Review Article

Hypersensitivity Pneumonitis

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ABSTRACT

Hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis is a non-IgE mediated hypersensitivity disease initiated by inhalation and subsequent sensitisation to organic antigens. These diseases have been described in different occupational groups and present in acute, subacute or chronic forms based on the exposure to antigens and host response. Clinical features are dependent upon the stage of the disease and can include fever, chills, cough, dyspnoea, and weight loss. The immunopathogenesis involves both cellular immunity and antibody responses to inhaled antigens. Antibody response to the implicated antigen can be demonstrated in HP patients, but such antibodies are also detected in antigen exposed asymptomatic individuals. Bronchoalveolar lavage demonstrates lymphocytosis and preponderance of CD8+ cells. Pulmonary function studies demonstrate a restrictive pattern with diffusion defects. The diagnosis is difficult as no single test is confirmatory, hence information from clinical, radiological, physiological, and immunological evaluations may be used together for a confirmative diagnosis of hypersensitivity pneumonitis. The treatment of choice is avoidance of antigen but systemic corticosteroids may be effective in suppressing the inflammatory response. The prognosis depends on early diagnosis and effective antigen avoidance. **[Indian J Chest Dis Allied Sci 2006; 48: 115-128]**

Key words: Hypersensitivity pneumonitis, Dyspnoea, BAL, Allergic alveolitis, Antigen.

INTRODUCTION

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is an immune mediated lung disease. This uncommon disease is caused by inhalation of and sensitisation to antigens derived from protozoa, molds, animals, insects, bacteria, chemicals, and other organic materials. The presentation of HP is with systemic and respiratory symptoms, but the mechanism is distinctly different from IgE mediated allergy; at times HP mimics the symptoms caused by fungal, bacterial, and viral infections. The symptoms include cough, dyspnoea, chest tightness, chills, sweating, malaise, fatigue, myalgia, and headache occurring four to six hours after antigen exposure once sensitisation has occurred. A complex interaction between exposure to antigens, susceptibility and immune response of the host and genetic factors are involved in the pathogenesis of HP. These factors together, or in combination, contribute to the presentation of the disease as acute, subacute or chronic forms. The pathology of these diseases involves the interstitium and alveoli as well as the middle and terminal airways. It is currently believed that inhalation of antigens present in the environment in these individuals results in a predominantly Th1 mediated response. The inflammatory cells associated with this disease also include CD8+ cytotoxic T-cells, macrophages and multinucleated giant cells. In most instances, serum IgG antibodies to the offending antigens are detected, although asymptomatic exposed individuals also may show elevated levels of antibodies. Both Type III and Type IV hypersensitivity mechanisms are discernable in HP. Pulmonary function studies demonstrate a restrictive pattern with diffusion defect resulting in hypoxemia in the acute form. Radiographic changes vary according to the stage of the disease and are best evaluated by high-resolution computerised tomography. Avoidance of antigen and early detection of the disease are the best control measures. Systemic corticosteroid therapy constitutes the treatment of choice to reduce the inflammatory response.

HISTORICAL BACKGROUND

A disease resembling HP was reported in grain sifters and measurers by Ramazzini in the early part of the 18th century[1]. He associated the disease with decay, weevils, and mold in the grain. Farmer's lung, the first classic and well-studied example of HP was described in England[2] in 1932. This was followed by reports of increased numbers of hypersensitivity lung diseases caused by a variety of antigens[1-13]. These syndromes include bagassosis, mushroom worker's lung, pigeon

[Received: October 28, 2005; accepted: November 10, 2005]

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breeder's disease, ventilation system induced lung diseases, and those caused by aerosols from industrial dusts, chemicals, and drugs[1].

ANTIGENS ASSOCIATED WITH HP

There are over 200 antigens known to be involved in various forms of HP. The antigens can be proteins or glycoproteins from animals, plants, bacteria, protozoa, and viral origins or small molecular weight chemicals and drugs. A list of the most frequently encountered antigens in HP is given in table 1.

Proteins derived from birds and animals constitute a significant source of antigens in causing diseases such as bird fancier's lung, furrier's lung, animal handler's lung, and gerbil keeper's lung, among others[3,4]. Pigeons are the principal source of avian allergen in HP, but several other birds have been cited as causative agents such as parakeets, parrots, doves, chickens, and turkeys[5-7]. The avian antigens may be from the droppings, serum or from the bloom and are inhaled as dust particles.

The antigens associated with farmer's lung are mainly from thermophilic actinomycetes and rarely

Table 1. Antigens associated with hypersensitivity pneumonitis

Antigen	Source	Disease
Bacteria: Thermophilic Actinomycetes		
Saccaropolyspora rectivirgula	Moldy hay, grain, compost, silage	Farmer's lung
Thermoactinomyces saccharii, T. vulgaris	Moldy sugarcane (bagasse)	Bagassosis
T. candidus, T. vulgaris, Saccharomonspora viridis	Humidifier, air conditioner Mushroom compost	Ventilation pneumonitis Mushroom picker's lung
Pseudomonas fluorescens, Acinetobacter lwoffii, Mycobacterium immunogenum	Contaminated metal working fluids	Machine operator's lung
Bacillus cereus, Klebsiella oxytoca	Ultrasonic cool mist humidifiers	Humidifier lung
Cephalosporium acremonium	Moldy wood floors	Floor finisher's lung
Bacillus subtilis	Enzyme dust, contaminated house dust	Enzyme / detergent worker's lung Familial HP
Bacillus subtilis (Subtilins)	Detergent / cleaning agent	
Fungi		
Aspergillus species (*e.g., fumigatus, clavatus*)	Moldy malt dust (in brewing) Moldy esparto grass (in stucco) Compost Moldy tobacco Contaminated water humidifier	Malt worker's lung Compost lung Tobacco worker's disease
Alternaria species	Moldy wood dust	Wood worker's lung
Rhizopus and *Mucor* species	Moldy wood trimmings	Wood trimmer's disease
Botrytis cinerea	Moldy grapes	Wine grower's lung
Aureobasidium pullulans	Moldy water in HVAC systems	Air–conditioner lung
Cladosporium species	Contaminated sauna water	Sauna taker's lung
Cephalosporium species	Contaminated basement (sewage)	
Penicillium frequentans	Moldy cork dust	*Suberosis*
P. caseii, P. roqueforti	Cheese mold	Cheese worker's / washer's lung
P. brevicompactum, Fusarium species	Moldy hay	Farmer's lung
Absidia corymbifera, Wallemia sebi	Moldy cowshed fodder	Farmer's lung (eastern France)
P. expansum, P. cyclopium, P. chrysogenum	Moldy wood dust	
P. camembertii, P. nalgiovense, P. chrysogenum	Salami seasoning	Salami worker's lung
Penicillium and *Monocillium* species	Moldy peat moss	Peat moss processor's lung
Pleurotus osteatus and *Hypsizigus marmoreus*	Indoor mushroom cultivation	Mushroom worker's lung
Trichosporum cutaneum, T. ovoides *Cryptococcus albidus*	Japanese house dust	Summer-type / summer house HP
Cryptostroma corticale	Wet maple bark	Maple bark stripper's disease
Rhodotorula rubra	Moldy cellar / bathroom walls	
Aureobasidium, Graphium and *Alternaria* species	Moldy redwood dust	Sequoiosis
Pezizia domiciliana	Moldy home from flooding	El Nino lung
Lycoperdon puffballs	Puff ball spores	Lycoperdonosis
Candida species	Moldy reed	Saxophonist's lung

