Occupation, Avocation, and Interstitial Lung Disease

Craig S. Glazer, M.D., M.S.P.H.

University of Texas Southwestern Medical School

Internal Medicine Grand Rounds

February 26, 2010

This is to acknowledge that Craig S. Glazer, M.D., M.S.P.H. has disclosed financial interests or other relationships with commercial concerns related indirectly to this Program. These relationships will not bias this activity. Dr. Glazer will be briefly discussing off-label uses in his presentation.

BIOGRAPHICAL INFORMATION:

Name: Craig S. Glazer, M.D., M.S.P.H.

Rank: Associate Professor

Division: Pulmonary and Critical Care Medicine

Interests: Occupational and environmental lung diseases

Occupational and environmental interstitial lung disease

Occupational granulomatous disease: chronic beryllium disease and bioaerosol induced lung disease

Pneumoconiosis

Interstitial lung diseases encompass approximately 200 distinct entities, all of which lead to the development of fibrosis and/or inflammation in the distal lung parenchyma. The epidemiology of this group of disorders remains poorly understood. Available data suggest there are approximately 100,000 hospitalizations per year in the United States. The annual incidence is approximately 30/100,000 and disease prevalence is approximately 70 per 100,000.[1] In addition, studies suggest the incidence and prevalence are increasing. However, these data suffer from significant limitations and little population based data exist regarding the various diseases within the category. The best available information in this regard comes from several available disease registries.[2-4] Review of these registries shows that idiopathic disease, especially idiopathic pulmonary fibrosis (IPF) and sarcoid, are the most common entities. However, occupational and environmental exposures account for 15-20% of all ILD in these various registries. The most common single disease within the occupational and environmental category is hypersensitivity pneumonitis. Occupational and environmental exposures thus represent a significant proportion of all ILD. In addition, ILD secondary to these exposures is preventable and in some cases treatable. Diagnosing these illnesses is thus important both for the individual patient and for coworkers and/or family members who may share the causative exposure.

Diagnosing an ILD secondary to an occupational or environmental exposure is often challenging. For example, detailed mineralogical microanalysis of lung biopsies in patients diagnosed with IPF indicate that in 25% of the cases an occupational exposure was the more likely cause.[5] Accordingly, a missed inhalational exposure is the most frequent reason ILD specialty centers will disagree with the diagnosis from a referring community physician.[6] In this study, hypersensitivity pneumonitis was the most frequently missed diagnosis.

The purpose of this paper is to review the clinical approach to making these diagnoses, focusing on the differentiation from idiopathic disease, especially the idiopathic interstitial pneumonias (IIP). We focus first on the diagnostic process beginning with when to suspect an occupational and environmental cause in general, followed by identification of clinical clues that suggest specific classes of exposure. We then review how to link an exposure with a disease and conclude with a brief overview of treatment.

When to Suspect an Occupational or Environmental ILD

As noted above, occupational or environmental exposures will account for one out of every 5 to 10 cases of ILD. In addition, there is tremendous pathologic overlap between idiopathic ILD including the various idiopathic interstitial pneumonias (IIPs), sarcoid and the various occupational and environmental exposures (see Table 1). No disease illustrates this better than hypersensitivity pneumonitis. Hypersensitivity pneumonitis (HP) is an ILD caused by inhalation and sensitization to a variety of organic antigens including bacteria, mycobacteria, fungi and animal proteins (especially avian) and a few reactive chemicals. The classic pathology is the triad of bronchiolitis, interstitial infiltrates with lymphocytes and plasma cells, and poorly formed granulomas.[7] However, it is now well shown that only one member of this triad may be present in any given individual. If that is the interstitial infiltrate then the histology is indistinguishable from Nonspecific Interstitial Pneumonia (NSIP).[8] Patients can also present as an isolated bronchiolitis.[9]

Table 1: Pathologic Patterns and the associated occupational/environmental causes

Pathology	Common Causative Exposures	Rare Causative Exposure
Granulomatous pulmonary inflammation	Hypersensitivity Pneumonitis (organic antigen, isocyanates, pyrethrum, anhydrides), Beryllium	Cobalt, aluminum, titanium, zirconium, talc
Usual Interstitial Pneumonia (UIP)	Asbestos, mixed dust, agents that cause hypersensitivity pneumonitis	Cobalt, wollastonite, attapulgite, sepiolite, mica, kaolin, rare earths, aluminum
Desquamative Interstitial Pneumonia (DIP)	No common exposures	Cobalt, aluminum, plutonium, asbestos, talc
Nonspecific Interstitial Pneumonia (NSIP)	Hypersensitivity Pneumonitis (organic antigen, isocyanates, pyrethrum, anhydrides)	Coal and silica can rarely cause a diffuse interstitial fibrosis similar to fibrotic NSIP
Organizing Pneumonia	NOx (silo-filler's lung)	Spray painting textiles – Acramin FWR;
Diffuse Alveolar Damage (AIP)	Irritant inhalational injury – NOx, SOx, cadmium, beryllium, chlorine, acid mists, etc.	
Giant Cell Interstitial Pneumonia (GIP)	Cobalt	
Pulmonary Alveolar Proteinosis	No common exposures	High level exposure to silica, titanium or aluminum dust
Constrictive bronchiolitis	Flavoring Workers (diacetyl), NOx, SOx, chlorine gas	

In addition, several recent studies show that Usual Interstitial Pneumonia (UIP), the pathology typically associated with IPF, can be the sole pathologic manifestation of chronic HP.[10, 11] Therefore, it is essential that the clinician consider occupational and environmental exposures whenever confronted with a patient suffering from ILD. One should not accept an idiopathic diagnosis until known causes are excluded. This includes connective tissue disease and drug reactions in addition to occupational and environmental exposures. The key to diagnosing an occupational or environmental cause is suspecting the possibility of an exposure related disease and then taking a thorough exposure history.

Although daunting, a careful history can provide several clues that can help the clinician suspect and define relevant exposures. For example, clusters of disease in coworkers, younger than expected age, and exposure to agents known to cause ILD should all suggest an occupational or environmental cause. There are also clues on the physiology, imaging and pathology that I will discuss below. Other historical clues are related to disease pathogenesis so a brief discussion of pathogenesis is warranted. This discussion is not intended to be comprehensive.

