The Acute Presentation of Interstitial Lung Disease

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Introduction

Interstitial lung disease (ILD) is often perceived as a group of chronic, progressive disorders associated with the insidious onset of cough, dyspnea and reticular opacities on imaging studies. Some forms of interstitial disease, however, present abruptly with severe respiratory complaints and alveolar flooding. The acute noninfectious interstitial lung diseases include acute lung injury and repair syndromes like acute interstitial pneumonia (AIP) and bronchiolitis obliterans organizing pneumonia (BOOP). In these conditions, it is a seemingly dysregulated "repair" process (excessive or persistent fibroproliferation) rather than the acute lung injury itself that dominates the clinicopathologic picture. The other major group of acute interstitial diseases are immunologically driven disorders including acute eosinophilic pneumonia (AEP), acute hypersensitivity pneumonitis (HP), diffuse alveolar hemorrhage (DAH), and immunologic pneumonias like acute lupus pneumonitis (ALP). The nature of these immune injuries varies. They may be caused by cellular immune activation (AEP and subacute/chronic HP), humoral activation (acute HP and some forms of DAH), or both (acute immunologic pneumonias). Finally, there are several forms of drug-induced pneumonitis that overlap considerably with these two broad categories. Some drugs may induce widespread acute lung injuries (diffuse alveolar damage or BOOP) while other produce a variety of "hypersensitivity" reactions (e.g., pulmonary eosinophilia or a lymphocytic alveolitis).

As a group, these conditions represent a collection of inflammatory and fibrosing disorders characterized by cough, dyspnea and a variety of constitutional complaints. Symptoms may evolve over hours, days or weeks. Certain historical elements, like the presence of hemoptysis or a history of bird exposure, may provide the only noninvasive means of separating these conditions from one another. Diagnosis is often delayed or missed entirely because these syndromes also mimic, clinically and radiologically, common disorders like pneumonia, heart failure or the acute respiratory distress syndrome (ARDS). Table 1 provides a summary of the major clinical, radiographic and pathologic features of the acute interstitial diseases.

Table 1. Essential clinical, radiographic and histologic features of the acute noninfectious forms of interstitial lung disease.

Diagnosis	Key Clinical Features	Radiographic Findings	Histopathology
AIP	ARDS	widespread GGO, consolidation	organizing DAD
BOOP	subacute cough, dyspnea viral prodrome common	peripheral/peribronchovasular consolidation	fibroblastic granulation tissue in bronchiolar/alveolar lumens
DAH	dyspnea, hemoptysis, anemia	bilateral alveolar filling process ground glass or consolidation	blood in alveolar lumens ± capillaritis
Acute HP	flu-like illness, cough, dyspnea spontaneous resolution in 1-2 days	GGO, mid-lung zone predominance	rarely biopsied
AEP	fever, hypoxemic respiratory failure	mixed interstitial/alveolar infiltrates effusions common	interstitial/alveolar eosinophils and mononuclear cells
ALP	fever, cough, dyspnea signs of lupus flare	bilateral basilar-predominant airspace disease	acute DAD, cellular interstitial pneumonia
Drug-induced pneumonitis	multiple syndromes	variable/nonspecific	cellular intersititial pneumonia, BOOP, DAD, DAH, fibrosis

GGO= ground glass opacification
DAD= diffuse alveolar damage
See text above for other abbreviations

The Fundamentals of Acute Lung Injury

An appreciation of acute interstitial disease first requires an understanding of the fundamental events associated with any acute lung injury. Although there are a plethora of different causes of acute lung injury, the lung is quite limited in its response to those events. Acute lung injuries are characterized by epithelial and endothelial necrosis. This is followed by interstitial edema, the development of intraluminal fibrin-rich exudates, inflammatory cell trafficking, alveolar collapse, and ultimately fibrosis. The fibrosis that is seen in response to these lung injuries is an active cellular process characterized by extensive fibroblast proliferation rather than predominant collagen deposition. This is the process of organization whereby interstitial mesenchymal cells migrate into the alveolar space or bronchiolar lumen along scaffolding provided by the fibrin provisional matrix.[1,2,3,4,5,6] These cells then proliferate and elaborate various extracellular matrix components. The intraluminal exudates are then said to be "organized."

The distribution and severity of the injury determines which histopathologic pattern of "wound healing" is observed: diffuse alveolar damage (DAD) or bronchiolitis obliterans organizing pneumonia (BOOP).[1] When widespread injury occurs to the distal gas exchanging apparatus, DAD is seen. When the injury focuses on bronchioles and peribronchiolar alveoli, BOOP develops (see section entitled *bronchiolitis obliterans organizing pneumonia*).[1]

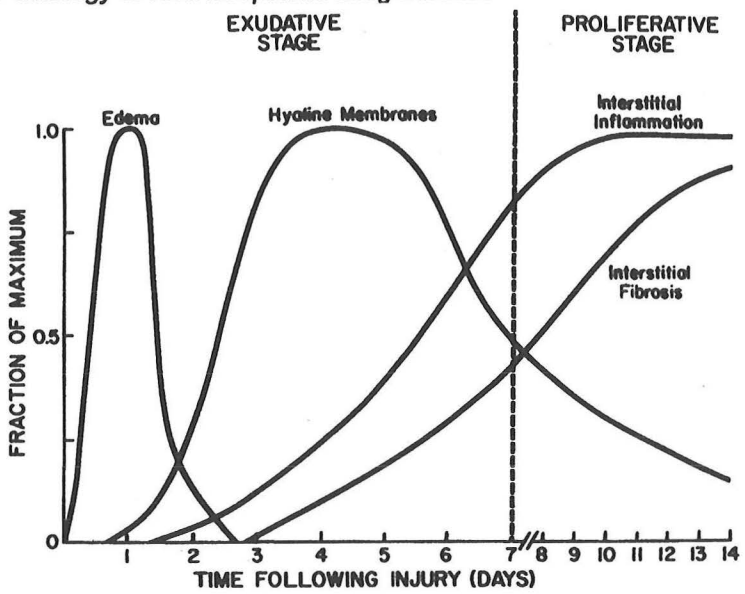
Table 2. Major causes of diffuse alveolar damage.

Infection/Sepsis	Radiation
Shock	Hypertransfusion
Aspiration injuries	Drug toxicity/overdose
Acute pancreatitis	Inhalational injury
Collagen vascular disease	Near drowning
Burns	Cardiopulmonary bypass
Fat embolism	Acute interstitial pneumonia

DAD is the histologic pattern that is usually associated with the adult respiratory distress syndrome, the sine qua non of acute lung injury.[1,7,8,9,10,11] The major causes of ARDS/DAD are detailed in table 2. When no cause can be identified, the patient is said to have acute interstitial pneumonia (AIP). DAD begins with an acute or exudative phase lasting about one week that is usually associated with acute hypoxemic respiratory failure (figure 1). In most instances, these patients require mechanical ventilatory support. Acute DAD is characterized histologically by the necrosis of type I epithelial cells that normally cover 95% of the alveolar surface. Interstitial and air space edema follow, and hyaline membranes accumulate within alveoli.[1,7,12,13] Type II cell hyperplasia is also stimulated. These cells are responsible for reepithelialization of denuded alveoli, and some will eventually differentiate into type I cells as the injury resolves. Injury to endothelial cells predisposes to the commonly identified arteriolar thrombi.[1,14]

The proliferative or organizing phase of DAD/ARDS begins within 72 hours and usually becomes the predominant process by 7-10 days (figure 1). The main histologic feature of this phase is fibroblast proliferation within the interstitium.[1] Edema fluid is largely resorbed and hyaline membranes become inconspicuous as alveolar macrophages clear particulate debris from the airspaces. Although the fibrosis is often extensive, it is associated with little mature collagen deposition and is potentially reversible. Long-term follow-up studies on ARDS survivors indicate only minor residual pulmonary function abnormalities in most subjects.[7,15]

Figure 1. Time course of histologic evolution in diffuse alveolar damage. Note the overlap between acute (exudative) and organizing (fibroproliferative) stages. From *Katzenstein and Askin's Surgical Pathology of Non-neoplastic Lung Disease*[1]



Acute Interstitial Pneumonia—A Variant of Diffuse Alveolar Damage

Acute interstitial pneumonia (AIP) is a fulminant disease process characterized by cough, dyspnea and frequently fever progressing rapidly to respiratory failure in most cases.[1,14,16,17] It represents a diffuse, and perhaps dysregulated, fibroproliferative repair response following severe acute lung injury.[1,7,14] The illness frequently begins with a viral-like prodrome and almost universally necessitates mechanical ventilatory support within one to three weeks of the onset of symptoms.[14,18,19] It usually occurs in previously healthy individuals. Some of these cases may be triggered by viral pneumonias, but extensive cultures, serologic investigations and ultrastructural examinations have revealed no evidence of infectious pathogens. Bilateral airspace disease is evident on plain chest radiographs.[14,20] Chest CT scans reveal patchy or diffuse ground glass attenuation (GGA) in all cases.[2,18,20,21] Zones of consolidation are also seen in most patients.

