

Eosinophilic Lung Diseases

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KEYWORDS

- Eosinophilic pneumonia • Eosinophils
- Eosinophilic lung disease • Churg-Strauss syndrome
- Allergic bronchopulmonary aspergillosis
- Hypereosinophilic syndrome

The eosinophilic lung diseases consist of a heterogeneous group of disorders characterized by an increased numbers of eosinophils in 1 or more compartments of the lung, radiographic abnormalities, or impaired pulmonary function, and commonly, but not universally, peripheral blood eosinophilia. These disorders may be idiopathic in nature, or the result of a well-defined disease process. Disease severity in these entities can vary from clinically silent disease noted incidentally on radiologic imaging to life-threatening disease. Accurate diagnosis is essential to optimizing patient outcomes but remains challenging. Signs and symptoms frequently overlap among the disorders, and because these disorders are infrequent, expertise is difficult to acquire. Still, these disorders are not rare, and most clinicians periodically encounter patients with one or more of the eosinophilic lung diseases and need to understand how to recognize, diagnose, and manage these diseases. This review focuses on the clinical features, general diagnostic workup, and management of the eosinophilic lung diseases.

CLASSIFICATION OF EOSINOPHILIC LUNG DISEASES

Eosinophilic lung diseases may be divided into primary disorders and secondary disorders (**Fig. 1**). The secondary disorders include those conditions in which the

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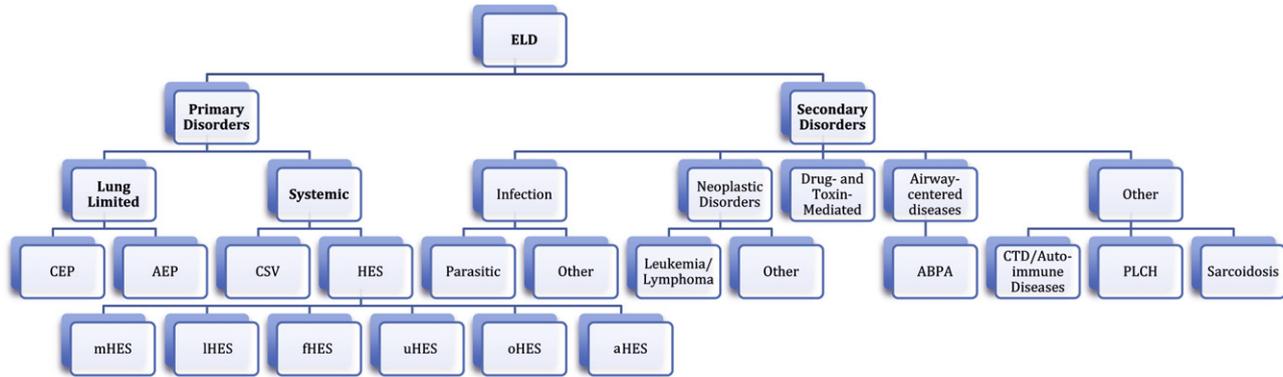


Fig. 1. Classification of eosinophilic lung diseases. aHES, associated variant hyper eosinophilic syndrome; CSV, Churg-Strauss vasculitis; CTD, connective tissue disease; ELD, eosinophilic lung disease; fHES, familial variant hyper eosinophilic syndrome; IHES, lymphocytic variant hyper eosinophilic syndrome; mHES, myeloproliferative variant hyper eosinophilic syndrome; oHES, overlap variant hyper eosinophilic syndrome; PLCH, pulmonary Langerhans cell histiocytosis. uHES, undefined variant hyper eosinophilic syndrome (benign and complex subtypes).

eosinophilia is believed to result from an identifiable, well-defined underlying cause or predisposition.¹ Secondary disorders are more common than primary disorders, and need to be definitively excluded before a primary disorder diagnosis is settled on. Examples of secondary disorders include infections (parasitic, fungal, mycobacterial, bacterial, and viral), drug/medication reactions, inhalant exposure (eg, crack cocaine), allergic bronchopulmonary aspergillosis (ABPA), primary connective tissue disease (eg, rheumatoid arthritis-related eosinophilic pneumonia), and primary malignancy (leukemias, lymphomas, myelodysplastic disorders, and lung carcinoma).

The primary eosinophilic diseases are commonly subdivided into organ-specific disorders and systemic disorders. Lung-limited entities include idiopathic chronic eosinophilic pneumonia (CEP) and idiopathic acute eosinophilic pneumonia (AEP), whereas systemic disorders include Churg-Strauss syndrome (CSS) and the hypereosinophilic syndromes (HES).¹

DIAGNOSTIC EVALUATION

Clinical Assessment

Once clinical suspicion for an eosinophilic lung disease is aroused, generally by the concurrent findings of pulmonary impairment or radiographic abnormalities plus increased numbers of eosinophils in the peripheral blood or lung tissue, the clinician embarks on a diagnostic evaluation directed toward making a more specific diagnosis (Fig. 2).¹ An in-depth medical history should include a detailed characterization of the clinical course, extent, and severity of the presenting disease course; a complete medication history (including not only current medications but previous medication history as well as supplement and nutraceutical use and illicit drug use); complete occupational and travel histories; and a detailed history of the patient's preexisting chronic medical conditions and immune status. In addition, a comprehensive review of systems is required to investigate all extrapulmonary signs and symptoms. Similarly, a comprehensive physical examination is crucial to identify all the potential manifestations (pulmonary and extrapulmonary) of the underlying disorder. For example, the identification of peripheral nervous system deficits consistent with mononeuritis multiplex may lead one toward a diagnosis of CSS, whereas findings of erythema nodosum and arthritis (Löfgren syndrome) argue for sarcoidosis.

Review of previous medical records may be of vital importance in uncovering the cause of the eosinophilic lung disease, particularly in those cases in which there is a protracted clinical course. In addition, previous documentation helps to provide objective baseline data, such as pulmonary physiology and imaging results, as well as highlighting the temporal relationships between potential exposures and the development of the eosinophilic lung disease.

The search for causation can be challenging. The diagnosis may remain elusive, particularly in the earlier stages of the disease. Signs and symptoms tend to be nonspecific and overlap among the various eosinophilic lung diseases. For example, if the clinician confirms a constellation of findings consisting of asthma, peripheral eosinophilia, constitutional symptoms (fatigue, malaise), chronic rhinosinusitis, and parenchymal pulmonary infiltrates on imaging, the differential diagnosis still includes CSS, idiopathic CEP (ICEP), ABPA, infectious causes of eosinophilic lung disease, drug/medication-induced eosinophilic lung disease, and undefined HES, because these findings are common to all of these disease states. Another common confounder to diagnosis is the use of empiric corticosteroids that nonspecifically ameliorates many of the signs and symptoms of eosinophilic lung disease and improves or resolves the peripheral or pulmonary eosinophilia before a definitive diagnosis being made.

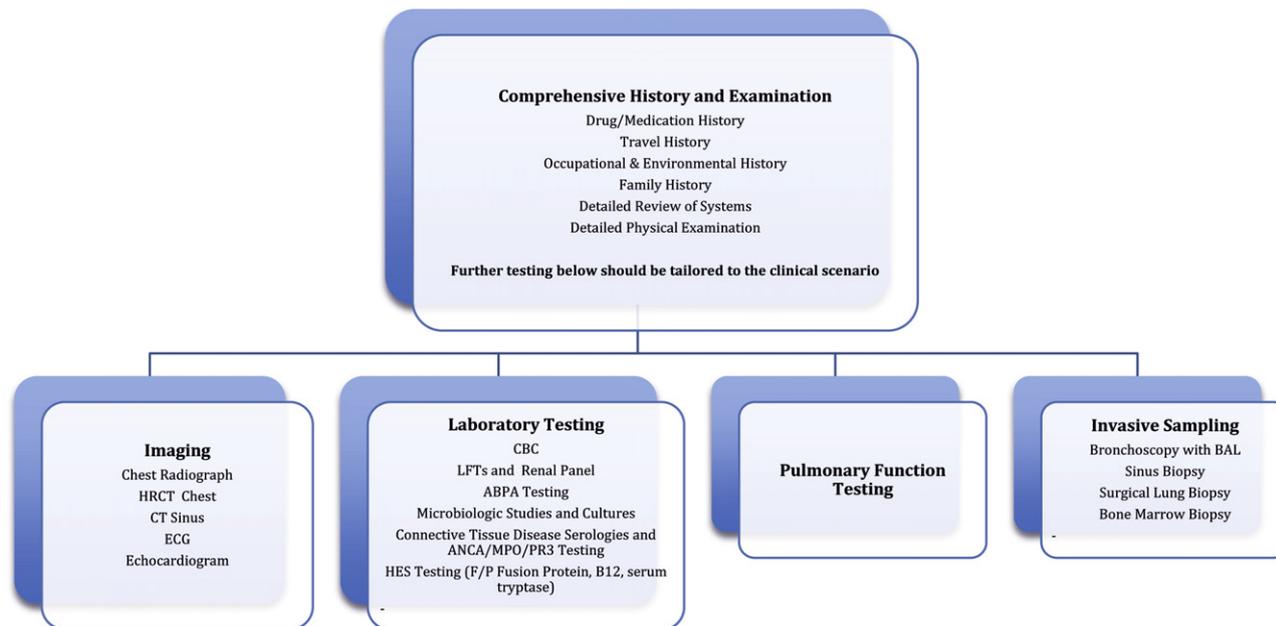


Fig. 2. Diagnostic approach to suspected eosinophilic lung disease. A multidisciplinary approach (eg, radiology, pathology) and appropriate subspecialty consultation as indicated by clinical presentation (eg, rheumatology, infectious disease, hematology-oncology) is recommended. ANCA, antineutrophilic cytoplasmic antibody; BAL, bronchoalveolar lavage; CBC, complete blood count; ECG, electrocardiogram; LFT, liver function test; MPO, myeloperoxidase; PR3, proteinase 3.

Recognizing the challenges surrounding the diagnosis and management of the eosinophilic lung disorders, the benefits of close collaboration among providers, and the importance of a multidisciplinary team approach cannot be overemphasized. Such an approach significantly facilitates the evaluation, diagnosis, and treatment of these conditions.

