

## Eosinophilia Associated Lung Diseases

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## Stephen P. Peters, MD, PhD Disclosure

- Basic and Clinical Research
  - NHLBI (AsthmaNet, SARP, SPIROMICS)
  - ALA (ACRC)
- Book Chapters
  - UpToDate
  - Merck Manuals
- Pharmaceutical Trials
  - Actelion, Amgen, Astra-Zeneca, Boehringer-Ingelheim, Centocor, Cephalon, Genentech, GlaxoSmithKline, Forest, Medimmune, Sanofi-aventis
- Advisory Boards
  - Array Biopharma, AstraZeneca, Aerocrine, Airsonett AB, Boehringer-Ingelheim, Experts in Asthma, Gilead, GlaxoSmithKline, Merck, Novartis, Ono Pharmaceuticals, Pfizer, PPD Development, Quintiles, Sunovion, Saatchi & Saatchi, Targacept, TEVA, Theron
- Speakers' Bureaus
  - Integrity CE
- Editorial Boards
  - Resp Med, Assoc Editor,
  - Resp Research, Assoc Ed
  - J Allergy
  - Case Reports in Medicine
  - US Resp Disease
  - J Pulm Resp Medicine
  - Clin Exp Med Sciences
  - JACI: In Practice

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## Eosinophilia Associated Lung Diseases: Learning Objectives

In a Clinical Approach:

- Review Important Eosinophil-Associated Lung Diseases
- Discuss the Differential Diagnosis and Distinguishing Features of These Disorders and Treatment Approaches

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## Eosinophilia and Eosinophilic Lung Disease

- **Peripheral Eosinophilia**
  - $\geq 400 - 500$  Eosinophils/ $\mu$ l
- **Pulmonary Eosinophilia**
  - Tissue Eosinophilia
  - BAL Fluid  $\geq 5\%$  (normal  $<1\%$ )
- **Mechanisms**
  - cytokine-mediated (mainly IL-5) increased differentiation and survival of eosinophils (extrinsic eosinophilic disorders)
  - Mutation-mediated clonal expansion of eosinophils (intrinsic eosinophilic disorders).

Campos, et al. J Bras Pneumol. 2009; 35:561-573  
Simon and Simon. J Allergy Clin Immunol 2007; 119:1291-1300

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## Case 1 - Presentation

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| <p>46 Yr Women Transferred from Central PA Hosp – “Severe Asthma”</p> <ul style="list-style-type: none"> <li>• 2 yr cough, wheeze, fatigue</li> <li>• HBP, depression, migraines</li> <li>• OCS, (ICS), Salm, Terbut. (PPI, Cipro, Estrogen)</li> <li>• Hairdresser</li> <li>• Hunter (Deer, Bear), Fishing</li> <li>• Exam – Cushingoid, Clear Lungs (PEF always low)</li> <li>• WBC 14K (86P, 1E)</li> <li>• ABG 7.42/42/70</li> </ul> | <ul style="list-style-type: none"> <li>• Spirometry                             <ul style="list-style-type: none"> <li>– FEV1/FVC 79% (nl)</li> <li>– FEV1 70% pred</li> <li>– FVC 72% pred</li> </ul> </li> <li>• TLC 76% pred (Restrict)</li> <li>• DLCO 50% pred</li> <li>• CXR, CT chest (nl with min atelectasis)</li> <li>• ECHO - WNL</li> <li>• Methacholine - WNL</li> <li>• Withdrew Medication</li> <li>• Resp Failure – ICU, OLBx</li> </ul> |
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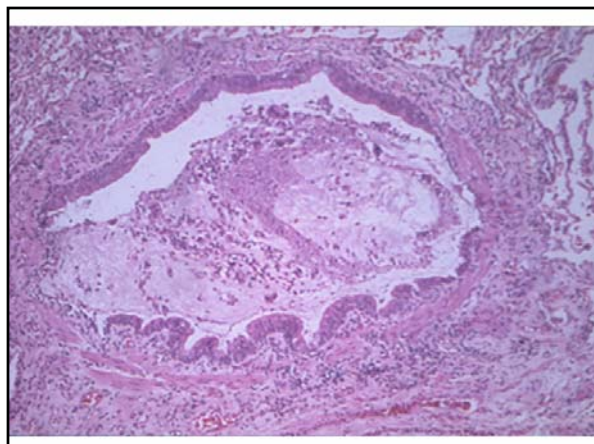
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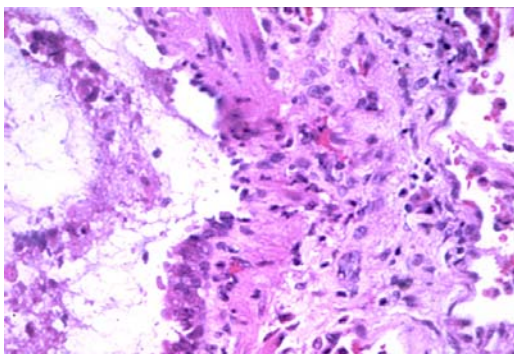
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**Eosinophilia Associated Lung Disease and Asthma Mimic – Eosinophilic Interstitial Pneumonitis**