Hamman and Rich were the first to describe this idiopathic and rapidly progressive fibrosing interstitial pneumonia that culminates in respiratory failure.[22] Histologically, organizing diffuse alveolar damage (DAD) is seen.[1,14] Remnants of hyaline membranes are often seen, but the main histologic finding is extensive interstitial fibroblast proliferation.[1,14] As indicated previously, a patient may be said to have AIP only if all other known causes of DAD such as sepsis, aspiration and trauma are excluded (table 2).[10,23,24,25] AIP is synonymous with the term Hamman-Rich syndrome.[12,19,22,26] It is considered to be an idiopathic form of ARDS. Many patients with AIP progress to respiratory failure soon after symptom onset similar to sepsis or pneumonia patients who develop ARDS. In one series of twelve patients from the University of Colorado, 77% of patients presented within one week (median 3 days) of the onset of symptoms (personal communication from Dr. Kevin Brown, manuscript in press). However, other cases have a more subacute presentation with progression of respiratory complaints over several days or a few weeks before mechanical ventilation is required. This is clearly not something seen in the classical form of ARDS. By the current definition, patients may have symptoms for up to two months, but such a prolonged prodrome is distinctly unusual.

When AIP patients present, they are often felt to have viral, atypical bacterial, or even opportunistic pneumonias. Surgical lung biopsies are usually delayed pending the results of cultures, bronchoscopy, serologic evaluation and empiric antibiotic therapy. When patients fail to respond, surgical biopsies are obtained which demonstrate changes indistinguishable from the fibroproliferative phase of ARDS.[14,19] Some patients do get biopsied early, but these patients have usually had symptoms for a week or more when they present, or they have already failed

outpatient antibiotic therapy. They too demonstrate organization (fibroproliferation) rather than acute DAD. This is intriguing since the most serious hypoxemia and greatest ventilatory support requirements in traditional forms of ARDS usually occur in the early exudative phase of the illness. AIP patients, on the other hand, actually present with already established fibroproliferation or they develop it by the time their clinical condition mandates biopsy. Thus, in some cases, the exudative phase of the acute lung injury is not sufficient to produce frank respiratory failure, but the organization phase is.

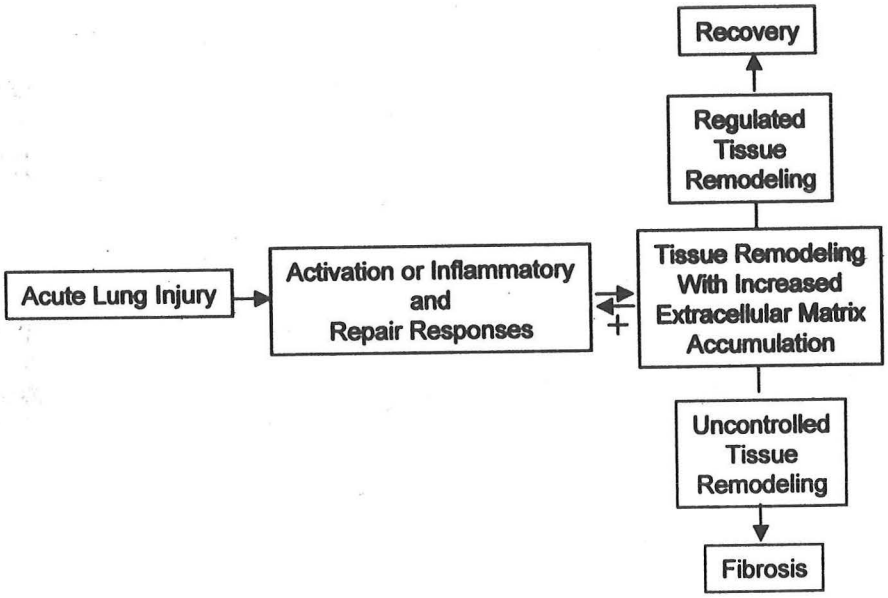
Patients with collagen vascular diseases can also develop an organizing DAD lesion like AIP. The presentation, natural history and histopathology of the conditions are, in fact, indistinguishable. However, the term AIP is currently reserved for *idiopathic* organizing DAD, so patients with underlying connective tissue disorders who develop this syndrome are usually not included under this heading. An argument can be made to change the nomenclature, however, since usual interstitial pneumonia (UIP) has both idiopathic (IPF) and collagen-vascular (e.g., rheumatoid lung) associations. Several collagen vascular diseases have been associated with an AIP/organizing DAD syndrome including rheumatoid arthritis, progressive systemic sclerosis, polymyositis/dermatomyositis and certain systemic vasculitides.[27,28,29,30,31]

The prognosis of AIP is poor. Mortality in most studies has ranged from 60%-100% at 6 months (average ~80%).[14,17,18,19,20] Most deaths occur within two months of diagnosis. Patients may succumb to progressive respiratory insufficiency or various nosocomial complications such as pneumonia, sepsis or venous thromboembolism. Interestingly, the mortality of ARDS where the etiology is known is usually not as high as that reported for AIP. The published mortality rate of ARDS is between 40 and 60%, and some recent reports indicate even better survival.[32,33,34,35,36,37,38] The difference is probably related to the lower frequency of protracted fibroproliferative reactions in typical ARDS. Most of the mortality in ARDS patients is traditionally attributed to sepsis or multisystem organ failure rather than respiratory failure.[36,37,39,40] Unfortunately, this concept underestimates the pivotal role of persistent fibroproliferation in determining outcome after an acute lung injury.[41,42,43,44,45,46,47] When one looks at autopsy specimens of ARDS patients who die, interstitial and intraalveolar fibrosis are reliable findings. In Clark's series of 25 patients with ARDS, all 15 subjects who lived demonstrated resolution of their respiratory failure in an appropriate time frame.[44] Of the ten patients who died, nine had persistent respiratory failure at the time of death, although death was attributed to non-pulmonary causes in eight of these cases.[44] Martin and colleagues performed transbronchial biopsies on twenty-five consecutive mechanically ventilated ARDS patients (at 10 $\pm$ 3 days from onset of respiratory failure) looking for evidence of fibrosis.[41] In the patients with fibrosis, the mortality rate was 57% (8 of 14 patients) compared to 0% in the remaining patients without evidence of fibrosis. Other studies have suggested that acute lung injury patients with higher levels of biologic markers for collagen synthesis have a worse prognosis.[44,48,49,50] Meduri indicates that most deaths in ARDS can be linked directly or indirectly to progressive pulmonary fibroproliferation.[43] Perhaps one quarter or one third of patients die as a direct consequence of refractory hypoxemia and/or hypercarbia. Indirectly, the marked reduction in lung compliance and increased physiologic dead space associated with fibroproliferation often necessitates prolonged ventilator dependence. This results in impaired pulmonary host defenses and an increased risk for nosocomial complications like sepsis, renal failure and thromboembolic events that are directly implicated in patient mortality.[43] Survival after an acute lung injury ultimately depends on the efficient restoration of normal gas exchange machinery. In some patients, this occurs fairly quickly leading to near complete physiologic recovery. On the other hand, patients who present with AIP have, in a sense, already been selected to do poorly. By definition, these are patients who have responded to their acute lung injury with a florid fibroproliferative reaction that seriously compromises gas exchange and pulmonary compliance. This may explain why their mortality is significantly worse in most studies compared to the average patient with ARDS, even though AIP patients do not have to contend with issues like shock, multiple trauma or sepsis at the time of presentation.[51,52]

Precisely what drives the relentless fibrogenesis in these patients is not clear. It may be related to the severity of the alveolar injury, the persistence of proinflammatory or profibrotic cytokines and growth factors, failure to completely resolve the root cause of the lung injury, or individual genetic differences.[3,45,46,53,54] Increased levels of procollagen peptides and plasma proteins are seen in the BAL fluid of nonsurvivors with ARDS reflecting early fibrosis and

increased alveolar-capillary leak.[44,45,48] Matthay argues that the presence of more protein in the air spaces, particularly in the form of insoluble hyaline membranes, produces a severely altered alveolar microenvironment.[45] This may prevent the required signaling between matrix elements and epithelial cells or fibroblasts that normally results in a controlled pattern of cell growth and matrix production. In normal lung, the extracellular matrix (ECM) is thought to provide mainly an inert scaffold for structural support of the gas exchanging apparatus. Increasing evidence, however, indicates a much broader role for newly deposited ECM elements in the setting of acute and chronic lung injury.[55] Matrix elements strongly influence both immune and non-immune cells via cell surface receptors that mediate chemotaxis, cell adhesion, migration, proliferation, differentiation and activation.[56,57,58,59] The precise role that these proteins and glycoproteins play in regulation of inflammatory and repair processes following lung injury is presently unknown. However, further research in this area could provide essential clues to the mystery of uncontrolled tissue remodeling (figure 2).[55]

Figure 2. General schematic of the processes involved in lung injury and repair. Injury triggers an early inflammatory response followed by tissue remodeling. Matrix deposition affects lung architecture but may also augment the inflammatory process and fibroproliferation. From Roman[55]

