# Pulmonary disorders, including vocal cord dysfunction

**Paul A. Greenberger, MD, and Leslie C. Grammer, MD** *Chicago, Ill*

**The lung is a very complex immunologic organ and responds in a variety of ways to inhaled antigens, organic or inorganic materials, infectious or saprophytic agents, fumes, and irritants. There might be airways obstruction, restriction, neither, or both accompanied by inflammatory destruction of the pulmonary interstitium, alveoli, or bronchioles. This review focuses on diseases organized by their predominant immunologic responses, either innate or acquired. Pulmonary innate immune conditions include transfusion-related acute lung injury, World Trade Center cough, and acute respiratory distress syndrome. Adaptive immunity responses involve the systemic and mucosal immune systems, activated lymphocytes, cytokines, and antibodies that produce $CD4^+$ $T_H1$ phenotypes, such as for tuberculosis or acute forms of hypersensitivity pneumonitis, and $CD4^+$ $T_H2$ phenotypes, such as for asthma, Churg-Strauss syndrome, and allergic bronchopulmonary aspergillosis.**
**(J Allergy Clin Immunol 2010;125:S248-54.)**

***Key words:*** *Innate, acquired, hypersensitivity, eosinophilia, lymphocyte, tuberculosis, aspergillosis, bronchopulmonary, bronchiectasis, immunologic*

*Abbreviations used*

| | |
|---|---|
| ABPA: | Allergic bronchopulmonary aspergillosis |
| ANCA: | Antineutrophil cytoplasmic antibody |
| ARDS: | Acute respiratory distress syndrome |
| BAL: | Bronchoalveolar lavage |
| COPD: | Chronic obstructive pulmonary disease |
| CSS: | Churg-Strauss syndrome |
| CT: | Computed tomography |
| FVC: | Forced vital capacity |
| HDAC: | Histone deacetylase |
| LT: | Leukotriene |
| PMN: | Polymorphonuclear leukocyte |
| RADS: | Reactive airways dysfunction syndrome |
| TLR: | Toll-like receptor |
| TRALI: | Transfusion-related acute lung injury |
| VCD: | Vocal cord dysfunction |

Pulmonary disorders can be organized according to whether the primary immune responses are characterized by innate or adaptive immune responses. The innate responses use complement activation or activation of polymorphonuclear leukocytes (PMNs) and occur without a period for sensitization. The adaptive responses include $T_H1$ or $T_H2$ lymphocytes, eosinophils, antibody mediated, and granuloma formation.[1] This chapter will review the various pulmonary disorders with a predominant immunologic pattern and also discuss vocal cord dysfunction (VCD), which can coexist with asthma or occur independently and results in cough, shortness of breath, and dyspnea.

## INNATE IMMUNE RESPONSES

### Transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) is a nonhemolytic transfusion reaction that occurs within 10 minutes to as long as 6 hours after infusion of a blood product and causes very severe noncardiogenic pulmonary edema, cyanosis, arterial hypoxemia, and respiratory failure.[2,3] The donor plasma typically contains antibodies to human neutrophil antigens or HLA class I or II antigens.[2,3] Neutrophil alloantibodies are found in 10% to 20% of female donors and 1% to 4% of male donors, yet the incidence of TRALI is about 1:5000 transfusions.[3] Alloantibodies are generated during pregnancy, but of course that would not explain the presence of such antibodies in men. Some recipients have antineutrophil antibodies. The immediate reaction, which might resemble anaphylaxis, involves sequestration of PMNs in the pulmonary vasculature, complement activation, and generation of TGF-β, IL-8, and IL-13.[2] Immune complexes activate PMNs and cause disruption of the endothelium barrier to plasma. TRALI is extremely rare after intravenous immunoglobulin infusions but occurs with infusions of platelets (suspended in plasma), whole blood, cryoprecipitates, and fresh frozen plasma.

The immediate management includes stopping the infusion, oxygen, mechanical ventilation if indicated, and treatment of hypotension with vasopressors. Donors should be deferred from future donations. Indeed, some transfusion experts have recommended that the donor pool should not include women who have been pregnant and that donor plasma be tested for alloantibodies.[2,3] Neither of these suggestions are standard practice.

### Acute respiratory distress syndrome and acute lung injury

Acute respiratory distress syndrome (ARDS) and acute lung injury represent diffuse pulmonary disease that can be fatal.[4] ARDS is a more severe form of acute lung injury. Causes include sepsis, pneumonia, trauma, or aspiration pneumonia.[4] Patients experience severe dyspnea, tachypnea, and hypoxemia. The chest roentgenogram and computed tomographic (CT) examination demonstrate bilateral infiltrates, alveolar consolidation, and "white out" of the lung. The alveoli collapse as they become filled with protein and fibrin-rich exudates (hyaline membranes), which inactivate surfactant.[4,5] Neutrophils release oxidant proteases, which damage the capillary endothelium. Bronchoalveolar lavage (BAL) reveals the presence of PMNs, procoagulant activity, IL-8 (chemotactic for PMNs), IL-2, IL-6, and TGF-β. There is reduced apoptosis of

From the Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine.

Supported by the Ernest S. Bazley Grant to Northwestern Memorial Hospital and Northwestern University

Disclosure of potential conflict of interest: P. A. Greenberger has served as an expert witness on the topics of immunotheraphy, remote practice, ABPA misdiagnosis, and anaphylaxis. L. Grammer has received research support from S&C Electric Company.

Received for publication May 18, 2009; revised August 28, 2009; accepted for publication September 2, 2009.

