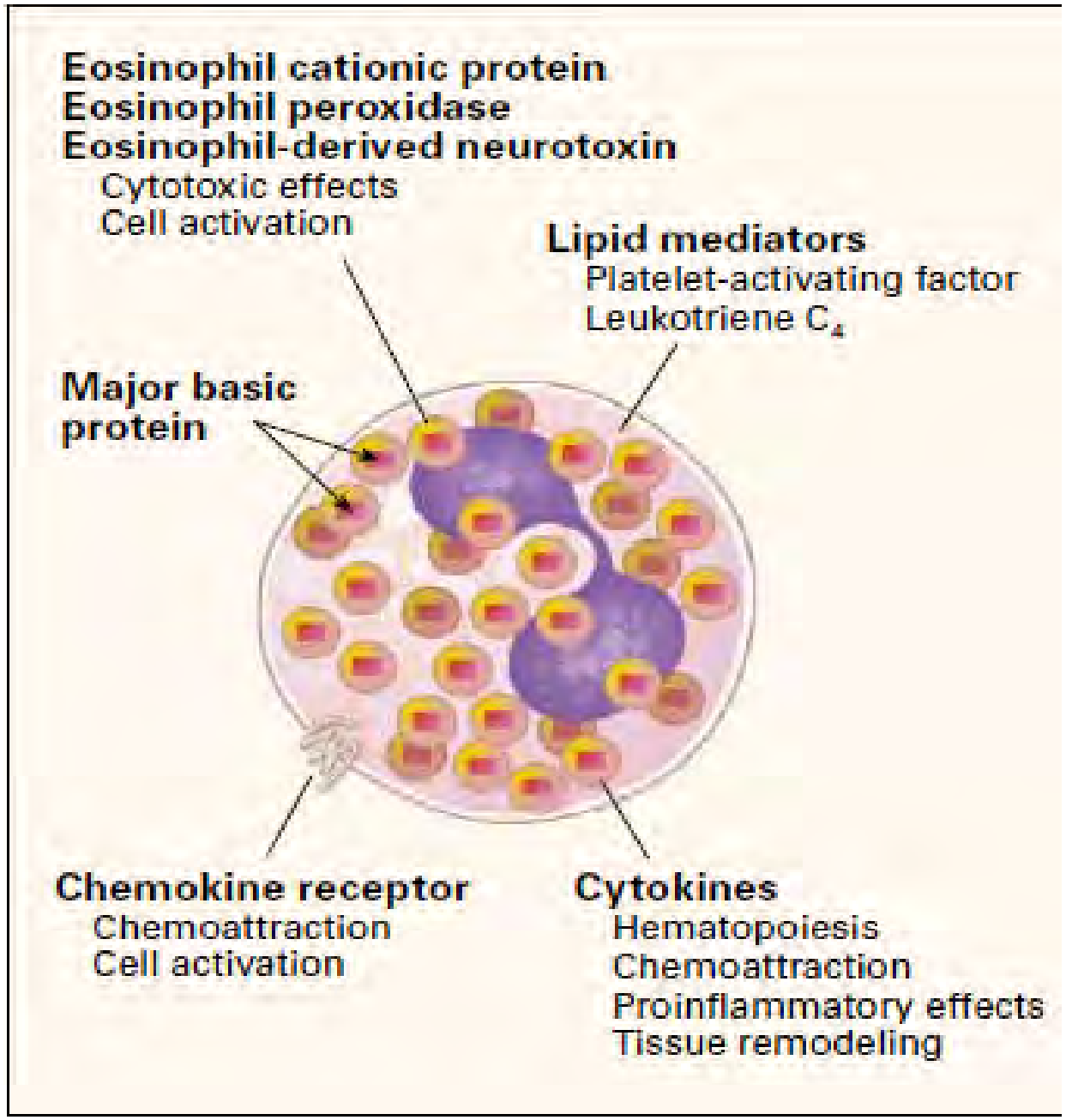
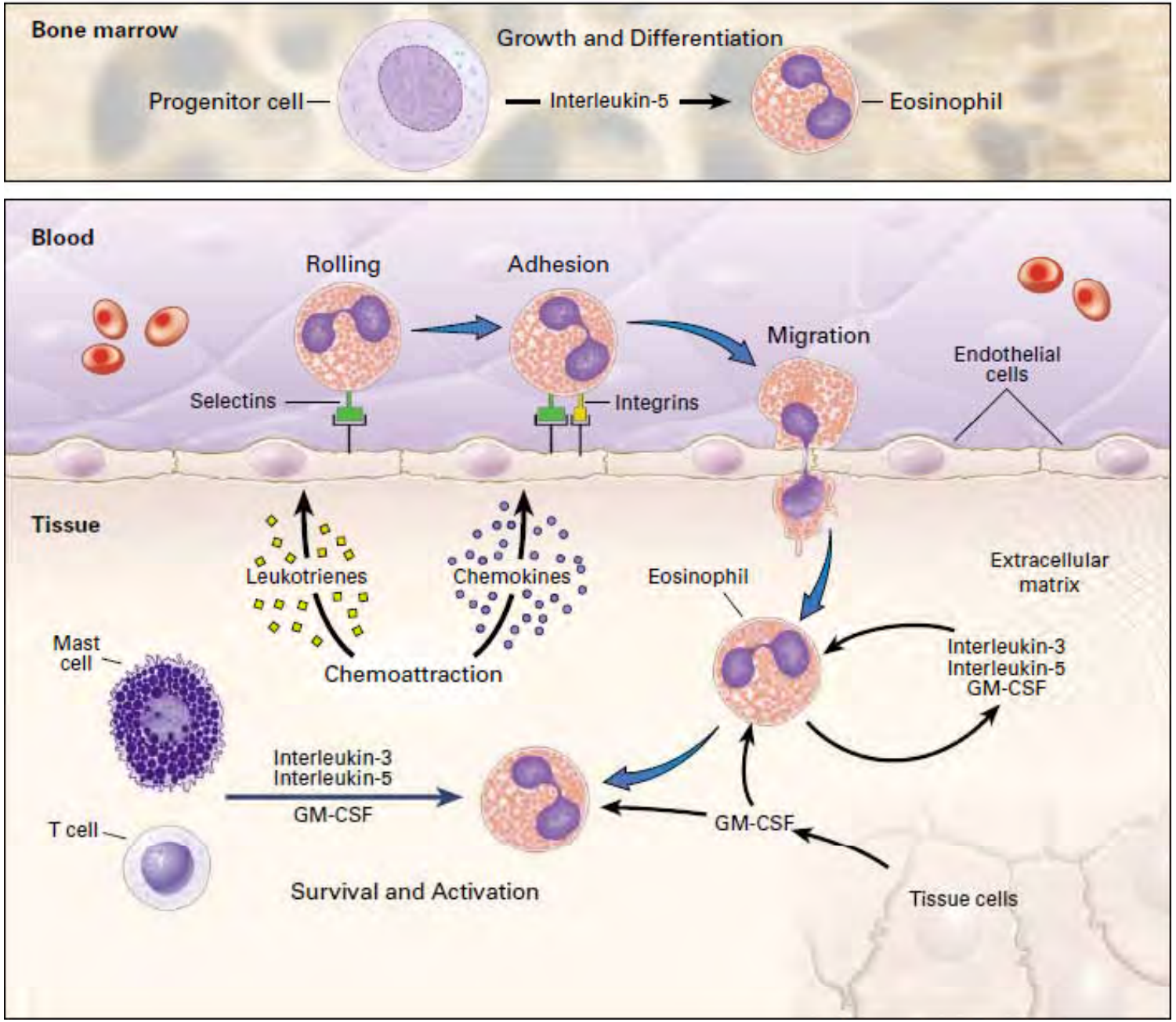
PULMONARY INFILTRATES WITH EOSINOPHILIA