Contd.

Table 1. ***Continued***

Antigen	Source	Disease
Epicoccum nigrum	Moldy basement shower	Basement shower HP
Fusarium napiforme	Moldy home	
Sacchoromonospora viridis	Dried grasses and leaves	Thatched roof disease
Streptomyces albus	Contaminated fertilizer	*Streptomyces albus* HP
Animal Protein		
Avian proteins	Pigeon (pets and wild), duck, chicken, turkey, love bird, dove, parrot, parakeet, Canada goose, owl	Bird fancier / breeder / handler's lung, pigeon breeder's disease, Budgerigar's disease, duck fever, plucker's lung, turkey handler's lung
Bovine and porcine proteins	Heterologous pituitary snuff	Pituitary snuff user's lung
Cat hair, animal pelts	Cat hair and fur dust	Furrier's lung
Rodent urinary proteins	Laboratory rat or gerbil urine	Laboratory worker's lung Gerbil keeper's lung
Oyster / mollusk shell protein	Shell dust	Oyster shell lung
Insect protein		
Sitophilus granarius	Infested wheat flour	Wheat weevil disease, Miller's disease
Silkworm larvae	Cocoon fluff	Sericulturist's lung disease
Amoebae		
Naegleria gruberi	Contaminated ventilation system	Ventilation pneumonitis
Acanthamoeba castellani		
Plant		
Soybean hull	Veterinary feed	
Tobacco leaves	Tobacco dust	Tobacco grower's lung
Coffee and tea dust	Coffee bean dust or tea leaves	Coffee worker's lung Tea grower's / worker's lung
Medications or Drugs		
Amiodarone, clozapine, cyclosporine, gold, procarbazine, minocycline, chlorambucil, sulfasalazine, nitrofurantoin, HMG-CoA, reductase inhibitor, methotrexate, beta blockers, intranasal herion, intravesicular BCG, mesalamine, fluoxetine	Medications	Drug-induced HP
Pauli's reagent	Laboratory reagent	Pauli's HP

Adapted from Fink and Zacharisen[100]

from thermotolerant or mesophilic fungi[8]. These organisms grow in compost, moldy hay, grain silage, sugarcane bagasse, and mushroom compost. The antigen load in the contaminated air from these sources may be very high and at times the inhaled spores may exceed over 750,000 per minute. Thus, a substantial amount of spores could be deposited in the lungs during work with contaminated materials.

Many different bacteria have also been implicated in HP and a number of case reports have appeared in the literature[9, 10]. Bacteria associated with HP include both saprophytic and non-pathogenic compared to those frequently causing other types of lung diseases. In recent outbreaks, bacteria contaminated metal working fluid exposure resulted in multiple cases of occupational HP. The significant bacteria associated with this condition are *Acinetobactor lwoffi* and *Mycobacterium immunogenum*[11, 12]. Other bacteria identified in causing HP are *B. cereum, B. subtitis*, *Klebsiella* sp., *pseudomonas sp.* and members belonging to the species of streptomyces[9,13]. Saprophytic fungi present in compost, decaying vegetables, contaminated ventilation systems and buildings are more frequently implicated in HP and have shown the greatest increase in recent years.

Despite changes in farming practices to reduce thermophilic organisms, farmers continue to be at risk for farmer's lung caused by fungi. Recent hay analyses in France identified fungi such as *Absidia corymbifera* and *Eurotorium amstelodami*[14] as causative organisms. Other fungal causes of farmer's lung include *Candida albicans* (by inhalation challenge) while the positive isolate from the environment was *Candida guiliermondii* which is more likely to be found in cattle-related

materials[15]. Three Canadian farmers died from chronic farmer's lung due to *Penicillium brevicompactum* and *P. olivicolor*[16].

Various occupations associated with fungal-related HP other than farmers include food workers in the malt, cheese, sausage, and soy sauce industries and commercial mushroom growing. Malt-workers in Scotland historically have a 5.2% incidence of HP. Workers are exposed to organic dusts of barley or other grains during the malting process. Enclosed malting systems using mechanical means such as conveyor belts or large drums decrease worker exposure and the incidence of HP[17]. Cheese workers develop HP to *Penicillium roqueforti* used in the manufacture of blue cheese[18]. In France, 5.2% of cheese workers making gruyere cheese had symptoms of HP[19]. Butchers who prepare sausage are exposed to airborne spores while brushing off excess mold[20] and an employee in a salami factory who worked near the area where the salami were seasoned with fungal inocula, developed HP from *Penicillium camembertii*[21]. A soy sauce brewer in Japan developed acute HP to *Aspergillus oryzae*, which produces a protease used to ferment soybeans[22].

Mushroom worker's lung has been shown to be caused by the inhalation of thermophilic actinomycetes from compost used to cultivate the common white button mushroom *Agaricus bisporus*[23,24]. In contrast to the thermophiles causing HP previously, the basidiospores of shiitake, and other mushrooms are themselves responsible for mushroom worker's lung[25, 26]. Similarly, outbreaks of HP related to cultivation of *Pleurotus osteatus*, *Hypsizigus marmoreus*, and Maitake mushrooms have been reported where indoor cultivation is practiced[27-29]. *Lyophyllum aggregatum*, also called *Shimeji* in Japanese, is a popular and common mushroom eaten throughout Asia. It has recently been cultivated in indoor greenhouses with high humidity (99%) for perennial production and distribution. Immediately after harvest, large quantities of 4.0 micron diameter spores are dispersed. Nine middle-aged non-smoking women who were involved with growing, picking or packing mushrooms were reported with HP[30]. The mean duration of symptoms was 9.8 years (range 7 months to 19 years). The initial symptoms were mild and episodic yet increased in frequency and severity consistent with subacute HP. Although the spores of these mushrooms are believed to be the antigens, precipitating antibody assays have proven unsuccessful. A women who cultivated vegetables in a plastic greenhouse in subtropical Japan experienced HP from *Aspergillus fumigatus* after tractor tilling and mixing straw and manure into the greenhouse soil[31].

