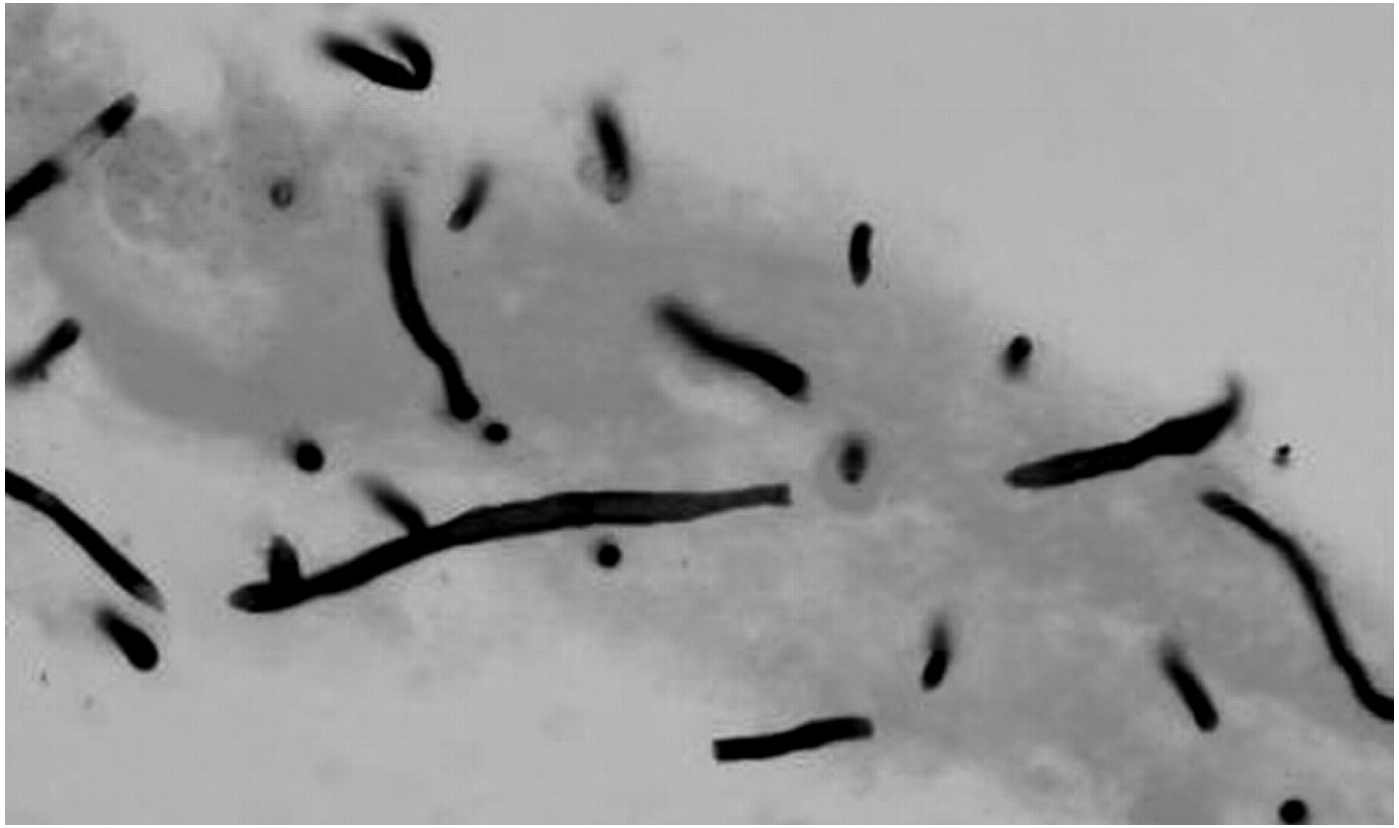
# CT-Case 1



# Bronchial cast- ABPA



# Silver stain, bronchial cast



# Revised Diagnostic Criteria for ABPA (ABPA)

- Elevated total serum IgE (≥ 417 IU/ml) (2 points)
- Positive specific IgE to *Aspergillus*/filamentous fungi (2 points)
- Previous history of asthma or asthma-like symptoms
- Blood eosinophilia ≥ 500 cells/$mm^3$
- Positive serum IgG (precipitins) for *Aspergillus*/filamentous fungi
- History of pulmonary infiltrates (variable to multifocal)
- Central bronchiectasis on CT
- Presence of high attenuation mucous plugs in central bronchi based on CT or removal of mucous plug via bronchoscopy (with or without fungal hyphae), or mucous plug expectoration history

Cai R, et al., J Asthma Allergy 2025;18:467-77

# ABPA

## Predisposing factors:

- Pre-existing asthma or cystic fibrosis
- Heterozygous CFTR mutants may be at increased risk
- HLA-DR2 (DRB1*1503) increases risk;  HLA-DQ2 protects