Dr Abhishek Goyal

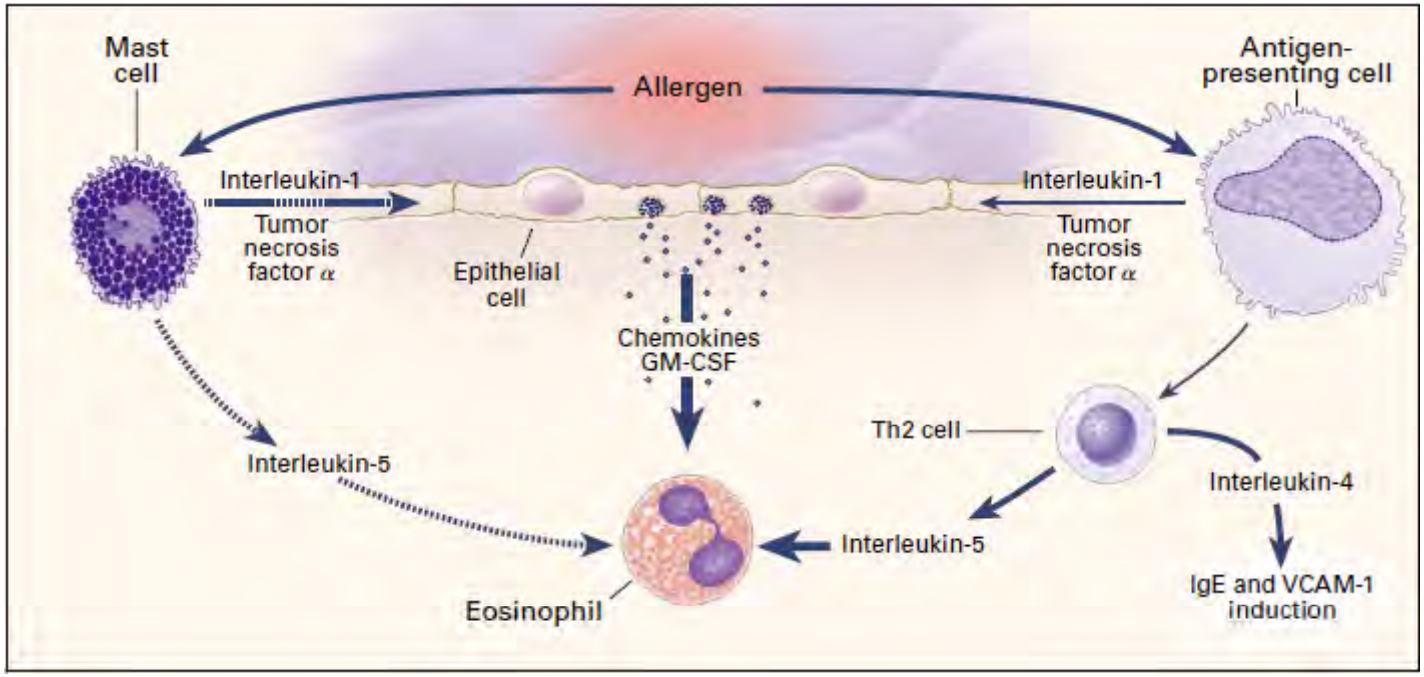
15/10/10



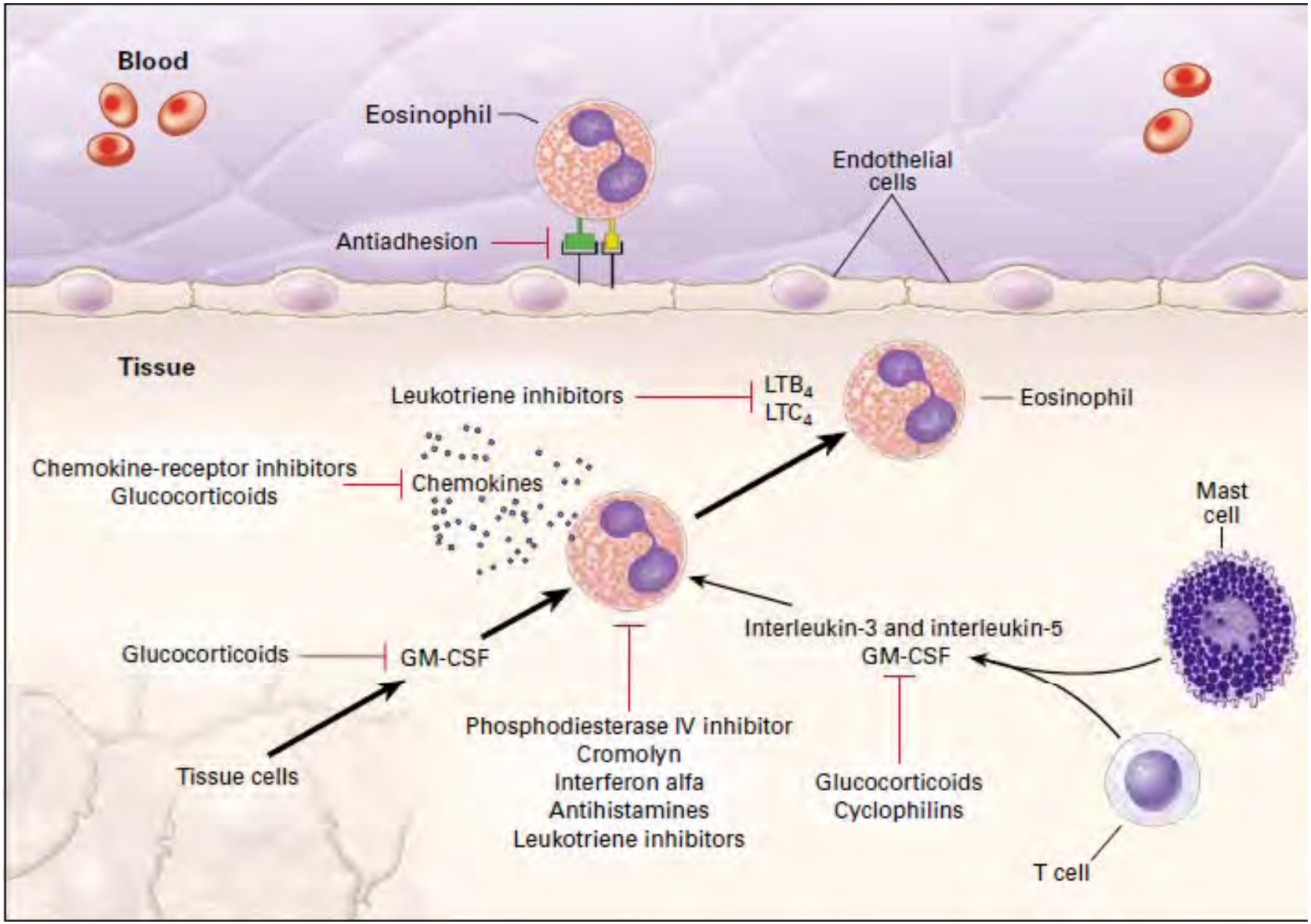
NEJM. Aug 2006



NEJM. Aug 2006



NEJM. Aug 2006



NEJM. Aug 2006

- Eosinophil-associated esophagitis
  - Primary EE (>15 eosinophils per high-power field without GERD)
    - Atopic
    - Nonatopic
    - Familial
  - Secondary
    - Eosinophilic disorders
      - Eosinophilic gastroenteritis
      - HES
    - Noneosinophilic disorders
      - Iatrogenic
      - Infection (typically helminthic)
      - GERD
      - Esophageal leiomyomatosis
      - Connective tissue disease (scleroderma)
- Eosinophil-associated gastroenteritis
  - Primary (mucosal, muscularis, and serosal forms)
    - Atopic
    - Nonatopic
    - Familial
  - Secondary
    - Eosinophilic disorders
      - HES
    - Noneosinophilic disorders
      - Celiac disease (typically not responsive to gluten avoidance alone)
      - Connective tissue disease (scleroderma)
      - Iatrogenic
      - Infection (typically helminthic)
      - Inflammatory bowel disease
      - Vasculitis (CSS)
- Eosinophil-associated colitis
  - Primary eosinophilic colitis (also allergic colitis of infancy)
    - Atopic
    - Nonatopic
  - Secondary
    - Eosinophilic disorders
      - Eosinophilic gastroenteritis