Laboratory Testing

The laboratory evaluation begins with a complete blood count and circulating eosinophil level count. A circulating eosinophil count greater than 400 cells/mm is abnormal and qualifies as eosinophilia. The terms high-grade eosinophilia or hypereosinophilia indicate a circulating eosinophil count exceeding 1500 cells/mm.¹ It is this finding of peripheral eosinophilia or hypereosinophilia that prompts further diagnostic evaluation.

Additional laboratory assessment, like the clinical evaluation, should be targeted toward assisting with the diagnosis and documenting the full extent of end-organ involvement and injury. Hence, screening for anemia, renal dysfunction, microscopic hematuria, and abnormal liver function tests is appropriate. Hypergammaglobulinemia, an increased erythrocyte sedimentation rate and an increased C-reactive protein level are all common abnormalities, but nonspecific. An increased total IgE level (>100 units/mL) is also common to many of the eosinophilic lung diseases; however, an IgE level greater than 1000 units/mL is more specific for entities such as ABPA, tropical pulmonary eosinophilia (TPE), and hyperimmunoglobulin E syndromes.

Microbiologic testing should be pursued based on clinical suspicion, taking into account the clinical presentation and the environmental and travel histories. Components of the evaluation may include sputum, urine, stool or blood cultures, stool sample for ova and parasites evaluation, and serologic assessments for evidence of parasitic infection (eg, strongyloidiasis, schistosomiasis.) Consultation with an infectious disease specialist is frequently beneficial in addressing potential infectious causes, especially in those patients with significant travel-related exposures.

Eosinophilic pneumonias in association with a primary rheumatologic condition commonly present once other clinical features of the rheumatologic disorder are established. However, in rare cases, pulmonary disease may occur before extrathoracic manifestations become apparent. Thus, the presence of autoantibodies may indicate an underlying collagen vascular disease or autoimmune disease. The choice of serologic testing must be driven by the clinical presentation, but in general terms, antineutrophilic cytoplasmic antibodies (ANCA) along with antimyeloperoxidase antibodies and antiproteinase 3 antibodies as measured by enzyme-linked immunosorbent assay testing are often obtained to assess for serologic evidence of Churg-Strauss vasculitis. Similarly, antinuclear antibodies (titer, pattern, and profile), anti-dsDNA, anticyclic citrullinated peptide antibodies, rheumatoid factor, anti-Scl-70 (topoisomerase), anti-Ro/SS-A, and anti-La/SS-B antibodies may also be obtained in those cases in which there is a clinical suspicion for a primary connective tissue disease.

Laboratory testing for primary hypereosinophilic syndromes generally includes a serum mast cell tryptase level test to evaluate for systemic mastocytosis and myeloproliferative HES (mHES), along with a serum vitamin B₁₂ concentration test for possible mHES.^{2,3} FIP1-like protein (FIP1L1) and the platelet-derived growth factor receptor α (PDGFR α) fusion protein (F/P) analysis by fluorescence in situ hybridization (FISH) or reverse transcriptase-polymerase chain reaction (RT-PCR) is used to evaluate for F/P-positive mHES (see later discussion) and may be performed on a peripheral blood sample or bone marrow biopsy.¹

An electrocardiogram and echocardiogram should be used to evaluate for cardiac involvement, which contributes heavily to the morbidity and mortality of CSS and HES. Pulmonary function testing rarely leads to a specific diagnosis but is useful in quantifying pulmonary impairment, in addition to monitoring disease progression and response to therapy.

Radiologic Evaluation

Imaging plays an integral role in the evaluation of the eosinophilic lung diseases. If the chest radiograph is abnormal, this may be the only modality required; however, high-resolution computed tomography (HRCT) of the chest is more sensitive than plain radiograph and provides valuable diagnostic insight in that it permits a more detailed characterization of the parenchymal abnormalities. Additional benefits of HRCT imaging may include the detection of nonparenchymal abnormalities (mediastinal lymphadenopathy, airways disease, or pleural or esophageal disease), prognostic information (eg, fibrotic changes as opposed to pure ground-glass attenuation), and the identification of an optimal location for bronchoalveolar lavage (BAL) or biopsy. Examples of characteristic HRCT patterns include middle and upper lobe predominant peripheral consolidation, also known as the photographic negative pulmonary edema seen in some patients with CEP,⁴ or the concomitant findings of bronchiectasis, mucous plugging, atelectasis, and areas of airspace consolidation/ground-glass attenuation in an upper and central lung zone predominant pattern characteristic of ABPA. If one identifies these findings on HRCT it is possible to distinguish these entities from other eosinophilic lung diseases in about 80% of cases.⁵

Imaging of other potential target organs, including sinuses, heart, and upper abdomen, may be helpful in specific cases. Sinus CT is commonly performed in patients with clinical evidence of sinus disease to characterize the pattern and extent of disease. Plain radiographs of the hands may be obtained to evaluate for the presence of an erosive arthropathy in those patients in whom a primary rheumatologic diagnosis is entertained. Abdominal ultrasonography or CT should be obtained when considering infectious causes of eosinophilia such as amebic liver abscess or echinococcal cysts, and also when screening for hepatosplenomegaly in patients with clinical HES. Cardiac magnetic resonance imaging (cMRI) for myocardial disease in CSS remains investigational, but may be performed in some centers with cMRI expertise.⁶ Similarly, positron emission tomography using [¹⁸F]fluoro-2-deoxy-D-glucose may be used in the evaluation of pulmonary and extrathoracic organ involvement in a subset of patients in whom malignancy is suspected.

Invasive Testing and Histopathology

Bronchoscopy with BAL is often a critical element of the evaluation of eosinophilic lung disease. Specifically, (1) differential cell counts on a formal BAL permit an accurate assessment as to whether or not there is an eosinophilic alveolitis consistent with histopathologic eosinophilic pneumonia, and (2) BAL fluid evaluation permits a more thorough evaluation for infectious processes. In normal individuals, the BAL differential cell count shows only a few lymphocytes, neutrophils, and eosinophils (<1%). If the BAL has more than 25% eosinophils (and even more convincingly >40% eosinophils), then the patient by definition has pulmonary eosinophilia or eosinophilic alveolitis, which in turn correlates with the histopathologic finding of eosinophilic pneumonia. There are 2 major caveats to this statement. First, normal airways have large numbers of eosinophils such that small volume lavages or bronchial washings commonly show eosinophilia. In our experience, for the differential cell count to be informative, the bronchoscope must remain in wedge position as serial lavage is

performed, and the lavage must use 3 to 4 instillations of 40 to 60 mL aliquots of saline (for a total volume of at least 120 mL, but no more than 240 mL), and achieve at least a 50% return volume.⁷ Second, the finding of an eosinophilic alveolitis or the histopathologic finding of eosinophilic pneumonia may be seen with several of the eosinophilic lung diseases and represents a pathologic finding, not a clinical diagnosis. It is still up to the clinician to integrate this important finding with the larger clinical picture to achieve a final clinical diagnosis.

Transbronchial biopsy is useful in the diagnosis of peribronchovascular disease such as that found in sarcoidosis, lymphangitic carcinomatosis, and lymphoma, and in processes with airspace consolidation. However, small specimen size and sampling error are significant limitations, and in general, transbronchial biopsy tends to confirm the findings (or lack thereof) identified on lavage. Endobronchial biopsies are helpful if ulcerative or exophytic tracheobronchial lesions are identified during bronchoscopy, such as those found in sarcoidosis, malignancy, or granulomatosis with polyangiitis (Wegener granulomatosis).

Video-assisted thoracoscopic surgery remains the surgical procedure of choice when a diagnosis cannot be obtained by less invasive tests and procedures. In our experience this surgery is required in only a few patients.¹

If a secondary cause for persistent high-grade eosinophilia cannot be found, and the patient does not meet criteria for reactive processes such as vasculitis, then evidence for a clonal expansion of eosinophils should be sought. Hematology-oncology consultation should be obtained and a bone marrow biopsy performed to exclude leukemia, lymphoma, myelodysplastic syndromes, and HES. An assessment for blasts, mast cells, and lymphocyte subpopulations should be performed, and conventional cytogenetic, clonality, and flow cytometry studies are often required.^{8,9}

PATHOLOGIC PATTERNS

Eosinophil longevity and survival are greater in peripheral tissues than in the circulation, and as a result, many eosinophils can be found in the lung even when the peripheral blood count is low or normal, and this is the case in AEP.¹⁰ In other cases, eosinophils are not a prominent component of the pulmonary cell infiltrate despite an increased blood eosinophil count. This scenario is frequently seen with malignancies. Any inflammatory eosinophilic reaction unrelated to host defense (ie, parasitic infection) is abnormal.¹¹ Although patients who smoke may have modest increases in pulmonary eosinophils, large numbers of eosinophils are unusual.^{12,13}

The key histopathologic feature of eosinophilic pneumonia is the presence of eosinophils within the alveolar airspace (**Fig. 3**). Its appearance ranges from the simple presence of modest numbers of eosinophils in an otherwise normal lung to dense collections of eosinophils admixed with fibrin and macrophages and associated with architectural distortion. In addition, there may be significant infiltration and expansion of the alveolar septa by a mixture of eosinophils and other inflammatory cells. Focal collections of eosinophils and areas of organizing pneumonia may also be seen. The recognition of associated histopathologic features in the proper clinical scenario of eosinophilic pneumonia may have diagnostic significance. Examples include the finding of diffuse alveolar damage in a patient with acute onset disease (ie, idiopathic AEP), extensive intra-alveolar hemorrhage (Goodpasture syndrome),¹⁴ or vasculitis with endothelial cell injury, eosinophilic abscess formation, and granulomatous inflammation (CSS).^{1,15} Still, it is worth reiterating that the finding of a histopathologic pattern of eosinophilic pneumonia frequently does not differentiate between eosinophilic lung disease considerations. Therefore, the clinical, physiologic,

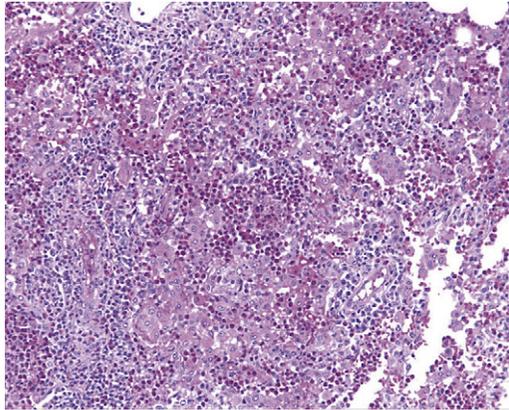


Fig. 3. Eosinophilic pneumonia. Histopathologic section of eosinophilic pneumonia showing airspaces filled with eosinophils, fibrin exudates, and macrophages. The adjacent septa are expanded by inflammation and show reactive pneumocyte hypertrophy.

radiographic, and laboratory findings must be integrated with the pathologic findings to make a specific diagnosis. A final caveat is that patients who received corticosteroid therapy before biopsy may have a paucity of eosinophils within the airspaces, thus producing patterns more similar to acute lung injury (ALI)/diffuse alveolar damage or organizing pneumonia, greatly complicating diagnosis.