Address for reprints: Paul A. Greenberger, MD, Division of Allergy-Immunology, 676 N St Clair Street, #14018, Chicago, IL 60611. E-mail: p-greenberger@northwestern.edu.

0091-6749/$36.00



doi:10.1016/j.jaci.2009.09.020

PMNs, which is attributable to increased concentrations of BAL fluid IL-2, IL-8, granulocyte colony-stimulating factor, GM-CSF, and growth-related oncogene α.[6] Alternatively, there is enhanced apoptosis of epithelial cells, resulting in the lack of a sufficient barrier between the alveoli and capillaries. TNF-related apoptosis-induced ligand levels are increased in BAL fluid in patients with ARDS and are recognized as proapoptotic for epithelial cells.[6]

Patients requiring mechanical ventilation benefit from smaller volumes, such as a tidal volume of 6 mL/kg, with positive end-expiratory pressures of 5 to 10 cm $H_2O$. Fluid replacement should be conservative. Corticosteroids and other interventions, such as nitric oxide and surfactants, are not effective.[7]

### Community-acquired pneumonia

Community-acquired pneumonia presents with a productive cough, fever, pleuritic chest pain, and abnormal chest roentgenographic results.[8] On auscultation, there can be crackles and bronchial breath sounds. Most pathogens include viruses, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, and *Legionella pneumophila*.[8] There might be no recovered organisms in some patients. Comorbidities influence survival.[8]

Levels of proinflammatory cytokines, such as TNF-α and IL-6, and the anti-inflammatory cytokine IL-10 are increased in those patients who succumb compared with survivors.[9] Impaired recognition of molecular patterns of bacteria is associated with decreased activation of innate immunity and worse clinical outcomes.[10] Toll-like receptors (TLRs) recognize pathogen-associated molecular patterns, and genetic polymorphisms have been identified in patients who had invasive *S pneumoniae* infections.[10] For example, polymorphisms of TLR4 impair its function in recognition of *S pneumoniae* pneumolysin, whereas polymorphisms of CD14, a coreceptor on monocytes for both TLR2 and TLR4, are associated with invasive *S pneumoniae* infections.[10] Polymorphisms in FCγRIIA increase the susceptibility to invasive disease. Current therapy includes early administration of antibiotics and supportive care. Future diagnosis might identify at-risk subjects proactively, and therapies will be able to strengthen the innate immune system.

## NONINFECTIOUS PULMONARY CONDITIONS

Byssinosis occurs from the inhalation of dusts from flax, cotton, sisal, and hemp. The dusts produce bronchoconstriction, typically on the first day of the workweek, but then tachyphylaxis develops with continued exposure. Byssinosis is not asthma or hypersensitivity pneumonitis.[1] At-risk workers include those who are exposed to endotoxin during the processing of raw cotton. In contrast, workers who spin cotton are not exposed to the high concentrations of endotoxin and are considered at low risk. Long-term exposure can result in symptoms of chronic bronchitis and cough. Modest reductions in $FEV_1$ and forced vital capacity (FVC) have been found, but concurrent smoking appears to be the major contributor as opposed to workplace exposures. Prevention includes methods to reduce the generation of endotoxins from gram-negative bacteria by reducing exposure to waste from cotton.

In contrast to byssinosis, the organic toxic dust syndrome is a toxic alveolitis that produces influenza-type symptoms of sudden-onset headache, chills, nonproductive cough, myalgias, arthralgias, and dyspnea. Crackles can be present on lung auscultation. The onset of symptoms is within 12 hours of inhalation of organic dusts. Although the clinical presentation might mimic that of acute hypersensitivity pneumonitis, there is no requirement for prior exposure or immunologic sensitization (see the later section on hypersensitivity pneumonitis). Various circumstances of exposure have been described, such as from organic mulch, endotoxin-rich vegetables and grass seeds, and contaminated seaweed. Massive inhalation of microbial products can cause an ARDS-like presentation, and this is designated as organic dust toxic syndrome or pulmonary mycotoxicosis.[11]

In patients with silo-unloader's disease, there is inhalation of nonorganic gases, such as NO, $NO_2$, or $N_2O_4$. These nitrogen oxides then generate nitric and nitrous acids that cause noncardiac pulmonary edema and, in some patients, methemoglobinemia. Deaths can occur, whereas survivors might have bronchiolitis obliterans.

Grain-handler's disease occurs in agricultural workers with a chronic cough, symptoms of chronic bronchitis, or wheeze after exposure to grain dusts. Concurrent cigarette smoking appears to be more injurious to the lung and associated with reductions in spirometric values. Measures to reduce exposure to dust are beneficial. Because of less implementation of safety standards, there is a major concern that workers will experience grain-handler's disease and other respiratory disorders in the world's emerging economies.

### Reactive airways dysfunction syndrome

The reactive airways dysfunction syndrome (RADS) describes a single unexpected inhalation of high concentrations of irritant fumes, vapors, fog, or smoke that results in acute cough, dyspnea, and wheezing within 24 hours.[12] An asthma-like syndrome begins that can last for months or years. Bronchial hyperreactivity can be demonstrated by means of methacholine challenge testing, and spirometry reveals normal or decreased $FEV_1$, FVC, and $FEV_1$/FVC ratio. There might be little to no bronchodilator response to albuterol. Bronchial biopsy specimens demonstrate loss of epithelium, subepithelial fibrosis, and infiltrates with lymphocytes but not eosinophils (as would be characteristic of asthma).

RADS might be confused with occupational asthma, where there is a sensitization period of months or years before symptoms begin, and with aggravation of underlying asthma. But RADS refers to the acute irritant-induced asthma.