- *SPA-2* variants correlate with severity
- *IL10* and *IL4RA* variants correlate with incidence

# ABPA

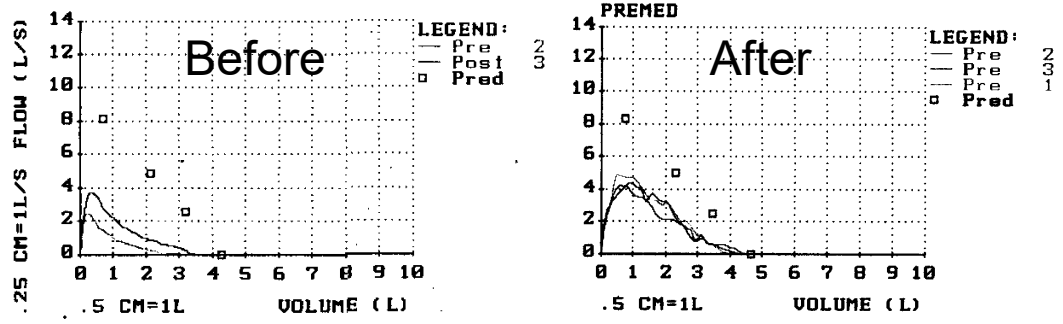
## Treatment:

- Systemic glucocorticoids
- Itraconazole (steroid-sparing in several studies)
- Omalizumab (several case reports showing potential steroid-sparing effect; no RCT)
- Multiple case reports and a small case series (DOI: 10.1016/j.jaip.2020.03.023) reporting improvement on mepolizumab
- Phase II clinical trial reports efficacy for dupilumab (anti-IL4Rα) https://doi.org/10.1164/ajrccm.2025.211.Abstracts.A5230

# Illustrative case 1

**Follow-up**:

- Clinically improved after prolonged course (6 weeks) of oral steroids but glycemic control problematic
- Nasal polyp developed once off prednisone
- IgE fell to 16,300 from 36,700
- Eosinophilia remains <100 on 7.5mg daily prednisone, Symbicort, montelukast
- Lost to follow up after 2 years