SPECIFIC EOSINOPHILIC LUNG DISEASES

Secondary Disorders

ABPA

Aspergillus sp pulmonary infections can manifest with (1) a chronic necrotizing process, (2) aggressive angioinvasive disease (most notably in immunocompromised hosts), or (3) a more indolent, saprophytic process (aspergilloma). However, *Aspergillus* colonization of the airways can also result in ABPA, a hypersensitivity immune response to *Aspergillus* conidial or mycelial antigens.

Approximately 1% to 2% of patients with asthma and 2% to 15% of patients with cystic fibrosis develop ABPA.¹⁶ More than 200 species of *Aspergillus* have been identified, and although ABPA is most commonly caused by *A fumigatus*, this identical hypersensitivity reaction has been described with other *Aspergillus* species as well as other fungal colonizers (and is then termed allergic bronchopulmonary mycosis). In susceptible hosts, the inhalation, colonization, and proliferation of *Aspergillus* in the airway leads to antigenic exposure within the tracheobronchial tree, and results in an intense CD4+ Th2-mediated eosinophilic inflammatory response, IgE, IgA, and IgG synthesis, and interleukin 8 (IL-8) mediated neutrophilic inflammation.¹⁷ The clinical ABPA phenotype is influenced by host genetic susceptibility factors (eg, CFTR gene mutations, class II HLA-DR2/5 antigens),^{18,19} host defense function, and underlying medical comorbidities, and organism virulence factors²⁰ such as the frequency and quantity of inhaled spores.¹⁶

Clinically, ABPA presents with severe, persistent asthma that is often steroid-dependent, chronic cough with expectoration of brown mucus plugs, constitutional symptoms (fatigue, malaise, weight loss, fever), recurrent, migratory pulmonary infiltrates, and cystic/varicoid bronchiectasis. ABPA preferentially affects persons in their third to fifth decades, but may be seen at any age. Chest CT frequently shows

characteristic abnormalities in ABPA, with bronchiectasis being found in about 90% of cases (typically proximal in location, and varicose or cystic in type).^{21,22} Peribronchial thickening, mucous plugging and impaction, migratory ground-glass opacities/consolidation, and bronchiolitis are common associated findings.^{5,23,24}

In terms of confirming a diagnosis of ABPA, the Rosenberg-Patterson criteria^{24,25} remain widely accepted (**Box 1**). Major diagnostic criteria include: (1) asthma, (2) radiographic infiltrates, (3) skin test positivity for *Aspergillus*, (4) peripheral eosinophilia, (5) positive serum precipitating antibodies to *Aspergillus*, (6) increased serum total IgE level (>1000 IU/mL), (7) increased *Aspergillus*-specific IgG and IgE, and (8) central bronchiectasis.^{24,25} Minor criteria include: (1) *Aspergillus* in the sputum, (2) the expectoration of brown mucus plugs, and (3) a positive delayed skin test reaction to *Aspergillus*. A confident diagnosis of ABPA may be made when at least 6 of the major Rosenberg-Patterson criteria are present.

Early diagnosis and treatment of ABPA is critical to preventing progressive and debilitating lung disease. Whereas systemic corticosteroid therapy clearly represents the primary treatment of ABPA, the dose and duration of optimal corticosteroid therapy remain unknown. One large cohort study using high dosages for a prolonged period appeared to be associated with higher rates of sustained disease remission compared with other historic case series.²⁶ On the other hand, the risk of adverse side effects increases with higher dosages administered for longer durations. Therefore, efforts should be made to minimize the total cumulative dose to the necessary dose required to control the disease, and the prescribed doses of corticosteroids must be carefully tailored to clinical, physiologic, and radiographic response.¹ In addition, both high-dose inhaled corticosteroids and oral itraconazole have been

Box 1**Rosenberg-Patterson criteria for diagnosis of allergic bronchopulmonary *Aspergillus****Major criteria*

1. History of asthma
2. Radiographic pulmonary opacities
3. Immediate skin reactivity (positive skin testing) to *Aspergillus* antigen
4. Peripheral blood eosinophilia
5. Precipitating antibodies to *Aspergillus* antigen
6. Increased serum total IgE level
7. Increased *A fumigatus*-specific IgE and IgG antibodies
8. Central bronchiectasis

Minor criteria

1. *A fumigatus* in sputum
2. History of expectorating brown plugs
3. Delayed skin reactivity to *Aspergillus* antigen

The presence of 6 of 8 major criteria makes the diagnosis of ABPA nearly certain.

Data from Patterson R, Greenberger PA, Halwig JM, et al. Allergic bronchopulmonary aspergillosis. Natural history and classification of early disease by serologic and roentgenographic studies. Arch Intern Med 1986;146(5):916-8; and Agarwal R, Gupta D, Aggarwal AN, et al. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in north India. Chest 2006;130(2):442-8.

associated with reduced oral corticosteroid requirements.^{27–32} A systematic review reported that the use of itraconazole, in addition to reducing corticosteroid dose, modifies the immunologic activation associated with ABPA and improves clinical outcomes.³³ Thus, itraconazole and high-dose inhaled corticosteroids should be strongly considered when treating corticosteroid-dependent ABPA patients and those with frequent exacerbations.

Anti-IgE monoclonal antibody therapy has been considered as a potential therapy for ABPA based on biologic plausibility, but no controlled studies of anti-IgE monoclonal antibody therapy have been reported in children or adults with ABPA. Although anti-IgE has been shown to improve respiratory function and reduce glucocorticoid administration in pediatric patients with ABPA with cystic fibrosis at the case report level, this therapy warrants further evaluation in a randomized, controlled trial.^{32,34,35}

The nonpharmacologic management of ABPA centers on close patient follow-up with regular monitoring of the total serum IgE level, blood eosinophil count, pulmonary function tests, and imaging studies; airway clearance techniques; pulmonary rehabilitation/regular exercise program to achieve and maintain musculoskeletal conditioning; appropriate vaccination; and the treatment of comorbid conditions. Moreover, given the frequent requirement for prolonged or repeated therapy with oral corticosteroids, screening (eg, periodic electrolytes and bone mineral density testing), prevention (eg, bone mineral preserving therapies), and treatment of glucocorticoid side effects (eg, diabetes) is recommended.

Infectious diseases

Infections, and especially parasitic infections, represent a major cause of eosinophilic lung disease. Infectious causes are often suggested by travel history, but not necessarily so, because the travel history may be remote to the onset of illness (eg, TPE). Fungi may cause pulmonary eosinophilia through direct infection of pulmonary tissue (eg, *Coccidioides*, *Blastomyces*, *Histoplasma*, *Paracoccidioides*) or by triggering an immunologic reaction when fungal antigens are inhaled (eg, ABPA). Also, yeastlike fungal infections (*Pneumocystis jiroveci*)³⁶ and viral infections (respiratory syncytial virus)³⁷ have been associated with eosinophilic pneumonia. Pulmonary disease associated with peripheral eosinophilia may be seen with a wide variety of infectious agents including bacteria, viral infections, mycobacterial pulmonary infections, and fungi.

Parasitic infections are common worldwide, especially in the tropical and subtropical regions. Parasitic pulmonary infections may be divided into those caused by protozoans and those caused by helminths. *Entamoeba histolytica* is spread by the fecal-oral route and is more common in areas with poor sanitation. Pulmonary involvement by *E histolytica* occurs mainly by extension from an amebic liver abscess (hepatopulmonary amebiasis).³⁸ Metronidazole is the mainstay of treatment.

In its broadest sense, simple pulmonary eosinophilia (also known as Löffler syndrome) is an acute, transient, and often mild hypersensitivity response to parasitic infections or medications/drugs characterized by migratory pulmonary infiltrates and eosinophilia (PIE syndrome). More narrowly, Löffler syndrome has generally been associated with intestinal (*Ascaris*, *Strongyloides*, *Trichinella*, *Ancylostoma*, and *Necator*) and tissue (*Toxocara*) roundworm infections, especially *Ascaris*, because *Ascaris* is the most prevalent roundworm infection worldwide, and hence, the most common parasitic cause of simple pulmonary eosinophilia. Infection is spread by ingestion of eggs from contaminated soil or food. Patients may be asymptomatic, or may present with a constellation of constitutional symptoms (fatigue, fever, night sweats, weight loss), dyspnea, or wheezing. Stool ova and parasite evaluation often confirms the diagnosis, albeit 6 to 12 weeks after the initial infection. At the time of pulmonary

symptoms, larvae may be identified in the sputum or on gastric aspirate. Mebendazole is the treatment of choice.