Pathogenesis

In general, the pathogenesis of ILD caused by occupational and environmental exposures can be divided into two categories. In the first group, activation of the adaptive or specific immune response is key to disease pathogenesis and thus host factors determine disease occurrence. In the second group, the offending agent leads to a nonspecific local inflammatory response. In this latter situation, specific exposures rather than host factors dominate pathogenic mechanisms.

Pathogenesis of Diseases where host factors predominate

The diseases that fall into this category include hypersensitivity pneumonitis, chronic beryllium disease (CBD) and possibly other metal induced disease including cobalt induced interstitial disease. CBD is a granulomatous disease clinically similar to sarcoidosis that is caused by the metal beryllium. All of these diseases are caused by repeated inhalation and subsequent sensitization to inhaled antigenic substances. The primary cell responsible is the activated T lymphocyte and in all these diseases T-helper memory cells with Th1 differentiation mediate the inflammation. For example, animal models of HP demonstrate that transfer of activated Th1 lymphocytes from a sensitized animal can transfer disease to an exposure naïve host. Transfer of plasma or Th2 lymphocytes does not transfer the disease. Interestingly, recent data also suggest a role for Th17 lymphocytes in the development of fibrosis.[12] The cell lines that can induce disease in a naïve animal demonstrate cellular markers consistent with an activated effector memory cell phenotype.[13]

This is the same cell type that is responsible for the inflammatory response in chronic beryllium disease (Figure1).

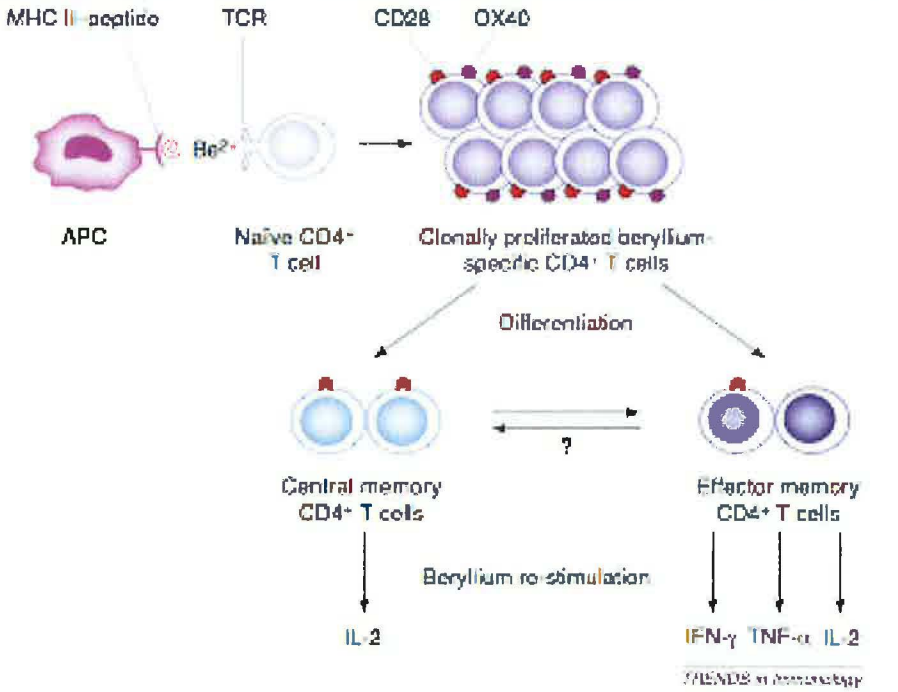

Figure 1: Immunopathogenesis of CBD, begins with presentation of antigen, clonal proliferation of specific T-cells and then differentiation to effector memory cells.[49]

CBD also illustrates why host factors dominate the pathogenesis of this group of illnesses. The risk for CBD development increases dramatically with certain HLA haplotypes. The primary HLA haplotype is an HLA-DPB1 with a glutamic acid at position 69 of the β-chain. This is a functional polymorphism that leads to a greater negative charge in an antigen binding pocket (Figure 2). This in turn facilitates its capacity to bind beryllium and present it to T-cells.

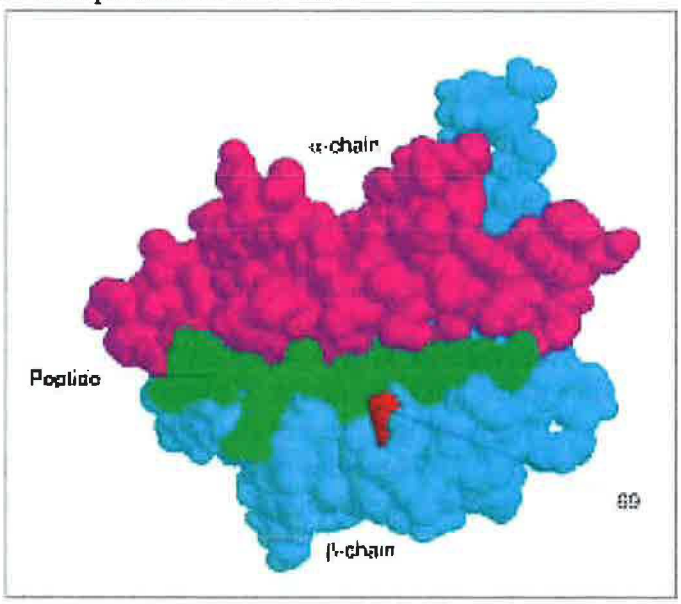

Figure 2: HLA DPB1 molecule illustrating the location of the glu 69 polymorphism in relation to the antigen binding pocket.[49]

Likewise, the T-cell receptor of the oligoclonal T-cell populations specific for CBD frequently express an aspartic acid at position 96 of the β chain within the complementarity-determining region. This also presents a negative charge that could interact with the above DP β chain with the positively charged Beryllium substrate acting as a bridging intermediary molecule.[14] This discussion illustrates that the development of one of the diseases in this group is in large part determined by the capacity of an individual's immune system to recognize and subsequently respond to an inhaled antigen. This is in contrast to diseases where exposure factors dominate the pathogenesis.