      - HES
    - Noneosinophilic disorders
      - Celiac disease
      - Connective tissue disease (scleroderma)
      - Iatrogenic
      - Infection
      - Inflammatory bowel disease
      - Vasculitis (CSS)

Intrinsic disorders	Extrinsic disorders
Mutations of hematopoietic stem cells	Cytokines released by T cells
Chronic eosinophilic leukemia	Allergic diseases
Acute myeloid leukemia	AD
Chronic myeloid leukemia	Urticaria
Myelodysplastic syndromes	Drug reactions
Idiopathic HES	Autoimmune diseases
	BP
	Dermatitis herpetiformis
	Infectious diseases
	HIV
	Ectoparasitosis
	Insect bites
	Erythema chronicum migrans
	Erythema toxicum neonatorum
	Hyper-IgE syndrome (Job syndrome)
	EPF
	Granuloma anulare
	Angiolymphoid hyperplasia with eosinophilia
	Eosinophilic fasciitis
	Eosinophilic cellulitis (Wells syndrome)
	HES
	Inflammatory clonal T-cell disease
	Cutaneous T-cell lymphoma
	Langerhans cell histiocytosis
	B-cell lymphomas
	Hodgkin lymphomas
	Acute T-cell leukemia/lymphoma

J Allergy Clin Immunol July 2010

- **PIE → > 1000/mm³ + Suggestive radiology**

BAL

- N < 1% eosinophil
- ICEP> 40% , IAEP>25%
- 3-40%→IPF,CTD-ILD , HP, sarcoidosis , BA, pneumoconiosis , infection
- Eosinophilic pneumonia→predominant cell eosinophil & > 25% (>40%)of DLC