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**Eosinophilic Lung Diseases**

Simon, et al. J Allergy Clin Immunol 2010; 126:3-13

TABLE II. Eosinophilic lung diseases

Disease	Prevalence of disease	Degree of peripheral blood eosinophilia*
Asthma	Common	Mild (up to moderate in SEs and with nasal polyposis)
Chronic obstructive pulmonary disease	Common	Mild
Eosinophilic bronchitis	Common (10% of chronic cough)	Mild

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**Eosinophilic Lung Diseases: Asthma**  
**Key Elements of Asthma**

- Reversible (partial) Airflow Obstruction
- Bronchial Hyperresponsiveness
- Intermittent Symptoms
- PFTs –
  - No Restriction (NI, Elevated TLC)
  - Diffusing Capacity ( $D_LCO$ ) NI (Elevated)
- Imaging – (CXT, CT) Usually Normal

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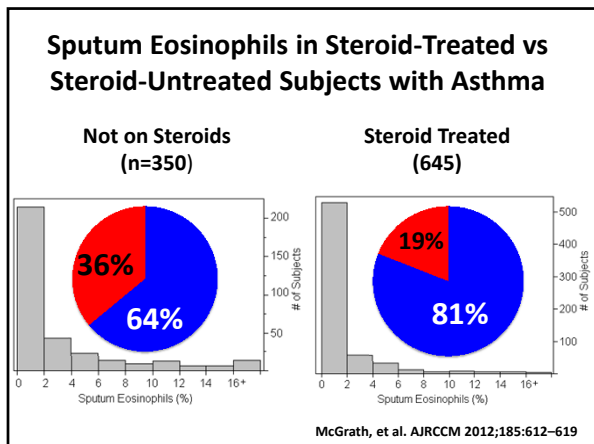
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### Characteristics of AECOPD Patients

Gao, et al. PLoS ONE 8(5): e57678. doi 10.1371

	Eosinophilic > 2.5%	Neutrophilic > 6.1%	Mixed granulocytic	Pauogranulocytic
N	10	38	5	32
Age (years)	64.8±11.9	65.9±10.5	66.4±11.4	62.8±10.0
BODE score	6(5-6.25) <sup>1</sup>	5.5(4-7) <sup>1</sup>	6(4.5-7.5) <sup>1</sup>	10(3-2.8)
GOLD I	0	5	0	7
GOLD II	6	19	1	25
GOLD IV	4	12	4	0
Post-FEV <sub>1</sub> (L)	0.99±0.20 <sup>2</sup>	1.24±0.52	0.61±0.06 <sup>2</sup>	1.34±0.53
Post-FEV <sub>1</sub> /pred (%)	31.4±5.1 <sup>2</sup>	38.5±9.8 <sup>2</sup>	22.8±5.0 <sup>2</sup>	46.7±18.3
FEV <sub>1</sub> /FVC (%)	57.3±12.3	59.3±7.0	56.1±5.9	58.7±8.5

12% COPD Patients General Population – Increased Blood Eosinophils (D Price)