Pathogenesis of Disease where exposure factors predominate

The disease that fall into this category include the inorganic dust induced diseases, or pneumoconioses. The classically described and most common diseases in this category include asbestosis, silicosis and coal worker's pneumoconiosis. In contrast to the above, these agents activate a non-specific local inflammatory response after inhalation and pulmonary deposition. The pathogenesis is dominated by exposure factors including fibrogenic potential of the inhaled agent and total exposure dose rather than its antigenic characteristics. There are numerous other dusts that have rarely been reported to cause pneumoconiosis but the incidence with the other agents is dramatically lower, likely due to the reduced fibrogenic potential of the other dusts. The initiation of the local inflammatory response in silicosis and asbestosis occurs via activation of the Nalp3 inflammasome. The Nalp3 inflammasome is a Nod-like receptor protein complex that activates caspase-1,

leading to the production of mature IL-1β (figure 3). Both silica and asbestos activate this after phagocytosis. [15] At least in the case of silica, it is clear that once taken up through phagocytosis the silica crystal destabilizes the lysosome, leading to its rupture. The NalP 3 inflammasome is then activated in response to the lysosomal rupture leading to the subsequent inflammatory process. [16] Persistent inflammation and lung injury, beginning with alveolar type I epithelial cell injury, then progresses to fibrosis and the occupational ILD detected clinically.[17]

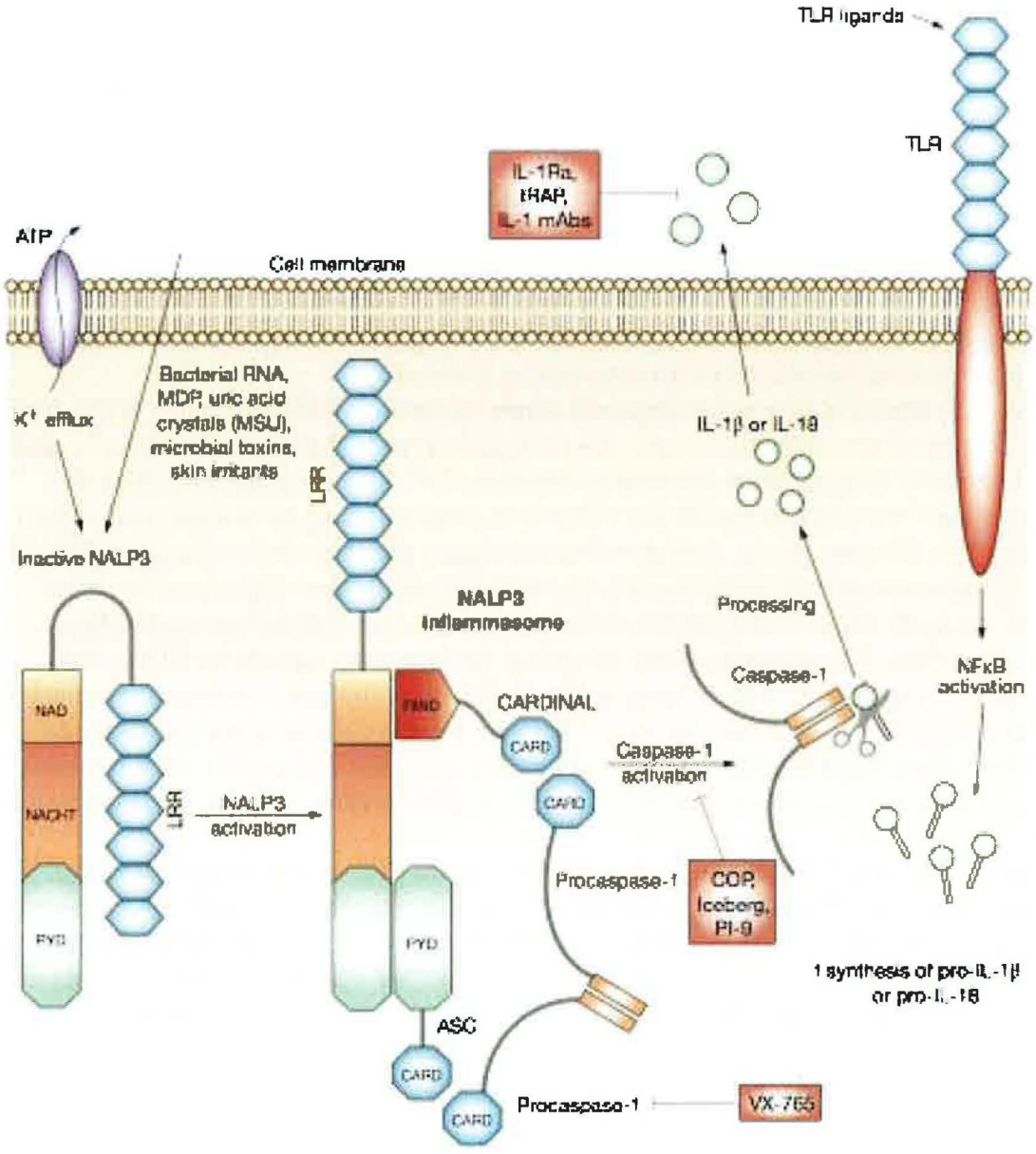

Figure 3: Illustration of the NALP3 inflammasome and function. It is activated with release of silica crystals into the cytosol upon lysosomal rupture. This leads to activation of caspase-1. Caspase 1 then activates Il-1B and Il-18, which initiate the inflammatory events culminating in fibrosis.[50]

The Effects of Pathogenesis on Clinical Features and the Exposure History

The two different classes of pathogenic routes to disease lead to several important differences in clinical presentation and historical features. These differences can help the clinician prioritize relevance in patients with multiple exposures. They can also help the clinician determine the likelihood that any given exposure is causative. In addition, there are several clues within each category of pathogenesis that can help separate exposure related ILD from the idiopathic interstitial pneumonias.

Clinical Features of Disease Where Host Factors Dominate Pathogenesis

The activation of the adaptive immune response leads to several important clinical features. First, this global immune response frequently leads to the development of constitutional symptoms including fever, chills, night sweats, weight loss, arthalgias and myalgias.[18, 19, 20] These symptoms are not typically seen in either pneumoconiosis or the IIPs. In addition, such constitutional symptoms may correlate with episodes of antigen exposure. In addition, pulmonary symptoms and lung function may worsen acutely with exposure but improve when the patient is removed from exposure. This temporal relationship between exposure and symptoms is an important diagnostic clue and the clinician should directly ask about it when taking a history.