Gold standard - Seldom necessary

Eosinophils

Macrophages

Eosinophilic granules

Charcot leydon crystals

Eosinophilic microabscess

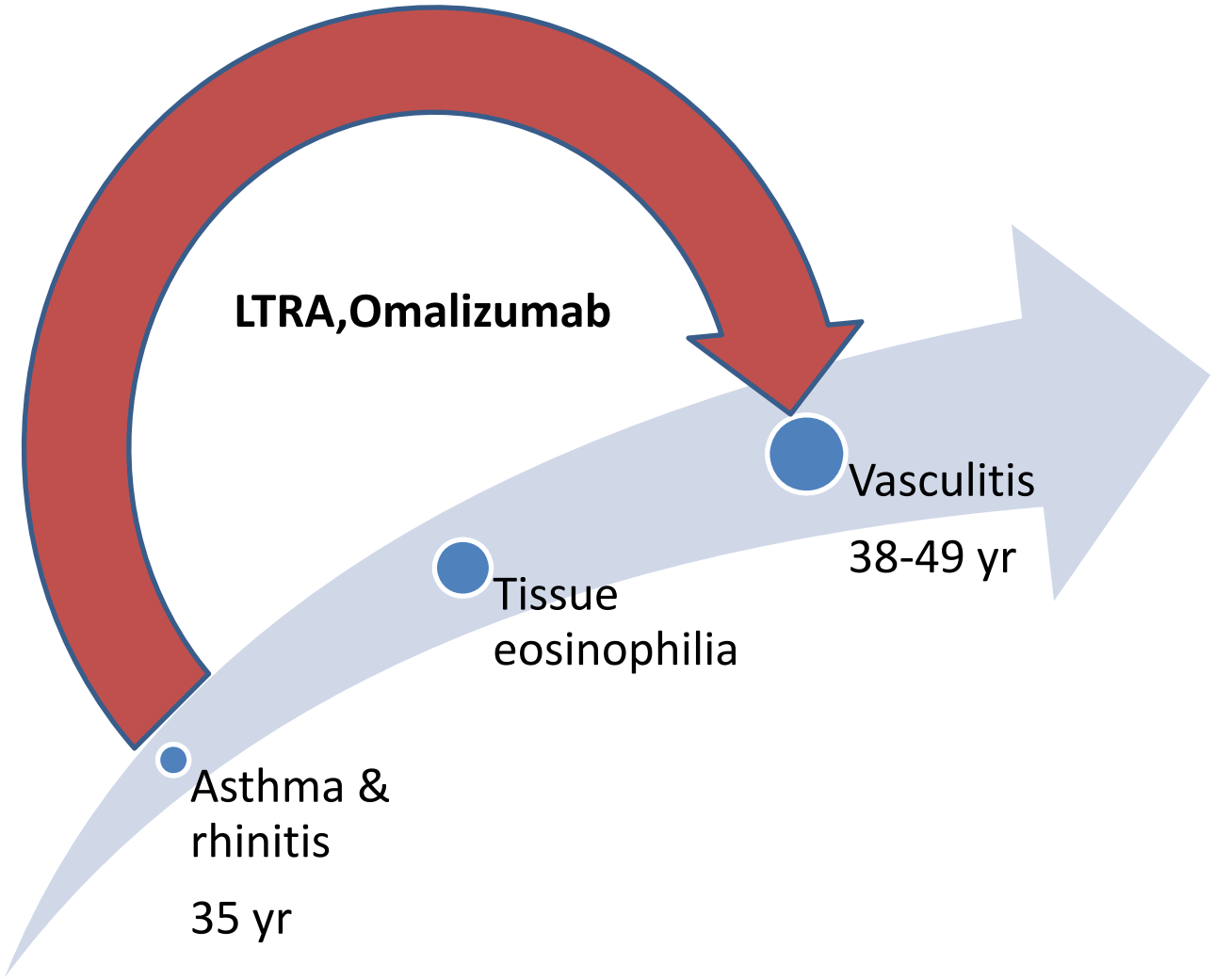
Global architecture of lung remains normal

Vasculitis (usually non necrotising)

DAD ,fibrinous exudates

Churg- Strauss syndrome (CSS)

- Eosinophil-rich and granulomatous inflammation.
- Necrotizing vasculitis affecting small to medium-sized vessels.
- Associated with asthma and eosinophilia.
- Possible defects in regulatory CD4+ CD25+ or CD4+ CD25- T-cell lymphocytes (producing IL-10 and IL-2) in CSS.
- ANCA + in 40 %


LTRA,Omalizumab
Vasculitis
38-49 yr
Tissue
eosinophilia
Asthma &
rhinitis
35 yr

Pulmonary manifestations

- Prodromic & eosinophilic phase
- Long standing asthma
- Loeffler’s like syndrome in 40% of pt
- Migratory ,nonlobar ,peripheral pulmonary infiltrates
- Nodular lesions (noncavitating)
- B/L pleural effusion

- Asthenia, weight loss, fever, arthralgias, and myalgias → often herald the development of the extrapulmonary manifestations of vasculitis.

- CCF – eosinophilic myocarditis/coronary arteritis/DCM

- Eosinophilic vasculitis in transplanted heart.

- Pericardial effusion/VTE

- Endomyocardial rare.

- Rhinitis/sinusitis (75%)
- PNS/CNS
- GIT
- Renal(26%)
- Dermatological(50%)
- Rheumatological

American College of Rheumatology criteria

Sensitivity 85% Specificity 99.7%

If 4/6present in a patient with proven systemic vasculitis.

- Asthma.
- Eosinophilia >10% DLC.
- Mononeuritis (including multiplex) or polyneuropathy.
- Fluctuating opacities on chest x-ray.
- Bilateral maxillary sinusal abnormalities.
- Presence of extravascular eosinophils on a biopsy including a vessel.

ANCA +ve vasculitic phenotype

- 38%

- Renal
- DAH
- Purpura
- PNS
- Vasculitic phenotype

ANCA –ve tissue disease phenotype

- 62%

- Cardiac
- Lung(except DAH)
- Eosinophilic lesion/organ fibrosis

Ann Intern Med 143:632–638, 2005
Arthritis Rheum 52:2926–2935, 2005.