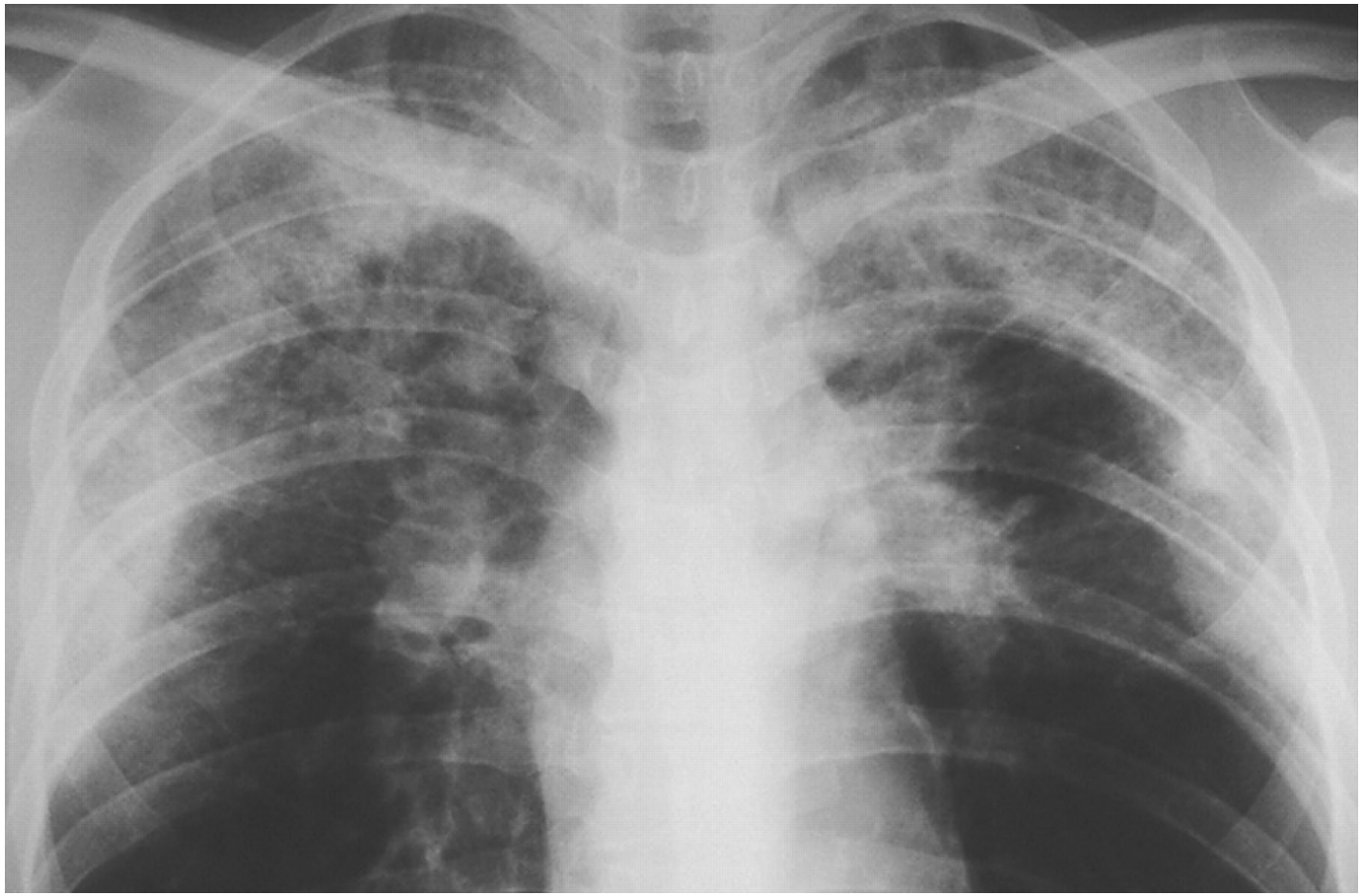

FVC = 4.59 L (98% of pred)
FEV1 = 2.78 L (69% of pred)