Second, since disease onset depends more on timing of the initiation of the immune response than on accumulated damage, the latency between the onset of exposure and disease is variable ranging from months to decades.[18, 21] This means that unlike the pneumoconioses, the clinician must consider both new and long term exposures when considering this disease group. Antigen characteristics are important when considering latency. In hypersensitivity pneumonitis, the antigens are either organic or reactive chemicals. As such, they do not persist in tissue and disease should not begin <u>after</u> exposure cessation. For example, if an individual farmed from age 20 to 40 but then developed ILD at age 50, Farmer's lung cannot be the explanation. On the other hand if that individual was still farming at age 50 then Farmer's lung would be quite possible. In contrast, beryllium does persist in tissue and as a result CBD can appear even decades after exposure cessation.[22] However, like HP, CBD can appear within months of exposure onset as well.[21]

Finally, as noted above, the pathogenesis is more dependent on an individual's capacity to respond to the antigen in question than on the exposure itself. As a result, large exposure doses are not required. This is demonstrated by the finding of HP in patients simply exposed to a feather duvet.[23] and by numerous CBD studies showing disease occurring at extremely small exposure doses including residential cases near beryllium production facilities.[24] Therefore, when obtaining an exposure history for agents in this category it is more important to determine the presence of exposure than to establish a high exposure dose.

Clinical Features of Disease Where Exposure Factors Dominate Pathogenesis

As discussed above, the pathogenesis of these diseases features a nonspecific local inflammatory response in the lung. As a result, systemic or constitutional symptoms are usually not seen. In addition, since the pathogenesis requires accumulation of injury the latency is always long, usually several decades.[25] In addition, high doses either because of a short but intense exposure or a long duration of exposure are typically required.

Therefore, the clinician considering a pneumoconiosis will need to ask questions designed to estimate exposure dose (see below).

In addition to the presence of a high dose exposure, one of the primary clinical clues that a patient is suffering from a pneumoconiosis relates to disease course. Unlike the IIPs, pneumoconiosis may remain stable over many years and when progression occurs it is typically much slower than in the idiopathic interstitial pneumonias (see figure 4).

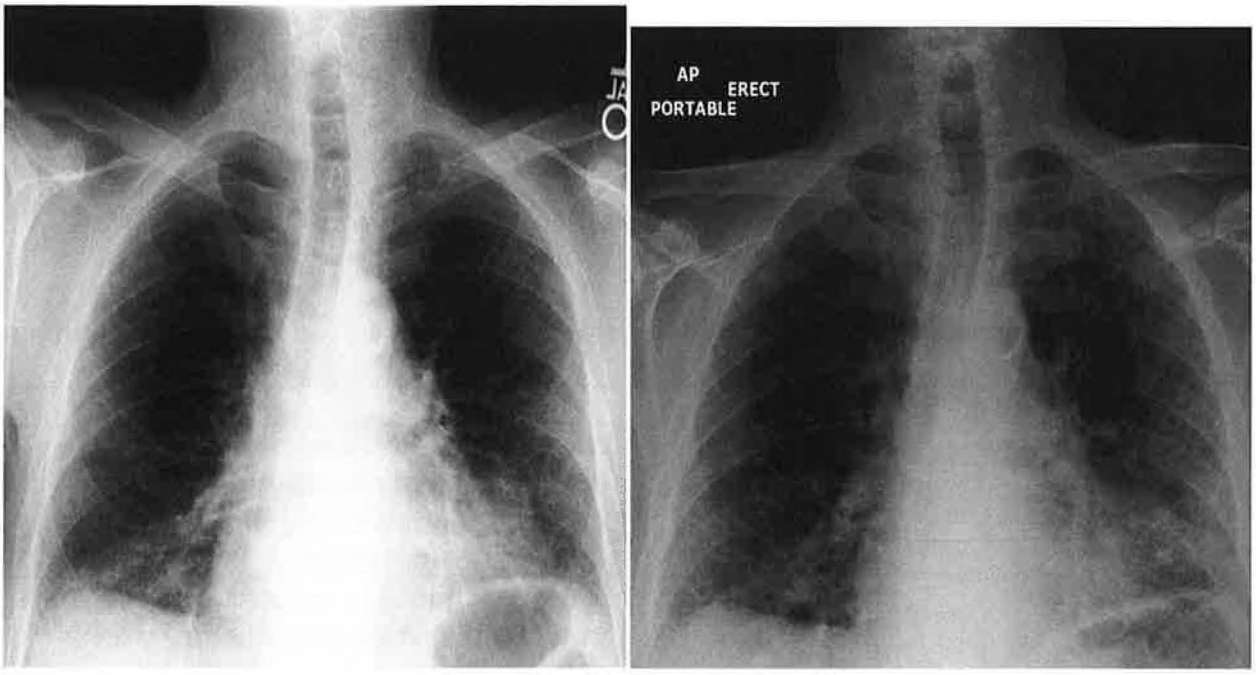

Figure 4– A) PA chest x-ray demonstrating the typical lower lobe predominant reticular infiltrate of asbestosis. B) follow-up film obtained from the same patient 6 years later demonstrating slow progression.

For example, in a recent study examining the progression of diffuse interstitial disease in silicosis it took an average of 12 years for end stage fibrosis to develop.[26] Likewise, in a Finnish study of asbestosis, the majority of patients did not progress over an 8 year follow-up. When progression did occur, the average time to increase one major ILO category was 5 years.[27] This stands in stark contrast to IPF where the average survival is only about 3 years from the time of diagnosis.

Other Clinical Clues That Suggest Occupational or Environmental ILD

Pulmonary Function

Restriction and a reduction in diffusion capacity are the most common physiologic abnormalities in patients with all forms of ILD. However, the presence of obstruction, with or without restriction, in a patient with ILD should suggest the possibility of an occupational or environmental cause. Idiopathic interstitial pneumonias do not typically cause obstruction on pulmonary function. When obstruction is seen in that setting it is typically from an alternative explanation, especially tobacco abuse. However, several of the

most common exposure related diseases can feature obstruction on PFTs. Sarcoid can also cause obstruction. Obstruction was first reported in patients suffering from HP in the 1960s.[28] This has been confirmed in several more recent studies.[29, 30] Emphysema can even occur independent of smoking as a long term sequelae of hypersensitivity pneumonitis.[31] Obstruction is also a common finding in CBD patients.[32] Silicosis and Coal-Worker's pneumoconiosis (CWP) also demonstrate obstruction or mixed obstruction/restriction on pulmonary function testing. In these diseases, symptoms often correlate better with the obstructive abnormality than restriction. [33] The pathogenesis of obstruction in silicosis and CWP is likely a combination of dust-induced excessive loss of FEV1 and emphysema.