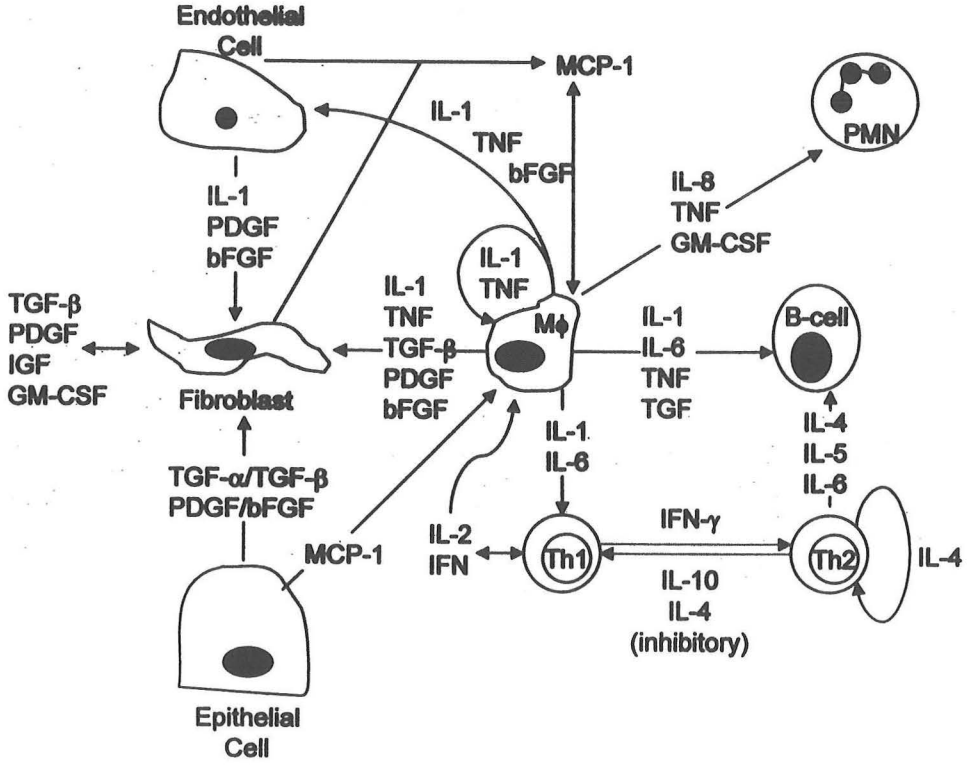


Of course, cytokine biology is another key force determining the outcome of tissue repair after acute lung injury. Meduri, for instance, has noted the presence of persistently high levels of proinflammatory cytokines like IL-6 in patients with unrelenting fibroproliferation.[51,52] In mice, TNF-α may be a key proximal effector of fibrogenesis following an acute lung injury.[60] Fibroblasts from TNF-α receptor knock-out mice do not proliferate or demonstrate significant collagen production in response to treatment with two agents that are believed to have a central role in the development of pulmonary fibrosis, PDGF and TGF-β.[60] The presence of these growth factors is crucial to normal wound healing, but dysregulated production could be an important factor leading to persistent fibrogenesis in acute and chronic interstitial disease (figure 3).[61,62,63]

One hypothesis suggests that differences in regulation of the Fas death receptor are responsible for differences in patient susceptibility to pulmonary fibrosis after exposure to various injurious agents.[53,64] Ligation of Fas normally leads to programmed cell death or apoptosis allowing for the removal of damaged or senescent cells without spillage of their contents that would incite inflammation. However, in some circumstances, Fas ligation can lead to the release of proinflammatory cytokines and tissue injury.[65,66] The earliest recognizable event in pulmonary fibrosis is the loss of alveolar epithelial cells.[3,67] Many different injuries like viruses, cytotoxic drugs and immunologic reactions can initiate epithelial cell apoptosis and have also been linked to the

development of acute or chronic fibrotic reactions in the lungs.[53] Interestingly, mice deficient in either Fas or Fas ligand are protected from fibrosis after exposure to bleomycin.[64] Precisely what happens after Fas ligation may depend on the relative influence of several pro-apoptotic and anti-apoptotic factors.[53] Chapman suggests that disruption of the balance between these counter-regulatory factors (due to genetic or environmental differences) may influence individual susceptibility to pulmonary fibrosis.[53] In addition to participating in the early stages of alveolar damage, Fas could play an essential role in the removal of excess fibroblasts after epithelial and endothelial repair are complete. Defective Fas ligation in fibroblasts could translate into persistent fibroproliferation preventing restoration of a functional alveolar-capillary membrane.

Figure 3. Schematic of cytokine networks involved in the pathogenesis of interstitial lung disease.



There is presently no established treatment for fibroproliferation. Anecdotal evidence in AIP and limited studies in late ARDS suggest that glucocorticoids are effective in some instances.[49,68,69,70,71,72] Initial therapy of AIP with pulse dose steroids is favored by some authors. Novel antifibrotic agents like perfenidone or interferon-γ may offer alternative avenues for pharmacologic intervention.[73,74,75,76] Theoretically, inhibition of fibroblast growth factor production or binding, or strategies designed to regulate fibroblast migration, differentiation and apoptosis may also be useful.[46]

Bronchiolitis Obliterans Organizing Pneumonia

Bronchiolitis obliterans organizing pneumonia (BOOP) is an inflammatory interstitial disorder whose pathologic hallmark is the presence of young fibromyxoid connective tissue within small airways, alveolar ducts and alveoli.[1,77,78,79] BOOP represents one general type of reparative or "wound healing" reaction following acute lung injury from a variety of causes.[1,80,81] After some lung injuries, plasma proteins and fluid exude into the airspaces, alveolar ducts and bronchioles. The coagulation cascade is activated leading to fibrin deposition. This is followed by an influx of fibroblasts and the elaboration of various extracellular matrix elements producing loose granulation tissue plugs.[5] As already discussed, this sort of intraluminal organization within alveolar sacs is

certainly not pathognomonic of BOOP, but can be seen prior to mural incorporation in the organizing phase of DAD (and hence, AIP) as well as other interstitial pneumonias like UIP, NSIP, hypersensitivity pneumonitis and chronic eosinophilic pneumonia.[1] Other histologic findings include a mononuclear cell interstitial infiltrate of variable intensity, patchy fibrin deposits, and foamy macrophages within alveoli (a consequence of persistent airway obstruction by organizing connective tissue).[82]

The distinct clinicopathologic entity known as idiopathic BOOP or cryptogenic organizing pneumonia (COP) was originally defined by Epler and Davison.[77,83] COP accounts for 50-90% of all cases of BOOP.[77,84,85,86] It is a diagnosis of exclusion because BOOP is known to have many different causes including drugs, infections, inhalation injuries, collagen vascular and other autoimmune diseases (table 3). Infections are a common cause of secondary BOOP, particularly atypical infections like mycoplasma, legionella, influenza, and HIV.[78,80,82,87,88,89,90,91] Histologically, BOOP would probably be identified frequently during the normal resolution of these illnesses if biopsies were obtained. Milder cases of post-infection BOOP resolve spontaneously with time, but in a few cases, the repair process seems to be dysregulated leading to excessive or persistent fibroblastic proliferation even after sterilization of the lung by antibiotics. BOOP then dominates the clinical picture leading to persistent fever, respiratory symptoms and pulmonary infiltrates. In this clinical setting, an empiric trial of short-course steroids is often indicated in lieu of a lung biopsy.

Another leading definable cause of BOOP, accounting for perhaps 10-15% of all cases, is collagen vascular disease.[77,84] BOOP may be seen with any of these disorders but is probably most common in systemic lupus erythematosus, rheumatoid arthritis, and the inflammatory myopathies.[29,77,84,92,93,94,95,96] The syndrome in these patients is indistinguishable from cryptogenic organizing pneumonia, but some have suggested that collagen vascular patients who develop BOOP have a worse prognosis.[77,84] This difference is probably a consequence of other systemic features of the connective tissue disorder. Alternatively, while BOOP may be present histologically, in some cases it occurs on the background of a much worse lesion like UIP in a patient with rheumatoid lung, or DAD in a patient with acute lupus pneumonitis. So it may not always represent the predominant pathologic reaction in these patients. This is particularly a concern if the diagnosis is made by transbronchial biopsy with its inherent risk of sampling error.

Table 3. Etiologies of bronchiolitis obliterans organizing pneumonia.
Adapted from Katzenstein[1] and Epler[82]

BOOP as principal cause of the respiratory illness
- Cryptogenic organizing pneumonia
- Collagen vascular disease
- Post-infectious organization
- Drug toxicity
- Inhalation injury
- Bone marrow/Lung transplantation
- HIV-related
- Immunologic disorders
  - Chronic thyroiditis
  - Inflammatory bowel disease
  - Common variable immunodeficiency

BOOP as nonspecific, peripheral reaction in other disease states
- Tumors
- Vasculitis
- Granulomatous disease
- Pulmonary infarction

BOOP as minor component within other interstitial reactions
- Chronic eosinophilic pneumonia
- Nonspecific interstitial pneumonia
- Hypersensitivity pneumonitis

BOOP is rarely seen in a variety of other autoimmune disorders including common variable immunodeficiency, chronic thyroiditis, and inflammatory bowel disease.[86,97,98,99] Drug-induced lung injury, hematologic malignancy and thoracic irradiation are other well documented clinical associations.[100,101,102,103,104,105,106,107] The clinical, radiologic and pathologic findings are similar regardless of whether an underlying cause is ascertained.[77,84] In most cases, patients present with a subacute onset (4-12 weeks) of symptoms following a flu-like prodrome or upper respiratory tract infection.[80,82,108,109,110,111] The principal features of the illness include cough, dyspnea and malaise (table 4).[77,84] Fever and weight loss are common.[84,108,112] Occasional patients complain of pleuritic chest pain or hemoptysis.[84,113,114] On auscultation, inspiratory crackles are usually heard. Signs of airflow limitation like wheezing are uncommon.[84] In most cases, physiologic assessment indicates a mild to moderate restrictive process and a low diffusing capacity.[77,115] Uncommonly, mixed or mainly obstructive pulmonary function tests are noted.[108,116]

Table 4. Clinical Characteristics of BOOP. Summary of available data from three of the largest series (Epler[77],Lohr[84],Boots[108]).