Non-food related industries associated with HP include cork makers, peat moss growers, plasterers and wood workers. Cork is obtained from the cork tree *Quercus suber* and depending on the desired end product stored in dark, humid conditions until moldy then sliced, punched and polished. Cork dust contaminated with *Penicillium frequentans* is considered the cause of suberosis first reported in 1955[32]. Other molds may colonize the cork such as *Aspergillus, Mucor* and *Rhizopus* species. A series of eight patients identified not only *P. frequentans*, but also *A. fumigatus* and suberin (non-contaminated cork antigen) as additional causes of suberosis[33].

Peat moss is harvested from sphagnum moss using a technique much like a giant vacuum cleaner sucking the loose dry material from the large open fields. It is used as an oil additive, home heating fuel and in the fabrication of organic filters. While abundant molds have been found in the stacks collected, HP has only been reported rarely[34]. In southwestern Spain, esparto grass (*Stipa tenacissima*) is produced for manufacturing ropes, baskets, paper paste and in the production of plaster for stucco. Stucco makers developed acute HP to *Aspergillus fumigatus* and thermophilic actinomycetes. In addition, the esparto grass itself has been implicated in causing HP termed Stipatosis[35-37].

Wood dust contaminated with *Penicillium*, *Paecilomyces*, *Aspergillus niger,* and other *Aspergillus* species, *Alternaria, Cryptostroma corticale*, and *Rhizopus* have been reported to cause HP[38-41]. It has been reported that wood dust itself, without mold contamination, can induce HP. Acute HP symptoms have been reported in wood workers with IgG antibodies to specific pine carbohydrates[42]. Homes and businesses contaminated with fungus from water incursion or contaminated vaporizers, saunas, cool mist humidifiers or air-conditioning systems are other important causes of HP[43].

Ultrasonic and cool mist humidifiers readily disperse droplets in size from 0.5 to 3 microns and have been identified as sources responsible for HP. Frequently the specific antigen is not identified[44-46]; specific yeast that has been implicated in *Rhodotorula* and *Debaryomyces*[47,48]. Furnace humidifiers or humidifiers associated with forced air heating systems can support the growth of thermophilic actinomycetes and have been implicated in humidifier lung[49-51]. Similarly, bacteria like *Klebsiella* have also been implicated in HP[9].

Plumbing leaks in schools and books contaminated with molds led to the development of HP[52,53] with precipitins to multiple organisms including *Alternaria tenuis*, *Aspergillus fumigatus*, *Botrytis cinerea*, *Cladosporium herbarum*, *Penicillium notatum*, *Pullullaria pullulans*, and *Rhizopus rhizopodiformis.*

Japanese investigators have described summer-type HP, as the major type of HP in Japan, caused by *Trichosporon asahii*, *T. dermatis*, and *Cryptococcus neoformans.* Summer type HP also exists as acute and chronic forms. Isolation of the responsible organism from the environment, presence of antibody and positive response to pulmonary challenge with culture filtrate antigens from these organisms constitute diagnosis of summer-type HP[54-56]. In almost 7% of summer-type HP in Japan, causative agent is not identified.

Low molecular weight chemicals such as isocyanates or phthalic anhydride, used in the plastic industry are responsible for causing occupational asthma. These molecules when inhaled act as haptens and forms neoantigens by coupling with respiratory proteins. These neoantigens sensitise the individuals and result in the development of HP. Workers in industry exposed to MDI (diphenylmethane diisocynate) or isocynate show a prevalence of 1-4.7% among the exposed workers[57, 58]. Acid hydrides used in the production of plastics, epoxy resins, printing inks, adhesives, and paints are highly reactive and can induce both HP and asthma. Pulmonary diseases resembling HP resulting from drugs such as amiodarone, gold, celiprolol (beta blocker), fluoxetine, sulfasalzine, nitrofurantons, chlorambucil, and others have been reported[59-62].

CLINICAL PRESENTATION

The clinical features of HP depend upon several factors. Some of the significant factors include the nature of the inhaled dust, such as antigenicity, particle size, intensity and frequency of exposure to the antigens, the immunological response of the host and concomitant bacterial or viral infections. Clinically HP can be categorised into acute, subacute, and chronic forms[63].

Acute Form

The acute form often presents after a high-level of exposure to the offending antigen over a short period of time. Symptoms usually develop within 4 to 8 hours and are similar to acute viral infection. Symptoms may include high fever up to 40 ^{o}C, chills, myalgia, fatigue, dyspnoea, and non-productive cough. The patient will usually recover in about 18 to 24 hours, once he is removed from the environment. Examination of the patient during an acute attack reveals an acutely ill, febrile and dyspneic individual. Bibasilar end-inspiratory rales are prominent and may persist for weeks after the fever subsides. Between attacks the subject may be completely normal.

Subacute Form

The symptoms are more insidious in the subacute form of HP due to the repeated low-level exposure. The features include progressive respiratory symptoms over weeks-to-months without acute systemic symptoms as noted with the acute form. Physical examination often reveals crepitant rales and hypoxemia especially with exertion. As with acute HP, removal of the patient from the offending environment improves symptoms.

Chronic Form

Chronic HP can be categorised as either chronic insidious or chronic recurrent HP[64]. The former results from prolonged and continuous exposure to low-levels of antigens leading to irreversible pulmonary damage without major acute attacks. Progressive dyspnoea, cough, malaise, weakness, anorexia, and weight loss are common. Fever is often not present. In the chronic form of HP, interstitial fibrosis is prominent. Lung examination may demonstrate dry crackles, but wheezing is uncommon. Since the chronic form of HP is characterised by fibrosing interstitial lung disease, avoidance of the offending antigen will not result in complete resolution of symptoms. Continued antigen exposure portends a poor prognosis.