TPE is caused by the host response to the mosquito-borne filarial parasites *Wuchereria bancrofti* and *Brugia malayi*.³⁹ In contrast to simple pulmonary eosinophilia, most patients are symptomatic with fever, fatigue, malaise, anorexia, weight loss, paroxysmal nocturnal cough, and breathlessness. However, clinical disease may not develop until months or years after the initial infection, greatly complicating diagnosis. Hypereosinophilia and markedly increased IgE levels (>1000 U/mL) are common in TPE. Chest imaging may show reticulonodular, interstitial infiltrates, but is variable, and may even be normal. TPE is commonly treated with diethylcarbamazine.

Drug-induced and toxin-induced eosinophilic lung disease

Illicit,⁴⁰ over-the-counter, and prescribed drugs as well as herbal remedies,⁴¹ radiation,⁴² environmental, and occupational inhalational exposures⁴³ have been associated with eosinophilic lung diseases. As the number of available drugs and medications expands, so does the incidence of drug-induced lung diseases. More than 120 medications have been associated with eosinophilic lung disease. An updated list can be found at <http://www.pneumotox.com>, a Web site database maintained by the Groupe d'Etudes de la Pathologie Pulmonaire Interrogative, which regularly updates thousands of bibliographical references of drug-induced lung diseases. Antibiotics and nonsteroidal antiinflammatory drugs are the most common causative agents.⁴⁴ Other classes of drugs implicated in eosinophilic lung disease are outlined in **Table 1**.⁴⁵

Drug-induced lung disease findings on histopathology and on high-resolution CT can resemble essentially any of the patterns described in the interstitial lung diseases,

Antibiotics	Anticonvulsants	Illicit drug
β-Lactams	Carbamazepine	Cocaine
Tetracyclines	Phenytoin	Heroin
Sulfa agents		
Nitrofurantoin		
Isoniazid		
Ethambutol		
Pentamidine		
Sulfonamides		
Nonsteroidal antiinflammatory drugs	Antidepressants	Chemotherapeutics
Ibuprofen	Amitriptyline	Bleomycin
Indomethacin	Trazadone	Camptothecin
Naproxen	Venlafaxine	
Diclofenac		
Sulindac		
Piroxicam		
Cardiovascular	Biologics	Nutraceuticals
Angiotensin-converting enzyme inhibitors	Infliximab	L-Tryptophan
Amiodarone	Interferon alpha	
β-blockers	Granulocyte-macrophage colony stimulating factor	

Data from Solomon J, Schwarz M. Drug-, toxin-, and radiation therapy-induced eosinophilic pneumonia. *Semin Respir Crit Care Med*. 2006;27(2):192–7; and Frankel SK. Drug-induced lung disease. In: Hanley M, Welsh C, editors. *Current diagnosis and treatment in pulmonary medicine*. New York: Lange Medical Books/McGraw-Hill; 2003. p. 337–47.

including desquamative interstitial pneumonia, diffuse alveolar damage, alveolar hemorrhage, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, organizing pneumonia, and eosinophilic pneumonia. Drug-related eosinophilic lung manifestations are remarkably common and varied, and may range from subclinical transient fleeting infiltrates (Löffler syndrome, the most common clinical presentation) to more pronounced presentations characterized by nonspecific constitutional symptoms, cough, dyspnea, and ground-glass infiltrates, and histopathologic findings of CEP. Drug-induced AEP may occur and present with life-threatening respiratory failure.^{46–49}

The diagnosis of drug-induced eosinophilic lung disease rests on the temporal association with a potential candidate agent or toxin and the development of disease. This relationship may be confirmed when prompt cessation of the offending agent leads to rapid improvement. In patients with significant symptoms or pulmonary impairment, systemic corticosteroids are often required, especially in those cases that do not resolve quickly and spontaneously, and in those patients who present with fulminant disease, especially those with respiratory distress/failure.

Neoplastic disorders

Eosinophilic lung diseases with or without peripheral blood eosinophilia may occur in the setting of malignancy as a result of opportunistic infections, as a side effect from chemotherapy or radiation therapy, as a host response to the neoplasm, or as a paraneoplastic manifestation. Peripheral blood eosinophilia results from the production of cytokines such as IL-3, IL-5, and granulocyte-macrophage colony stimulating factor that promote eosinophil differentiation and survival. An eosinophilic response may be seen with leukemia, lymphoma, acute graft versus host disease,⁵⁰ myelodysplastic disorders, systemic mastocytosis, and solid organ neoplasms including lung cancer.^{50–53} In contrast to primary lung neoplasms or thoracic metastases of solid tumors, peripheral blood eosinophilia in blood and bone marrow malignancies is generally considered to be an ominous sign and important factor for determining disease-free survival.^{54,55}

Primary Disorders

Lung-limited

ICEP ICEP is an uncommon interstitial lung disease. The true incidence and prevalence are unknown, but based on 2 registry studies, ICEP seems to represent approximately 1% to 2.5% of interstitial lung disease cases.^{56,57} The gender distribution favors a female predominance in most series. No clear genetic predisposition exists, but patients frequently have a previous history of asthma or other atopic disease. The relationship between asthma and ICEP is not well understood. Although both entities share similar inflammatory responses and cytokine/chemokine profiles, the precise mechanisms that produce pulmonary parenchymal eosinophilic inflammation in ICEP compared with those associated with asthma alone await further research.^{58,59}

Clinical manifestations of ICEP include cough, dyspnea on exertion, exercise intolerance, and systemic symptoms such as fever, chills, night sweats, anorexia, and malaise that evolve insidiously over weeks to months. Chest auscultation may reveal wheeze, consolidative findings, or crackles, but the remainder of the physical examination is largely unremarkable. Signs of pulmonary hypertension as a result of pulmonary fibrosis may be present in advanced cases.

Frequent laboratory findings include peripheral blood eosinophilia or hypereosinophilia, increased inflammatory markers, and increased total IgE levels.⁶⁰ Chest films commonly reveal migratory, patchy, bilateral, peripheral-predominant, ground-glass,

or consolidative infiltrates. Shadows parallel to the pleural surface (ie, the photonegative pulmonary edema) are virtually pathognomonic⁶¹; however, this imaging pattern is found in fewer than 25% of patients with CEP.⁶² Progressive interstitial changes, including reticular infiltrates and honeycombing, consistent with pulmonary fibrosis have been described.⁶³ Pulmonary function testing is nonspecific and may show obstructive, restrictive, or mixed patterns of disease, or may be normal. BAL eosinophilia greater than 25% is characteristic in treatment-naïve patients. This finding in the correct clinical scenario, and in the absence of alternative diagnostic considerations (ie, drug-induced and infectious causes have been excluded) can obviate a surgical lung biopsy. If a biopsy is performed, histopathologic specimens show an inflammatory and eosinophilic cellular infiltrate involving the interstitium and filling the alveolar space. Occasionally, areas of organizing pneumonia can be seen.⁶²

The natural history of ICEP is unpredictable at the time of the diagnosis. Some patients may resolve their disease after an initial course of corticosteroid therapy without further recurrence of the disease, whereas others may experience one or more episodes of disease relapse. Still others may have progressive disease despite therapy. It is unclear if these different natural histories represent distinct phenotypes of ICEP or if the natural history is influenced by other factors such as asthma. Among patients with ICEP, asthmatics may have a lower frequency of relapse than nonasthmatics, whereas the occurrence of ICEP in asthmatics is often associated with the development of more severe asthma.⁶⁴

ICEP is typically exquisitely responsive to systemic corticosteroids. Rapid improvement in symptoms and radiographic infiltrates is often noted within days after the initiation of therapy. However, the disease commonly recurs after corticosteroid therapy is discontinued, and this is especially true for those patients for whom the steroid therapy is quickly tapered.^{60–62,65} Steroid-resistant cases should raise the question of a competing diagnostic entity (eg, CSS). No randomized controlled trials have been conducted with corticosteroid monotherapy in ICEP. As with ABPA, the dose and duration of systemic corticosteroids need to be tailored to the severity of disease and individual circumstances. In general, we initiate therapy with 0.5 to 1 mg/kg/d of prednisone or equivalent followed by a gradual tapering over a period of 6 to 12 months. The duration of therapy can be extended beyond 12 months if the disease course is marked by relapses.⁶² Screening for and prevention of corticosteroid-related adverse side effects is highly recommended (eg, osteoporosis, diabetes, electrolyte abnormalities, ophthalmologic complications). In addition, *Pneumocystis* prophylaxis should be considered for patients who are on high-dose corticosteroids (eg, ≥ 20 mg/d of prednisone or equivalent) for 1 month or longer or if used in combination with another immunosuppressive drug. Steroid-sparing agents may be considered on a case-by-case basis for remission maintenance in patients requiring chronic moderate-dose to high-dose oral corticosteroids (>15 mg/d of prednisone) in an attempt to limit steroid-related toxicity and in patients who develop unacceptable side effects with the doses necessary to control ICEP.¹ The addition of high-dose inhaled corticosteroids, especially in those with concomitant asthma, may reduce ICEP recurrence or total oral corticosteroid requirements.^{1,64,66,67}

AEP AEP is a severe and acute illness that clinically resembles ALI/acute respiratory distress syndrome (ALI/ARDS). AEP is often indistinguishable from ALI/ARDS or severe community-acquired pneumonia at the time of initial presentation. However, unlike ALI/ARDS, AEP is rare, making diagnosis challenging. The predominant histologic feature of AEP is eosinophilic pneumonia, although elements of diffuse alveolar damage may also be seen in conjunction with the dominant eosinophilic process.