# Illustrative case 2

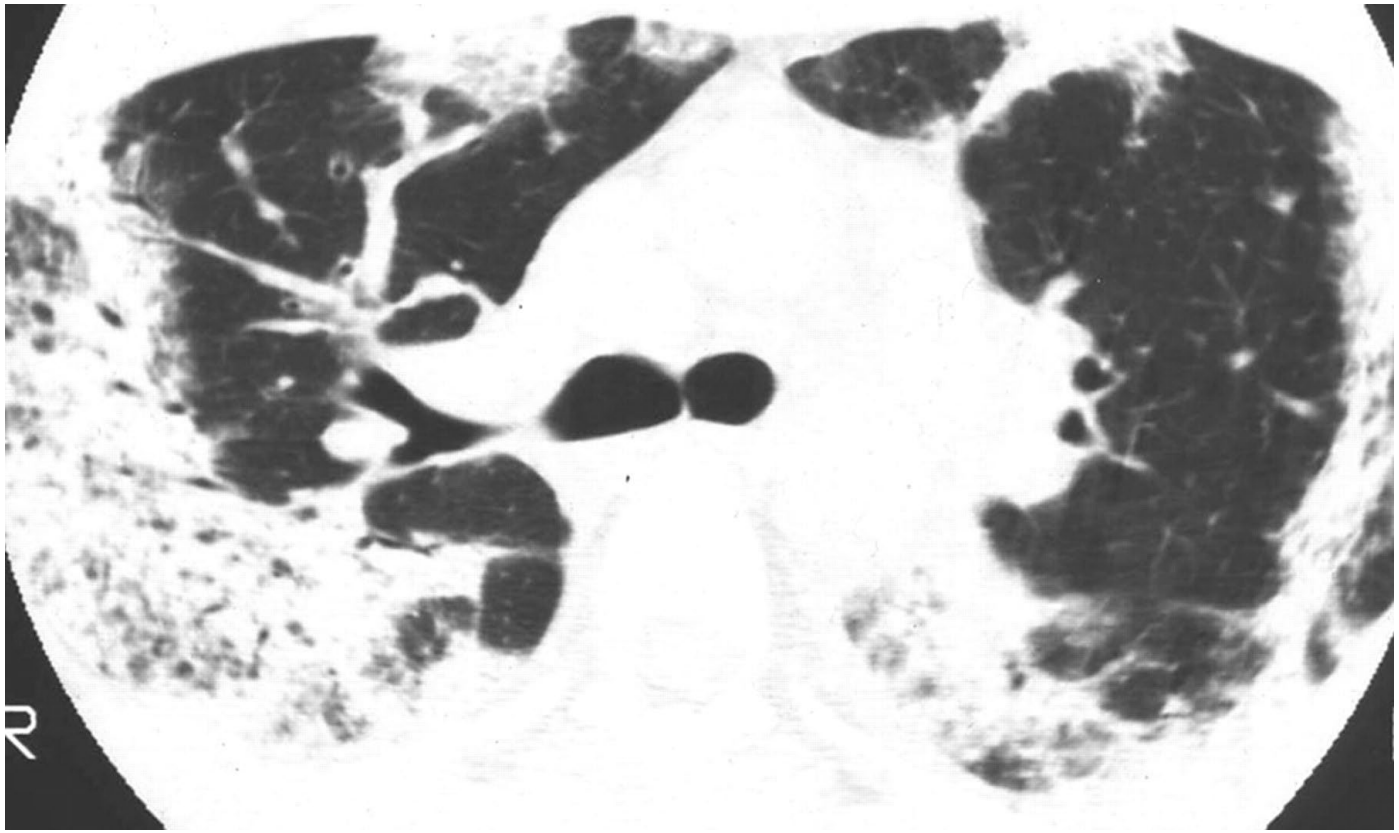
**29-year-old male with longstanding asthma**

- 3-month history of productive cough, wheeze, dyspnea- no improvement with antibiotics
- Recent 10-pound weight loss, night sweats
- Exam- Wheezing and dense crackles on lung auscultation, no nasal polyps, no rash or extrapulmonary signs
- Lung function: FVC 76% of predicted, FEV1 65% of predicted; increases of 8 and 12%, respectively, with bronchodilator
- Labs: significant eosinophilia (WBC 6,700, 27.5% eosinophils- TEC 1842)
- Total IgE 127, skin testing positive for *Aspergillus* but precipitins negative