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- ### Obstructive Lung Diseases Differentiating Asthma from COPD
- COPD
    - Emphysema (Decreased D<sub>L</sub>CO)
    - Chronic Bronchitis (History - Cough & Spit)
  - Asthma
    - Normal Diffusing Capacity (Could be increased with Exacerbation and Hyperinflation)
    - Chronic Sputum Production Less Common

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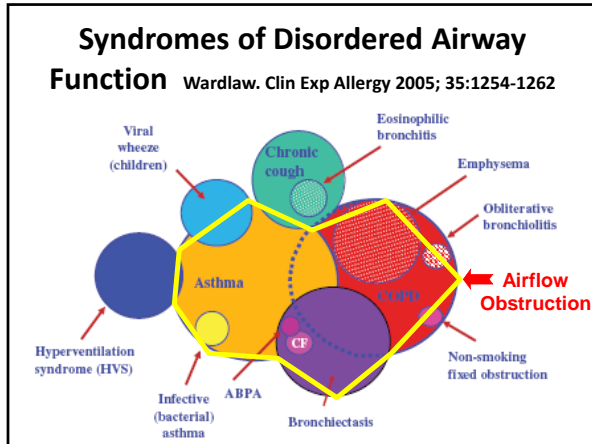
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### Case 2 - Recurrent Post-Partum Pulmonary Eosinophilia

Davies, et al. Thorax 1997; 52:1095-1096

23 year old woman developed idiopathic eosinophilic pneumonia which was successfully treated with corticosteroids. She subsequently developed two identical relapses in the post-partum period.

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### Principal Forms of Pulmonary Eosinophilia (clinical-radiological presentation)

Campos, et al. J Bras Pneumol. 2009; 35:561-573

- 1) Simple pulmonary eosinophilia (Löffler's)
- 2) Chronic eosinophilic pneumonia (CEP)
- 3) Acute eosinophilic pneumonia (AEP)

Not all cases have Peripheral Eosinophilia  
Peripheral Infiltrates on Imaging  
BAL Eosinophilia Characteristic

Differentiating Factors

- Chronicity - < 30 Days (Loeffler's) ± Steroids vs CEP
- Acute Respiratory Failure (AEP)

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## Eosinophilic Lung Diseases

Simon, et al. J Allergy Clin Immunol 2010; 126:3-13

TABLE II. Eosinophilic lung diseases

Disease	Prevalence of disease	Degree of peripheral blood eosinophilia*
Fungal airway colonization	Regarded as unusual but probably common in patients with more severe disease	Mild to moderate
Eosinophilic pneumonia (EP)	Unusual	Moderate to severe

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## Allergic Bronchopulmonary Aspergillosis (ABPA)

Greenberger. J Allergy Clin Immunol. 2002; 110:685-692

### Clinical Features of ABPA

- Asthma-Like Syndrome
- May Have Sputum (“black plugs”)
- Pulmonary Infiltrates (may be “fleeting” and recurring in same areas)
- Airway Obstruction which can Progress to Restriction
- Corticosteroid Responsive

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## Allergic Bronchopulmonary Aspergillosis (ABPA)

Greenberger. J Allergy Clin Immunol. 2002; 110:685-692

### Diagnosing ABPA

- Asthma with central bronchiectasis (late and “pathopneumonic”) or pulmonary infiltrates
- Total IgE levels greater than 1,000 ng/ml
- Positive skin test reactivity to *Aspergillus sp.*
- IgE or IgG against *Aspergillus sp.* in the blood

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### Case 3 – Presentation

Wechsler. JAMA 1998; 279:455-457

Healthy Woman, Sinusitis and Asthma at 40 yr

- ICS, theo, β-Ag, frequent OCS
- Zafirlukast – Improved over 2 mo; D/C OCS
- 2 wk – Rash, Fever, Diarrhea, Dyspnea
- Tachycardia, Wheezes
- Unilateral Foot Drop
- WBC 26K, 37% Eos
- CXR – Patchy Infiltrates
- ECHO – Global Hypokinesia, EF 35-40%
- Skin Bx – lymphocytic and eos perivascular infiltrates
- Lung Bx – Necrotizing, granulomatous vasculitis
- Treatment – Corticosteroids and Cyclophosphamide