However, the most telling difference between AEP and ALI/ARDS is that AEP improves dramatically within hours of corticosteroid administration. Thus, the ability to make a prompt diagnosis has important implications for the management and outcome of this disease: AEP may be fatal if not recognized, but has excellent outcomes in most cases that are promptly diagnosed and treated. Therefore, early BAL showing an increased percentage in the total number of eosinophils (>25%) is of paramount importance in the early diagnosis of this disorder. In contrast to patients with ICEP, peripheral blood eosinophilia is usually not a prominent feature. Moreover, a history of asthma or atopy is unusual, and relapses of the idiopathic form of this disease are rare.^{68,69}

A temporal relation has been reported between the development of AEP and several inciting factors such as heavy dust exposure,⁴³ drugs,^{46,70} and several occupational exposures.^{68,71} However, cigarette smoke is the most frequently implicated trigger in susceptible individuals.^{68,69,72}

Patients with AEP typically present with the abrupt onset (≤ 7 days) of cough, dyspnea, fatigue, malaise, myalgias, fever, chest discomfort, and ultimately hypoxemic respiratory failure, hence the difficulty distinguishing AEP from ALI/ARDS or severe community-acquired pneumonia. On auscultation, crackles are frequently audible although clear lungs have been reported.^{1,68,71} Radiographically, the findings are indistinguishable from those of cardiogenic pulmonary edema or ARDS and include bilateral infiltrates (which may be patchy or asymmetric) and in some cases pleural effusions. In the absence of features to suggest cardiovascular dysfunction or other causes of ALI/ARDS, AEP should be suspected.⁷³

Significant eosinophilia in BAL fluid is essential for the diagnosis. In the absence of alternative explanations, BAL eosinophilia can help provide a presumptive diagnosis on which to base treatment.⁶⁹ Biopsy is usually not necessary, but when obtained, reveals eosinophilic pneumonia with or without a component of acute or organizing diffuse alveolar damage.^{1,74}

High-dose, intravenous corticosteroids (1 g/d in divided doses) typically produce rapid and dramatic improvement in clinical symptoms and radiographic abnormalities. Once disease activity is controlled, the corticosteroids may be transitioned to oral therapy. Corticosteroid taper may be performed over approximately a 3-month period, and resolution without recurrence after treatment is characteristic for this disorder.¹

Primary Disorders, Systemic

CSS

CSS, first described by J. Churg and L. Strauss in 1951,⁷⁵ is a distinct clinicopathologic entity characterized by necrotizing vasculitis affecting small to medium-sized vessels, granulomatous inflammation, and eosinophilic tissue infiltration associated with asthma and peripheral eosinophilia.^{76,77} CSS is one of the ANCA-associated small-vessel vasculitides, a category that also includes granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis.

Although the pathogenesis of CSS is unknown, several environmental, drugs, and putative triggering factors have been identified.^{78,79} Familial clustering of CSS suggests that genetic factors may confer susceptibility to this disease.^{80,81} CSS is rare, with an estimated annual incidence of 2.7 cases per million of total population.⁸² The disease occurs almost exclusively in asthmatics, with an estimated incidence in this subpopulation of 35 to 67 cases per million person-years.^{83,84} The incidence of CSS increases with age until the sixth to seventh decades of life and is more common in men than women.

Given the overlapping signs and symptoms common to both the other ANCA-associated vasculitides and the other eosinophilic lung disorders, careful exclusion

of alternative causes through multidisciplinary collaboration is of the utmost importance for a correct diagnosis. Although multiple classification schemes have been proposed, none of the diagnostic schemes identifies all patients with CSS.⁸⁵ The diagnosis is usually made or excluded when a preponderance of data derived from the clinical, radiographic, laboratory, and histopathologic findings support or refute a diagnosis of CSS.

CSS has classically been characterized as evolving through 3 distinct phases with different clinical, histopathologic, and radiographic manifestations; and although a useful paradigm, the phases are not necessarily progressive and may overlap. The first stage described is a prodromal allergic/atopic phase and consists of atopic disease, rhinitis, and asthma. Asthma is near universal in patients with CSS, and although the asthma may vary in severity from patient to patient, it is more commonly severe and progressive. Similarly, sinus involvement is present in most patients, but unlike granulomatosis with polyangiitis, lacks destructive features and is more similar to the eosinophilic/allergic rhinosinusitis that is seen in the other eosinophilic lung disorders.^{1,79,85} The second phase is described as the eosinophilic phase, which consists of peripheral blood eosinophilia or end-organ eosinophilic infiltration, particularly of the lung, heart, and gastrointestinal tract. Migratory infiltrates consistent with eosinophilic pneumonia may be noted on imaging studies. On the other hand, cardiac and gastroenterologic involvement may present with life-threatening complications.^{79,85–87} The third phase is the vasculitic phase and presents with manifestations commonly seen in the other ANCA-associated vasculitides and is often life threatening. At any point throughout the disease process, nonspecific constitutional symptoms may develop, and most patients ultimately complain of fatigue, malaise, anorexia, fever, myalgias, and arthralgias during their disease course.¹

Recent studies evaluating clinical phenotypes in CSS have suggested that ANCA status may distinguish between 2 different clinical phenotypes of CSS.⁸⁸ Patients who are ANCA or myeloperoxidase (MPO)-positive seem to preferentially present with features of small-vessel vasculitis, whereas ANCA-negative patients typically have a clinical presentation dominated by eosinophilic tissue infiltration. The latter population clinically shares more commonality with the HES (see later discussion) and other eosinophilic lung diseases. Whereas the vasculitic phenotype has an increased frequency of neurologic (eg, mononeuritis multiplex), renal (necrotizing glomerulonephritis), and cutaneous (eg, leukocytoclastic vasculitis) manifestations, those with an eosinophilic phenotype typically have more frequent cardiac and pulmonary involvement. Cardiac involvement may be seen in 10% to 50% of patients with CSS and carries an attributable mortality of 33% to 83% of CSS-related deaths.^{79,89,90} Common cardiac manifestations include conduction abnormalities, cardiomyopathy, coronary arteritis, heart failure, and pericardial disease.^{91–95}

Approximately one-half to two-thirds of patients have a positive ANCA, and there is compelling evidence that ANCA are important in the pathogenesis of the vasculitis. Most CSS patients who are ANCA positive show a perinuclear pattern, called p-ANCA, which in turn corresponds most commonly to autoantibodies directed against MPO. In ANCA-positive patients with CSS, ANCA titers are poor markers of therapeutic response.⁷⁹ Furthermore, patient survival and relapse are independent of ANCA status.^{96,97}

As with other eosinophilic lung diseases, the radiological findings are nonspecific and most commonly include bilateral, patchy, ground-glass opacities or airspace consolidations. Associated findings may include airway wall thickening, nodules, or pleural effusions.¹ Serial imaging frequently shows migratory infiltrates.^{1,98–100} In those patients who undergo biopsy, the classic pathologic findings in the lung include

a combination of eosinophilic pneumonia, granulomatous inflammation, and the presence of a small or medium-sized vessel necrotizing vasculitis.^{77,101} However, all, some, or none of the 3 findings may be present.

Clinical management in CSS is based on disease extent, severity, and response to treatment. The recently revised French Vasculitis Study Group 5-factor score system (FFS) may be used to grade disease activity and predict the need for cytotoxic agents when poor prognostic factors are present.¹⁰² Of the 5-FSS, 4 of the elements are associated with a poor prognosis (age ≥ 65 years, renal insufficiency, cardiac involvement, and gastrointestinal manifestations) and the presence of each of these elements is assigned a weight of +1 point, whereas the fifth factor (ear nose and throat involvement) is associated with a better prognosis, and the absence of upper airway manifestations is scored as +1 point. The 5-year mortality for scores of 0, 1, and 2 or more were 9%, 21%, and 40%, respectively.¹⁰²

With regard to treatment, patients with CSS with FFS of 0 may successfully be treated with corticosteroid monotherapy (0.5–1 mg/kg per day of oral prednisone or equivalent) as first-line treatment. Intermittent intravenous cyclophosphamide (CYC) is used in combination with corticosteroids for those patients with an FFS of 1 or more or who present with life-threatening disease manifestations (eg, central nervous system disease or diffuse alveolar hemorrhage). Intravenous CYC is preferable to daily oral CYC in terms of reducing drug-specific toxicity. Unlike the other ANCA-associated vasculitides, a shorter CYC pulse regimen may be less effective in controlling CSS than a longer regimen. A prospective multicenter trial comparing 6 versus 12 CYC pulses (given in conjunction with corticosteroids) in 48 patients with CSS showed that those receiving 6 pulses had significantly more disease relapses than those receiving 12 pulses of therapy (94% vs 41%).¹⁰³ Nevertheless, once disease remission is achieved, corticosteroid therapy is slowly tapered. Similarly, once CYC therapy is complete, patients are transitioned to a less toxic agent of moderate potency such as azathioprine or methotrexate for maintenance of disease remission. The recommended duration of moderate potency immunosuppressive therapy for the maintenance of disease remission remains controversial, but most experts seem to favor between 1 and 4 years, barring evidence of disease relapse.

Rituximab, an anti-CD20 monoclonal antibody, may represent an attractive alternative in CSS ANCA-positive patients intolerant or refractory to CYC, and this agent is currently the subject of a phase II/III clinical trial for the treatment of CSS. A recent randomized, controlled, multicenter trial of rituximab versus CYC for the induction of disease remission in patients with granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis showed that the rituximab-based regimen was not inferior to CYC for induction of remission at 6 months in severe ANCA-associated vasculitis and was more efficacious than the CYC-based regimen for inducing remission of relapsing disease.¹⁰⁴ However, further studies are needed to establish whether or not there is a role for rituximab in CSS.

Other agents that may be considered for refractory disease to conventional therapy include α -interferon,¹⁰⁵ intravenous immune globulin,¹⁰⁶ anti-tumor necrosis factor agents,¹⁰⁷ and anti-IgE therapy,¹⁰⁸ although the quality of evidence informing the use of these agents is limited and based on observational uncontrolled data. Anti-IL-5 monoclonal antibodies are under investigation as a potentially novel therapy for the treatment of CSS in both the United States and Europe.¹⁰⁹

When addressing the total disease management of the patient with CSS, the clinician must also recall that the disease is characterized by severe, steroid-dependent asthma, chronic rhinosinusitis, and oral corticosteroid use, and additional therapies should be directed toward each of these elements. Specifically, most patients require

additional therapy directed toward their severe persistent/steroid-dependent asthma including high-potency inhaled corticosteroids, a long-acting β -agonist, and a rescue inhaler. Although leukotriene antagonists were suspected of potentially facilitating a biologic conversation of severe asthma toward Churg-Strauss vasculitis, more recent studies seem to support the notion that the use of leukotriene antagonists permits reductions in oral corticosteroid doses such that incidentally treated, underlying CSS is unmasked and no causal link between leukotriene antagonists and CSS has been reported.¹¹⁰ The addition of a leukotriene antagonist is often appropriate for patients with CSS whose asthma continues to require oral corticosteroids as per National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program Asthma Guidelines.¹¹¹ Similarly, if patients meet criteria for omalizumab use for management of their severe asthma, are taking no other biologic agents, and there is no other contraindication to their use, then the presence of CSS does not by itself mitigate against their use, and the agent may be used for the management of the severe asthma. Moreover, aggressive therapies directed toward the management of concomitant sinus disease (nasal saline irrigation and topical corticosteroids) and gastroesophageal reflux disease (eg, proton pump inhibitor therapy) may improve asthma control. Up to 10% of the attributable mortality in CSS is caused by asthma/status asthmaticus.