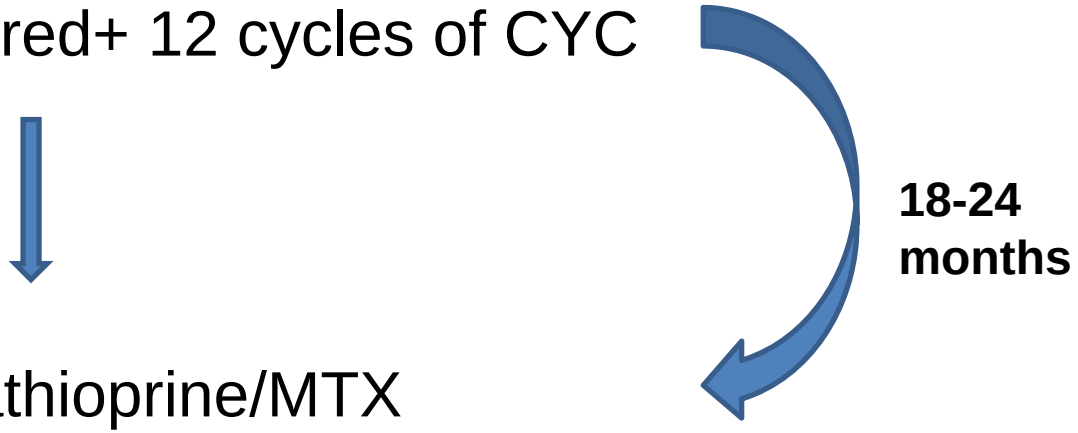
FFS

- Proteinuria greater than 1 g/day.
- Renal insufficiency ,serum creat> 1.58 mg/Dl.
- Gastrointestinal tract involvement
- Cardiomyopathy
- Central nervous system

Medicine (Baltimore) 1996; 75:17-28.

- FFS = 0→ Steroids ± MTX

- FFS >0→Pulse methypred+ 12 cycles of CYC



Taper/stop steroids ± Azathioprine/MTX

Rituximab → role in ANCA +; bronchospasm in ANCA –ve

Rheumatology (Oxford) 2008; 47:1104-1105.

- Imatinib
- Anti IL-5/Mepolizumab

Am J Respir Crit Care Med 2003; 167:1655–1659.

- Infliximab/Etarnecept

ICEP (Idiopathic chronic eosinophilic pneumonia)

- Female:male - 2:1
- 45 yrs
- ?Smoking protective
- H/O atopy in half
- Asthma 2/3of pt

Clinical features

- SOB X mths
- Chest pain
- Dry cough→ min mucoid sputum
- Hemoptysis(10%)
- Wt loss=10 kg (10%)
- URT(rhinitis/sinusitis)
- Wheeze 1/3 rd

Peripheral consolidation with eosinophilia

- CEP
- SPE
- CSS
- Drug induced
- Sarcoidosis
- DIP

- ↑ESR, ↑ IgE
- ↑ ↑urinary EDN(eosinophil degranulation)
- PFT→ obstructive/restrictive
- T/t→ steroids ;dramatic response

  >6 mth /relapses

IAEP

- 1. Acute onset of febrile respiratory manifestations (<1 mth)
- 2. Bilateral diffuse opacities on chest radiography
- 3. Hypoxemia, with PaO2 on room air < 60 mm Hg, and/or PaO2/FiO2 <300 mm Hg, and/or sPO2 on room air < 90%
- 4. Lung eosinophilia, with >25% eosinophils on BAL DLC(or eosinophilic pneumonia at lung biopsy)
- 5. Absence of infection, or of other known causes of eosinophilic lung disease (especially drug induced)

N Engl J Med 321:569–574, 1989. Allergy 60:841–857, 2005.

- Average age -30 yr but can be <20/>40
- Male
- <7 to <30 days
- Asthma-/atopy ±
- Recent alterations in smoking habits seem to play a major role in the onset of “idiopathic” AEP.
- Outdoor activities??

Chest 2008; 133:1174-1180.

- Increased levels of (1 3)-beta-D-glucan (a major component of the cell wall of most fungi and also one of the components of cigarette smoke) have been reported in BAL fluid

Chest 2007; 131:1234-1237.

- Peripheral AEC- <300 ; may↑↑ during course
- BAL eosinophil 37-54%
- PFT - restrictive
- MV/NIV is necessary in a majority of patients for ALI or ARDS.
- shock is exceptional ; extrapulmonary organ failure does not occur.
- T/t →methylprednisolone; spontaneous
- Prognosis better than ALI/ARDS

Hypereosinophilic syndrome

Old definition: idiopathic hypereosinophilic syndrome	Proposed new definition: HESs
1. Blood eosinophilia of greater than 1500/mm^3 for at least 6 mo 2. Unknown trigger of eosinophilia 3. Signs and symptoms of organ involvement	1. Blood eosinophilia of greater than 1500/mm^3 on at least 2 occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked blood eosinophilia 2. Exclusion of secondary causes of eosinophilia, such as parasitic or viral infections, allergic diseases, drug-induced or chemical-induced eosinophilia, hypoadrenalism, and neoplasms