Symptom	**Number Affected/Total (%)**
Cough	99/129 (77%)
Dyspnea	91/128 (71%)
Malaise	13/15 (87%)
Weight loss	30/69 (43%)
Night sweats	22/55 (40%)
Flu-like prodrome	39/122 (32%)
Pleuritic chest pain	16/66 (24%)
Hemoptysis	11/125 (9%)
Sign	
Crackles	104/129 (81%)
Wheezes	16/124 (13%)
Fever (T>38°C)	38/76 (50%)

Plain chest radiographs typically show patchy alveolar infiltrates that favor the lung periphery.[77,84,85,108,112,117,118] As the process evolves, it is common to see a gradual increase in the size and/or number of these opacities. In a few cases, the infiltrates have been noted to spontaneously migrate;[108,119,120] and when the disease recurs, it often involves a previously unaffected region of lung. Cavitation, nodules, mass-like infiltrates or pleural effusions are seen in a minority of patients.[77,84,108,114,121,122] Uncommonly, bibasilar interstitial infiltrates are seen that may even mimic UIP. These patients have a worse prognosis, but many have other types of interstitial pneumonias that simply show BOOP-like features.[1,86,115] Chest CT scans typically identify subpleural or peribronchovascular consolidation.[103,123,124,125] Other patterns seen concomitantly or in lieu of consolidation include bronchial wall thickening and dilatation, nodules and ground glass or reticular opacities.[122,123,125]

Bronchoalveolar lavage may assist in making or excluding this diagnosis. Increased cellularity is found in BOOP with a marked elevation in lymphocytes (usually ≥ 25%).[84,108,115,116,126,127,128] The CD4:CD8 ratio is reduced.[108,126,127,128] Increased numbers of neutrophils (around 10%) and eosinophils (around 5%) are also seen. Some data indicate a role for mast cell activation in BOOP as well.[116]

Definitive diagnosis requires a surgical (open or thoracoscopic) lung biopsy, but when a patient has typical clinical and radiologic findings, a transbronchial biopsy may suffice.[84,126,129,130] This is particularly true, according to Epler, when both bronchiolar and alveolar elements demonstrate fibroblastic granulation tissue plugs.[82] However, in one study by Lohr and colleagues, 36 patients were diagnosed with organizing pneumonia by transbronchial biopsy and only one of these demonstrated bronchiolar polyps.[84] In patients with less than classic imaging studies or atypical symptoms, a transbronchial specimen cannot be relied upon to make or exclude the diagnosis.

Uncommonly, BOOP is a fulminant illness which may progress rapidly to respiratory failure over a period of days.[131,132,133,134,135,136] Acute, severe BOOP may be seen with idiopathic or

secondary forms of organizing pneumonia. Distinguishing this variant from AIP (or DAD of other cause) is clinically impossible, and may be challenging even for the pathologist.[1]

With BOOP, spontaneous recovery is unusual.[77,108,136] Corticosteroids are the mainstay of therapy. Prednisone is given at a dose of 0.75-1.0 mg/kg/day for 4-8 weeks before slow tapering to 10-15 mg a day or every other day.[80,109,111] Symptoms improve quickly in about 80% of patients,[77,109,115,126,137] but complete radiographic resolution may take several weeks, and about one third demonstrate residual radiographic or physiologic abnormalities.[77,85,118,126] Approximately 15% of patients have refractory and progressive disease leading to fibrosis and architectural distortion of the underlying lung parenchyma.[115,131,135] Death occurs in 3-12% of affected patients.[77,85,86,118] Progression of infiltrates shortly after initiation of treatment is not rare and was seen in 40% of 15 cases in one series.[108] In most instances, this is not reason for concern. However, in rapidly evolving BOOP associated with respiratory failure, aggressive treatment with up to one gram per day of methylprednisolone is warranted. Unfavorable prognostic features include a sudden onset of disease with rapid progression, reticulonodular infiltrates, severe hypoxemia at presentation, and serious underlying conditions like collagen vascular disease or malignancy.[84,115,131,132,138]

Relapses are frequent (20-35%) during tapering or after withdrawal of steroid therapy, particularly when short course treatment regimens are utilized.[77,84,108,115,138,139] Still, because of the wide range of untoward effects associated with long term corticosteroid use, an argument can be made to limit treatment to three or four months in complete responders. Cordier suggests that long-term therapy up to 12 months can be reserved for patients who relapse.[80] In some cases, relapse can be prevented with very low dose alternate day regimens. In one case, BOOP was purportedly cured by standard dose inhaled corticosteroids after prolonged treatment.[140] Such reports have to be interpreted cautiously since some forms of BOOP (particularly post-infectious BOOP) may resolve spontaneously with enough time. In progressive cases, cytotoxic therapy[133] or macrolide treatment[141] may be considered. Macrolide antibiotics have a variety of direct antiinflammatory effects and have been used with great success in diffuse panbronchiolitis.[142] Their use is now being investigated in a variety of other small airways diseases.

Immunologic Forms of Acute Interstitial Lung Disease

Acute Eosinophilic Pneumonia

Acute eosinophilic pneumonia (AEP) is a rapidly evolving febrile illness that is commonly associated with hypoxemic respiratory failure (table 1).[143] It was first described in 1989.[144,145] There appears to be either an increased incidence or increased awareness of this disorder in Southeast Asia because many of the reports in the literature have originated from this region.[146,147,148,149,150,151,152] Its major symptoms consist of cough, dyspnea and fever.[143,153,154] The mean temperature elevation in the two largest series was 101.4°F.[143,153] Headache, malaise, chest pain and myalgias are also common. Physical examination usually reveals diffuse or basilar-predominant crackles; but occasionally, auscultation is normal or mild wheezing is appreciated.[143,153,154] Spirometry indicates mild restrictive impairment in most cases.[143,144]

Radiographs initially show bilateral interstitial infiltrates. Kerley B lines are often seen. Within a short period of time (hours to a few days), most patients develop alveolar filling.[143,146,153] Pleural effusions are common. Chest CT scans show patchy bilateral ground glass opacities in almost all patients.[146,147] Interlobular septal thickening, zones of frank consolidation and poorly-defined nodules can also be seen. The clinical and radiographic features are completely nonspecific and suggest an atypical pneumonia. Hypoxemia is usually severe, and mechanical ventilatory support is required in many cases.[143,145,153] Peripheral eosinophilia is usually absent or modest at the time of presentation, although it frequently is seen during the resolution phase of the illness.[143,148] Significant leukocytosis with a neutrophil predominance is usual, reinforcing initial misconceptions that the lesion is of infectious origin.

Bronchoalveolar lavage is the key to diagnosis in most cases (see table 5 for diagnostic criteria). BAL almost uniformly reveals a marked increase in eosinophils (≥ 25% of the cellular differential).[143,147,153] BAL lymphocytes and neutrophils are also increased. Rare cases do not

show BAL eosinophilia but nevertheless have diagnostic histopathology.[149] Biopsies are not usually required to secure the diagnosis but demonstrate features of acute and organizing diffuse alveolar damage with prominent interstitial and alveolar eosinophils, mononuclear cells and macrophages.[143,146,155,156] In contrast to Churg-Strauss syndrome which is also associated with pulmonary infiltrates and eosinophilia, vasculitis and granulomas are not a feature of AEP.

Table 5. Diagnostic criteria for acute eosinophilic pneumonia. Adapted from Pope-Harman[143] and Tazelaar[155]

Acute febrile illness of ≤ 7 days duration
Severe hypoxemia often with respiratory failure
Diffuse alveolar, interstitial or mixed pulmonary infiltrates
BAL eosinophilia ≥ 25% or diagnostic histopathology (surgical biopsy)
Absence of infection, drug toxicity, vasculitis
Prompt and complete response to corticosteroids
Absence of relapse after steroid tapering

Patients with AEP usually respond rapidly to treatment with systemic corticosteroids.[143,144,145,153,155,157,158] High dose steroids (methylprednisolone 40-125 mg IV q6) are recommended for initial treatment of patients requiring mechanical ventilation, but there are also multiple reports of patients improving spontaneously in the hospital within one or two weeks with only supportive care (and empiric antibiotics).[146,147,150,151] When steroids are employed, they are usually tapered over a couple of weeks to a couple of months. Unlike chronic eosinophilic pneumonia, recurrences are extremely rare.[143,144,150,151]

AEP is a diagnosis of exclusion. Other conditions associated with pulmonary infiltrates and eosinophilia are listed in table 6. AEP is not synonymous with Löeffler's syndrome (simple pulmonary eosinophilia). That disorder is characterized by very mild symptoms, mild peripheral eosinophilia, and fleeting pulmonary infiltrates.[159]

Table 6. Major causes of pulmonary eosinophilia.