As with ICEP and ABPA, screening for, prevention of, and treatment of steroid-related side effects cannot be overemphasized. Patients should routinely be evaluated for complications of corticosteroid use, including but not limited to osteoporosis/vascular necrosis, diabetes, electrolyte abnormalities, cataract formation, hypertension, and opportunistic infections. Bone mineral-preserving therapies and *Pneumocystis carinii* pneumonia prophylaxis should be strongly considered. Vaccination against pneumococcal disease and influenza is appropriate, as is a regular exercise program, efforts to achieve and maintain optimal body weight, good nutrition, and regular medical follow-up that includes assessments for disease activity, complications of the medications used to manage the disease, opportunistic infections, and the development of comorbid conditions.

HES

HES are a group of rare and heterogeneous disorders characterized by the presence of hypereosinophilia and end-organ damage.¹¹² The diagnostic criteria for HES have historically included: (1) persistent eosinophilia of 1500 cells/mm³ or more for longer than 6 months; (2) the absence of known causes of eosinophilia; and (3) signs and symptoms of end-organ damage.¹¹³ Despite the seemingly straightforward nature of these criteria, the diagnosis of HES is complicated by several issues.¹¹⁴ For example, the first criterion may exclude recognized variants of HES, even those with recognized molecular abnormalities, that present without peripheral blood hypereosinophilia. Second, it is unlikely that a patient with symptomatic HES would remain untreated for 6 months.¹¹⁴ Likewise, the third criterion would exclude patients with evolving HES who do not yet have documented end-organ injury.^{112,114} As a result, the definition of HES was refined in a recent National Institutes of Health workshop summary report to include those disorders in which (1) eosinophils are markedly increased in the peripheral blood (≥ 1500 mm³), (2) this degree of eosinophilia is documented on more than 1 occasion, and (3) a secondary cause cannot be identified.¹¹² The new classification scheme subdivides HES into the following subtypes (see **Fig. 1**): myeloproliferative, lymphocytic, familial, undefined (benign if asymptomatic and without evidence of end-organ involvement, complex if symptomatic or with end-organ damage), overlap (hypereosinophilia in the setting of single organ

involvement), and associated (hypereosinophilia associated with another distinct cause, such as CSS) HES.¹¹² However, the diagnostic classification scheme will likely continue to evolve with increasing knowledge regarding the pathogenesis of disease variants and the identification of specific clinical phenotypes.

The 2 most well-characterized pathogenic HES variants (mHES and lymphocytic HES [IHES]) are associated with dramatic differences in clinical profiles, prognosis, and responses to therapy.¹¹⁵ The mHES variant is a male-predominant disease subdivided into FIP1L1-PDGFR α F/P-positive mHES, F/P-negative mHES, and chronic eosinophilic leukemia.¹¹² In F/P-positive patients, a deletion on chromosome 4q12 results in fusion of the FIP1L1 and PDGFR α genes.¹¹⁶ RT-PCR or FISH testing commonly detects the FIP1L1-PDGFR α F/P. Because the CHIC2 gene is located in this deleted genetic segment, a FISH probe for the CHIC2 deletion is also available. The F/P has constitutive tyrosine kinase activity, and F/P-positive patients are amenable to therapy with the tyrosine kinase inhibitor imatinib mesylate (Gleevec).^{116–119} Although additional cytogenetic abnormalities/constitutively active kinase activities have been identified^{114,120} not all patients with a clinical phenotype of mHES can be explained at the molecular level. In the absence of the F/P protein, a presumptive diagnosis of mHES is based on a patient having 4 or more of the following criteria: (1) an increased serum tryptase level; (2) an increased serum B₁₂ level; (3) splenomegaly; (4) anemia; (5) thrombocytopenia; (6) increased circulating myeloid precursors; (7) bone marrow hypercellularity with reticulin or collagen fibrosis; or (8) increased numbers of atypical (CD25+) mast cells.^{119,121}

The IHES is characterized by the expansion of CD3-CD4+ T cells that elaborate IL-3 and IL-5, which in turn drive the polyclonal expansion and survival of eosinophils.¹²² In some cases, the aberrant T-cell population is clonal.^{1,123} In these cases, malignant transformation into T-cell lymphoma may occur. However, other cases of IHES do not have an identifiable clonal T-cell population. Clinically, patients with IHES present with cutaneous atopic disease such as urticaria or angioedema, increased IgE levels, and increased serum thymus and activation-regulated chemokine (a marker of T-cell eosinophil hematopoietin expression). In contrast to those with mHES, IHES affects men and women equally, rarely results in cardiac involvement, and is typically more steroid responsive.¹²⁴

Virtually any organ system may be involved in HES. Of 188 patients evaluated in a multicenter, retrospective study,¹¹⁵ the most common presenting manifestations of HES were dermatologic (37%), pulmonary (25%), and gastrointestinal (14%) in nature. Six percent of patients in this series presented with clinically asymptomatic eosinophilia. Less than 5% of patients had cardiac manifestations at the time of diagnosis; however, as with CSS, cardiac involvement in patients with HES (especially mHES) represents a major cause of morbidity and mortality. Pulmonary manifestations of HES include chronic eosinophilia pneumonia, AEP, and ARDS.¹²⁵

Systemic corticosteroids are the first-line therapy for most HES subtypes. Imatinib is indicated for mHES F/P-positive patients, and may result in dramatic improvement, but is not useful in IHES. Second-line modalities include hydroxyurea and interferon- α . One notable concern regarding interferon- α is that it may inhibit clonal CD3-CD4+ T-cell apoptosis, potentially promoting T-cell survival, and therefore it is not used as monotherapy for IHES.¹²⁶ Use of monoclonal anti-IL-5 antibody, mepolizumab, and anti-CD52 antibody, alemtuzumab,¹²⁷ are under investigation for potential use in refractory disease. A recently completed trial of mepolizumab found that patients who received the agent had clinically significant reductions in corticosteroid dosage, and in some cases, corticosteroid discontinuation.¹²⁸ The JAK (janus kinase) signaling pathway has been shown to promote eosinophil activation and survival in human eosinophils and may represent a novel target for future HES therapies.^{129–131}

SUMMARY

Eosinophilic lung diseases encompass a heterogeneous group of disorders unified by the presence of peripheral and/or tissue eosinophilia combined with pulmonary impairment and/or radiographic abnormalities. Because their course and prognosis are highly variable, an accurate diagnosis is essential to optimizing outcomes. Therefore, a thorough clinical evaluation using a multidisciplinary care model is recommended to achieve accurate diagnosis and optimize patient outcomes. Although much progress has been made over the last decade, resulting in more accurate diagnosis and decreased morbidity and mortality for these disorders, much remains to be done.

REFERENCES

1. Li H, Groshong SD, Lynch D, et al. Eosinophilic lung disease. *Clin Pulm Med* 2010;17(2):66–74.
2. Chang HW, Leong KH, Koh DR, et al. Clonal origin of eosinophils in the hyper-eosinophilic syndrome detected by PCR analysis of DNA polymorphisms of the X linked human androgen receptor gene. *Int J Hematol* 1996;64:S43.
3. Chang HW, Leong KH, Koh DR, et al. Clonality of isolated eosinophils in the hypereosinophilic syndrome. *Blood* 1999;93:1651–7.
4. Kagohashi K, Ohara G, Kurishima K, et al. Chronic eosinophilic pneumonia with subpleural curvilinear shadow. *Acta Medica (Hradec Kralove)* 2011;54(1):45–8.
5. Johkoh T, Muller NL, Akira M, et al. Eosinophilic lung diseases: diagnostic accuracy of thin-section CT in 111 patients. *Radiology* 2000;216(3):773–80.
6. Marmursztejn J, Vignaux O, Cohen P, et al. Impact of cardiac magnetic resonance imaging for assessment of Churg-Strauss syndrome: a cross-sectional study in 20 patients. *Clin Exp Rheumatol* 2009;27(1 Suppl 52):S70–6.
7. Bronchoalveolar lavage constituents in healthy individuals, idiopathic pulmonary fibrosis, and selected comparison groups. The BAL Cooperative Group Steering Committee. *Am Rev Respir Dis* 1990;141(5 Pt 2):S169–202.
8. Kwong YL, Chan LC. Involvement of eosinophils in acute myeloid leukemia with monosomy 7 demonstrated by fluorescence in situ hybridization. *Br J Haematol* 1994;88:389–91.
9. Luppi M, Marasca R, Morselli M, et al. Clonal nature of hypereosinophilic syndrome. *Blood* 1994;84:349–50.
10. Giembycz MA, Lindsay MA. Pharmacology of the eosinophil. *Pharmacol Rev* 1999;51(2):213–340.
11. Kariyawasam HH, Robinson DS. The eosinophil: the cell and its weapons, the cytokines, its locations. *Semin Respir Crit Care Med* 2006;27(2):117–27.
12. Lams BE, Sousa AR, Rees PJ, et al. Immunopathology of the small-airway submucosa in smokers with and without chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158(5 Pt 1):1518–23.
13. Dippolito R, Foresi A, Chetta A, et al. Eosinophils in induced sputum from asymptomatic smokers with normal lung function. *Respir Med* 2001;95(12):969–74.
14. Komadina KH, Houk RW, Vicks SL, et al. Goodpasture's syndrome associated with pulmonary eosinophilic vasculitis. *J Rheumatol* 1988;15(8):1298–301.
15. Travis WD. Pathology of pulmonary vasculitis. *Semin Respir Crit Care Med* 2004;25(5):475–82.
16. Agarwal R. Allergic bronchopulmonary aspergillosis. *Chest* 2009;135(3):805–26.