Radiology

The classic radiographic clue to the presence of an exposure related ILD is the presence of upper-lobe predominant disease (Table 2).

Table 2: Occupational and Environmental ILDs with Upper Lobe Predominance on CXR and select exposure scenarios

Common Exposures/Diseases	
Beryllium/CBD	Nuclear weapons, electronics, aerospace, ceramics, metal recycling, dental prostheses,, alloy machining, defense industries, automotive
Silica/Silicosis	Hard rock mining, construction, road work, tunneling, sandblasting, foundry work, granite/stone workers, silica flour production/use, ceramics, glass manufacture
Coal/Coal Worker's Pneumoconiosis	Coal Mining or processing
Hypersensitivity Pneumonitis	Bird exposure, water damaged environments, hot tubs, humidifiers, contaminated organic materials (wood, hay), farming, metal working fluids
Uncommon Exposures/Diseases	
Other Carbon compounds: Carbon black, graphite, oil shale	Tires, pigments, paints, pencils, foundry linings, mining, metallurgy, carbon electrodes, plastics
Silicon Carbide	Abrasive, refractory materials, ceramics, metal matrix composites
Diatomaceous earth (when heated above 450°C it converts to crystalline silica)	Foundries, filter production, abrasives, dry lubricant
Cobalt	Hard metal manufacture or tool use (metal grinding, cutting or drilling tools), diamond polishing

In contrast, the majority of idiopathic interstitial pneumonias display lower lobe predominance. However, this clue does not help one distinguish sarcoid, typically an upper lobe process, from an occupational or exposure related ILD. It is also important to realize that although the presence of an upper lobe predominant distribution suggests an inhalational exposure its absence does not exclude exposure related ILD. Hypersensitivity pneumonitis, Cobalt-related ILD and CBD can all involve the mid to lower lung zones. Silica and coal have recently been associated with a lower lobe predominant diffuse interstitial fibrosis in addition to their classic upper lobe predominant nodular pattern. [26, 34] More importantly, several fibrogenic exposures including asbestos are typically lower lobe predominant (Table 3)

Table 3: Occupational and Environmental ILDs with Lower Lobe Predominance on CXR and select exposure scenarios

Common Exposures/Disease	
Asbestos/Asbestosis	Construction trades, building maintenance, mining, milling, production of asbestos products, shipbuilding and repair, automobile and railroad workers, electrical wire insulation, as a contaminant in talc or vermiculite
Uncommon Exposures/Disease	
Fibrous silicates (wollastonite, attapulgite, sepiolite)	Asbestos Substitute, fuller's earth, paint thickeners, drilling mud, mining and milling, ceramics
Plutonium	Nuclear weapons and nuclear power (high dose exposure)
Mica	Boiler and furnace lining, electronics industry, building materials (tiles, cements), acoustic products, grinding
Kaolin	Kaolin mining, paper product manufacture, ceramics, refractory materials, ceramics
Rare Earths	Glass manufacturing, photoengraving, lens polishing, electronics, carbon arc lamp

An additional radiologic clue is the involvement of multiple compartments of the lung, such as concomitant pleural and interstitial disease or interstitial disease with findings suggestive of bronchiolar involvement. This type of multiple compartment involvement is not usually seen in the IIPs. However, many exposure related illnesses can involve multiple pulmonary compartments . Asbestos is a well described cause of both pleural and interstitial disease (figure 5).

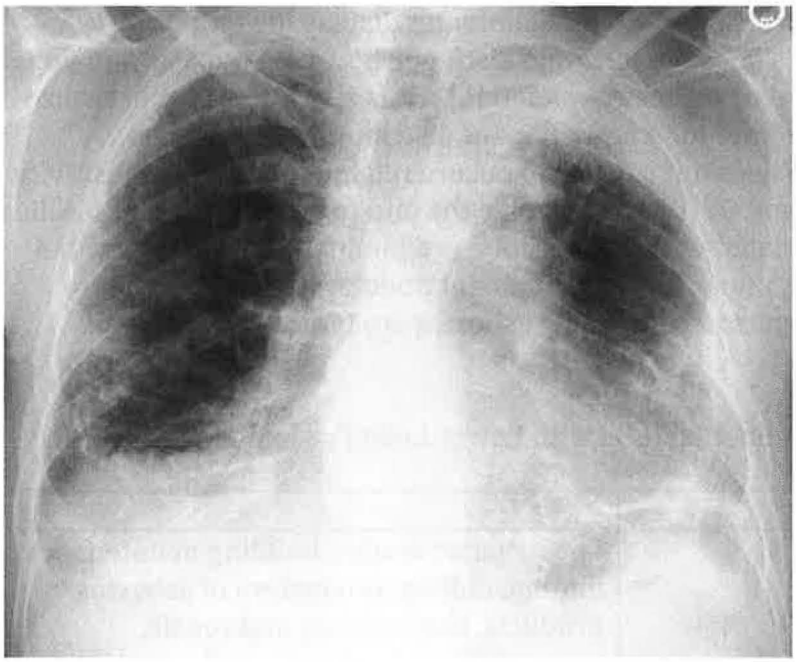

Figure 5– A) PA chest x-ray showing pleural and parenchymal involvement (en face plaques and diffuse pleural thickening) in a patient with a history of asbestos exposure from naval shipyards.