Acute eosinophilic pneumonia	Löeffler's syndrome
Chronic eosinophilic pneumonia	Parasitic infection
Allergic bronchopulmonary mycoses	Churg-Strauss syndrome
Fungal infection	Drug toxicity
Idiopathic hypereosinophilic syndrome	

In many cases, AEP appears to represent an acute hypersensitivity reaction to various antigens, most of which are inhaled.[145,160] Certain exposures are known or believed to cause acute eosinophilic pneumonia, but the majority of cases are idiopathic.[143,153] A number of reports have indicated an association with tobacco abuse, especially the recent onset of cigarette smoking (often ≤ 2 weeks in duration).[153,161,162,163,164] In a few cases, recurrence of AEP symptoms has been confirmed after rechallenging patients with exposure to tobacco smoke.[161] Some cases are incited by exposure to *Trichosporon* or *Trichoderma* species from soil or dust in the home.[150,151,165] One subject developed AEP after intentional inhalation of 1,1,1-trichloroethane (Scotchguard).[166] Others occurred after initiating treatment with venlafaxine, a 5-hydroxytryptamine and norepinephrine reuptake inhibitor[167], trazodone[168], pentamidine[169], and GM-CSF[170]. Simple pulmonary eosinophilia is a fairly common reaction to several other drugs, but these agents have been associated with a true acute eosinophilic pneumonia and severe respiratory embarrassment.

Some early reports stressed the lack of association with atopic disease, but others have indicated a frequent history of allergic rhinitis, allergic dermatitis and/or elevated serum IgE levels.[147,148,151,171] Unlike chronic eosinophilic pneumonia, asthma (or significant airflow limitation) is not a feature of this disease although some patients develop transient wheezing.[143,148]

BAL levels of IL-5 are elevated in patients with AEP.[152,164,172] This cytokine is thought to be a central mediator in the pathogenesis of eosinophilic pneumonia. IL-5 promotes eosinophil chemotaxis, adherence and degranulation while prolonging survival through inhibition of eosinophil

apoptosis.[173,174,175,176,177] IL-5 is increased in the serum of some patients with AEP as well.[152] GM-CSF has been detected in high concentrations in BAL fluid and could also contribute to eosinophil activation and recruitment in the lung.[164] Significant differences have been noted with respect to adhesion molecule expression in BAL eosinophils compared to peripheral blood eosinophils.[152] This may be an important factor contributing to compartmentalization of the injury, limiting eosinophil-mediated damage to the lung.

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is a syndrome resulting from sensitization to a wide variety of inhaled organic dusts.[178,179,180,181] These complex organic particulates may be derived from animal, plant, bacterial, fungal or amebic origin. The source may be in the home or the workplace, and is sometimes linked to specific hobbies. Among the more common causes are thermophilic actinomycetes found in wet hay (farmer's lung), avian proteins (bird fancier's disease)[182,183], and various fungi or molds like *Alternaria* (wood worker's disease),[184,185] *Cladosporium* (sauna-takers disease)[186], *Aspergillus* (malt-worker's lung) or *Trichosporon* species (summer type hypersensitivity pneumonitis).[187,188] Certain highly reactive chemicals like toluene diisocyanate and trimelletic anhydride can also cause HP.[189,190] These substances are used in the manufacture of paints and plastics and are capable of forming protein-hapten complexes that are immunogenic.

Depending on the antigen involved, 5-15% of repeatedly exposed persons will develop HP.[191,192] Many more asymptomatic subjects show serologic evidence of an immunologic response to the antigen but fail to develop disease. Importantly, in about 10% of patients with HP, precipitating antibodies (serum precipitins) cannot be detected by currently available methods.

Acute, subacute and chronic presentations of HP are recognized.[193] This discussion will focus on the more acute forms of the disease. These syndromes are not merely different stages of one disease. Acute HP uncommonly progresses to the chronic form, and many patients with chronic HP have no history of acute flares.[194,195] Notwithstanding, some patients with subacute HP and persistent antigen exposure will progress to fibrosis. The nature of the presentation is largely dependent on the intensity and duration of antigen exposure. Brief exposure to large antigen loads produces the acute syndrome, while chronic HP results from long-term low-level exposure.[196] Other factors influencing the clinical response include the type of inhaled antigen and ill-defined host factors relating to modification of the immune response.[181]

Acute HP is by far the most prevalent reaction. Once sensitization has occurred, a single high intensity antigen exposure may elicit a violent reaction four to eight hours later characterized by high grade fever, chills, cough, chest tightness and dyspnea. Malaise, myalgias, arthralgias and headache are also common. Physical examination may indicate a toxic appearance with bilateral crackles and cyanosis in severe cases. The white blood cell count is elevated with a left shift. Mild eosinophilia is seen occasionally. Hypergammaglobulinemia is typical, but IgE levels are normal. Chest films in the acute form of HP reveal widespread ground glass or alveolar infiltrates usually with a middle lung zone predominance.[197,198] The subacute form is often characterized by fine nodular (miliary-like) or reticulonodular opacities with variable ground glass attenuation.[197] In chronic HP, a primarily reticular pattern is seen that may have an upper lung zone predominance. Importantly, acute and subacute forms of the disease are commonly associated with normal chest roentgenograms despite rather impressive symptoms.[199,200,201] Pulmonary function tests in acute HP typically show a restrictive defect with a reduction in diffusing capacity.[202,203] As bronchiolitis develops in subacute or chronic HP, an element of airflow limitation may be seen as well.[204,205]

The signs and symptoms of acute HP generally abate within 24-48 hours with no specific therapy other than removal from the antigenic source. The symptoms tend to recur, however, upon repeat exposure. For patients who are not in a high risk group (e.g., farmers or bird breeders), the diagnosis may not be considered until the patient returns three or four times with the same flu-like syndrome. Most physicians have a low index of suspicion for this disorder. The symptom complex and radiographic findings are indistinguishable from atypical infections like viral pneumonia or mycoplasma.[206] To further complicate matters, patients may even have a nonspecific increase in antibody titers to these atypical infectious agents during an HP flare.[207] In

farmers presenting with symptoms like these, the differential should also include silo-filler's disease (mediated by NO_2 inhalation) and the organic dust toxic syndrome (ODTS) caused by massive exposure to bacterial endotoxins or fungal mycotoxins in moldy hay.[208,209,210,211] ODTS presents similarly with fever, chills, malaise, myalgias and arthralgias. Respiratory complaints in ODTS range from nasal and throat irritation to cough, dyspnea, chest tightness and wheezing. It is not a hypersensitivity reaction and does not require previous sensitization. The subacute form of HP has a broad differential diagnosis that includes miliary tuberculous and fungal disease, sarcoidosis and many other forms of diffuse infiltrative lung disease.[212,213]

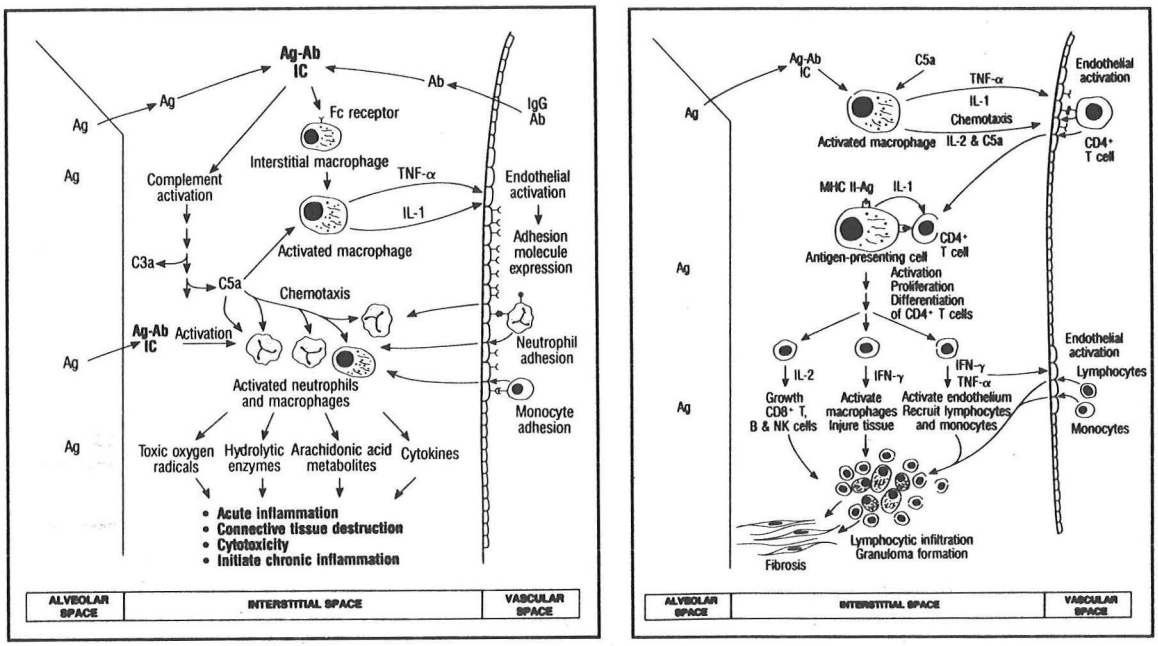
Hypersensitivity pneumonitis may be considered a paradigm of immunologic lung injury, both acute and chronic. Normally, of course, cellular and humoral immune responses protect against antigen-mediated injury. Unfortunately, dysregulated or particularly intense immune responses are themselves capable of inducing tissue damage. The pathogenesis of HP involves both a type III immune complex (Arthus) reaction and a type IV delayed type hypersensitivity reaction.[214,215] The acute form of HP represents an immune complex mediated form of acute lung injury (figure 4a).[180,215,216] Serum-derived IgG present in lung tissue and alveolar spaces combines with the inhaled antigen and activates macrophages promoting the release of proinflammatory cytokines like IL-1 and TNF-α.[217,218,219] They also activate complement by the alternate pathway.[220] Together, these substances incite a neutrophilic (and lymphocytic) alveolitis.[215,221, 222,223,224] Neutrophil activation is associated with the release of toxic oxygen species, proteases and additional proinflammatory cytokines.[225,226] The subsequent injury to the alveolar-capillary membrane results in increased vascular permeability with interstitial edema and a proteinaceous alveolar exudate.[221] The antigens associated with HP are not directly toxic to the lung, and only cause injury because of these inflammatory responses.[180,227]