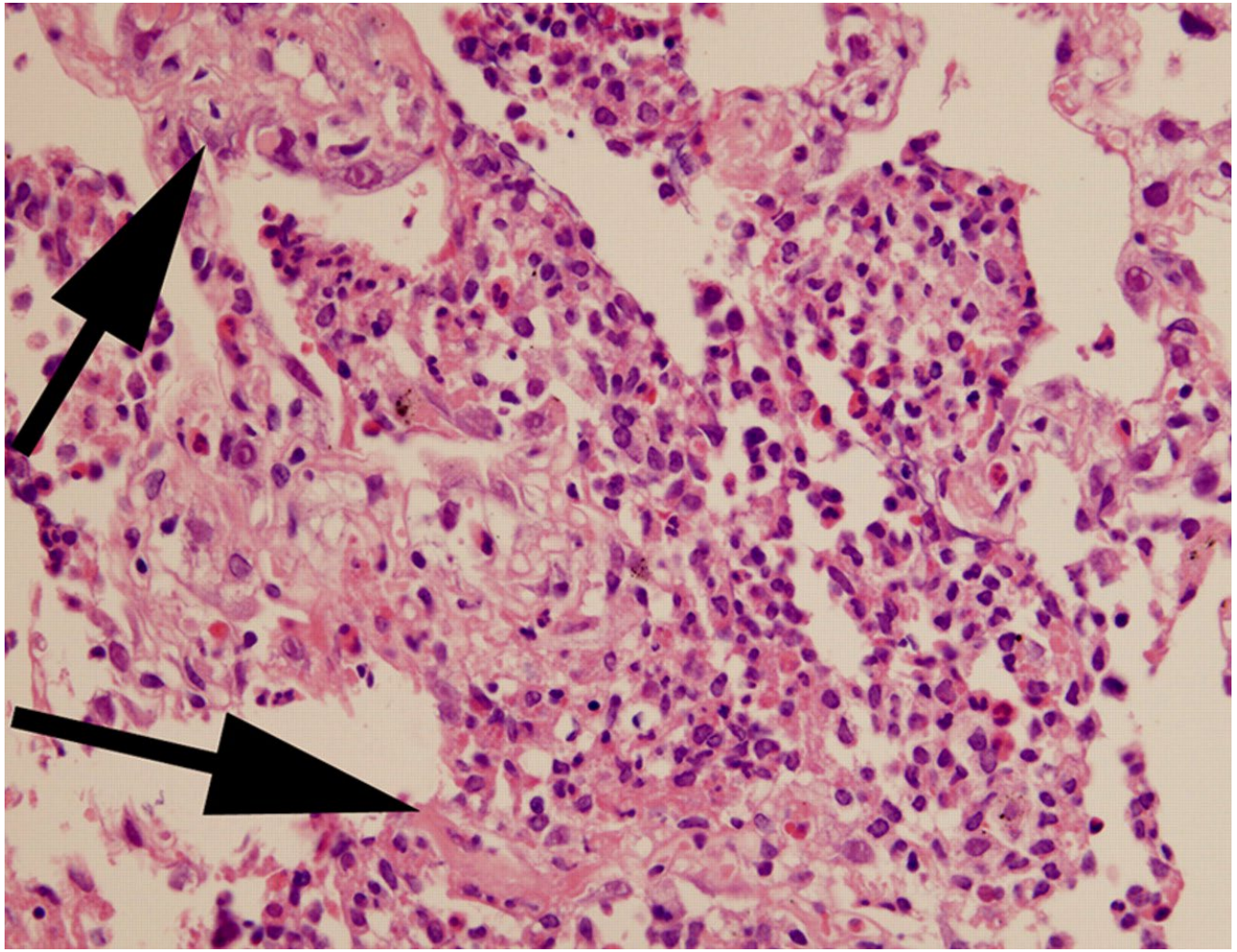
# CXR-Case 2



# CT-Case 2



# Lung biopsy-Case 2



# Chronic Eosinophilic Pneumonia (CEP)

- First reported in 1968 (Carrington, NEJM)
- Usually middle-aged asthmatics
- Indolent, slowly progressive
- Blood eosinophilia common but not uniform
- BAL fluid eosinophilia
- Alveolar filling with eosinophils, macrophages
- Fibrosis with longstanding disease
- Steroid-responsive, high rate of recurrence
- Mepolizumab efficacious in a “real world” study (Brenard E., et al. Lung 2020;198:355-360)-no RCT published