### World Trade Center cough

The first responders to the 2001 collapse of the World Trade Center in New York City experienced a very troublesome cough within 24 hours of beginning rescue operations.[13,14] The exposures included acrid smoke, fires that burned for 3 months, asbestos, glass fibers, lead, and aromatic compounds. Many responders did not use protective masks. Subsequent evaluations identified methacholine hyperreactivity in 24% and a reduced $FEV_1$/FVC ratio of less than 0.75 in 16% of affected subjects.[13] The high exposures would be consistent with a diagnosis of RADS in some subjects.[14]

### VCD

VCD is a form of "functional" or nonanatomic upper airway obstruction.[15] The inspiratory tracing on a flow-volume loop is truncated (Fig 1) or incompletely performed. Other causes of nonanatomic inspiratory obstruction include vocal cord paralysis,

neuromuscular disorders, and sleep disorders.[15] In contrast, some anatomic abnormalities that cause a truncated inspiratory loop include a large goiter, tracheal stenosis, and an obstructing tumor. Symptoms of VCD include dyspnea, wheeze, tightness in the neck, shortness of breath, inability to breathe deeply or satisfactorily, and coughing. Some patients with VCD have concurrent asthma and chronic rhinosinusitis with postnasal drainage or gastroesophageal reflux or atypical (laryngopharyngeal) reflux. VCD can be intermittent and might not be present when the patient is distracted, sedated, or asleep. VCD can masquerade as or coexist with severe asthma.[16]

Recognition of VCD might begin with the truncated inspiratory loop of the flow-volume tracing, especially when the patient is symptomatic. Alternatively, it can be suspected when the patient's difficulty breathing surpasses the physical findings, such as clear chest on auscultation, wheezes over the neck but not lower airways, whispering instead of talking loudly, and refusal to inspire to total lung capacity or produce an appropriate forced expiratory maneuver. Bronchoscopy might be of value in excluding other causes. Fiberoptic laryngoscopy can help demonstrate the adduction of vocal cords during inspiration. When methacholine challenge tests are performed in patients with VCD, there might or might not be apparent flattening of the inspiratory flow-volume loop or, in fact, quite severe airways obstruction, even stridor or respiratory arrest. The latter can occur in patients with major psychiatric diagnoses and even should be anticipated in considering a methacholine challenge test in such patients with VCD.

Some patients benefit from speech therapy, which can emphasize breathing through the abdomen as opposed to thoracic breathing. Nevertheless, other patients with psychologic or psychiatric conditions might not overcome their VCD. When this is the case, it is important to avoid continued treatment with systemic corticosteroids unless it is demonstrated that there is both persistent asthma and VCD.

## GRANULOMATOUS $T_H1$ INFLAMMATORY CONDITIONS

The granulomatous $T_H1$ conditions comprise sarcoidosis, tuberculosis, berylliosis, and hypersensitivity pneumonitis. CD4 $T_H1$ lymphocytes participate in granuloma formation. Some cytokines include IL-2, IL-12, and IFN-γ. IFN-γ, which is generated by CD4 $T_H1$ and $CD8^+$ lymphocytes, can be measured in patients with tuberculosis, and the US Food and Drug Administration has approved an assay that helps in the diagnosis of tuberculosis.[17] Class I MHC–restricted $CD8^+$ lymphocytes can function as memory cells to *Mycobacterium tuberculosis*.[18] In patients with advanced pulmonary tuberculosis, the BAL fluid reveals increased numbers of $CD4^+$ lymphocytes and increased $CD4^+$/$CD8^+$ ratios. There is evidence for pulmonary sequestration or compartmentalization of the $CD4^+$ lymphocytes because the peripheral blood $CD4^+$ lymphocytes can be decreased relatively and the $CD4^+$/$CD8^+$ ratio is reduced because of increases in the numbers of $CD8^+$ lymphocytes.[19] In patients with HIV/AIDS, the low numbers of $CD4^+$ lymphocytes are associated with greater susceptibility and more severe tuberculosis,[20] including decreased delayed hypersensitivity responses (type IVa1).

Granulomas help limit the replication of mycobacteria; however, lung architecture is destroyed in the process. $CD4^+CD25^+$ regulatory T cell numbers are increased in patients with tuberculosis and are thought to help control or attempt to control the intensity of the $CD4^+$ $T_H1$ granulomatous responses.[21] The expression of the transcription factor forkhead box protein 3 is increased and is indirect evidence of regulatory T-cell suppression of the granulomas.

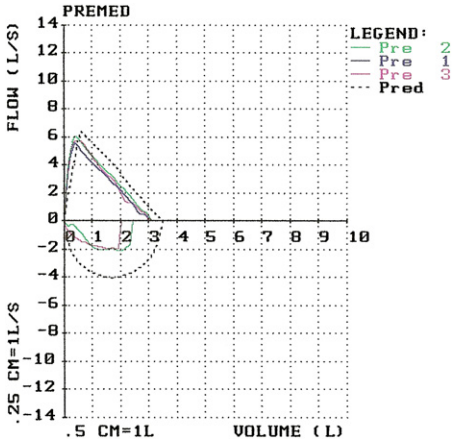


**FIG 1.** Flow-volume loop of a 26-year-old woman with shortness of breath, wheezing, and cough. Note blunting of the inspiratory phase versus predicted value. FVC was 3.19 L (91%), $FEV_1$ was 2.75 L (91%), and $FEV_1$/FVC ratio was 0.86. Notably, forced expiratory flow at 50%/forced inspiratory flow at 50% of FVC was increased at 1.62 (normal value is <1).