Immune complex formation is probably not instrumental in the pathogenesis of HP beyond the first few days. As the acute phase of the injury subsides, it is replaced by a T-cell mediated delayed hypersensitivity reaction which may perpetuate lung damage in patients with continued antigen exposure (figure 4b).[228] The BAL neutrophilia disappears as a lymphocytosis, mediated in part by IL-2, evolves.[229] CD4+ T-cells are the main effectors of delayed type hypersensitivity reactions, including experimental forms of HP, and it is curious that the BAL indicates a predominance of CD8+ lymphocytes in most cases (CD4:CD8 <1).[230,231,232,233] This is not to say that there is not an absolute increase in BAL CD4+ cells as well. Most of the CD8+ cells do not exhibit a cytotoxic phenotype, but may augment CD4 cell mediated reactions through the release of cytokines.[180,234,235] In some cases, CD4+ cells do predominate.[236] If a bronchoalveolar lavage is performed immediately after antigen challenge in patients with subacute or chronic HP, a transient neutrophil predominance will also be seen.[222,224]

Acute HP is a clinical diagnosis where a temporal association is established between the candidate exposure and the onset of symptoms. When symptoms flare upon repeat exposure to the suspect environment, a presumptive diagnosis can be made. Serum precipitins are a marker of exposure and indicate an immune response by the host, but their mere presence does not confirm a causal role for a particular antigen in the development of lung disease. Occasionally, provocation testing is performed when the diagnosis is uncertain.[237,238] These tests available only in specialized centers, and the lack of standardized antigen preparations and dosing recommendations severely limits the value of laboratory-based inhalational challenges. It is often more useful and practical to expose the patient to the suspect natural environment while monitoring his or her response. Lung biopsies are almost never obtained since the syndrome clears so quickly. High resolution computed tomography (HRCT) shows patchy or diffuse ground glass opacification sometimes with frank consolidation.[239,240] HRCT is considerably more sensitive than routine chest radiographs in patients with acute HP.[241] Physicians must remember not to exclude this diagnosis simply because plain films fail to indicate any abnormalities.

Figure 4. Schematic of the primary pathophysiologic mechanisms involved in acute (4a) and subacute (4b) hypersensitivity pneumonitis. In acute HP, immune complex triggered interstitial inflammation results in cellular injury and edema formation. If antigen stimulation persists, a T cell mediated delayed-type hypersensitivity reaction develops within the interstitium producing a lymphoplasmacytic infiltrate and granuloma formation. From Kaltreider[180]

4a) 4b)



The diagnosis of subacute HP is based on principles similar to those described above. However, when the onset of disease is more insidious, and particularly when intermittent flu-like symptoms are absent, definitive diagnosis requires histologic confirmation. Typical findings on a surgical biopsy specimen include a lymphoplasmacytic interstitial infiltrate and poorly formed noncaseating granulomas.[1,242,243] Early on, proteinaceous alveolar exudates are seen.[244] Air spaces commonly contain abundant foamy macrophages. Constrictive (BO) or proliferative (BOOP) bronchiolitis may also be seen.[205,245] Other features supportive of a diagnosis of subacute HP include the presence of serum precipitins and a marked BAL lymphocytosis usually with a predominance of CD8 positive T cells.[223,246,247] In addition to zones of ground glass opacification or airspace disease (as seen in acute HP), HRCT scans often indicate ill-defined centrilobular nodules reflecting the bronchiolocentric inflammatory changes.[201,239,240] Since the trigger for this type of injury gains access to the lungs by inhalation, it is not surprising that the inflammatory response is often accentuated around the small airways. If a patient has a good history for subacute HP, compatible HRCT findings and a BAL lymphocytosis (typically >50% of recovered cells), that is sufficient for diagnosis. Serum precipitins are helpful, but are negative in 10% of cases.

The cornerstone of therapy for HP is early recognition and antigen avoidance. Unfortunately, some immunogenic peptides such as bird antigens may persist for extended periods of time despite intensive clean-up efforts.[248] Moreover, bird breeder's are notorious for refusing to part with their avian friends, and for a farmer, changing occupations is frequently implausible.[249] Interestingly, though, many patients with acute HP who have persistent antigen exposure do not go on to develop chronic, fibrotic lung disease, and may even stop having acute attacks.[195,250] This is probably a result of antigen-specific immunologic tolerance.[251] OSHA-approved dust masks are useful but impractical when they must be worn for extended periods of time or during physical labor.[252] Corticosteroids are the mainstay of therapy in severe acute HP and in progressive forms of the disease. Like sarcoid, steroids accelerate recovery in HP, but it is unclear whether they affect the long-term physiologic outcome in these patients.[253] As a general

rule, patients without steroid tolerance issues (i.e., diabetics) are given 1 mg/kg/day of prednisone for one month before gradual tapering. Long-term treatment may be required if the disease flares as immunosuppressive therapy is weaned. Anecdotal data suggest a possible role for high dose inhaled steroids in HP.[254,255]

The mortality rate of acute HP, especially related to farmer's lung, appears to be quite low, perhaps 1%.[250,256] Patients with chronic bird-related disease may not fare as well. The 5 year mortality in one large study was 25%.[257] Because many of these patients have low level, long-term exposure histories, they often have a more insidious onset of symptoms. They may have no history of recurrent "attacks" or flu-like syndromes and, instead, present with established fibrosis. Some of these cases continue to progress similar to idiopathic pulmonary fibrosis even if antigen exposure is eliminated.

The Alveolar Hemorrhage Syndromes

The alveolar hemorrhage syndromes are characterized by widespread bleeding from the pulmonary microvasculature into the airspaces. Although diffuse alveolar hemorrhage (DAH) is uncommon, it can occur in association with a large number of mostly immune-mediated disorders (see Table 7).[258,259,260,261] The presentation is similar regardless of the underlying cause. Symptoms usually evolve over hours to several days. Patients complain of cough, dyspnea, and hemoptysis.[259,262,263] Hemoptysis, however, is present in only two thirds of affected individuals at the time of presentation. It eventually develops in almost everyone.[259,264,265,266] Because the site of hemorrhage is so distal within the pulmonary parenchyma, massive expectoration of blood is unusual.[267] In fact, the degree of hemoptysis often seems disproportionately low compared to the extent of alveolar filling. Fever (T > 38°C) is seen in one third of subjects and some patients complain of chest pain. Anemia and/or a falling hematocrit are uniformly identified in patients with active DAH. In some cases, the hemorrhage progresses rapidly to hypoxemic respiratory failure necessitating mechanical ventilatory support.

Chest radiographs usually reveal bilateral alveolar consolidation with sparing of the apices. A symmetrical, perihilar predominance is sometimes seen, but the infiltrates may be patchy or asymmetrical, especially early on. Sometimes an ill-defined nodular (acinar) or ground glass pattern is seen.[259,268,269,270,271] The chest x-ray may even be normal in up to 20% of patients.[268] When the hemorrhage stops, blood is resorbed from the airspaces quickly over two or three days. The alveolar consolidation gives way to a more reticular appearance that usually clears over a couple of weeks.[271] The radiographic patterns are nonspecific and difficult to distinguish from atypical pneumonia, cardiogenic and noncardiogenic pulmonary edema, eosinophic pneumonia, BOOP, proteinosis and certain malignancies (i.e., lymphoma and alveolar cell carcinoma). Each of these disorders has the potential to produce a rather explosive airspace filling process.

A marked elevation in the diffusing capacity for carbon monoxide (CO) is usually seen in DAH due to the large extravascular pool of erythrocytes that are capable of binding CO.[272,273] This may be useful for detecting fresh bleeding within about 48 hours. It may also suggest that alveolar hemorrhage is the cause of the diffuse parenchymal lung disease in cases that are not associated with hemoptysis. It is most useful when baseline tests are available and less useful when patients are acutely ill as many of these subjects are. Nevertheless, it may also help determine if active bleeding is occurring in patients on therapy who have persistent radiographic abnormalities or a drifting hematocrit. See table 8 for the routine diagnostic approach to patients with suspected diffuse alveolar hemorrhage.

In most instances, DAH results from cellular (i.e., neutrophilic) or humoral (i.e., ABMA or immune complex) immune-mediated acute lung injury. Many of the disorders that cause alveolar hemorrhage are systemic illnesses. Extrapulmonary manifestations like skin rashes, arthritis, sinus and renal disease may provide valuable insight into the underlying etiology. Patients frequently present with a pulmonary-renal syndrome (hematuria, proteinuria, and/or an elevation in serum creatinine along with alveolar hemorrhage). These disorders include the anti-neutrophil cytoplasmic antibody (ANCA)-related systemic vasculitides, anti-basement membrane antibody (ABMA) disease, idiopathic rapidly progressive glomerulonephritis (RPGN) and several collagen vascular diseases.[259]

Table 7. Main Causes of Diffuse Alveolar Hemorrhage.