DIAGNOSIS OF HYPERSENSITIVITY PNEUMONITIS

The diagnosis of HP is usually difficult especially in children and patients with the chronic form of the disease. Because of the diverse presentation of the disease, a team approach including allergists, pulmonologists, immunologists, lung pathologists, and industrial hygienists will be helpful. The recommended criteria for the diagnosis[65] are listed in table 2. Other criteria such as bibasilar rales, decreased lung diffusion capacity, and arterial hypoxemia at rest or during exercise may be present in HP, but may also be present in many other interstitial lung diseases. Recently, a clinical prediction rule for the diagnosis was developed by Lacasse *et al*[66] based on the presence and absence of history, physical examination, and basic laboratory features (Table 2). When these predictors are present, the probability of diagnosis of HP is at least 98 percent.

Differential Diagnosis

Many disorders can present features similar to HP and these depend on several factors including presentation, age, and underlying conditions of the patient. Acute HP can be easily misdiagnosed as acute viral or atypical pneumonia or bronchitis. Nasopharyngeal swab for respiratory viruses and serological analysis for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species are required. Blood cultures are useful to demonstrate bacteremia.

The organic dust toxic syndrome (ODTS) refers to the group of non-infectious febrile illnesses that have been described by various terms such as grain fever, pulmonary mycotoxicosis and toxic alveolitis. Workers with large exposures to dusts contaminated with bacterial and fungal species can develop cough, chest tightness and fever, with normal spirometry, diffusing capacity and chest radiograph. Large amounts and a variety of fungal spores can be cultured from the sputum or demonstrated from lung biopsies. The typical positive serology of farmer's lung is absent and lung biopsy lacks granulomata.

ODTS has been reported especially in farmers who may inhale dense clouds of mold spores while forking

Table 2. Diagnostic criteria for hypersensitivity pneumonitis

Major Criteria (Four major criteria need to be present)

1. History of symptoms compatible with HP
2. Evidence of exposure to the offending antigen by history or through detection in serum or BAL fluid antibody
3. Changes of characteristic HP on chest radiograph (reticulonodular infiltrates, linear opacities) or HRCT of the chest (ground-glass opacities, micronodules, honeycombing, linear opacities, air trapping)
4. Demonstration of BAL fluid lymphocytosis, if BAL is performed
5. Demonstration of histologic changes consistent with HP, if lung biopsy is performed, such as alveolitis, noncaseating granulomas, giant cells, foamy alveolar macrophages, or fibrosis
6. Positive 'natural challenge' that produces symptoms and objective abnormalities either through controlled inhalational challenge or after re-exposure to the offending environment

Minor Criteria (Two minor criteria need to be present)

1. Bibasilar rales
2. Decreased diffusion capacity
3. Arterial hypoxemia, either at rest or with exercise

Clinical Prediction

1. Exposure to known offending antigen
2. Positive precipitating antibody to the offending antigen
3. Recurrent episodes of symptoms
4. Respiratory crackles in physical examination
5. Symptoms occurring between 4 to 8 hours after exposure
6. Weight loss

Adapted from Schuyler and Cormier (1997)[65]

off the top layer of a silo or cleaning a dry silo. A Swedish survey suggested ODTS was 30 to 50 times more common than HP and occurs more commonly in the summer months and is usually seen among younger individuals. In the Midwest U.S., 36% of the farmers surveyed had symptoms of cough and chest tightness consistent with ODTS[67]. Farmers working in swine confinement had nearly twice the frequency than those who did not work in swine confinement. Grain dust and dusts in swine confinement and poultry-raising buildings, as well as laboratory animal quarters, can cause similar symptoms. The respiratory symptoms in animal-confinement buildings are not due solely to endotoxin but are also related to ammonia and hydrogen sulfide gases as well. Evidence of sensitisation including precipitating antibodies to agents commonly implicated in HP may be there because concurrent exposures are common in these workers. In patients with ODTS lavage fluid has usually shown increased numbers of total cells, polymorphonuclear cells and spore and fungal elements.

Humidifier fever occurs in environments where recirculated water is sprayed into the air for humidification or cooling or for cleaning manufacturing equipment. The recirculated water becomes contaminated with gram-negative organisms producing endotoxins. Affected workers develop fever, malaise, and mild cough with chest tightness, 4 to 8 hours after exposure[68]. Chest radiographs are normal and pulmonary function tests are either normal or show mild airway obstruction without impairment of gas transfer. The symptoms resolve completely in a few hours. Serologic tests may be positive to microbial antigens from the environment but inhalation challenges with these antigens do not consistently reproduce symptoms. Inhalation of endotoxin, however, does provoke effects in about half of previously unexposed volunteers[69].

LABORATORY EVALUATION

No single clinical or unique diagnostic laboratory test is available for the diagnosis of HP. A combination of several evaluation procedures may be essential in most patients to establish conclusive diagnosis.

Precipitin Antibodies Against Sensitising Antigens

Precipitating antibodies to antigens associated with HP are frequently present in the serum and in the bronchoalveolar lavage fluids. The presence of precipitating antibodies indicates exposure and sensitisation to respective antigens. These antibodies are present in most patients and in a sizable number (40-50%) of all exposed individuals[70]. Hence, the presence of precipitins is only indicative of exposure and not *per se* the presence of the disease. The majority of individuals with HP will have positive precipitins. However, false negative tests may result from the poor quality of antigens, low sensitivity of tests and procedures and the use of irrelevant antigens. If the diagnosis of HP is strongly indicated in spite of a negative panel, additional antigen preparations from the suspected environment are strongly indicated to demonstrate the immunologic response in patients. In addition to serum

precipitins, IgG antibodies may be detected by ELISA, although this test has less specificity but greater sensitivity than does gel diffusion.

Cell Mediated Immunity Studies

Although normal individuals may show a positive antigen induced proliferation of lymphocytes, patients with HP respond more frequently and strongly to the offending antigens[71]. Macrophages from HP patients suppress the lymphoproliferation in response to phytohemagglutinin (PHA) as compared to asymptomatic exposed subjects and normal controls[72]. Macrophages from the lungs of HP patients frequently have an enhanced lympho-proliferative response, while this response is not seen with lymphocytes from normal subjects. This response of macrophages leads to lymphocytic alveolitis seen in HP patients. However, these techniques are still restricted to research laboratories and have no direct diagnostic applications.