Sarcoidosis remains a disease of unknown cause that produces noncaseating, epithelioid granulomas that can affect most organ systems.[22] BAL fluid recoveries demonstrate very high numbers of activated $CD4^+$ lymphocytes, which are sustained by IL-2.[22] $CD4^+$ $T_H1$ lymphocytes participate in formation of the granuloma, in association with IFN-γ, and activated macrophages. IL-18, derived from monocyte/macrophages and airway epithelial cells, upregulates expression of IL-2 and supports IFN-γ production.[23] IL-18 levels are increased in BAL fluid and plasma and have been associated with progression of sarcoidosis.

Although not all patients are treated because up to two thirds have a spontaneous remission, initial pharmacotherapy is with oral corticosteroids. In an attempt to reduce the granulomatous response, TNF-α inhibitors have been administered to patients with sarcoidosis[22]; their role is not established, however. Endobronchial sarcoidosis is a rare cause of cough and wheezing.

## GRANULOMATOUS $T_H2$ INFLAMMATORY CONDITIONS

Churg-Strauss syndrome (CSS) is a systemic, necrotizing, eosinophil-laden granulomatous vasculitis. The presentation can be that of (1) asthma with pulmonary infiltrates, (2) peripheral blood eosinophilia, (3) peripheral neuropathy (mononeuritis multiplex), or (4) palpable purpura. When a patient with asthma experiences palpable purpura on the shins or upper extremities or if foot or wrist drop occurs, CSS should be suspected. A decrease in oral corticosteroids or in high-dose inhaled corticosteroids might be associated with onset of fever and eosinophilic pneumonia, purpura, or wrist drop, any of which should raise the possibility of CSS. Histologic evidence for CSS can be obtained by means of skin biopsy or biopsy of nerves (eg, sural) or pulmonary tissue.

Laboratory findings demonstrate peripheral blood eosinophilia (20% to 60%), $CD4^+$ $T_H2$ lymphocytes, increased total IgE concentrations, and antineutrophil cytoplasmic antibodies (ANCAs). Approximately 60% of patients have the perinuclear pattern of

ANCAs, which on ELISA is positive for antibodies to myeloperoxidase, whereas 10% of patients have positive results for cytoplasmic staining, with antibodies directed against proteinase-3.[1] Although the presence of a perinuclear pattern of ANCAs is helpful in supporting a diagnosis, the ANCA titers do not provide prognostic information for disease management.[24,25] Similarly, eosinophil-derived major basic protein and cationic protein have not been demonstrated to have utility in guiding treatment.[24] Urinary concentrations of leukotriene (LT) $E_4$, the major metabolite of $LTC_4$ and $LTD_4$, and eosinophil-derived neurotoxin and 3-bromotyrosine, a marker for oxidation of eosinophils, are increased in patients with CSS.[26]

The 6-year survival has been reported to be 70%.[24] Long-term survival, up to 26 years, has also been reported.[27] The most effective therapy has been with oral corticosteroids.[24,27] Additional corticosteroid-sparing and immunosuppressive therapies include cyclophosphamide, azathioprine, IFN-α, mepolizumab (anti–IL-5), omalizumab (anti-IgE), and rituximab (anti-CD20 B lymphocytes). There are potential untoward effects from cyclophosphamide (cytopenias, hemorrhagic cystitis, and malignancy potential), azathioprine (cytopenia, nausea, and vomiting), and IFN-α (depression and progressive multifocal leukoencephalopathy). Often patients can be managed long-term with prednisone administered on an alternate-day schedule with or without immunosuppressive therapy, such as with azathioprine. Abrupt discontinuation of prednisone is not advisable because it can result in fever, eosinophilia, and pulmonary infiltrates within a few days, demonstrating that the CSS might be controlled but is not in remission.

## $T_H1$-RELATED INFLAMMATORY CONDITIONS

### Hypersensitivity pneumonitis

Hypersensitivity pneumonitis is a $CD4^+$ $T_H1$ and $CD8^+$ lymphocyte–predominant alveolitis that results in noncaseasting granulomas and pulmonary fibrosis. Clinical stages include acute, subacute (clinically similar to acute), and chronic. In the acute and subacute stages inhalation of organic antigens causes cough, shortness of breath, myalgias, and fever within 4 to 6 hours. The physical examination would reveal pulmonary crackles. A patient might self-treat for "flu" or be given an improper diagnosis of community-acquired pneumonia. When there is continued or repeated exposure to antigens, such as bird excreta, patients might have subacute episodes or evolve into chronic hypersensitivity pneumonitis where typical flu-like illness does not occur. The latter patients experience a nonproductive cough and progressive dyspnea and, in advanced cases, oxygen requirements. Pulmonary function tests in the acute and subacute stages typically are described as restrictive; however, especially with bird fanciers, obstructive findings can occur and mimic asthma. The restrictive findings are associated with a decreased diffusing capacity for carbon monoxide. In contrast, the diffusing capacity for carbon monoxide in patients with asthma is normal or even increased.

High-resolution CT scans demonstrate small nodules (<5 mm) that indicate alveolitis or areas of pulmonary fibrosis. Mosaic findings of fibrosis are present in patients with chronic hypersensitivity pneumonitis. An example of pulmonary fibrosis and traction bronchiectasis from avian hypersensitivity pneumonitis is shown in Fig 2.