Churg-Strauss: LTRA and Systemic Steroid Discontinuation

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### Churg-Strauss Syndrome

Campos, et al. J Bras Pneumol. 2009; 35:561-573

- 1) **Allergic phase:** presence of asthma or rhinitis
  - 2) **Eosinophilic phase:** presence of severe persistent peripheral eosinophilia (eosinophil count greater than 1,500 cells/mm<sup>3</sup>) for more than 6 months
  - 3) **Vasculitic phase:** presence of systemic manifestations and small vessel vasculitis, represented by the involvement of two or more extrapulmonary organs.
- However, it is important to remember that the three phases can be dissociated. Asthma is present in 100% of cases.*

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### Xolair<sup>R</sup> (Omalizumab) – PI July 2008

#### Eosinophilic Conditions

In rare cases, patients with asthma on therapy with Xolair may present with serious systemic eosinophilia sometimes presenting with clinical features of vasculitis consistent with **Churg-Strauss syndrome** a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between Xolair and these underlying conditions has not been established.

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**Principal Forms of Pulmonary Eosinophilia  
(clinical-radiological presentation)**

Campos, et al. J Bras Pneumol. 2009; 35:561-573

- 4) Allergic bronchopulmonary aspergillosis
- 5) Pulmonary eosinophilia associated with a systemic disease:
  - Churg-Strauss syndrome
  - Hypereosinophilic syndrome

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**Asthma Plus Disorders**

- Churg-Strauss Syndrome – Vasculitis, GI involvement, ?Medications
- Allergic Bronchopulmonary Aspergillosis – Infiltrates, Obstruction and Restriction, Elevated IgE
- Occupational Asthma (vs RAD –Reactive Airways Dysfunction) – History, PFTs
- Anaphylaxis – Multisystem, Serum Tryptase

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**Eosinophilic Lung Diseases**

Simon, et al. J Allergy Clin Immunol 2010; 126:3-13

TABLE II. Eosinophilic lung diseases

Disease	Prevalence of disease	Degree of peripheral blood eosinophilia*
CSS	Rare	Severe
Idiopathic pulmonary fibrosis (IPF)	Unusual	Mild
Lung carcinoma	Common	Mild to severe
Infection with helminthic parasites	Common in countries where parasite infection is endemic	Severe

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## Etiology of Pulmonary Eosinophilia

Campos, et al. J Bras Pneumol. 2009; 35:561-573

1) Primary or idiopathic

2) Secondary

a) Known cause

- Drugs
- Parasites
- Toxic products/irradiation
- Fungal and mycobacterial infection

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## Drugs Associated with Eosinophilia

Simon and Simon. J Allergy Clin Immunol 2007; 119:1291-1300

Drug group	Drug examples
Aromatic anticonvulsants	Carbamazepine Phenobarbital Phenytoin Primidone
Nonaromatic anticonvulsants	Lamotrigine Valproic acid Gabapentin Benzodiazepines
Anticancer drugs	Allopurinol
Antimicrobial agents	Minocycline Terbinafine Nitrofurantoin Isoniazid Abacavir
Sulfa drugs	Sulfonamides Dapsone Sulfasalazine
Nonsteroidal anti-inflammatory drugs	Oxicam Thalidomide
Antihypertensive drugs	Captopril
Antidiabetics	Diltiazem Sorbinil

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## Parasites Causing Eosinophilia

Simon and Simon. J Allergy Clin Immunol 2007; 119:1291-1300

Phylum	Species
Cestode	<i>Mesocestoides corti</i> *
Nematode	<i>Hymenolepis diminuta</i>
	<i>Angiostrongylus</i> species*
	<i>Anisakis</i> species
	<i>Ascaris lumbricoides</i>
	<i>Ancylostoma</i> species
	<i>Baylisascaris</i> species
	<i>Brugia</i> species*
	<i>Enterobius vermicularis</i>
	<i>Heligmosomoides polygyrus</i>
	<i>Litomosoides</i> species*
	<i>Nippostrongylus</i> species*
	<i>Onchocerca</i> species*
	<i>Strongyloides</i> species*
	<i>Toxocara</i> species
	<i>Trichinella</i> species*
<i>Trichuris</i> species	
Trematode	<i>Wucheria bancrofti</i>
	<i>Fasciola</i> species
	<i>Schistosoma</i> species*