Capillaritis	**Bland pulmonary hemorrhage**
Wegener's granulomatosis	Idiopathic pulmonary hemosiderosis
Systemic necrotizing granulomatosis	Goodpasture's syndrome**
Collagen vascular disease*	Coagulation disorders
Isolated pulmonary capillaritis	Mitral stenosis
Henoch-Schönlein purpura	Drug-induced DAH
Behçet's disease	Trimellitic anhydride exposure
Cryoglobulinemia	
Pauci-immune glomerulonephritis	
Diffuse alveolar damage	**Miscellaneous**
Systemic lupus erythematosis	Lymphangioleiomyomatosis
Cytotoxic drug therapy	Pulmonary veno-occlusive disease
Crack cocaine	Pulmonary capillary hemangiomatosis

* may be associated with capillaritis, bland hemorrhage or diffuse alveolar damage
** some cases also associated with capillaritis

ABMA, or Goodpasture's syndrome, typically affects young men.[262] It usually produces a "bland" pulmonary hemorrhage without evidence of inflammation in alveolar walls.[1,274,275] In the kidney, a rapidly progressive crescentic glomerulonephritis is seen.[262,276] The pathologic hallmark of ABMA disease is linear staining on immunofluorescence studies. This pattern is detectable in both lung and renal biopsies, but immunohistochemical stains of lung tissue are significantly more challenging. Interestingly, patients with ABMA disease who smoke have a much greater risk of developing DAH, while nonsmokers often manifest only renal involvement.[277] This is presumably because smoking independently impairs the integrity of the alveolar-capillary membrane ("two-hit" hypothesis).

Patients with Wegener's granulomatosis (WG) typically have a triad of sinus, pulmonary and renal involvement in addition to a positive serum cANCA antibody directed against proteinase 3.[278,279] This disease is characterized by necrotizing granulomatous inflammation of medium and small vessels.[278,280] Nodules and localized infiltrates (often cavitating) are classically seen on chest x-ray, but not in the fewer than 10% of patients who develop DAH. When diffuse alveolar hemorrhage does occur in WG, it is often the initial manifestation of the disease. It is also usually associated with rapidly progressive glomerulonephritis. Consequently, compared to patients with a more classical presentation of WG, these patients do much worse. Up to two-thirds die with the first episode. The distinctive histologic finding in this population of WG patients is widespread pulmonary capillaritis.[261,280,281]

Capillaritis is a unique form of interstitial pneumonitis characterized by neutrophilic infiltration of alveolar septae.[1,261,282] The lesion is similar to the skin disorder known as leukocytoclastic vasculitis. Some of these neutrophils have fragmented or pyknotic nuclei. Fibrin thrombi appear within alveolar capillaries, and capillary walls are destroyed by a process called fibrinoid necrosis. This allows for the extravasation of erythrocytes and inflammatory cells into alveolar spaces. Since capillaries represent the major anatomic structure in the alveolar wall, the entire septum may vanish in some areas.[1,282]

Capillaritis is certainly not unique to WG. In one series examining DAH of various etiology, 30 (88%) of 34 patients demonstrated this lesion.[260] Other common causes include systemic necrotizing vasculitis (SNV), sometimes called microscopic polyangiitis, and collagen vascular disease. In a few cases, a clearly definable association cannot be identified (idiopathic capillaritis). In others, capillaritis is a transient finding. For instance, Travis noted that

occasionally, capillaritis identified by surgical lung biopsy was no longer apparent at autopsy several days later in patients who expired.[260]

Systemic necrotizing vasculitis (microscopic polyangiitis) is another important ANCA-associated disease that may cause DAH.[260,283,284,285,286] Like WG, this lesion is predominantly a capillaritis (and venulitis/arteriolitis), but medium-sized vessels are sometimes involved.[1] Granulomatous features are lacking and large zones of necrosis are not seen. Diffuse alveolar damage may be associated with this disorder.[1,287,288] Immunofluorescence studies indicate a perinuclear (p-ANCA) staining pattern in neutrophils. These are mainly anti-myeloperoxidase antibodies that can, like cANCAs, stimulate leukocytes to produce endothelial injury.[289] Notably, though, all of the ANCA-related vasculitides are pauci-immune lesions with little or no evidence of immune deposits in affected tissues.[290] This is in contrast to either ABMA disease or hemorrhage associated with collagen vascular disease. In one study of 36 patients with capillaritis and pulmonary hemorrhage, 27 (75%) demonstrated pANCAs while 9 (25%) had cANCAs.[290] The pANCA alveolar hemorrhage group includes not only subjects with SNV but also patients with idiopathic crescentic GN and occasional patients with WG.

Table 8. Diagnostic evaluation in suspected diffuse alveolar hemorrhage.

Historical considerations
- Drugs, autoimmune disease symptoms, cardiac or coagulation disorders
- Hematuria or decreased urine output
- Exclude aspiration of blood from upper airway or gastrointestinal tract source

Plain chest radiographs (bilateral alveolar or ground glass infiltrates)

Bronchoscopy with bronchoalveolar lavage
- Serial aliquots to confirm alveolar source (should see increasingly bloody effluent)

Laboratory assessment
- CBC
- BUN, creatinine
- U/A with microscopic
- ANA, RF, C3, C4
- ANCA, ABMA, circulating immune complexes, cryoglobulins
- DLCO
- Blood/BAL cultures

Diffuse alveolar hemorrhage is an infrequent manifestation of collagen vascular disease.[259,291,292,293,294] Still, this represents another manifestation of acute immune-mediated lung injury that must be differentiated from diffuse alveolar damage (acute lupus pneumonitis or AIP), rapidly progressive BOOP, drug-induced lung disease, uremic pneumonitis, myocarditis with heart failure, and pulmonary infection (opportunistic and otherwise).[295,296] Almost all of the DAH in connective tissue disorder patients is seen in systemic lupus erythematosus.[293,295] Occasional cases are seen in rheumatoid arthritis, polymyositis, progressive systemic sclerosis and mixed connective tissue disease.[258,292,297,298,299] Even among SLE patients, only 2% ever develop this life-threatening complication.[258,266,291,293] The reported mortality has ranged from 25-90%.[266,291,297] The mortality is higher in patients with a concomitant infection, and infection may be a precipitating factor in DAH.[293,300] Usually, there is overt clinical and serologic evidence of a systemic collagen vascular disease flare (including nephritis) when these patients develop pulmonary hemorrhage.[293] In about 20% of patients who develop lupus-related DAH, pulmonary hemorrhage is actually the presenting feature of the autoimmune disease.[293] Granular deposits of immune complexes (and complement) are seen on immunofluorescence studies of involved tissues, along with capillaritis in the majority of cases.[258,269,293,301,302,303] Immune complex deposition with DAH is not unique to the collagen vascular diseases, but has also been reported in disorders like Henoch-Schönlein purpura and cryoglobulinemia.[304,305,306,307,308] Occasionally, a bland pulmonary hemorrhage is identified, and sometimes the dominant underlying histologic reaction is diffuse alveolar damage.[1,293,309] DAD may be a direct consequence of the autoimmune disorder (i.e., acute lupus pneumonitis), or it may be caused by infection. Vascular invasion by fungi with hemorrhagic infarction can also result in DAH in these immunosuppressed patients.

Pulse steroid therapy is the cornerstone of initial treatment in all forms of immune alveolar hemorrhage.[259,291,293,301] Concomitant cytotoxic therapy is often employed as well. Cyclophosphamide is preferred in Wegener's granulomatosis and systemic necrotizing vasculitis.[259,261,278] Azathioprine is utilized more frequently in DAH associated with the collagen vascular diseases, but some prefer cyclophosphamide here as well.[261,293,291] Plasmapheresis is useful in the management of ABMA disease, but it has not been proven effective in SLE even though this appears to be an immune complex mediated disease.[310] In general, it is important to treat any underlying infection, avoid excessive filling pressures, and address all coagulation issues including uremic platelet dysfunction.[259,311] Since tobacco abuse alters permeability of the alveolar-capillary membrane and increases the risk for developing DAH, smoking cessation is also essential.[277]

Acute Immunologic Pneumonia

In addition to AIP, BOOP and DAH, patients with collagen vascular diseases, particularly systemic lupus erythematosus and polymyositis, may develop acute immunologic pneumonias.[29,295,312,313,314] Pulmonary capillaritis is actually one type of acute immunologic pneumonia, but acute lupus pneumonitis (ALP) is the archetypal example of this syndrome.[301,312] It is characterized clinically by a usually abrupt onset of fever, cough and dyspnea.[312,315] Hypoxemic respiratory failure may ensue.[312,316] Pleuritic chest pain and hemoptysis are fairly common. In most cases, patients show evidence of a systemic lupus flare with arthritis and nephritis.[312] Chest films usually reveal bilateral infiltrates often favoring the lung bases, but unilateral or asymmetrical changes can occur.[295,312,316] Pleural or pericardial effusions may also be seen.[312,313] ALP develops in 1-12% of lupus patients at some time during the course of their disease.[312,313] It is the presenting manifestation of lupus in up to half of those affected.[312] The mortality of this syndrome approaches 50%, but patients do not always die of respiratory failure. Some of the deaths are linked to other autoimmune injuries such as acute renal failure or cerebritis, while others are related to nosocomial complications like infection or pulmonary embolism.