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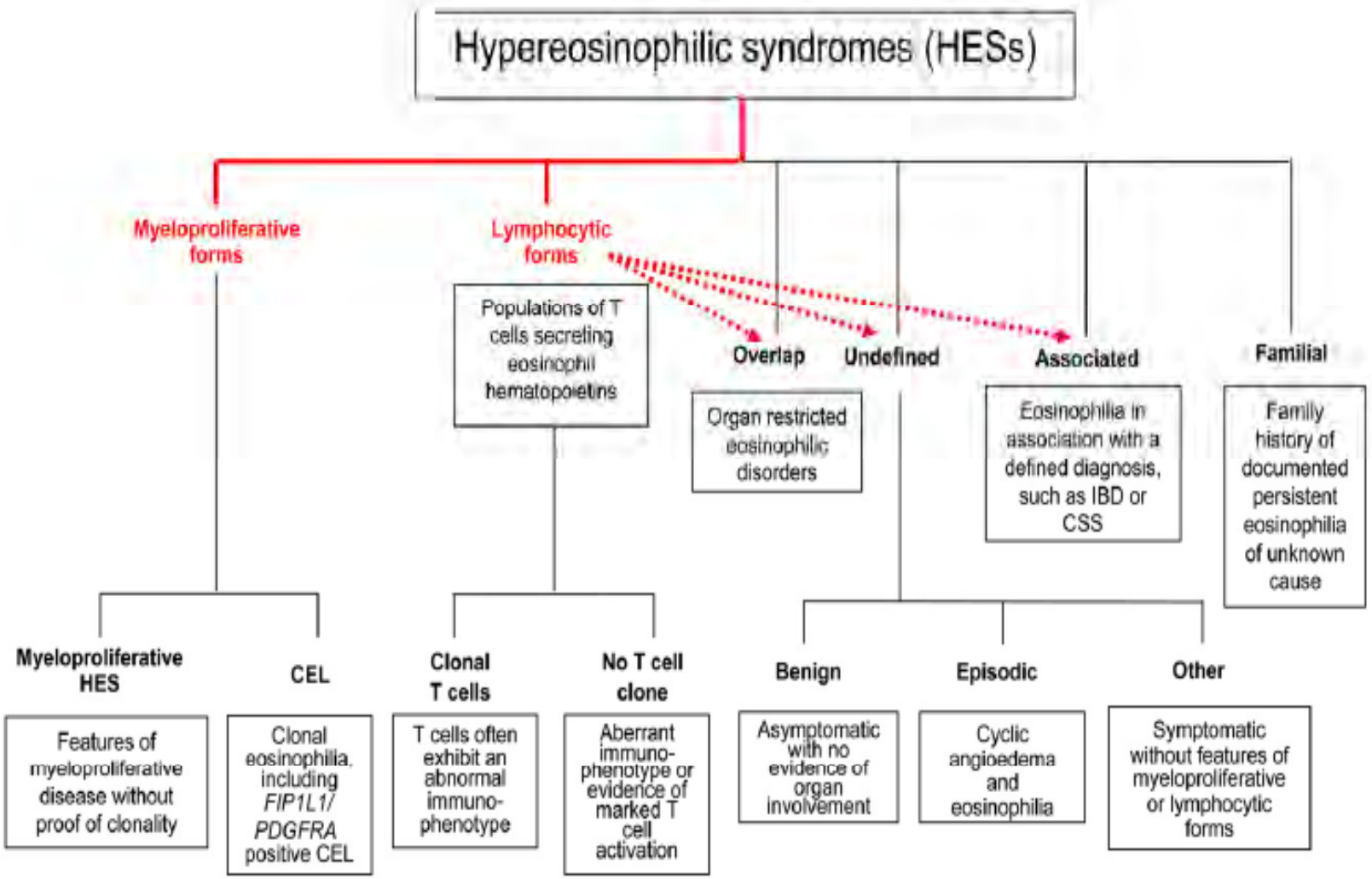

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Available in most hospital settings

- Complete blood count with leukocyte differential
- Microscopic examination of peripheral blood smear
- Serum IgE
- Serum IgG, IgA, IgM
- Serum Vitamin B12
- Leukocyte alkaline phosphatase score
- Bone marrow smear and biopsy (with staining for tryptase and reticulin)
- Lymphocyte phenotyping
- TCR gene rearrangement analysis (Southern blot and polymerase chain reaction)
- Conventional cytogenetic analysis on peripheral blood and bone marrow
- Abdominal ultrasound (measurement of liver and spleen)
- Echocardiogram and cardiac magnetic resonance imaging when possible

Investigations referred to qualified laboratories

- Serum tryptase
- Serum TARC (thymus and activation-regulated chemokine)
- FIP1L1-PDGFRα fusion
  RT-PCR, FISH
- Lymphocyte phenotyping*
  including CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD25, CD27, CD45RO, TCRα/β, TCRγ/δ, HLA-DR, CD95
- TCR gene rearrangement analysis*
  eventually on a FACS-sorted phenotypically aberrant population
- Conventional cytogenetic analysis*
  in presence of rIL-2 in addition to usual mitogens
- Cytokine profile of T-cell populations
  IL-4, IL-5, IL-13, IL-3, GM-CSF
  intracellular cytokines at the single cell level by flow cytometry
  cytokines in PBMC culture supernatants

Semin Respir Crit Care Med 2006;27:158–170

Treatment

- m-HES→ imatinib mesylate 100-400 mg/d

  side effects- nausea, vomitting, fluid overload

  cardiotoxic

- L-HES→corticosteroids
- Prognosis

  survival 12%at 3 yrs→70% at 10 yrs

Novel Therapies

- Nilotinib
- dasatinib
- Sorafenib
- PKC412

- Anti-IL5 therapies :

  mepolizumab

  reslizumab
- Alemtuzumab : anti -CD52 Mab

The Norwegian journal of medicine 2010;68:7/8

Loeffler syndrome(SPE)

- a/k/a Simple pulmonary eosinophilia
- Any age
- Self limting resp symptoms
- Mod- marked eosinophilia
- ?hypersensitivity to ascaris lumbricoides

- PFT – restrictive; dec DLco
- Stool R/E- WNL until 8 weeks of onset of respiratory syndrome→ so F/U over 3 mth period
- Search for other etiology
- T/t→bronchodilators ±steroids±mebendazole

- Eosinophilic pneumonia due to parasites almost always occurs during larval migration to the lungs.
- Initially (in the pulmonary infiltrate phase) parasitological stool examination results are negative, because the worms are still in the larval phase and therefore do not produce eggs.
- Stool examination results remain negative for up to 8 weeks after the onset of pulmonary symptoms.

Tropical pulmonary eosinophilia

- 2^{nd}-3^{rd} decade
- Males
- C/F- immune response of the host to the parasites.
- Nocturnal cough ± SOB/wheeze
- LOA/fever

- do not usually have clinical features of lymphatic filariasis.
- Microfilariae are usually not found in the blood or the lung. The circulating microfilariae are trapped in the lung vasculature where they release their antigenic contents, further triggering the inflammatory pulmonary reaction.

- BAL(54%) & blood(2000) eosinophilia
- IgE levels >10,000 ng/mL
- ↑ ↑ antifilarial IgG.
- Persisting irregular basilar opacities in 2/3 of patients after 1 year.
- “reticulonodular pattern” in majority of patients ±bronchiectasis/air trapping/mediastinal lymphadenopathy
- T/t → DEC 2mg/kg tds X 2-3 weeks ± steroids

Diagnostic criteria

- cough worse at night
- residence in a filarial endemic area
- eosinophil count> 3300 cells/mm3
- clinical and hematologic response to DEC

Respir Med 1999; 93:655-659.