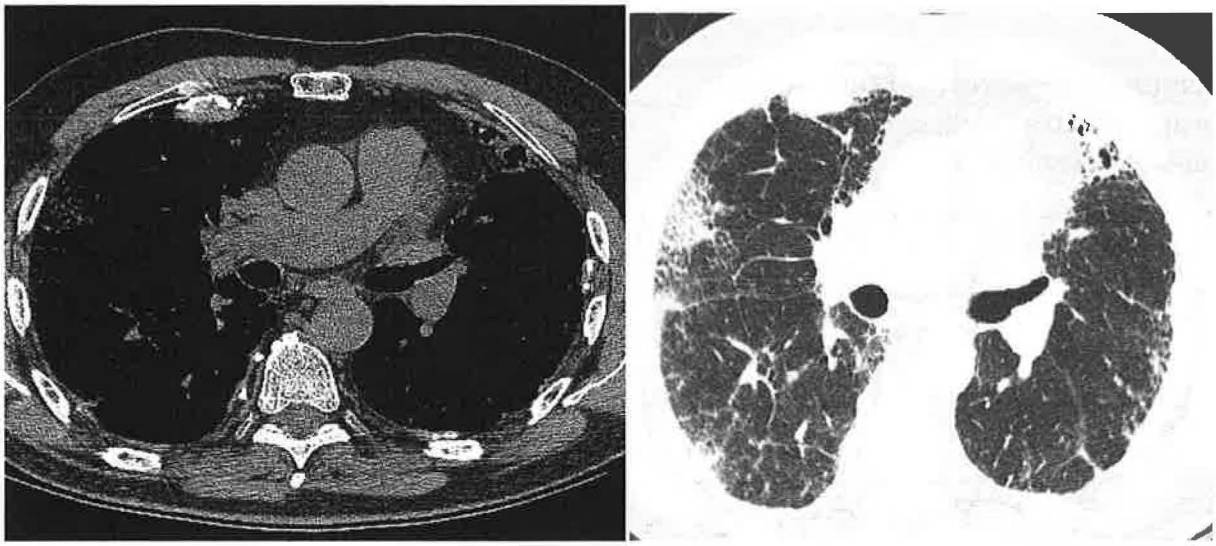

Figure 5B) HRCT mediastinal window from the same patient demonstrating the calcified pleural plaques. C) HRCT lung window at the same level demonstrating subpleural intralobular septal thickening and honeycombing from asbestosis.

Pleural thickening is also a common finding on HRCT in advanced silicosis and CWP.[35] Centrilobular nodules and lobular areas of decreased attenuation on HRCT are findings suggestive of bronchiolar involvement (figure 6). The presence of these findings can help differentiate HP from NSIP and UIP on HRCT.[36]

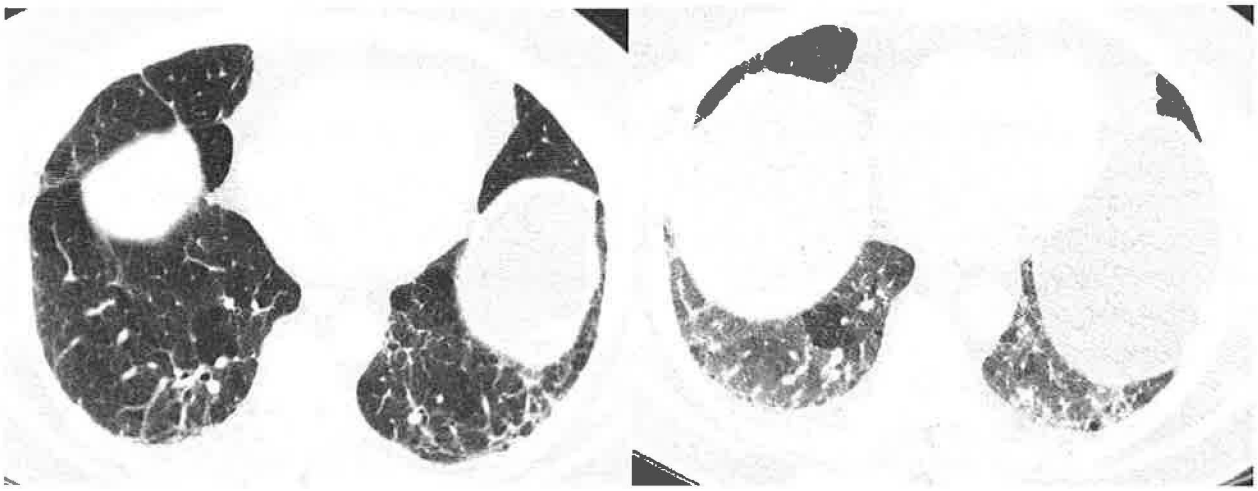

Figure 6 – Inspiratory (a) and Expiratory (b) HRCT from an individual with bird related hypersensitivity pneumonitis demonstrating fibrotic changes including septal thickening and traction bronchiectasis and a lobular area of decreased attenuation.

The Occupational and Exposure History

Once one suspects an exposure related illness, the key to establishing a diagnosis is obtaining a thorough exposure history. This is difficult but essential. Several published resources are available to assist the clinician[37] and the key components are shown in Box 1. Things to consider when obtaining an exposure history include a lifetime history of occupations and industries in which the individual has worked, hobbies, and current condition of the individual's work and living environments. One should also consider bystander exposures so a spouse work and hobby history, information about industry surrounding a patient's home and place of work, and a description of coworkers tasks are also important. In addition, one needs to consider latency. As discussed above, latency is defined as the time between the onset of exposure and the onset of disease. Finally, new exposures continue to be described so the clinician should be willing to consider new exposures.

Many of the important clues one should seek in the history were discussed above. As noted, when one is considering a disease where host factors dominate the pathogenesis discovering the presence of an exposure is more important than eliciting a high dose. For example, a large cohort study designed to develop a clinical rule to help confirm a diagnosis of hypersensitivity pneumonitis found that the most predictive feature by far is the presence of an exposure (OR = 38.8).[38]

Box 1: The Occupational and Environmental Exposure History

Points to Consider while taking the Occupational and Environmental Exposure History:

1. Latency
2. Exposure Dose
3. Disease Course
4. Don't accept a disease as idiopathic until a complete exposure history is negative.
5. Keep an open mind regarding new exposures.
6. Temporal relationships between symptoms and exposure

1. Job Type and Activities

Employer, job title, detailed description of job tasks or activities and surrounding activities within the worksite, temporal association between symptoms and days worked.

2. Exposure Estimate

Visible dust or mist in the air, dust on surfaces, visible dust in sputum (or nasal drainage) at end of work shift, hours worked per day and days per week, years worked, personal protective equipment used.

4. Bystander Exposures

Work – job activities and materials used at surrounding workstations, timing of worksite cleaning (during or post-shift), individual performing cleanup and process used (wet vs. dry).

Home – spouse's job, does spouse wear work clothes home and who cleans, surrounding industries.

5. Other

Hobbies, pets, problems with home heating or air-conditioning, humidifier and hot tub use, water damage in the home.