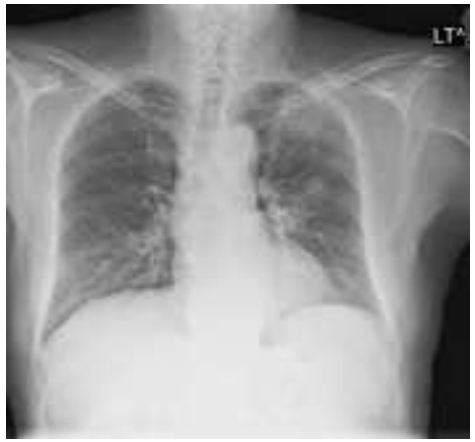
# Illustrative Case 3

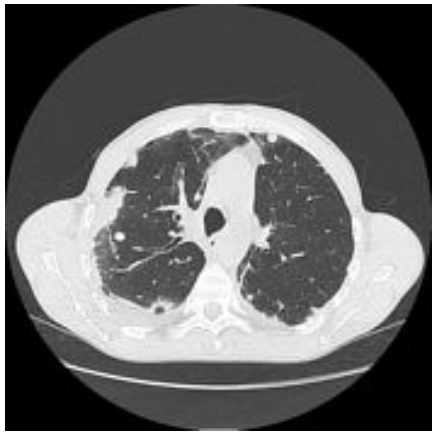
**34-year-old male with longstanding history of asthma and allergic rhinitis presents with worsening dyspnea, cough, one episode of mild hemoptysis**

- Worsening sinus congestion, epistaxis
- Recent nocturnal fevers, numbness of left hand
- Abdominal pain and rash (nodules)
- Exam: palpable nodules on lower extremities, diffuse wheezing, nasal polyps
- CBC: HCT 29, WBC 8600, 15% eos (AEC 1290), IgE 675, ANCA negative, CRP 36

# Illustrative Case 3

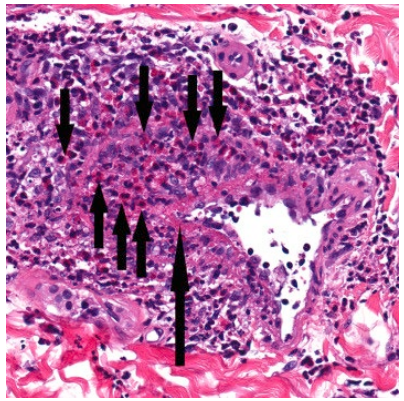
No “classical” radiographic features (nodules, infiltrates, sometimes peripheral)





Skin biopsy:

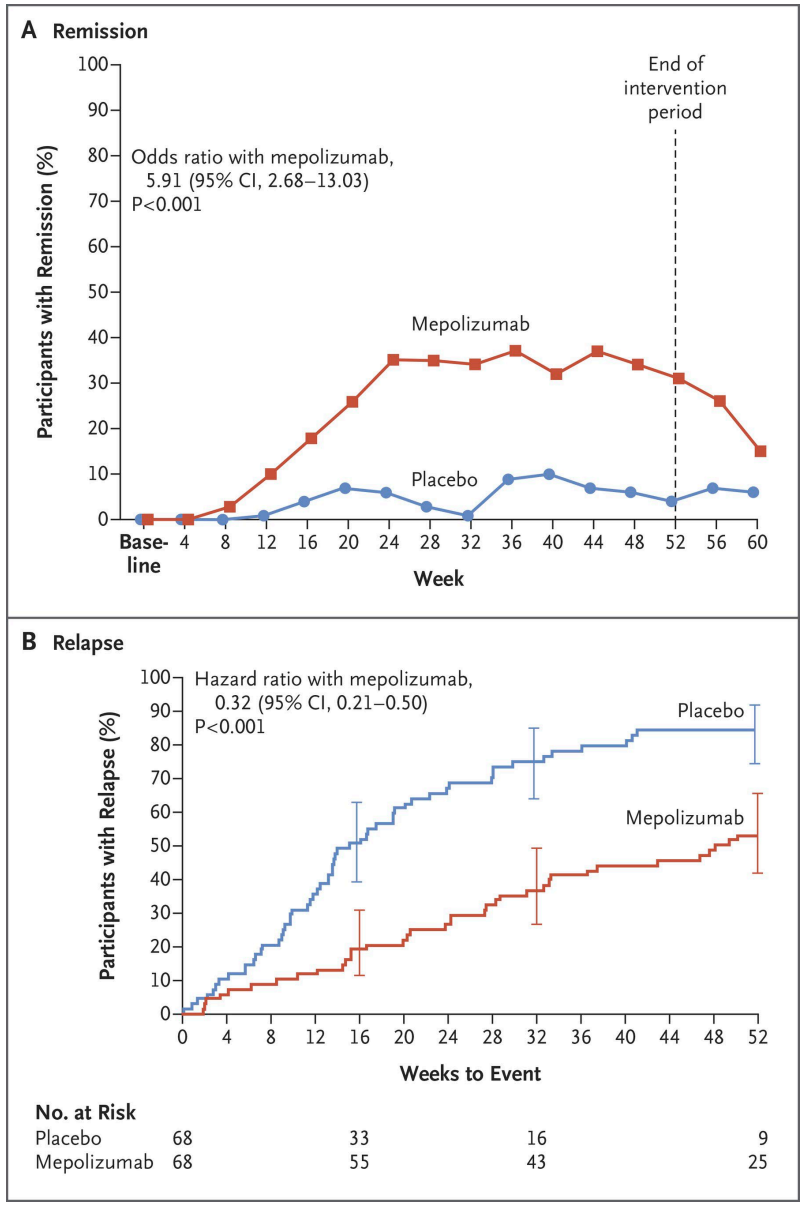
Necrotizing small vessel vasculitis with extravasated eosinophils