Blood Tests

Blood tests may not always be diagnostic, but may provide additional information in the diagnosis. Although peripheral blood eosinophilia is characteristically absent, there is usually a marked blood neutrophilia and lymphopenia in HP patients with the acute form[73]. Elevation of non-specific markers of inflammation such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and serum lactose dehydrogenase (LDH) may be present[74]. Enhanced rheumatoid factor may be detected in over 50% of the patients. An increase in serum IgA, IgG, and IgM levels, but not IgE has been reported in HP patients.

Skin Hypersensitivity Tests

There have been conflicting reports on the usefulness of skin testing in HP. A number of studies have demonstrated the presence of immediate skin test reactivity to diluted bird serum and fecal extracts in bird fancier's disease[75]. Similar immediate reactivity to hay extract and *Saccharopolyspora rectivirgula* extract in farmer's lung patients was reported with much lower reactivity in exposed normal subjects. Given the conflicting results, the high proportion of subjects without the disease with positive reactions and the lack of standardised extracts, skin testing currently has limited value in the diagnosis of HP.

Pulmonary Function Testing

Several pulmonary function abnormalities may be demonstrable during an acute episode of HP. Pulmonary function tests typically reveal a restrictive pattern with a reduction in lung volumes and a decrease in diffusion capacity (DLCO). A decrease in airway compliance is also often seen with a shift in the pressure-volume curve down and to the right[73,76]. Hypoxemia is also observed on arterial blood gas analysis with an increase in the alveolar-arterial oxygen gradient. The hypoxemia and reduced DLCO reflect a filling of the alveolar space with fluid and inflammatory cells. Oxygen desaturation with exercise or with sleep may also be seen. Patients with subacute and chronic HP have a mixed restrictive and obstructive impairment, and occasionally patients with chronic HP may have only on obstructive disease. Patients with chronic HP also have a significant decrease in DLCO and exhibit hypoxemia. A number of patients (20-40%) display a nonspecific airway hyper-reactivity and 5-10% have asthma. In patients with farmer's lung, there is an increased risk by developing asthma after a diagnosis of HP. The bronchial hyper-reactivity seen in some individuals with HP may be secondary to the bronchiolitis found in these patients[77].

Radiologic Findings

Radiologic findings in HP correlate with the stage of disease. In acute HP, chest radiography usually demonstrates poorly defined, nodular infiltrates, but patchy ground-glass opacities, or diffuse infiltrates may also occur[78]. It is important to note that patients with acute HP may have a normal chest radiograph after cessation of exposure and resolution of the acute episode. High-resolution computed tomography (HRCT) of the chest typically demonstrates ground-glass opacities in acute HP, but the presence of ground-glass opacities is generally a nonspecific finding[79]. Ground-glass opacification represents cellular interstitial infiltration, small granulomas or both within the alveolar septa. These opacities may be found either centrally or peripherally, but are predominantly in the lower lung zones with sparing of the apices in acute HP.

In subacute HP, a reticulonodular appearance with fine linear shadows and small nodules is typically present on the chest radiograph, although the chest radiograph may also be normal as seen in acute HP[74]. HRCT of the chest typically demonstrates centrilobular nodules associated with larger areas of ground-glass opacity, as well as air trapping and mosaic perfusion. Centrilobular nodules correspond to the presence of poorly marginated granulomas and active alveolitis, while mosaic perfusion indicates the re-distribution of blood flow, and air trapping denotes obstructive bronchiolitis[79].

Chronic HP is characterised by diffuse reticulonodular infiltrates, volume loss, and coarse linear opacities on chest radiography[74]. The findings in chronic HP appear to be more severe in mid to upper zones of the lung. HRCT often demonstrates fibrotic changes that include irregular linear opacities, honeycombing, and traction bronchiectasis. These changes can also be found in several other disorders such as sarcoidosis, interstitial pulmonary fibrosis and collagen vascular diseases. Centrilobular nodules are often found in chronic HP when ongoinng antigen

exposure is occurring. The radiographic findings in chronic HP, unlike acute HP, are unlikely to resolve when antigen exposure ceases. There are several findings that are not frequently found, but may be helpful in differentiating HP from other disorders. Pleural effusions or pleural thickening as well as cavitation, calcification and atelectesis are usually absent in HP. Hilar adenopathy, commonly seen in sarcoidosis, is rarely seen in HP[80].

BAL Findings

Bronchoalveolar lavage (BAL) from normal individuals typically reveals a preponderance of alveolar macrophages with approximately 10% lymphocytes that have a CD4+ / CD8+ ratio of 1.8[81]. BAL in patients with HP within 48 hours of acute exposure reveals a predominance of neutrophils. This is followed by a lymphocytic alveolitis that comprises 60% or greater of the white blood cells. In adults, there is a characteristic increase in the number of CD8+ T cells in the BAL fluid and an increase in the natural killer cells (NK). This leads to a decrease in the ratio of CD4+ / CD8+ T cells to less than one. In contrast, this elevation in CD8+ T cells is not seen in sarcoidosis where an increase in the number of CD4+ T cells is observed[74]. The CD4+ / CD8+ T cell ratio in sarcoidosis is often greater than 3.5:1. An elevation in the concentration of specific IgG, IgA, and IgM antibodies is also found in the BAL fluid, but appears to decline after a week of antigen exposure[82]. As the disease progresses to the chronic form, an increase in the CD4+ / CD8+ T cell ratio is seen along with an increase in neutrophils.

Bronchoalveolar lavage evaluated in chidren with HP reveals a significant increase in the percentage of lymphocytes with a mean of 80% *versus* 12% in age-matched controls[83]. Additionally, foamy macrophages have been observed in the patients with HP and all patients were found to either have an increased expression of HLA-DR (7 of 8 children) on BAL lymphocytes or an increase in NK cells (5 of 8 children) in the BAL fluid. Importantly, there were no significant differences between normal controls and patients with HP with respect to CD4+ / CD8+ T cell ratio; however, the mean for both groups was less than one indicating a difference in ratios among healthy children and healthy adults.

Histopathology

Lung biopsy is not usually required for diagnosis and is reserved for cases when the afore-mentioned studies do not yield a definitive diagnosis of HP. Little data exists regarding the histologic features of acute HP, but acute bronchiolitis with a neutrophilic infiltrate has been described. Subacute HP is characterised by a triad of histologic changes that includes a diffuse interstitial lymphocytic infiltrate, scattered small poorly formed granulomas, and a cellular bronchiolitis; these findings are seen in 50-75% of patients with HP. Other typical histopathologic features in subacute HP are plasma cells, mast cells, foamy alveolar macrophages, and giant cells. B-cell follicular formation may also be seen in interstitial spaces[84]. Bronchiolitis obliterans may also be found. Additionally, 15-25% of patients with HP have bronchiolitis obliterans with organising pneumonia (BOOP) on biopsy. The presence of an interstitial infiltrate adjacent to and distant from the noncaseating granulomas may help in differentiating HP from sarcoidosis, as the inflammatory infiltrate in sarcoidosis typically only occurs adjacent to the granulomas[74]. Vasculitis and eosinophilia are not seen.