There is striking BAL lymphocytosis of 60% to 80% from acutely ill patients.[28,29] The classic finding is a CD4/CD8 ratio of less than 1, whereas in patients with sarcoidosis, the CD4/CD8 ratio is as high as 8 because of the $CD4^+$ alveolitis.[30] In patients with hypersensitivity pneumonitis, levels of $T_H1$ cytokines are increased, including IL-12, IL-18, and TNF-α. $CD8^+$ lymphocytes serve as effector cells but are not sufficiently functional.[28,31,32] In contrast, in patients with chronic hypersensitivity pneumonitis, there can be an increase in the CD4/CD8 ratio as the CD4 (and $T_H2$) lymphocytes increase and $CD8^+$ lymphocytes decrease.[32] It has been suggested that the effector $CD8^+$ lymphocytes become "exhausted." These data suggest that chronic hypersensitivity pneumonitis is associated with "skewing" toward $T_H2$ lymphocytes, IL-4 production, and pulmonary fibrosis.[32] IL-17, which is proinflammatory, increases activation and numbers of neutrophils, and upregulates IL-6, IL-8, and TNF-α, might participate in hypersensitivity pneumonitis.[33,34]

Treatment includes early identification of patients with hypersensitivity pneumonitis, avoidance/remediation of the antigens involved, oral corticosteroids for short-term use, and monitoring of overall respiratory status depending on the stage that is present.

### Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterized by fixed dyspnea, lack of fully reversible airways obstruction, and progressive loss of $FEV_1$ over time. Cessation of cigarette smoking and use of oxygen have proved of value. Pharmacotherapy includes short- and long-acting bronchodilators and anticholinergic medications. For patients with moderate–to–very severe COPD, when the $FEV_1$ is less than 50% and the $FEV_1$/FVC ratio is less than 70%, combination inhaled corticosteroid/long-acting β-agonist therapy is recommended. Treatment with combination fluticasone propionate and salmeterol has resulted in fewer exacerbations but not fewer deaths.[35] In a study of patients with COPD in whom fluticasone/salmeterol or salmeterol was added to tiotropium, there was no additional benefit over tiotropium in the primary outcome of exacerbations of COPD.[36] Secondary outcomes did demonstrate increases in $FEV_1$, fewer hospitalizations, and improved quality-of-life measures in those patients receiving fluticasone/salmeterol.[36] An unexpected finding has been increased numbers of cases of pneumonia in patients with COPD receiving high-dose fluticasone propionate.[35,37]

The pathogenesis of COPD includes cigarette smoking (most cases), viral or bacterial infections (or a combination), genetic susceptibility, oxidative stress, and little to no response to high-dose corticosteroids. Sputum often harbors PMNs, but eosinophils can be present with either viral or combined viral and bacterial infections.[38] In patients with COPD, not only is there presence of PMNs and macrophages, there are also increases in CD4 $T_H1$ and CD8 lymphocyte numbers.[39]

The impaired response to corticosteroids helps differentiates COPD from asthma in most cases. After absorption, the corticosteroid binds to its receptor and traverses the cytoplasm and enters the nucleus, where it interacts with glucocorticoid response elements of DNA.[40] Then corticosteroids can reduce levels of the proinflammatory transcription factors nuclear factor κB and activator protein 1. It is thought that these transcription factors would have been upregulated by viral upper respiratory tract infections. Transcription factors can be generated as the DNA-histone complex "unwinds" during a process of acetylation by histone acetyltransferase.[40] Histone acetyltransferase levels are increased in some but not all cases of COPD, whereas in patients

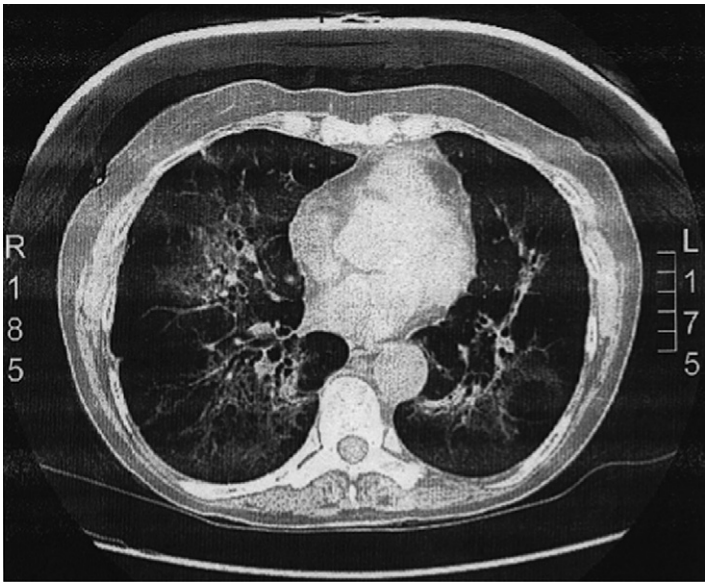


**FIG 2.** A 62-year-old woman who presented with "uncontrolled asthma" and had pulse oxygenation of 83% on room air reported shortness of breath for 6 years. She had 5 birds at home and worked at an exotic animal house. The CT examination revealed widened (bronchiectactic) bronchi, honeycomb fibrosis, and some opacities near the bronchi. The bronchiectasis occurred because of traction by the lung parenchyma/interstitium on the bronchi. The diffusion capacity of the lung for carbon monoxide was 39%, and the FVC was 74%. $FEV_1$ was 84% of predicted value, with a 6% improvement with albuterol.

with asthma, they are increased consistently.[40] Gene repression can occur when the DNA is deacetylated by histone deacetylase (HDAC) as the DNA is compacted. HDAC levels are reduced in both patients with COPD and those with asthma, but corticosteroids will increase HDAC levels in patients with asthma but not those with COPD.[40] Lack of deacetylation of the DNA in patients with COPD can favor sustained proinflammatory action and lack of response to corticosteroids, which is in contrast to what occurs in patients with asthma.