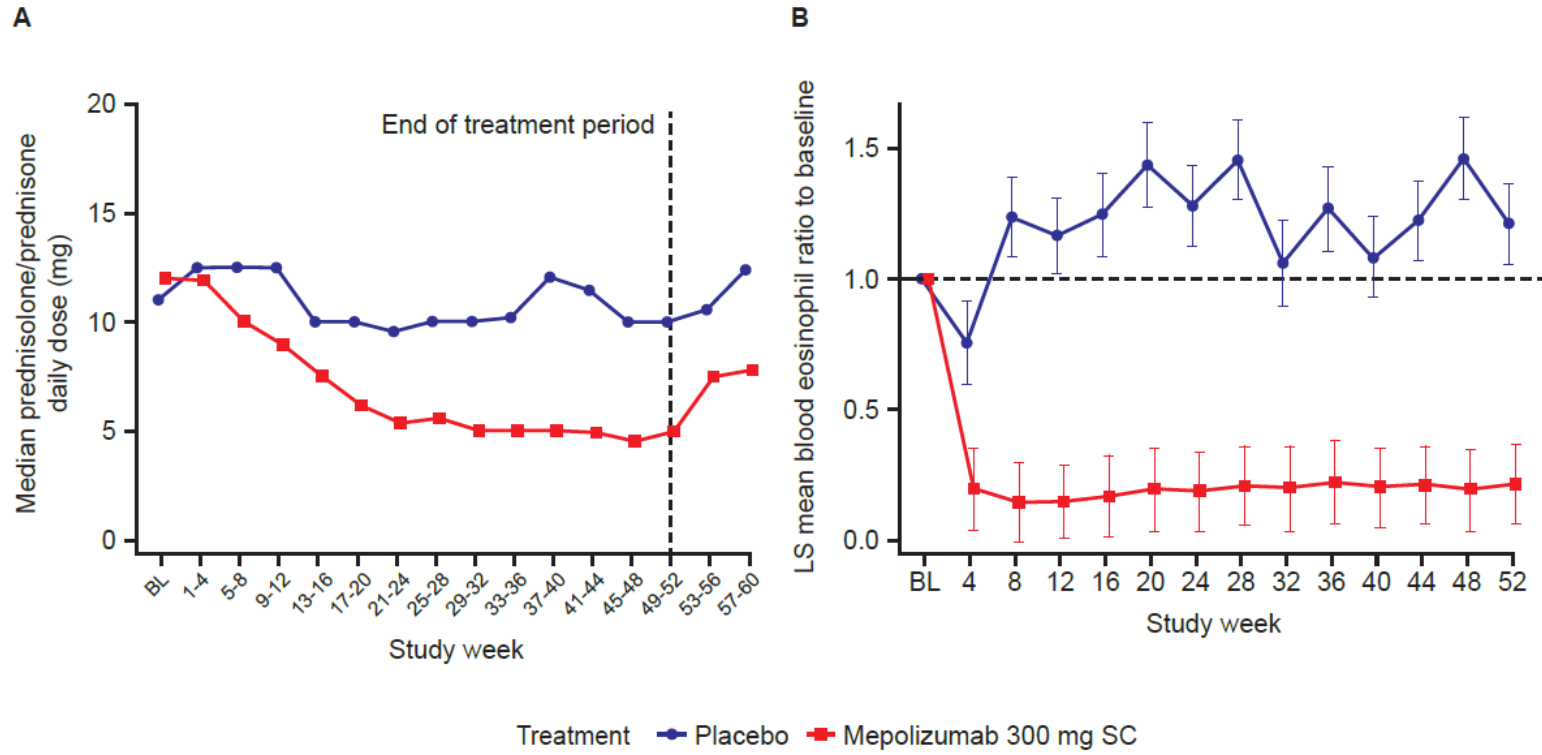
# EGPA diagnostic criteria

| **American College of Rheumatology classification criteria (1990)** ‡ |
| --- |
| Asthma |
| Eosinophilia >10% of total WBC |
| Neuropathy |
| Pulmonary infiltrates nonfixed |
| Paranasal sinus abnormalities |
| Extravascular eosinophils |
| **Revised Chapel Hill Consensus Conference Nomenclature of Vasculitides (2012)** |
| Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small-to-medium vessels, and associated with asthma and eosinophils. ANCA is more frequent when glomerulonephritis is present. |

# Mepolizumab for EGPA (FDA approved in 2019)






Benrilizumab (anti-IL-5Rα) non-inferior to mepolizumab for inducing remission in EGPA

**Weschler, M. et al, NEJM 2019**
**Weschler, M., et al. NEJM 2024**

# CONCLUSIONS

**Eosinophilic lung disorders**

- Asthma-associated; ABPA, CEP, EGPA
- Not asthma-associated; AEP, Loeffler's, tropical eosinophilia
- Suspect diagnoses in patients with loss of asthma control, eosinophilia, or (in the case of EGPA) prominent extrapulmonary symptoms
- Eosinophilia is the common thread; associated lab, radiographic, and clinical features help distinguish
- Anti-IL-5 and -IL-5Rα antibodies are efficacious for EGPA; await studies in other disorders
- Dupilumab may be efficacious in ABPA