Interstitial fibrosis with an interstitial cellular infiltrate that is primarily lymphocytic with a large number of plasma cells is usually observed in chronic HP. The degree of fibrosis varies and honeycombing may be found in advanced stages. There is normally a decrease or absence of noncaseating granulomas in this stage of HP. Although the above findings are commonly seen in the respective stages of HP, none are pathognomonic for the disease and may be found in other pathologic processes.

IMMUNOPATHOGENESIS OF HP (Figure)

Although HP is an immunologic disorder, the exact mechanism involved in the disease are not yet fully understood. The initial event in the pathogenesis of HP is sensitisation to an environmental antigen by inhalation. The level and duration of antigen exposure required to produce disease in susceptible individuals is not known. Once an individual is sensitised, all subsequent exposures may result in expression of the signs and symptoms of HP[85]. Both cellular and humoral pathways have been suggested in the disease process.

Antibody Mediated Responses

Serum precipitating antibodies specific to the antigen can be found in most patients; however, precipitins can be detected in a majority of asymptomatic exposed individuals. The precipitating antibodies are usually of IgG type, but can be of IgM or IgA types. IgG antibodies may play a role in antibody mediated cell cytotoxicity (ADCC) by NK cells or in the antigen-antibody immune inflammation. Direct activation of the alternate complement cascade by organic dust antigens together with the production of IL-1 and TNF-α by pulmonary macrophages participate in the inflammatory cascade[86]. Activation of the complement cascade could lead to enhanced vascular permeability through C3a and chemoattraction of neutrophils and macrophages[87] via C5a. Secretion of IL-1 and TNF-α may lead to adhesion molecule expression on leukocytes and endothelial cells, thus promoting adherence prior to leukocyte migration

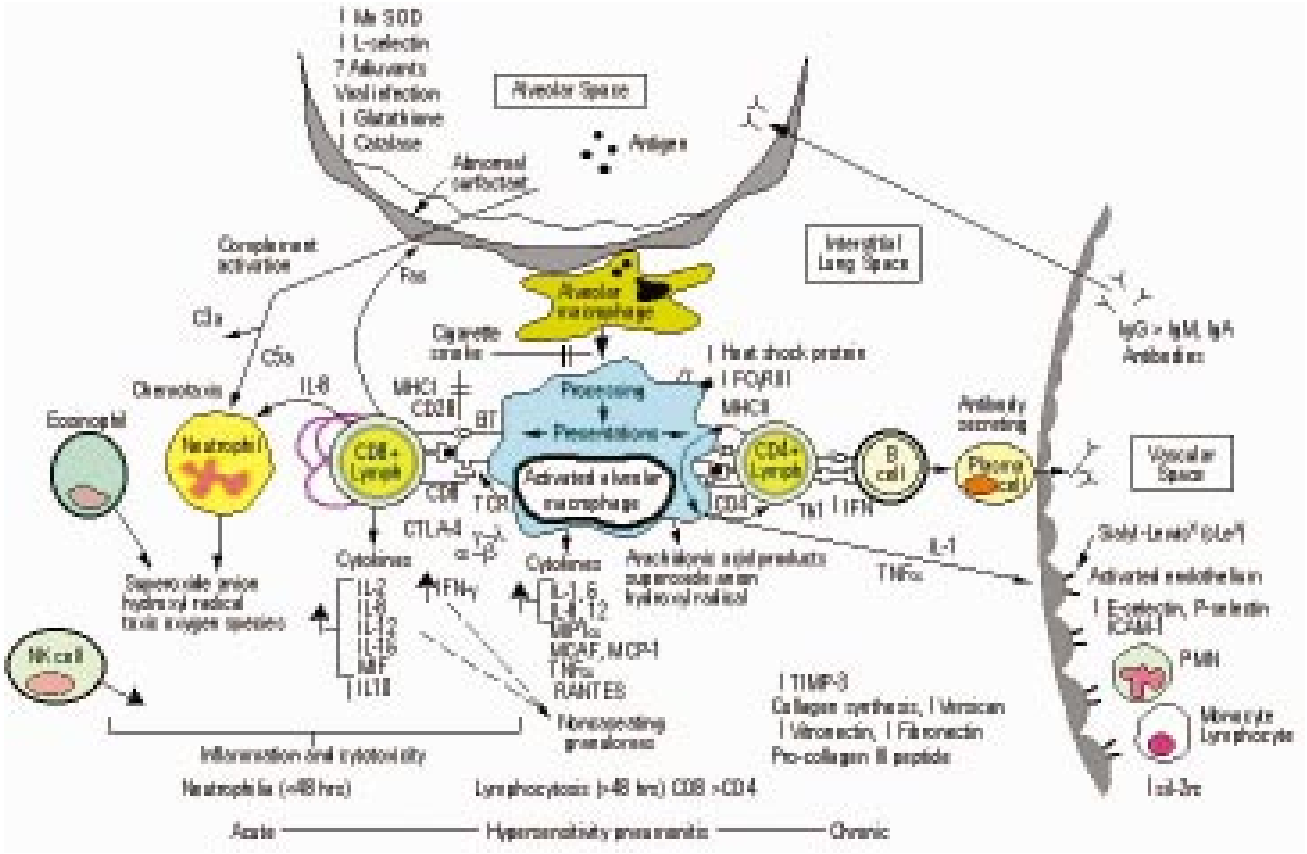

Figure 1. Pathogenesis of hypersensitivity pneumonitis. The antigen that enters the alveoli is engulfed by alveolar macrophages, which become activated and interact with both CD4+ and CD8+T lymphocytes, resulting in the release of various chemokines and inflammatory mediators typical of Th1 profile. Many factors, including environmental influences, adjuvants, surfactant proteins, and balance of cytokines and chemokines that influence the inflammatory response. This response eventually leads to granuloma formation of the interstitial lung space and alveoli.

into the alveolar interstitium. Additionally, pulmonary macrophages secrete IL-8, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, and RANTES that act as chemotactic factors for a variety of cells[86]. IL-8 is a chemotactic factor for neutrophils, and MIP-1α is a chemotactic factor for CD8+ T cells. MIP-1α also promotes polarisation of CD4+ Th0 cells to Th1 cells, which, in turn, produce interferon gamma (IFN-γ). IFN-γ has been shown to be essential for the expression of granulomatous reactions in a mouse model of HP[88]. Treatment of acute HP patients with antigen avoidance and corticosteroids has been shown to decrease the synthesis of both MIP-1α and IL-8 in alveolar macrophages, further implicating their role in the pathogenesis of this disorder[81].