Strongyloidosis

- Loeffler's like symptoms following transcutaneous infection
- Chronic → by autoinfection→ recurrent asthma like symptoms which worsen with steroid
- Hyperinfection syndrome in defective CMI/GI disorder→ prolong therapy
- Ivermectin/thiabendazole/albendazole

- Ankylostomiasis→ creeping eruption

  self limiting(no specificT/t)

- Toxocara canis→ visceral larva migrans

  ↑TLC,IgG &E,hepatomegaly

  self limiting

  albendazole/steroids hasten recovery

DRUGS WITH TYPICAL PULMONARY EOSINOPHILIA
Acetylsalicylic acid
Captopril
Diclofenac
Ethambutol
Fenbufen
Granulocyte-macrophage colony-stimulating factor
Ibuprofen
Minocycline
Naproxen
Para (4)-aminosalicylic acid
Penicillins
Phenylbutazone
Piroxicam
Pyrimethamine
Sulindac
Sulfamides-sulfonamides
Tolfenamic acid
Trimethoprim-sulfamethoxazole

DRUGS WITH OCCASIONAL PULMONARY EOSINOPHILIA
Bleomycin
Carbamazepine
Chlorpromazine
Cocaine
Desipramine
Dapsone
Febarbamate
Gold salts
Heroin
Imipramine
Isoniazid
Loxoprofen
Mephenesin
Methotrexate
Methylphedinate
Nitrofurantoin
Nomifensine
Pentamidine
Perindopril
Phenytoin
Propranolol
Sulfasalazine
Trimipramine

Interstitial Lung Disease (4th ed).London: BC Dekker, 2003, pp 657–700.

Manifestation	Drugs
Generalised rash with or without fever	Any drug is a possibility Mostly seen with antibiotics
Interstitial nephritis with eosinophiluria	Antibiotics, gold compounds, allopurinol
Pulmonary infiltrates	Nitrofurantoin, minocycline, naproxen, penicillins, phenylbutazone, sulindac, piroxicam, sulphonamides, nimesulide, tolfenamic acid
Pleuropulmonary manifestations	Dantrolene sodium, bleomycin, methotrexate
Hepatitis	Phenothiazines, penicillins, tolbutamide, allopurinol, methotrexate, fluoroquinolones
Leucocytoclastic vasculitis	Allopurinol, phenytoin
Chronic rhinosinusitis with nasal polyposis and asthma	Aspirin
Eosinophilia-myalgia syndrome	L-tryptophan
DRESS syndrome (drug rash with eosinophilia and systemic symptoms)	Carbamazepine, allopurinol, antibiotics, etc.

- Eosinophilic- myalgia syndrome
- Toxic oil syndrome- dSSc like / spain 1981 Acute→ resp failure- death

Chronic→ HTN/SSc/hepatic/sicca/polyneuropathy/jt contractures/chronic pulmonary sequelae

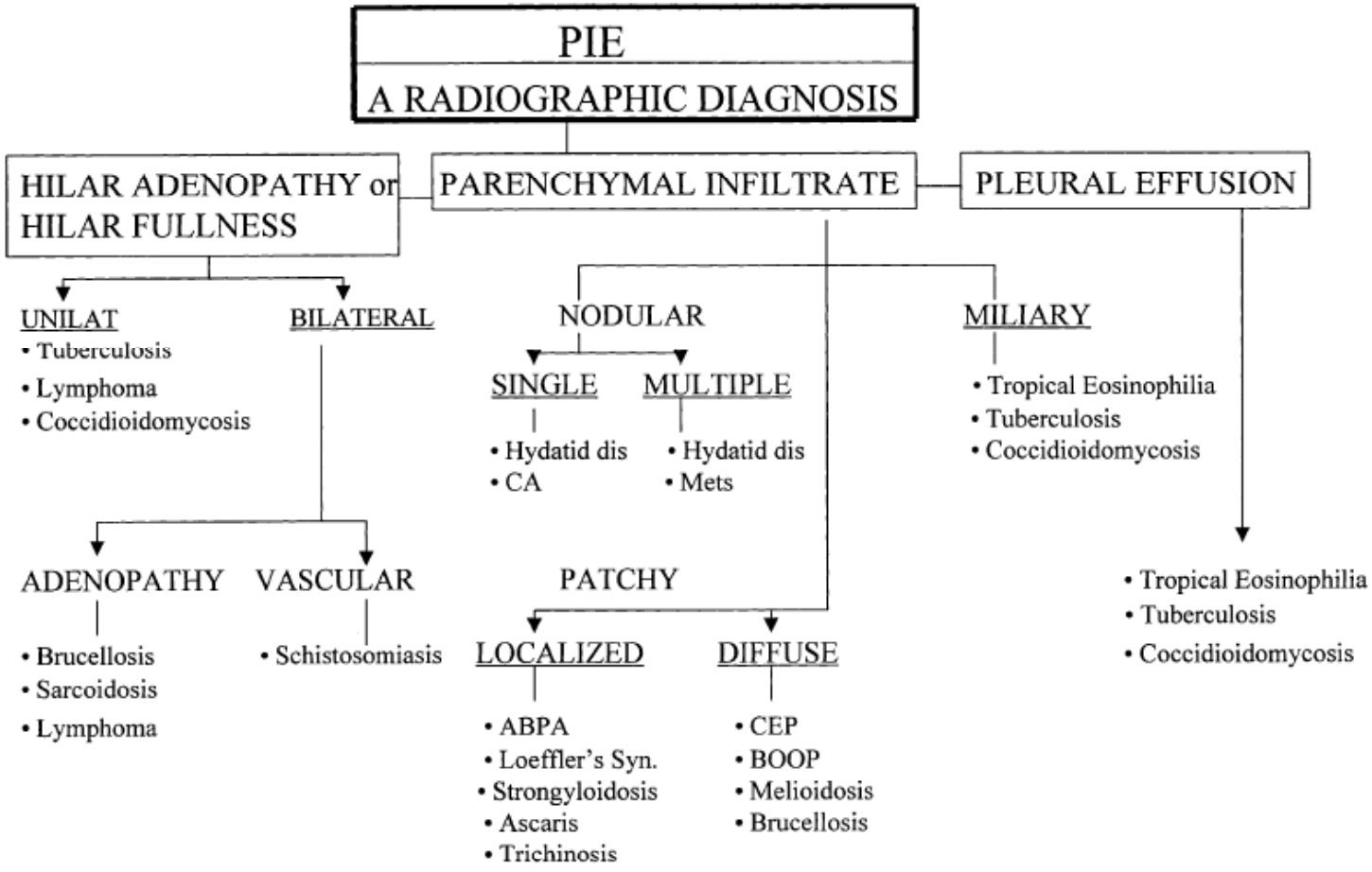
- May resemble

  ICEP/IAEP/CSS
- Stop drugs
- Corticosteroids±

Bronchocentric granulomatosis

- inflammatory and destructive process beginning within the bronchiolar walls and further extending into the surrounding parenchyma with a peribronchiolar distribution of the lesions.
- 50% pt are asthmatics.
- Scattered fungal hyphae .
- blood eosinophilia >1000 eosinophils/mm3.