17. Gibson PG, Wark PA, Simpson JL, et al. Induced sputum IL-8 gene expression, neutrophil influx and MMP-9 in allergic bronchopulmonary aspergillosis. *Eur Respir J* 2003;21(4):582–8.
18. Chauhan B, Santiago L, Hutcheson PS, et al. Evidence for the involvement of two different MHC class II regions in susceptibility or protection in allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol* 2000;106(4):723–9.
19. Eaton TE, Weiner Miller P, Garrett JE, et al. Cystic fibrosis transmembrane conductance regulator gene mutations: do they play a role in the aetiology of allergic bronchopulmonary aspergillosis? *Clin Exp Allergy* 2002;32(5):756–61.
20. Tomee JF, Kauffman HF. Putative virulence factors of *Aspergillus fumigatus*. *Clin Exp Allergy* 2000;30(4):476–84.
21. Mitchell TA, Hamilos DL, Lynch DA, et al. Distribution and severity of bronchiectasis in allergic bronchopulmonary aspergillosis (ABPA). *J Asthma* 2000;37(1):65–72.
22. Ward S, Heyneman L, Lee MJ, et al. Accuracy of CT in the diagnosis of allergic bronchopulmonary aspergillosis in asthmatic patients. *AJR Am J Roentgenol* 1999;173(4):937–42.
23. Agarwal R, Gupta D, Aggarwal AN, et al. Clinical significance of hyperattenuating mucoid impaction in allergic bronchopulmonary aspergillosis: an analysis of 155 patients. *Chest* 2007;132(4):1183–90.
24. Rosenberg M, Patterson R, Mintzer R, et al. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann Intern Med* 1977;86:405–14.
25. Patterson R, Greenberger PA, Halwig JM, et al. Allergic bronchopulmonary aspergillosis. Natural history and classification of early disease by serologic and roentgenographic studies. *Arch Intern Med* 1986;146(5):916–8.
26. Agarwal R, Gupta D, Aggarwal AN, et al. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in north India. *Chest* 2006;130(2):442–8.
27. Imbeault B, Cormier Y. Usefulness of inhaled high-dose corticosteroids in allergic bronchopulmonary aspergillosis. *Chest* 1993;103(5):1614–7.
28. Balter MS, Rebuck AS. Treatment of allergic bronchopulmonary aspergillosis with inhaled corticosteroids. *Respir Med* 1992;86(5):441–2.
29. Wark PA, Hensley MJ, Saltos N, et al. Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial. *J Allergy Clin Immunol* 2003;111(5):952–7.
30. Stevens DA, Schwartz HJ, Lee JY, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. *N Engl J Med* 2000;342(11):756–62.
31. Skov M, Hoiby N, Koch C. Itraconazole treatment of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. *Allergy* 2002;57(8):723–8.
32. Kanu A, Patel K. Treatment of allergic bronchopulmonary aspergillosis (ABPA) in CF with anti-IgE antibody (omalizumab). *Pediatr Pulmonol* 2008;43(12):1249–51.
33. Wark PA, Gibson PG, Wilson AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. *Cochrane Database Syst Rev* 2004;3:CD001108.
34. van der Ent CK, Hoekstra H, Rijkers GT. Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. *Thorax* 2007;62(3):276–7.
35. Zirbes JM, Milla CE. Steroid-sparing effect of omalizumab for allergic bronchopulmonary aspergillosis and cystic fibrosis. *Pediatr Pulmonol* 2008;43(6):607–10.

36. Acute eosinophilic pneumonia. *N Engl J Med* 1990;322(9):634–6.
37. Rosenberg HF, Dyer KD, Domachowske JB. Respiratory viruses and eosinophils: exploring the connections. *Antiviral Res* 2009;83(1):1–9.
38. Shenoy VP, Vishwanath S, Indira B, et al. Hepato-pulmonary amebiasis: a case report. *Braz J Infect Dis* 2010;14(4):372–3.
39. Ong RK, Doyle RL. Tropical pulmonary eosinophilia. *Chest* 1998;113(6):1673–9.
40. Forrester JM, Steele AW, Waldron JA, et al. Crack lung: an acute pulmonary syndrome with a spectrum of clinical and histopathologic findings. *Am Rev Respir Dis* 1990;142(2):462–7.
41. Kobashi Y, Nakajima M, Niki Y, et al. [A case of acute eosinophilic pneumonia due to Sho-saiko-to]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1997;35(12):1372–7 [in Japanese].
42. Cottin V, Frogner R, Monnot H, et al. Chronic eosinophilic pneumonia after radiation therapy for breast cancer. *Eur Respir J* 2004;23(1):9–13.
43. Rom WN, Weiden M, Garcia R, et al. Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. *Am J Respir Crit Care Med* 2002;166(6):797–800.
44. Solomon J, Schwarz M. Drug-, toxin-, and radiation therapy-induced eosinophilic pneumonia. *Semin Respir Crit Care Med* 2006;27(2):192–7.
45. Frankel SK. Drug-induced lung disease. In: Hanley M, Welsh C, editors. *Current diagnosis and treatment in pulmonary medicine*. New York: Lange Medical Books/McGraw-Hill; 2003. p. 337–47.
46. Salerno SM, Strong JS, Roth BJ, et al. Eosinophilic pneumonia and respiratory failure associated with a trazodone overdose. *Am J Respir Crit Care Med* 1995;152(6 Pt 1):2170–2.
47. Fleisch MC, Blauer F, Gubler JG, et al. Eosinophilic pneumonia and respiratory failure associated with venlafaxine treatment. *Eur Respir J* 2000;15(1):205–8.
48. Hayes D Jr, Anstead MI, Kuhn RJ. Eosinophilic pneumonia induced by daptomycin. *J Infect* 2007;54(4):e211–3.
49. Honore I, Nunes H, Groussard O, et al. Acute respiratory failure after interferon-gamma therapy of end-stage pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;167(7):953–7.
50. Paralkar VR, Goradia A, Luger SM, et al. Severe eosinophilia as a manifestation of acute graft-versus-host disease. *Oncology* 2008;75(3–4):134–6.
51. Pandit R, Scholnik A, Wulfekuhler L, et al. Non-small-cell lung cancer associated with excessive eosinophilia and secretion of interleukin-5 as a paraneoplastic syndrome. *Am J Hematol* 2007;82(3):234–7.
52. Wilson F, Tefferi A. Acute lymphocytic leukemia with eosinophilia: two case reports and a literature review. *Leuk Lymphoma* 2005;46(7):1045–50.
53. Slungaard A, Ascensao J, Zanjani E, et al. Pulmonary carcinoma with eosinophilia. Demonstration of a tumor-derived eosinophilopoietic factor. *N Engl J Med* 1983;309(13):778–81.
54. Enblad G, Sundstrom C, Glimelius B. Infiltration of eosinophils in Hodgkin's disease involved lymph nodes predicts prognosis. *Hematol Oncol* 1993;11(4):187–93.
55. Utsunomiya A, Ishida T, Inagaki A, et al. Clinical significance of a blood eosinophilia in adult T-cell leukemia/lymphoma: a blood eosinophilia is a significant unfavorable prognostic factor. *Leuk Res* 2007;31(7):915–20.
56. Coultas DB, Zumwalt RE, Black WC, et al. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med* 1994;150(4):967–72.
57. Thomeer MJ, Costabe U, Rizzato G, et al. Comparison of registries of interstitial lung diseases in three European countries. *Eur Respir J Suppl* 2001;32:114s–8s.

58. Tateno H, Nakamura H, Minematsu N, et al. Eotaxin and monocyte chemoattractant protein-1 in chronic eosinophilic pneumonia. *Eur Respir J* 2001;17(5):962–8.
59. Alam M, Burki NK. Chronic eosinophilic pneumonia: a review. *South Med J* 2007;100(1):49–53.
60. Marchand E, Reynaud-Gaubert M, Lauque D, et al. Idiopathic chronic eosinophilic pneumonia. A clinical and follow-up study of 62 cases. The Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). *Medicine (Baltimore)* 1998;77:299–312.
61. Gaensler EA, Carrington CB. Peripheral opacities in chronic eosinophilic pneumonia: the photographic negative of pulmonary edema. *AJR Am J Roentgenol* 1977;128:1–13.
62. Jederlinic PJ, Sicilian L, Gaensler EA. Chronic eosinophilic pneumonia. A report of 19 cases and a review of the literature. *Medicine (Baltimore)* 1988;67(3):154–62.
63. Yoshida K, Shijubo N, Koba H, et al. Chronic eosinophilic pneumonia progressing to lung fibrosis. *Eur Respir J* 1994;7(8):1541–4.
64. Marchand E, Etienne-Mastroianni B, Chanez P, et al. Idiopathic chronic eosinophilic pneumonia and asthma: how do they influence each other? *Eur Respir J* 2003;22(1):8–13.
65. Durieu J, Wallaert B, Tonnel AB. Long-term follow-up of pulmonary function in chronic eosinophilic pneumonia. Groupe d'Etude en Pathologie Interstitielle de la Societe de Pathologie Thoracique du Nord. *Eur Respir J* 1997;10:286–91.
66. Naughton M, Fahy J, FitzGerald MX. Chronic eosinophilic pneumonia. A long-term follow-up of 12 patients. *Chest* 1993;103(1):162–5.
67. Minakuchi M, Niimi A, Matsumoto H, et al. Chronic eosinophilic pneumonia: treatment with inhaled corticosteroids. *Respiration* 2003;70(4):362–6.
68. Philit F, Etienne-Mastroianni B, Parrot A, et al. Idiopathic acute eosinophilic pneumonia: a study of 22 patients. *Am J Respir Crit Care Med* 2002;166(9):1235–9.
69. Allen J. Acute eosinophilic pneumonia. *Semin Respir Crit Care Med* 2006;27(2):142–7.
70. Liegeon MN, De Blay F, Jaeger A, et al. A cause of respiratory distress: eosinophilic pneumopathy due to minocycline. *Rev Mal Respir* 1996;13(5):517–9 [in French].
71. Pope-Harman AL, Davis WB, Christoforidis AJ, et al. Acute eosinophilic pneumonia: a summary of fifteen cases and review of the literature. *Medicine (Baltimore)* 1996;75:334–42.
72. Shintani H, Fujimura M, Ishiura Y, et al. A case of cigarette smoking-induced acute eosinophilic pneumonia showing tolerance. *Chest* 2000;117:277–9.
73. King MA, Pope-Harman AL, Allen JN, et al. Acute eosinophilic pneumonia: radiologic and clinical features. *Radiology* 1997;203:715–9.
74. Tazelaar HD, Linz LJ, Colby TV, et al. Acute eosinophilic pneumonia: histopathologic findings in nine patients. *Am J Respir Crit Care Med* 1997;155:296–302.
75. Churg J, Strauss L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. *Am J Pathol* 1951;27(2):277–301.
76. Lanham JG, Elkon KB, Pusey CD, et al. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine (Baltimore)* 1984;63:65–81.
77. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994;37(2):187–92.