Although several aspects of the disease, such as time course of clinical symptoms after exposure and the presence of precipitating antibodies against the offending agent support a type III immune complex hypersensitivity immune reaction, other aspects of the disease remain unexplained. For instance, precipitating antibodies to the offending antigen can be found in a high percentage of individuals who have a history of exposure but lack clinical disease. Additionally, histologic examination of the lung does not reflect a vasculitic immune-complex mediated disorder. In a study of 60 patients with farmer's lung who underwent lung biopsy, Reyes *et al*[89] found that the most common features identified were interstitial pneumonitis (100%), unresolved pneumonias (65%), granulomas (70%), interstitial fibrosis (65%), and bronchiolitis obliterans (50%). Vasculitis was not observed in any of the cases.

Cell-Mediated Responses

Cell-mediated immune responses are thought to predominate with continued antigen exposure. The increased expression of FCγ RIII receptors on pulmonary macrophages suggests a role for macrophage activity in the pathogenesis of HP. Activated pulmonary macrophages secrete several cytokines such as IL-1, TNF-α, IL-6, IL-12, and MIP-1α, and have increased expression of CD80 / CD86[78]. IL-12 and MIP-1α secretion by alveolar macrophages promotes polarisation of CD4+ Th0 cells to the Th1 phenotype. IL-1 and TNF-α cause fever and acute phase reactions and stimulate Th1 cells to produce IFN-γ. IFN-γ production by Th1 cells

causes alveolar macrophages to secrete more IL-1 and TNF-α, thus creating a positive feedback loop. An earlier study indicate that IFN-γ is essential for the development of HP in mice as IFN-γ knockout mice developed only minimal inflammation and no granulomas on exposure to *Saccharopolyspora rectivirgula*, a causative agent in farmer's lung disease[88]. However, these mice developed inflammation and granulomas when given replacement IFN-γ. Other factors that are IFN-γ inducible, such as IL-10, and I-TAC, are increased in the lungs of wild-type mice during exposure to *S. rectivirgula*, while IFN-γ knockout mice had reduced levels of these chemokines in the lungs after exposure[90].

Th1 and Th2 cytokine profiles have been analysed from BAL and peripheral blood (PB) T cells in patients with HP. Although there was no difference in IL-12 production between BAL and PB T cells, there was an increase in high affinity IL-12R in BAL T cells and an increase in production of IFN-γ when rIL-12 was added, in the BAL T cell group only[91]. Further support for the role of Th1 cytokines includes the demonstration that only Th1 CD4+ T cell lines were able to adoptively transfer experimental HP in mice exposed to *S. rectivirgula*[92]. Additionally mice susceptible to HP have a Th1 bias (C57BL/6 mice), while Th2 cytokine mRNA was less stable in Th2 biased mice (DBA/2 mice). However, the expression of T-bet (Th1), GATA-3 (Th1), and nuclear factor of activated T cells transcription factor (NFATc, Th1) was not significantly different between the two groups[93]. Therefore, regulation of cytokine mRNA stability may play a role in Th1/Th2 polarisation, and hence, the development of HP.

Several other cytokines and chemokines play a role in HP. IL-6 and IL-8, chemotactic factors for CD8+ T cells and neutrophils has been found to be increased in the BAL fluid of HP patients. IL-10, necessary in preventing a severe granulomatous response in mice, was found to be decreased when BAL cells of patients with HP were stimulated[91]. CD8+ T cells are the most predominant T cell found in the BAL fluid and the lung tissue of patients with HP. These cells are mostly cytotoxic T-suppressor cells and may produce Th1 or Th2 cytokines and modulate granuloma formation.

Natural killer cells are increased in the BAL and lung tissue of patients with HP and appear to provide a protective effect[83]. BAL cells in acute HP have significant NK cell activity. In patients with farmer's lung, this activity increases with treatment. In a mouse model of HP, NK cell depleted mice challenged with *S. rectivirgula* displayed an increased cellular recruitment in the BAL and an increased fibrotic response compared to control mice[94].

Costimulatory Molecules

An upregulation of CD80 and CD86 on alveolar macrophages has been demonstrated in patients with HP. These costimulatory molecules are involved in the differentiation and activation of T cells. These molecules on antigen presenting cells (APCs) interact with either CD28 or CTLA-4 during the presentation of antigens to the T cells via MHC T-cell receptor (TCR) interactions. CD28 is expressed on resting or activated T cells and promotes T cell differentiation, while CTLA-4 negatively regulates T cell proliferation. CTLA4-Ig treatment in mice exposed to intranasal *S. rectivirgula* has been shown to decrease inflammatory cell numbers in both BAL and in lung tissue. There was also decreased production of IL-4, IL-10, and IFN-γ in IL-2 stimulated pulmonary T cells[95]. The CD28 costimulatory pathway has been considered causal for the accumulation of lymphocytes in the lungs of HP patients. The expression of Bcl-xL, an anti-apoptotic product of the Bcl-2 gene family, and IL-2, which can inhibit apoptosis of inflammatory cells, are both increased through CD28 stimulation[96]. It has been demonstrated that patients with HP have increased levels of soluble Fas and an increased quantity of intracellular, inducible anti-apoptotic gene Bcl-xL product in BAL fluid compared with normal patients. An increase in soluble Fas would prevent cross-linking between Fas antigen (CD95) and Fas ligand (FasL, CD95L), thus inhibiting apoptosis[96].

Adhesion Molecules

Adhesion molecules may also play a role in the pathogenesis of HP. TNF-α induces the expression of adhesion molecules and chemoattractants, thus promoting the adhesion, activation and migration of circulating leukocytes. It has been demonstrated that HP patients have elevated levels of L-selectin in BAL fluid, and increased levels of E-selectin and P-selectin in peripheral blood compared to controls[97]. L-selectin, which is normally expressed on leukocytes, and E-selectin, which is normally expressed on endothelial cells, actively participate in leukocyte/endothelial cell interactions. P-selectins are involved in neutrophil migration at endothelial borders. Inhibition of E-and P-selectins in a murine model of SR induced HP, resulted in infiltration of decreased numbers of lymphocytes in BAL fluid and a decrease in the severity of the inflammatory response[98].