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## Etiology of Pulmonary Eosinophilia

Campos, et al. J Bras Pneumol. 2009; 35:561-573

### b) Diseases that can lead to pulmonary eosinophilia

- **Diffuse lung diseases:** cryptogenic organizing pneumonia; hypersensitivity pneumonia; idiopathic pulmonary fibrosis; Langerhans cell histiocytosis; sarcoidosis.
- **Malignant diseases:** leukemia; lymphoma; lung cancer; adenocarcinoma involving multiple organs; squamous carcinoma involving multiple organs.
- **Connective tissue diseases:** rheumatoid arthritis; Sjögren's syndrome.

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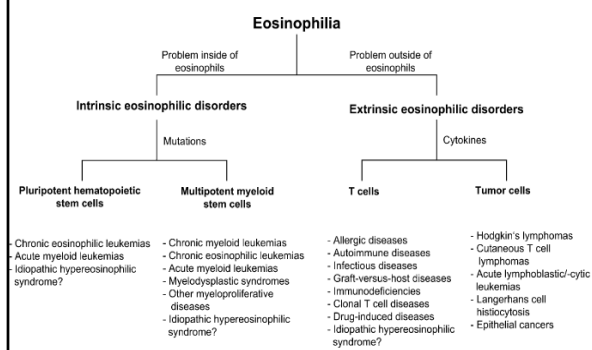
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## Approach to Eosinophilia

Simon and Simon. J Allergy Clin Immunol 2007; 119:1291-1300




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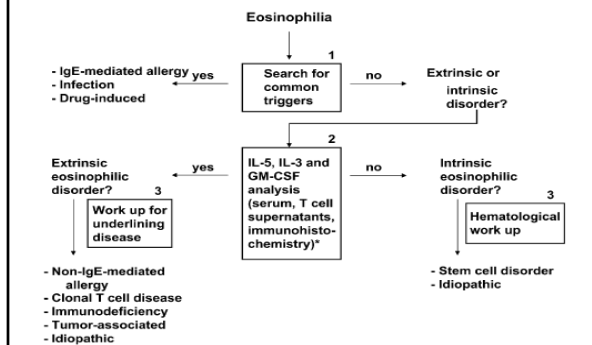
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## Algorithm for Diagnosing Eosinophilic Disorders

Simon and Simon. J Allergy Clin Immunol 2007; 119:1291-1300




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### Eosinophilic Lung Diseases

Simon, et al. J Allergy Clin Immunol 2010; 126:3-13

- Asthma
- COPD
- Eosinophilic Bronchitis
- Drug-Induced
- Fungal Airway Disease
- Eosinophilic Pneumonias
- Chrug-Strauss Syndrome
- Parasitic Lung Diseases
- Diffuse Lung Diseases (e.g. Idiopathic Pulmonary Fibrosis [IPF])
- Carcinoma (e.g. Lung Cancer, Hodgkin's Disease)
- Connective Tissue Disease (RA, Sjögren's)
- Hypereosinophilic Syndrome (HES)
- Stem Cell or Tumor Cell Disorders

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### Eosinophilia Associated Lung Diseases Conclusions

- Peripheral and/or Lung Eosinophilia is Found in a Number of Common Lung Diseases (asthma COPD) or as Incidental Findings (malignancies, CTDs)
- Initial Steps are Directed Toward R/O Extrinsic Factors (e.g. drugs, parasites)
- Key Differential Factors
  - Presence and Nature of Pulmonary Infiltrates
  - Characteristics of Onset
  - Nature of Extra-pulmonary Involvement
- Hematologic Evaluation (bone marrow) Indicated When Diagnosis Unclear
- Treatment – Corticosteroids, anti-IL-5 (biologics)

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### Eosinophilia Associated Lung Diseases

Questions?

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