Hypersensitivity pneumonitis is primarily caused by exposure to organic antigens. Most cases are secondary to exposure to either avian antigen or microbial organisms. The history should thus focus on detecting these two exposures. Asking about exposure to avian antigen either from live birds or feather products is thus crucial. In order to have an exposure to microbial organisms there must be a source or location where they can grow to levels above typical background concentrations. Since these organisms cannot thrive without water the history should focus on indoor water sources or contamination (Box 2).[39]

Box 2: Questions to ask when considering hypersensitivity pneumonitis

Home Environemnt
1. Water Contamination - Water damage (floods, roof leaks, broken pipes), visible mold or mildew, build-up of material on HVAC vents or filters, foundation type and if pier and beam is there water in the crawl space under the home, musty odors
2. Water Sources – central humidifier, portable humidifier or vaporizer, hot tub or pool, use of exercise facilities with hot tub, pool, or steam room, swamp cooler.
3. Hobbies – woodworking, gardening, use of compost
4. Avian – birds as pets or feather products (pillows or duvets)

Work Environment
1. Organic Antigens - Same as above and questions for other water sources or contaminated materials. Farming, moldy hay, indoor environments with high humidity (green house or mushroom farming), contaminated cork, wood or other organic material (ex. Peat moss), metal working fluids.
2. Reactive chemicals – isocyanates (furniture manufacture, car painting, foam production), anhydrides (resins), pyrethrum (insecticide)

Likewise, the clinician considering CBD or cobalt related disease needs to take a history focused on metal exposure or work in high risk industries (Box 3). Finally, if the patient doesn't know what they were exposed to the clinician should obtain Material Safety Data Sheets (MSDS) from the patient's worksite when possible. The health effect information on these forms is notoriously inaccurate but they do list hazardous substances within the products used and the clinician can then seek further information on those hazards from more reliable sources.

Box 3: Questions for beryllium and other metals

1. Direct Questions – use of beryllium, beryllium alloys, beryllium ceramics. Use of hard metal, other sintered alloys, other metal work including welding, grinding, cutting, brazing and machining of metals.
2. High Risk Industry –
   A. Beryllium - Electronics, computers, nuclear weapons, aerospace, defense, metal recycling, dentistry, automotive, sparkless tools, beryllium production facilities
   B. Cobalt - –Diamond polishing, cutting and polishing metals, grinding tools, and drilling holes in metal

When considering pneumoconiosis the history must include two critical points. First, the pneumoconioses all have a long latency so a lifetime work history is always required. Second, disease requires a high exposure dose. This may be a dusty environment for long periods of time. However, short duration high dose exposures are well-reported

causes. The classic example is the individual whose only asbestos exposure came during several months spent working in a shipyard during WWII. Questions that can help the clinician determine dose are presented in Box 1. Absence of exposure to dusty work environments or to dust transported home from one of those environments on the clothes of family members makes pneumoconiosis unlikely. Knowledge of high-risk industries is also helpful as work in one of these industries should trigger the clinician to take a more careful history (Table 4). As noted above, bystander exposures in the above industries should also be sought.

Table 4: Industries with high risk for exposure to fibrogenic dusts and possible exposures

Industry	**Potential Exposures**
Construction	Asbestos, silica, mica, fibrous silicates
Mining/Quarrying/Stone work	Silica, fibrous silicates including asbestos
Foundry	Silica, Diatomaceous earth, other carbon compounds
Drilling (oil and gas)	Asbestos, other fibrous silicates
Glass and Ceramics	Silica, silicon carbide, kaolin, other fibrous silicates, rare earths
Manufacture or repair of metal products (automotive, aerospace, etc)	Metal dust, welding, asbestos, isocyanates (paints)

Going From Knowledge of Exposures to Attribution

Once the clinician suspects the disease, takes a thorough history of occupational and environmental exposures, and identifies potential exposures he/she must then decide if the exposures detected are causing the ILD. This can be a very difficult step as the mere presence of an exposure does not mean the exposure was the cause of disease in any given individual. One must still exclude other known causes including autoimmune disease and medications. For some of these diseases, clear criteria exist regarding diagnosis confirmation. In addition, some of the clues discussed above that made one suspect an occupational or environmental cause also provide evidence for attribution. Otherwise, the approach does vary some according to the two categories of pathogenesis.

Attribution in Disease Where Host Factors Dominate Pathogenesis

As noted above, some of these patients will note an improvement in symptoms and more importantly objective testing including pulmonary function and imaging with removal from exposure (figure 7). Objective improvement with removal from exposure can confirm the cause especially if combined with objective worsening with reexposure. Absence of improvement with removal from exposure does not exclude that exposure though for several reasons. First, many of the metals will be retained in tissue and thus the biologic exposure will continue. Second, patients may continue to progress despite removal especially if fibrosis is already present at the time of diagnosis. When fibrosis is present improvement may not occur but absence of further progression after removal from exposure should be considered a positive response.

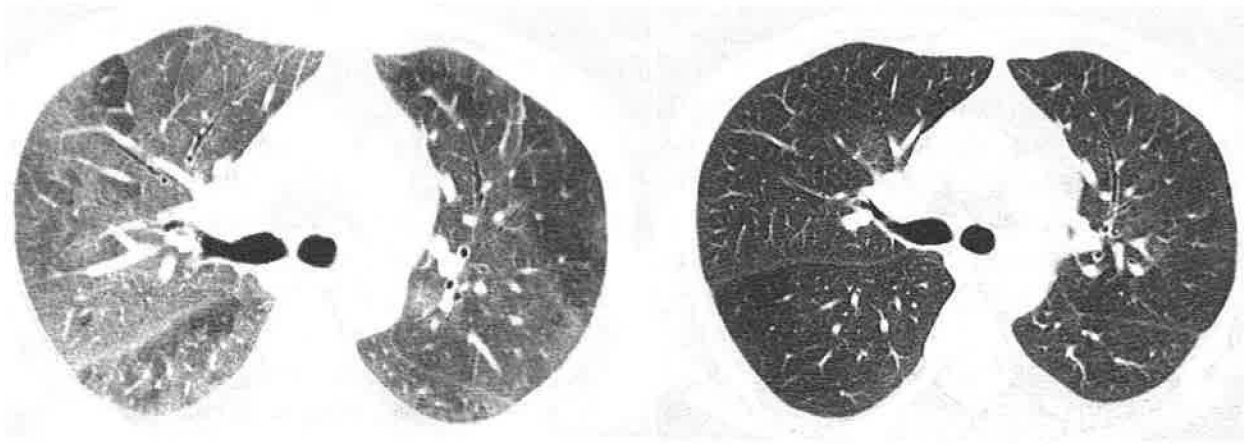

Figure 7– A) HRCT of an individual with Hypersensitivity pneumonitis from home mold exposure at presentation. It demonstrates ground glass, septal thickening and lobular areas of decreased attenuation. B) HRCT from the same individual at approximately the same level obtained 6 months after removal from exposure