## $T_H2$-RELATED INFLAMMATORY CONDITIONS

It has been reported that the half-life of eosinophils in peripheral blood is 8 to 18 hours and 2 to 5 days or longer in tissue.[41] In addition, perhaps there are at least 100 times as many eosinophils in tissue than in peripheral blood.[41] In the bone marrow eosinophils differentiate and proliferate from $CD34^+$ progenitors (see Chapter 6) with the major cytokines IL-3, IL-5, and GM-CSF.[42] Potent chemoattractants for eosinophils include RANTES, CCL11 (eotaxin-1), platelet-activating factor, and $LTB_4$.[42] The interaction of very late antigen 4 on eosinophils with vascular cell adhesion molecule 1 on endothelium results in firm adhesion to the endothelial cells. During allergic reactions, IL-4, IL-13, and TNF-α will upregulate vascular cell adhesion molecule 1, enhancing this process.

In Table I there is a list of prototype pulmonary eosinophilia syndromes or conditions. One prototype condition is allergic bronchopulmonary aspergillosis (ABPA), which complicates both asthma and cystic fibrosis.[43,44] ABPA might overlap with either hyper-IgE syndrome or chronic granulomatous disease.[45] Patients with asthma who have ABPA typically experience pneumonias or pulmonary infiltrates with eosinophilia (10% to 30%) but not peripheral blood eosinophilia as high as 40% to 60%, which occurs with CSS or parasitism. All patients have immediate skin reactivity to *Aspergillus fumigatus*. Because some commercial mixtures of *Aspergillus* species or mold mixes contain little or no *A fumigatus*, it is advisable to use a reactive extract for screening. Negative skin test results help to exclude ABPA for nearly all patients unless there is an allergic bronchopulmonary mycosis present. High-resolution CT examination demonstrates proximal bronchiectasis (inner two thirds of the lung field) in contrast to the distal bronchiectasis that occurs in some patients with COPD or recurrent infections. In patients with cystic fibrosis, there is proximal and distal bronchiectasis, and such a finding should suggest the possibility of concomitant (usually pancreatic sufficient) cystic fibrosis. In patients with ABPA, the predominant response is that of $CD4^+$ $T_H2$ lymphocytosis; eosinophilia; increased total serum IgE and anti–*A fumigatus* IgE, IgG, and IgA antibody levels; precipitating antibodies *to A fumigatus* and a genetically restricted susceptibility profile; and increased responsiveness to IL-4 stimulation.[43,46,47]

Treatment includes avoidance/remediation of areas in a home/workplace of obvious mold growth that can occur from unplanned water entry, oral corticosteroids to clear the pulmonary infiltrates and manage asthma, antiasthma medications as indicated, monitoring of the total serum IgE concentration because doubling over baseline values indicates a possible current new pulmonary infiltrate, and assessment of pulmonary function and respiratory status over time.[43] For initial treatment of a patient with newly diagnosed ABPA, the dose of prednisone is 0.5 mg/kg given each morning for 1 to 2 weeks, with conversion to alternate day-therapy for 2 months. The radiographic findings can be expected to clear or be reduced, as demonstrated by means of high-resolution CT examination in 2 months. Then the prednisone can be tapered and discontinued. It is not necessary to continue prednisone indefinitely in the absence of new infiltrates or development of severe (prednisone dependent) asthma. With use of the alternate-day prednisone, serious adverse effects are avoided or minimized.

**TABLE I.** Pulmonary eosinophilia syndromes or conditions

| |
|---|
| Asthma (allergic and nonallergic) |
| Asthma with atelectasis from mucus plugging |
| ABPA |
| Allergic bronchopulmonary mycosis |
| CSS |
| Collagen vascular disease (rare) |
| Drug allergy with pulmonary eosinophilia |
| Eosinophilic pneumonia |
| Acute (BAL fluid eosinophilia 25% to 60% with little or no peripheral blood eosinophilia) |
| Chronic (high peripheral blood eosinophilia) |
| Simple eosinophilia (Loffler syndrome) |
| Tropical pulmonary eosinophilia |
| Hypereosinophilic syndromes (interstitial infiltrates and pleural effusions, thromboembolism) |
| Neoplasms |
| Parasitism (helminthic) |
| Sarcoidosis (very rare) |

Adapted with permission from Greenberger.[1]

Antifungal therapies have been used for the treatment of ABPA and are considered adjunctive.[48,49] A potentially good candidate for antifungal therapy is a patient with sputum plugs harboring *A fumigatus* despite prednisone therapy. There are reports of the use of omalizumab[50] for patients with ABPA, but it remains to be established whether this treatment will help to prevent new infiltrates or improve asthma symptoms.

Eosinophilic pneumonias are divided into 4 types: acute, chronic, simple, and tropical (Table I). Acute eosinophilic pneumonia can masquerade as severe community-acquired pneumonia and present with respiratory failure. When there is no or little peripheral blood eosinophilia, the diagnosis can be made with bronchoscopy and BAL showing eosinophilia of 25% to 60%. Alternatively, there might be peripheral blood eosinophilia as high as 42%.[51] Drugs, nonprescription products, parasitism, and other causes of widespread pulmonary infiltrates should be considered.