78. Lane SE, Watts RA, Bentham G, et al. Are environmental factors important in primary systemic vasculitis? A case-control study. *Arthritis Rheum* 2003;48(3): 814–23.
79. Guillevin L, Cohen P, Gayraud M, et al. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999;78(1):26–37.
80. Tsurikisawa N, Morita S, Tsuburai T, et al. Familial Churg-Strauss syndrome in two sisters. *Chest* 2007;131(2):592–4.
81. Manganelli P, Giacosa R, Fietta P, et al. Familial vasculitides: Churg-Strauss syndrome and Wegener's granulomatosis in 2 first-degree relatives. *J Rheumatol* 2003;30(3):618–21.
82. Watts RA, Lane SE, Bentham G, et al. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum* 2000;43(2):414–9.
83. Harrold LR, Andrade SE, Go AS, et al. Incidence of Churg-Strauss syndrome in asthma drug users: a population-based perspective. *J Rheumatol* 2005;32(6): 1076–80.
84. Loughlin JE, Cole JA, Rothman KJ, et al. Prevalence of serious eosinophilia and incidence of Churg-Strauss syndrome in a cohort of asthma patients. *Ann Allergy Asthma Immunol* 2002;88(3):319–25.
85. Keogh KA, Specks U. Churg-Strauss syndrome: clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. *Am J Med* 2003;115(4):284–90.
86. Conron M, Beynon HL. Churg-Strauss syndrome. *Thorax* 2000;55:870–7.
87. Pagnoux C, Mahr A, Cohen P, et al. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. *Medicine (Baltimore)* 2005;84:115–28.
88. Kallenberg CG. Churg-Strauss syndrome: just one disease entity? *Arthritis Rheum* 2005;52(9):2589–93.
89. Solans R, Bosch JA, Perez-Bocanegra C, et al. Churg-Strauss syndrome: outcome and long-term follow-up of 32 patients. *Rheumatology (Oxford)* 2001; 40(7):763–71.
90. Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)* 1996;75(1):17–28.
91. Hasley PB, Follansbee WP, Coulehan JL. Cardiac manifestations of Churg-Strauss syndrome: report of a case and review of the literature. *Am Heart J* 1990;120:996–9.
92. Morgan JM, Raposo L, Gibson DG. Cardiac involvement in Churg-Strauss syndrome shown by echocardiography. *Br Heart J* 1989;62:462–6.
93. Ramakrishna G, Connolly HM, Tazelaar HD, et al. Churg-Strauss syndrome complicated by eosinophilic endomyocarditis. *Mayo Clin Proc* 2000;75:631–5.
94. Stollberger C, Finsterer J, Winkler WB. Eosinophilic pericardial effusion in Churg-Strauss syndrome. *Respir Med* 2005;99:377–9.
95. Val-Bernal JF, Mayorga M, Garcia-Alberdi E, et al. Churg-Strauss syndrome and sudden cardiac death. *Cardiovasc Pathol* 2003;12:94–7.
96. Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum* 2005;52(9):2926–35.
97. Sable-Fourtassou R, Cohen P, Mahr A, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 2005;143(9):632–8.

98. Choi YH, Im JG, Han BK, et al. Thoracic manifestation of Churg-Strauss syndrome: radiologic and clinical findings. *Chest* 2000;117:117–24.
99. Silva CI, Muller NL, Fujimoto K, et al. Churg-Strauss syndrome: high resolution CT and pathologic findings. *J Thorac Imaging* 2005;20:74–80.
100. Worthy SA, Muller NL, Hansell DM, et al. Churg-Strauss syndrome: the spectrum of pulmonary CT findings in 17 patients. *AJR Am J Roentgenol* 1998;170:297–300.
101. Katzenstein AL. Diagnostic features and differential diagnosis of Churg-Strauss syndrome in the lung. A review. *Am J Clin Pathol* 2000;114(5):767–72.
102. Guillevin L, Pagnoux C, Seror R, et al. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* 2011;90(1):19–27.
103. Cohen P, Pagnoux C, Mahr A, et al. Churg-Strauss syndrome with poor-prognosis factors: a prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. *Arthritis Rheum* 2007;57(4):686–93.
104. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010;363(3):221–32.
105. Metzler C, Csernok E, Gross WL, et al. Interferon-alpha for maintenance of remission in Churg-Strauss syndrome: a long-term observational study. *Clin Exp Rheumatol* 2010;28(1 Suppl 57):24–30.
106. Tsurikisawa N, Taniguchi M, Saito H, et al. Treatment of Churg-Strauss syndrome with high-dose intravenous immunoglobulin. *Ann Allergy Asthma Immunol* 2004;92(1):80–7.
107. Arbach O, Gross WL, Gause A. Treatment of refractory Churg-Strauss-Syndrome (CSS) by TNF-alpha blockade. *Immunobiology* 2002;206(5):496–501.
108. Pabst S, Tiyerili V, Grohe C. Apparent response to anti-IgE therapy in two patients with refractory "forme fruste" of Churg-Strauss syndrome. *Thorax* 2008;63(8):747–8.
109. Kim S, Marigowda G, Oren E, et al. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. *J Allergy Clin Immunol* 2010;125(6):1336–43.
110. Bibby S, Healy B, Steele R, et al. Association between leukotriene receptor antagonist therapy and Churg-Strauss syndrome: an analysis of the FDA AERS database. *Thorax* 2010;65(2):132–8.
111. Weller PF, Plaut M, Taggart V, et al. The relationship of asthma therapy and Churg-Strauss syndrome: NIH workshop summary report. *J Allergy Clin Immunol* 2001;108(2):175–83.
112. Klion AD, Bochner BS, Gleich GJ, et al. Approaches to the treatment of hyper-eosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol* 2006;117(6):1292–302.
113. Chusid MJ, Dale DC, West BC, et al. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine (Baltimore)* 1975;54:1–27.
114. Klion A. Hypereosinophilic syndrome: current approach to diagnosis and treatment. *Annu Rev Med* 2009;60:293–306.
115. Ogbogu PU, Bochner BS, Butterfield JH, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol* 2009;124(6):1319–25. e1313.
116. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by the fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003;348:1201–14.

117. Klion AD, Noel P, Akin C, et al. Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. *Blood* 2003;101(12):4660–6.
118. Vandenberghe P, Wlodarska I, Michaux L, et al. Clinical and molecular features of FIP1L1-PDFGRA(+) chronic eosinophilic leukemias. *Leukemia* 2004;18:734–42.
119. Klion AD, Robyn J, Akin C, et al. Molecular remission and reversal of myelofibrosis in response to imatinib mesylate treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome. *Blood* 2004;103(2):473–8.
120. Curtis CE, Grand FH, Musto P, et al. Two novel imatinib-responsive PDGFRA fusion genes in chronic eosinophilic leukaemia. *Br J Haematol* 2007;138(1):77–81.
121. Sheikh J, Weller PF. Clinical overview of hypereosinophilic syndromes. *Immunol Allergy Clin North Am* 2007;27(3):333–55.
122. Cogan E, Schandene L, Crusiaux A, et al. Brief report: clonal proliferation of type 2 helper T cells in a man with the hypereosinophilic syndrome. *N Engl J Med* 1994;330:535–8.
123. Roufosse F, Cogan E, Goldman M. Recent advances in pathogenesis and management of hypereosinophilic syndromes. *Allergy* 2004;59:673–89.
124. Ogbogu PU, Rosing DR, Horne MK 3rd. Cardiovascular manifestations of hypereosinophilic syndromes. *Immunol Allergy Clin North Am* 2007;27(3):457–75.
125. Winn RE, Kollef MH, Meyer JI. Pulmonary involvement in the hypereosinophilic syndrome. *Chest* 1994;105(3):656–60.
126. Schandene L, Roufosse F, de Lavareille A, et al. Interferon alpha prevents spontaneous apoptosis of clonal Th2 cells associated with chronic hypereosinophilia. *Blood* 2000;96(13):4285–92.
127. Verstovsek S, Tefferi A, Kantarjian H, et al. Alemtuzumab therapy for hypereosinophilic syndrome and chronic eosinophilic leukemia. *Clin Cancer Res* 2009;15(1):368–73.
128. Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008;358(12):1215–28.
129. Ochiai K, Tanabe E, Ishihara C, et al. Role of JAK2 signal transductional pathway in activation and survival of human peripheral eosinophils by interferon-gamma (IFN-gamma). *Clin Exp Immunol* 1999;118(3):340–3.
130. Gotlib J. World health organization-defined eosinophilic disorders: 2011 update on diagnosis, risk stratification, and management. *Am J Hematol* 2011;86(8):677–88.
131. Jones AV, Kreil S, Zoi K, et al. Widespread occurrence of the JAK2 V617F mutation in chronic myeloproliferative disorders. *Blood* 2005;106(6):2162–8.