In addition, the involvement of the adaptive immune response also provides the opportunity to prove immune system activation and this provides powerful supportive evidence of causation. This is best illustrated in chronic beryllium disease. The current diagnostic criteria for CBD include the presence of granulomatous inflammation in target organs and demonstration of an immune response to beryllium. The immune response is demonstrated by the beryllium lymphocyte proliferation test (BeLPT).[40] This is a clinically available test performed at a few specialty laboratories that effectively quantifies the cellular or Th1 immune response. Lymphocytes collected from either blood or bronchoalveolar lavage (BAL) fluid are cultured in the presence and absence of beryllium salts. Proliferation is measured by uptake of radiolabeled DNA precursors and a stimulation index is calculated by comparing the uptake in the cells cultured with beryllium to those cultured without it. A single positive BAL BeLPT or two positive blood BeLPT are considered proof of immune reactivity to beryllium and when combined with the presence of granulomatous inflammation equal a diagnosis of CBD.[41]

Positive tests of immune system reactivity also provide supportive information in hypersensitivity pneumonitis.[38] The test most frequently studied in HP is serum precipitins. Serum precipitins have a questionable role in disease pathogenesis for the reason noted above and the sensitivity and specificity of precipitins for the diagnosis of HP is suboptimal. Despite these limitations, a study by Lacasse et al. found positive precipitins to be predictive of HP.[38] However, they and others correctly point out that negative precipitins should <u>never</u> be used to exclude disease. This is especially true in fibrotic disease where the sensitivity is at its worst.[10] In a study of bird breeder's HP where diagnosis was established on the basis of a positive exposure challenge only 18% of fibrotic cases demonstrated positive antibodies. Lymphocyte proliferation testing to avian antigen had a much higher sensitivity of about 90% regardless of the presence or absence of

fibrosis.[10] These findings are consistent with data from CBD and are not surprising given the role of the cellular immune response in the disease. Unfortunately, lymphoctye proliferation tests for HP antigens are not commercially available.

Bronchoscopy can also be a helpful tool for this group of diseases. For CBD, the yield of bronchoscopic biopsy is similar to the excellent yield seen in sarcoidosis. In addition, a BAL can obtain cells for the BeLPT and the sensitivity of that test is greater than the blood sensitivity. In hypersensitivity pneumonitis, elevated lymphocytes are typically seen on BAL and provide supportive evidence.[10, 42] However, the classically described finding of a reduced CD4:CD8 ratio is of questionable value as more recent data shows that the CD4:CD8 ratio varies by antigen and stage of disease.[42, 43] Transbronchial biopsy can provide diagnostic findings but the yield is typically lower than in sarcoid or CBD.[44] Bronchoscopy can even be diagnostic of cobalt-related disease if one finds cannibalistic giant cells on either BAL or biopsy.[45]

Attribution in Disease Where Exposure Factors Dominate Pathogenesis

Disease attribution with the pneumoconioses typically follows the approach set forth in the American Thoracic Society guidelines for attribution of non-malignant respiratory disease caused by asbestos.[46] In a patient with established ILD these criteria include a history of significant exposure, an adequate latency for the development of ILD (as above, this is typically decades), exclusion of other known causes, and a consistent clinical picture. The last criterion includes typical radiologic findings and a consistent disease course (i.e. slow progression as described above). The history of significant exposure can be documented by the exposure history or if that's not clear the finding of elevated concentrations of the mineral in pathologic samples can function as a substitute. Although the above guidelines only address asbestosis it is reasonable to apply a similar approach to the other fibrogenic dusts.

The Role of Surgical Lung Biopsy

Surgical lung biopsy may be required in certain situations in order to establish a diagnosis. Surgical biopsy should not be performed solely for purposes of compensation. One should consider obtaining a surgical biopsy in patients with atypical presentations or disease course, when considering new or poorly characterized exposures, in the setting of multiple potential etiologies, or if results may affect therapy. For example, if a patient has a CT consistent with UIP but also has an unavoidable exposure to an agent that can cause hypersensitivity pneumonitis, then a biopsy would be indicated to attempt to distinguish IPF from chronic HP. Although HP can cause a UIP pattern of fibrosis, there are some pathologic clues that suggest HP over IPF. These include a bronchiolocentric distribution of fibrosis and the presence of either giant cells or granulomas.[47, 48] These considerations emphasize the importance of an experienced pulmonary pathologist to differentiate IPF from UIP caused by HP.

A helpful diagnostic feature for non-organic agents is the finding of the foreign material in question throughout the areas of fibrosis.[5] Therefore, the clinician needs to ask the surgeon to have one piece immediately frozen in OCT and a separate piece fixed in glutaraldehyde for subsequent electron microscopy if necessary. The pathologist should also review the samples with polarized light as many, but not all, agents will be visible with this methodology.

Management

The most important intervention for all occupational and environmental ILDs is removal from exposure. This is especially important for some of the diseases, especially hypersensitivity pneumonitis, but is considered prudent for all the occupational and environmental ILDs. In the better characterized pneumoconioses it is based on the association between disease progression and cumulative exposure dose. The clinician should also remember that diagnosing an occupational or environmental ILD in one patient also identifies an at risk population (i.e. individuals who share the exposure). These diagnoses are thus also an opportunity for primary and secondary prevention in the at risk population.

With regards to the pharmacologic management, there are no controlled trials in any of these illnesses. Any pharmacologic management is only a supplement to the primary intervention of exposure removal. The typical approach in patients with diseases that feature activation of the immune system (i.e. CBD, HP, etc.) is to initiate anti-inflammatory therapy, typically beginning with prednisone. In CBD, the treatment algorithms follow those used for sarcoid. In hypersensitivity pneumonitis, prednisone may accelerate recovery. If patients cannot be weaned off of prednisone, azathioprine is considered the best second or steroid sparing agent. There are no known effective pharmacologic interventions for any of the pneumoconioses. For diseases that also feature obstructive lung physiology treatment according to published guidelines for COPD may improve symptom control. Diuretics may be needed if cor pulmonale is present. Standard preventive medicine including oxygen for hypoxia, immunizations, and pulmonary rehabilitation are also important in all cases.

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