Chronic eosinophilic pneumonia is characterized by respiratory symptoms for at least 2 weeks, peripheral blood eosinophilia of at least 1000/mm$^3$ or BAL eosinophilia of greater than 25%, and bilateral pulmonary infiltrates.[52] In classic presentations the infiltrates are in the periphery, suggesting the photographic negative of pulmonary edema. Most patients require years of oral corticosteroid treatment. The radiographic infiltrates and surges of peripheral blood eosinophilia can be controlled with modest doses of prednisone.

Simple pneumonia (Loffler syndrome) is a mild condition lasting less than 4 weeks and has transient pulmonary infiltrates.

Tropical pulmonary eosinophilia is characterized by widespread pulmonary infiltrates and high levels of peripheral blood eosinophilia. Mediastinal lymph nodes might be enlarged and can harbor activated eosinophils. Patients typically have lived in endemic areas of parasites before tropical pulmonary eosinophilia occurs.

## SUMMARY

The immunologic features of pulmonary disorders can be used to categorize various conditions and provide focus for potential innovative therapies. Although usually there is not a single treatment that antagonizes a critical component of either the innate or acquired immune system and results in clinical improvement, complex conditions might be amenable to immunologically based treatments in the future. A more ambitious goal is primary prevention of many of the pulmonary conditions discussed in this chapter. The ability to diagnose pulmonary conditions and the masquerader of asthma, VCD, continues to improve, which should result in earlier diagnoses and improved outcomes.

### REFERENCES

1. Greenberger PA. 7. Immunologic lung disease. J Allergy Clin Immunol 2008; 121(suppl):S393-7.
2. Eder AF, Herron R, Strupp A, Dy B, Notari EP, Chambers LA, et al. Transfusion-related acute lung injury surveillance (2003-2005) and the potential impact of the selective use of plasma of male donors in the American Red Cross. Transfusion 2007;47:599-607.
3. Eder AF, Benjamin RJ. TRALI risk reduction: donor and component management strategies. J Clin Apher 2009;24:122-9.
4. Tsushima K, King LS, Aggarwal NR, De Gorordo A, D'Alessio FR, Kubo K. Acute lung injury review. Intern Med 2009;48:621-30.
5. Bastarache JA, Wang L, Geiser T, Wang Z, Albertine KH, Matthay MA, et al. The alveolar epithelium can initiate the extrinsic coagulation cascade through expression of tissue factor. Thorax 2007;62:608-16.
6. Lee KS, Choi YH, Kim YS, Baik SH, Oh YJ, Sheen SS, et al. Evaluation of bronchoalveolar lavage fluid from ARDS patients with regard to apoptosis. Respir Med 2008;102:464-9.
7. Calfee CS, Matthay MA. Nonventilatory treatments for acute lung injury and ARDS. Chest 2007;131:913-20.
8. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(suppl):S27-72.
9. Reade MC, Yende S, D'Angelo G, Kong L, Kellum JA, Barnato AE, et al. Differences in immune response may explain lower survival among older men with pneumonia. Crit Care Med 2009;37:1655-62.
10. Yuan FF, Marks K, Wong M, Watson S, de Leon E, McIntyre PB, et al. Clinical relevance of TLR2, TLR4, CD14 and FCγRIIA gene polymorphisms in *Streptococcus pneumoniae* infection. Immunol Cell Biol 2008;86:268-70.
11. Perry LP, Iwata M, Tazelaar HD, Colby TV, Yousem SA. Pulmonary toxicosis: a clinicopathologic study of three cases. Mod Pathol 1998;11:432-6.
12. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. Chest 1985;88:376-84.
13. Prezant DJ, Weiden M, Banauch GI, McGuinness G, Rom WN, Aldrich TK, et al. Cough and bronchial responsiveness in firefighters at the world trade center site. N Engl J Med 2002;347:806-15.
14. Banauch GI, Alleyne D, Sanchez R, Olender K, Cohen HW, Weiden M, et al. Persistent hyperreactivity and reactive airways dysfunction in firefighters at the world trade center. Am J Respir Crit Care Med 2003;168:54-62.
15. Sterner JB, Morris MJ, Sill JM, Hayes JA. Inspiratory flow-volume curve evaluation for detecting upper airway disease. Respir Care 2009;54:461-6.
16. Moore WC, Peters SP. Severe asthma: an overview. J Allergy Clin Immunol 2006; 117:487-94.
17. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med 2007;146:340-54.
18. Guyot-Revol V, Innes JA, Hackforth S, Hinks T, Lalvani A. Regulatory T cells are expanded in blood and disease sites in patients with tuberculosis. Am J Respir Crit Care Med 2006;173:803-10.
19. Tsao TCY, Chen H-C, Jong J-H, Hsieh M-J, Tsao K-C, Lee C- H. Shifts of T4/T8 T lymphocytes from BAL fluid and peripheral blood by clinical grade in patients with pulmonary tuberculosis. Chest 2002;122:1285-91.
20. Glynn JR, Murray J, Bester A, Nelson G, Shearer S, Sonnenberg P. Effects of duration of HIV infection and secondary tuberculosis transmission on tuberculosis incidence in the South African gold mines. AIDS 2008;22:1859-67.
21. Richeldi L. An update on the diagnosis of Tuberculosis infection. Am J Respir Crit Care Med 2006;174:736-42.
22. Callejas-Rubio JL, Lopez-Perez L, Ortego-Centeno N. Tumor necrosis factor-alpha inhibitor treatment for sarcoidosis. Ther Clin Risk Manag 2008;4:1305-13.
23. Kieszko R, Krawczyk P, Jankowska O, Chocholska S, Krol A, Milanowski J. The clinical significance of interleukin 18 assessment in sarcoidosis patients. Respir Med 2007;101:722-8.