- CXR→ The radiographic features consist of masses, alveolar opacities or pneumonic consolidation, or reticulonodular opacities, which predominate in the upper lobes and are u/l in majority.
- Most of these patients fulfill the criteria for ABPA.
- corticosteroids are efficient with an excellent prognosis, although recurrences are common

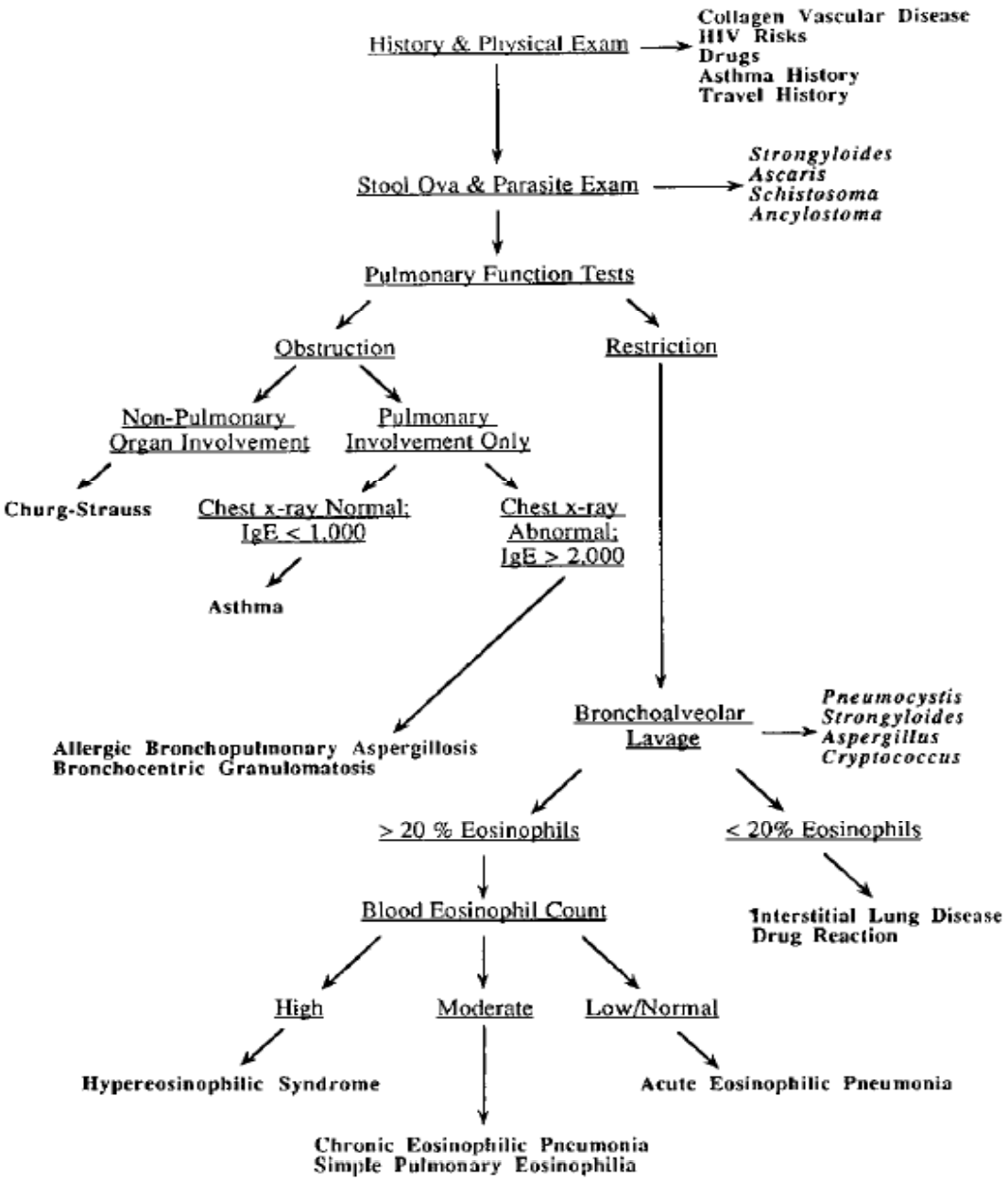


D.M. Savani, O.P. Sharma / Clin Chest Med 23 (2002) 377–396

Initial workup

- Drug history
- Travel history ?
- Serology testing for selective helminths
- 3 stool specimen & urine specimen for ova & larvae
- Asthma history
- PFT
- ANA/ANCA
- HIV

- Serial complete Hgm
- Serum IgE
- Vitamin B12
- ECG,ECHO
- HRCT thorax
- BAL
- Specific IgE,IgG
- Serum precipitins



Am J Respir Crit CareMed 150:1423–1438, 1994.)

Serum IgE levels in pulmonary infiltration with eosinophilia syndrome

Normal (IU)	Mildly high (<500 IU)	Moderately high (500–1000 IU)	Extremely high (>1000 IU)
Tuberculosis	Coccidioidomycosis	Strongyloidiasis	Allergic bronchopulmonary aspergillosis
Brucellosis	Drug-induced	Schistosomiasis	Tropical pulmonary eosinophilia
Hydatid cyst (encapsulated)	Loeffler's syndrome	Paragonimiasis	Churg-Strauss syndrome
Amebiasis	Sezary syndrome	Hydatid cyst (if cyst leaks)	
Polyarteritis nodosa			
Langerhan's cell granulomatosis			
Sarcoidosis			

D.M. Savani, O.P. Sharma / Clin Chest Med 23 (2002) 377–396