The pathology of acute lupus pneumonitis is variable.[1,312,317,318,319] Acute or exudative diffuse alveolar damage with hyaline membranes, interstitial and alveolar edema is usually the main histologic finding in ALP. These patients may also have a prominent cellular (lymphoplasmacytic) interstitial pneumonia. Foci of BOOP may be seen, and alveolar hemorrhage is common.

No controlled trials of therapy are available for acute lupus pneumonitis. In most cases, patients are treated initially with high dose corticosteroids.[312,320] Cytotoxic agents like azathioprine or cyclophosphamide are frequently employed as well.[312,313,321] Plasmapheresis is sometimes used in refractory cases.[322]

Drug-Induced Acute Interstitial Lung Disease

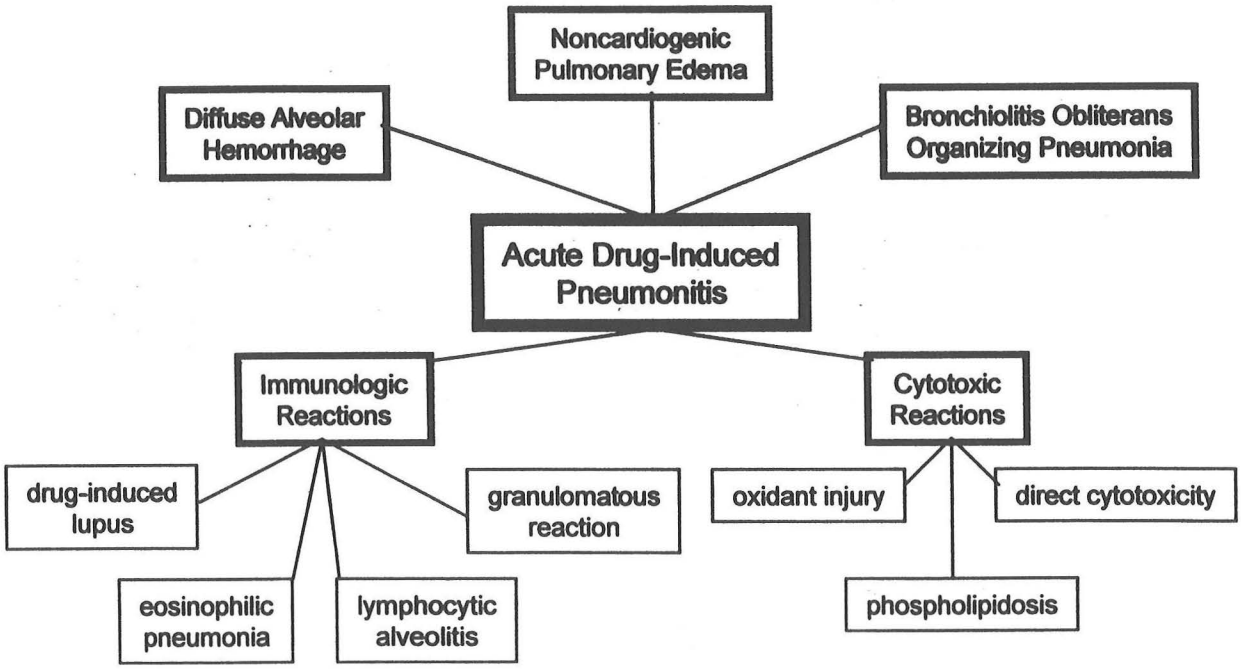
Drug toxicity is always a consideration when patients present with diffuse parenchymal lung disease. More than 100 different drugs are known to produce adverse effects in the lung ranging from simple cough or bronchospasm to acute respiratory failure with widespread pulmonary infiltrates.[323,324,325,326,327,328] Among the more serious acute or subacute drug-induced injuries are noncardiogenic pulmonary edema, diffuse alveolar damage, a cellular interstitial pneumonia with or without fibrosis, BOOP, and DAH.[323,329] Because drug reactions are commonly associated with fever and patchy "mixed" infiltrates, they may be easily confused with atypical pneumonias.

Most drugs that cause pulmonary infiltrates do so by either cytotoxic or immunologic mechanisms (figure 5). Within these broad categories are several subsets. Drugs that induce immune-mediated lung injury do so by several mechanisms including drug-induced lupus, eosinophilic pneumonia, granulomatous inflammation or, more commonly, other "hypersensitivity" reactions associated with a lymphocytic alveolitis.[325,329] These conditions are notable for a generally good prognosis and a high degree of reversibility provided that they are recognized early. Simple discontinuation of the offending drug is usually sufficient for patients who are not

severely ill. For others, corticosteroids may speed recovery and hasten resolution of radiographic opacities.

Unfortunately, cytotoxic drug injuries are much more likely to be associated with irreparable damage and fibrosis.[324,329,330] These agents induce type 1 and type 2 cell atypia, and also have varied means of producing cellular injury. Many chemotherapeutic drugs, for example, are directly cytotoxic to the alveolar-capillary membrane. Others produce cytotoxicity through oxidant metabolites or the generation of toxic oxygen species like superoxide, hydrogen peroxide or hydroxyl radicals. These drugs may synergize with other sources of oxidant stress like high inspired fractions of oxygen or concomitant radiation therapy to increase the chance of developing serious lung injury. Amphophilic drugs like amiodarone may produce extensive phospholipid deposition (phospholipidosis) within several cell types in the lung. This is also thought to have a cytotoxic effect on alveoli. Proinflammatory substances released from damaged or dying cells tend to perpetuate the injury. The lung's reparative response to cytotoxic damage usually takes the form of either diffuse alveolar damage or a chronic interstitial pneumonia with fibrosis. Occasionally, BOOP is seen as well.

Figure 5. Mechanisms of Drug-Induced Pneumonitis.



Other pharmaceutical agents cause acute pulmonary syndromes that cannot be classified as "cytotoxic" or "immunologic" injuries. These include noncardiogenic pulmonary edema, diffuse alveolar hemorrhage and BOOP (table 8).[323,328,329] Cessation of the offending drug and supportive care form the backbone of treatment in patients with noncardiogenic edema. Steroids are employed in drug-induced BOOP and certain types drug-induced alveolar hemorrhage. Interestingly, some drugs have several different ways of producing acute or chronic lung injury. For instance, amiodarone may cause BOOP, diffuse alveolar hemorrhage, diffuse alveolar damage, lipoid pneumonia or a chronic interstitial pneumonia with fibrosis as a result of cytotoxic or immunologic responses.

Table 8. Drugs or drug classes linked to acute pulmonary reactions.

Cytotoxic agents
Alkylating agents
- Cyclophosphamide
- Busulfan

Nitrosoureas
- BCNU

Cytotoxic antibiotics
- Bleomycin
- Mitomycin

Antimetabolites
- Methotrexate
- Cytosine arabinoside

Noncardiogenic edema
Salicylates
Narcotics/naloxone
Hydrochlorothiazide
Tricyclic antidepressants
Cytosine arabinoside

Alveolar hemorrhage
Amiodarone
Penicillamine
Nitrofurantoin
Mitomycin
Thrombolytics
Cocaine

BOOP
Gold
Amiodarone
Sulfasalazine
Penicillamine
Bleomycin
Methotrexate
Mitomycin
Cyclophosphamide

Hypersensitivity lung disease
Pulmonary eosinophilia
- Multiple antibiotics

Nonsteroidal agents
- Antidepressants
- GM-CSF

Granulomatous reaction
- Methotrexate
- BCG

"Hypersensitivity pneumonitis"
Nitrofurantoin
- Nonsteroidal agents
- Paclitaxel
- Sulfasalazine
- Drug-induced lupus
- Procainamide
- Hydralazine

Conclusion

The acute forms of interstitial lung disease are important to consider whenever patients present with the recent onset of cough, dyspnea and pulmonary infiltrates. The radiographic features of these syndromes are nonspecific, and these disorders are commonly confused with atypical pneumonias, heart failure or, in severe cases, ARDS. A thorough medical history is invaluable along with a high clinical index of suspicion whenever one is faced with an acute pulmonary syndrome of uncertain etiology. In most cases, some form of invasive testing (e.g., bronchoalveolar lavage, transbronchial or surgical lung biopsy) will be required to solidify these diagnoses.

In general, acute interstitial lung diseases are either immune-mediated injuries or they are linked to excessive fibroproliferation following cytotoxic, infectious or other inflammatory insults. Even among the immunologically driven disorders, considerable variation is evident with respect to pathogenesis. In some cases, eosinophils are the dominant effector cells. In others, a neutrophilic or lymphoplasmacytic infiltration develops within the interstitium. Still others are mediated by immune complex deposition or autoantibody formation.

In some patients a specific trigger or clinical association can be identified. Other cases are idiopathic. Even though most cases of BOOP are cryptogenic, for example, the same clinicopathologic syndrome can be induced by such varied injuries as infection, drugs, collagen vascular disease or radiation therapy. It is probably best, therefore, to think of the acute forms of ILD as distinctive patterns of lung injury and repair rather than specific diseases. The precise pattern observed may depend on a number of variables: 1) the nature of the injurious agent or disease trigger; 2) the intensity of exposure; 3) whether the trigger induces primarily a cytotoxic or

immunologic response; 4) individual differences governing the control of fibroproliferation; and 5) the major focus of injury (for example, the peribronchiolar tissues bear the brunt of the injury/remodeling process in BOOP and HP, while many drug-induced syndromes and AIP result from widespread alveolar-capillary membrane injury).

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