24. Klion AD, Bochner BS, Gleich GJ, Nutman TB, Rothenberg ME, Simon H-U, et al. Approaches to the treatment of hypereosinophilic syndrome: a workshop summary report. J Allergy Clin Immunol 2006;117:1292-302.
25. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Cassassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore) 1999;78:26-37.
26. Highashi N, Mita H, Taniguchi M, Turikisawa N, Higashi A, Ozawa Y, et al. Urinary eicosanoid and tyrosine derivative concentrations in patients with vasculitides. J Allergy Clin Immunol 2004;114:1353-8.
27. Vemuri P, Greenberger PA, Patterson R. Churg-Strauss syndrome: survival for 26 years. Ann Allergy Asthma Immunol 2002;88:640-3.
28. Fink JN, Ortega HG, Reynolds HY, Cormier YF, Fan LL, Franks TJ, et al. Needs and opportunities for research in hypersensitivity pneumonitis. Am J Respir Crit Care Med 2005;171:792-8.
29. Agostini C, Calabrese F, Poletti V, Marcer G, Facco M, Miorin M. CXCR3/CXCL10 interactions in the development of hypersensitivity pneumonitis. Respir Res 2005;6:20.
30. Hamagami S, Miyagawa T, Ochi T, Tsuyuguchi I, Kishimoto S. A raised level of soluble CD8 in bronchoalveolar lavage in summer-type hypersensitivity pneumonitis. Am J Respir Crit Care Med 1999;159:1830-4.
31. Chen B, Tong Z, Nakamura S, Costabel V, Guzman J. Production of IL-12, IL-18 and TNF-alpha by alveolar macrophages in hypersensitivity pneumonitis. Sarcoidosis Vasc Diffuse Lung Dis 2004;21:199-203.
32. Barrera L, Mendoza F, Zuniga J, Estrada A, Zamora AC, Melendro EI, et al. Functional diversity of T-cell subpopulations in subacute and chronic hypersensitivity pneumonitis. Am J Respir Crit Care Med 2008;177:44-55.
33. Joshi AD, Fong DJ, Oak SR, Trujillo G, Flaherty KR, Martinez FJ, et al. Interleukin-17-mediated immunopathogenesis in experimental hypersensitivity pneumonitis. Am J Respir Crit Care Med 2009;179:705-16.
34. Selman M, Pardo A, Barrera L, Estrada A, Watson SR, Wilson K, et al. Gene expression profiles distinguish idiopathic pulmonary fibrosis from hypersensitivity pneumonitis. Am J Respir Crit Care Med 2006;173:188-98.
35. Calverly PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89.
36. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourdeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2007;146:545-55.
37. Weddzicha JA, Calverly PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008;177:19-26.
38. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med 2006;173:1114-21.
39. Fabbri LM, Luppi F, Beghe B, Rabe KF. Update in chronic obstructive pulmonary disease 2005. Am J Respir Crit Care Med 2006;173:1056-65.
40. Ito K, Ito M, Elliott WM, Cosio B, Caramori G, Kon OM, et al. Decreased histone deacetylase activity in chronic obstructive pulmonary disease. N Engl J Med 2005;352:1967-76.
41. Kita H, Adolphson CR, Gleich GJ. Biology of eosinophils. In: Adkinson NF, Yunginger JW Jr, Busse WW, Bochner BS, Holgate ST, Simons FER, editors. 6th ed. Philadelphia: Mosby; 2003. p. 305-32 Middleton's allergy: principles and practice.
42. Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. J Allergy Clin Immunol 2006;117(suppl):S450-6.
43. Greenberger PA. Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 2002;110:685-92.
44. Stevens DA, Moss RB, Kurup VP, Knutsen AP, Greenberger PA, Judson MA, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art: Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis 2003;37(suppl 3):S225-64.
45. Eppinger TM, Greenberger PA, White DA, Brown AE, Cunningham-Rundles C. Sensitization to Aspergillus species in the congenital neutrophil disorders chronic granulomatous disease and hyper-IgE syndrome. J Allergy Clin Immunol 1999;104:1265-72.
46. Knutsen AP, Kariuki B, Consolino JD, Warrier MR. IL-4 alpha chain receptor (IL-4Ralpha) polymorphisms in allergic bronchopulmonary aspergillosis. Clin Mol Allergy 2006;4:3.
47. Kurup VP, Knutsen AP, Moss RB, Bansal NK. Specific antibodies to recombinant allergens of *Aspergillus fumigatus* in cystic fibrosis patients with ABPA. Clin Mol Allergy 2006;4:11.
48. Wark PA, Hensley MJ, Saltos N, Boyle MJ, Toneguzzi RC, Epid GD, et al. Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial. J Allergy Clin Immunol 2003;111:952-7.
49. Moss RB. Critique of trials in allergic bronchopulmonary aspergillosis and fungal allergy. Med Mycol 2006;44:269-72.
50. van der Ent CK, Hoekstra H, Rijkers GT. Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. Thorax 2007;62:276-7.
51. Shorr AF, Scoville SL, Cersovsky SB, Shanks GD, Ochenhouse CF, Smoak BL, et al. Acute eosinophilic pneumonia in US Military personnel deployed in or near Iraq. JAMA 2004;292:2997-3005.
52. Tsuirkisawa N, Saito H, Tsuburai T, Oshikata C, Ono E, Mitomi H, et al. Differences in regulatory T cells between Churg-Strauss syndrome and chronic eosinophilic pneumonia with asthma. J Allergy Clin Immunol 2008;122:610-6.