Surfactant Proteins

There are several other factors reported to play a major role in the pathogenesis of HP. These include surfactant proteins, extracellular matrix and free radical formation. Normal surfactant has been shown to inhibit the release of inflammatory cytokines by macrophages[99]. However, surfactant from HP patients has been shown to have a higher content of surfactant protein A (SP-A) which stimulates inflammatory cytokine release, immunoglobulin production and mitogen induced

proliferation[99]. In a study, surfactant proteins isolated from normal individuals and HP patients were added to alveolar macrophages and peripheral blood monocyte cell co-cultures[95]. It was demonstrated that surfactant proteins from control subjects inhibited alveolar macrophage induced lymphocyte proliferation in patients with HP, while surfactant from HP patients had a lower inhibitory effect on alveolar macrophage induced lymphocyte proliferation. This may indicate that changes in surfactant composition may lead to decreased suppressive activity of alveolar macrophages in patients with HP. However, a decrease in the SP-A concentration in the BAL fluid was also reported in patients with HP. Fatty acid composition of lung surfactant in patients with HP has not been shown to be significantly different from controls.

Other Factors

Free redicals have been implicated in the inflammation of lung parenchyma through the oxidative action of lung neutrophils[100]. Glutathione is an antioxidant normally found in the lungs and has been shown to be decreased in the BAL fluid of patients with farmer's lung compared to asymptomatic farmers after a controlled antigen challenge[101]. Manganese superoxide dismutase (MnSOD) and catalase are two intracellular antioxidant enzymes that are involved in lung defense[102]. Catalase has been found to be constitutively expressed, but not upregulated, in patients with a variety of interstitial lung diseases, including HP. MnSOD, however, was found to be markedly upregulated in patients with interstitial lung disease, including those with HP. This would suggest that these antioxidants are involved in protecting the lung from the progression of interstitial lung disease. Variants in the promotor region of tissue inhibitor of metalloproteinases (TIMP) -3 have been shown to decrease the susceptibility of patients with pigeon breeders disease[103]. Matrix metalloproteinases are zinc dependent proteinases that are involved in the degradation and turnover of extracellular matrix, and TIMPs are inhibitory to these proteinases. Therefore, TIMPs exert a regulatory role over the turnover of the extracellular matrix. TIMP-3 has been implicated as a fibrosis promoting factor in mice. Deposition of the proteoglycan versican in the extracellular matrix has also been shown to be specific for the early remodeling process in granulomatous lung diseases such as HP[103].

MANAGEMENT

As with other allergic lung diseases, the most important aspect of management is identification of the inciting antigen so that avoidance measures can be implemented. Frequently, avoidance alone is sufficient intervention. In occupational diseases this may include changing professions and job retraining, changing working materials, adding fungicides to water-based products, and/or instituting personal respiratory protection[107]. In an effort to reduce farmer's lung, treatment of hay with a buffered propionic acid significantly decreased the concentration of fungal species and thermophilic actinomyces without the deleterious effects on farm machinery or cattle. While hay conditioners and dryer systems can be effective, implementation can be at times cost prohibitive. In residential case of fungal-induced HP, remediation measures by trained professionals may include dehumidification, removal of moldy carpet, wallboard, wood and insulation, and decontamination with bleach or other fungicides. Preventive measures in Japan have improved summer type HP.

Pharmacologic Therapy

Pharmacologic therapy with supplemental oxygen and parenteral corticosteroids is indicated for ill patients with abnormalities on lung function testing, radiographs or with hypoxemia, For acute symptoms, oral prednisolone at 40-80 mg daily for 1-2 weeks may be sufficient while subacute and chronic HP may require 40-80 mg daily with a taper over several months depending on the response to improvement in symptoms and functional abnormalities[100].

Other treatments have only been described in isolated cases. After oral steroids, inhaled beclomethasone 400 mcg daily in hydrofluoroalkane-134a (HFA) propellant has been successfully used to treat an adult with mild mushroom spore-induced HP. The extra mist associated with this propellant is considered to improve the drug delivery to the distal airways and alveoli. Antihistamines and inhaled cromolyn sodium are ineffective for treatment. Short-acting bronchodilators and inhaled steroids may be helpful if an obstructive component with reversibility is established.

Pentoxifylline, a nonselective phosphodiesterase inhibitor used for the treatment of vascular insufficiency, was found to decrease cytokine production (TNF-alpha and IL-10) from alveolar macrophages from nine patients with HP[104]. Low dose, long term macrolide antibiotics have been demonstrated to have anti-inflammatory effects in subjects with chronic lower respiratory tract inflammation. In a murine model of HP, erythromycin significantly suppressed the early influx of neutrophils, inhibiting the up-regulated expression of intercellular adhesion molecules.

PROGNOSIS

Early treatment of acute or subacute disease results in a complete recovery for most patients while those with the chronic form may experience permanent sequelae such as progressive interstitial fibrosis, emphysema or

even asthma-like symptoms. The clinical course is variable, however, and even a single severe episode can result in sequelae while individuals with subacute or chronic disease can progress despite avoidance or remain stable despite continued exposure[105]. Most of these data are from pigeon breeder's disease and farmer's lung and no direct comparisons can be made with other causes of HP. Treatment with oral steroids has been demonstrated to improve symptoms and resolve hypoxemia, but has not been shown to affect the long-term prognosis.

CONCLUSIONS

Hypersensitivity pneumonitis is a complex immune-mediated reaction to various environmental antigens that can affect both children and adults. Cases may be epidemic or sporadic in nature and originate from contamination with fungal, bacterial, avian or other antigens in occupational or residential exposures. Despite the varied nature of the antigens, the presentation is similar with acute, subacute or chronic forms and if not identified and left untreated, may progress to irreversible lung disease with fibrosis. However, with early recognition, treatment with avoidance and systemic steroids, the prognosis is excellent. The immunopathogenesis is poorly understood. No standardised immunodiagnosis is currently available.

ACKNOWLEDGEMENTS

This work has supported by the US Veteran Affairs Medical Research and the editorial assistance of Donna Schrubbe is gratefully acknowledged.

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