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Identification and Remediation of Environmental Exposures in Patients With Interstitial Lung Disease

Evidence Review and Practical Considerations

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A relationship between inhalational exposure to materials in the environment and development of interstitial lung disease (ILD) is long recognized. Hypersensitivity pneumonitis is an environmentally -induced diffuse parenchymal lung disease. In addition to hypersensitivity pneumonitis, domestic and occupational exposures have been shown to influence onset and progression of other ILDs, including idiopathic interstitial pneumonias such as idiopathic pulmonary fibrosis. A key component of the clinical evaluation of patients presenting with ILD includes elucidation of a complete exposure history, which may influence diagnostic classification of the ILD as well as its management. Currently, there is no standardized approach to environmental evaluation or remediation of potentially harmful exposures in home or workplace environments for patients with ILD. This review discusses evidence for environmental contributions to ILD pathogenesis and draws on asthma and occupational medicine literature to frame the potential utility of a professional evaluation for environmental factors contributing to the development and progression of ILD. Although several reports suggest benefits of environmental assessment for those with asthma or certain occupational exposures, lack of information about benefits in broader populations may limit application. Determining the feasibility, long-term outcomes, and cost-effectiveness of environmental evaluation and remediation in acute and chronic ILDs should be a focus of future research. CHEST 2021; 160(1):219-230

KEY WORDS: environmental lung disease; hypersensitivity pneumonitis; pulmonary fibrosis

Although hypersensitivity pneumonitis (HP) and pneumoconioses are archetypal environmental lung diseases, environmental exposures likely contribute to the pathogenesis of some idiopathic interstitial pneumonias, including idiopathic pulmonary fibrosis (IPF). HP occurs following inhalational exposure and immune-mediated sensitization to organic/protein antigen(s),[1–3] and pneumoconiosis occurs following chronic exposure to respirable dust. A key component of the

ABBREVIATIONS: HAA = high attenuation areas; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; JEM = job exposure matrix; NIOSH = National Institute for Occupational Safety and Health; PCR = polymerase chain reaction; VGDF = vapors, gas, dust, or fumes

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FUNDING/SUPPORT: This study was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health [Grant K23HL141539].

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DOI: https://doi.org/10.1016/j.chest.2021.02.021

diagnostic evaluation for environmental lung disease includes elucidation of a compatible exposure history[1-4]; without this information, the diagnosis may remain in question. Accurate identification of environmental exposures driving disease development may also influence outcomes. For example, an inciting antigen is not identified in up to 50% of patients with HP, and these individuals have shortened survival.[5] Patients with IPF who are exposed to higher levels of particulate air pollutants have an increased risk for adverse events such as acute disease exacerbation and lung function decline.[6,7] Unfortunately, there is no standardized approach to evaluation for, or remediation of, potentially harmful environmental exposures in home or workplace environments for patients with HP or other interstitial lung diseases (ILDs).

The current article summarizes the evidence for a pathologic role of various environmental factors in ILD, presents two complementary cases illustrating aspects of exposure identification and remediation, discusses evidence for use of a formal (ie, professional) evaluation for environmental factors contributing to ILD development and progression, and reviews practical considerations surrounding exposure identification and remediation.

ILD and the Environment

Two key reasons for query of environmental exposures among all patients with ILD include identification and removal of ongoing sources of lung injury and for diagnostic classification. The current paradigm of fibrotic ILD pathobiology involves recurrent injury to the lung epithelium, with consequent fibroblast activation and accumulation of collagen and other extracellular matrix components in the interstitium, in genetically susceptible individuals. Extrinsic exposures are increasingly recognized as a source of epithelial injury.[8-10] Previously termed "extrinsic allergic alveolitis," HP results from inhalation and sensitization to organic protein antigens (eg, environmental molds), with consequent infiltration of the lungs by lymphocytes, granuloma formation, and, in some cases, development of pulmonary fibrosis.[3,11] Multiple studies have linked specific exposures or occupations with increased risk for having IPF, HP, and other ILDs (Table 1).[12-25] An American Thoracic Society/European Respiratory Society statement estimated the occupational/environmental burden of IPF to be substantial, with an occupationally related population-attributable fraction of 26% (95% CI, 10-41) for vapors, gas, dust, or fumes (VGDF) exposures.[26]

Further supporting a role of the environment in ILD pathobiology, features of occupational and domestic exposures have important prognostic implications. In IPF, people exposed to dusts, molds, or higher levels of air pollutants have earlier disease onset and worse outcomes.[6,27-29] Patients with HP with a longer duration of antigen exposure have worse prognosis and less lung function recovery following antigen removal.[30] Higher quantity of bird antigen detected in household dust samples has also been associated with faster decline in FVC and increased mortality among avian-associated HP.[31] A subset of patients with HP do not have an identifiable antigen, and they experience shortened survival even after accounting for other disease severity measures such as the presence of fibrosis, presumably due to ongoing occult exposure(s).[5,32-36]

Diagnosis of specific ILDs is driven in part by disease morphology (ie, specific patterns or findings on high-resolution CT scanning and/or lung biopsy); however, existing guidelines for the diagnosis of IPF, HP, and others also require elucidation of a compatible exposure history (or lack thereof) for higher confidence diagnostic classification.[3,37,38] HP diagnosis is intimately tied to identification of an inciting antigen, with lengthy lists of potential antigens and named subsyndromes (eg, mushroom worker's lung, bagassosis).[2,3,11] Some environmental risk factors, particularly exposure to organic dusts and birds, have been linked to increased risk for both HP and IPF.[12,13,20,21,24] Identification of similar risk factors could be related to diagnostic uncertainty (eg, difficulty separating fibrotic HP from IPF morphologically) or variation around case definition in practice (eg, a bird-exposed patient with usual interstitial pneumonia on surgical lung biopsy specimen diagnosed with HP at one center and IPF at another).[22,39,40] Unfortunately, little consensus exists to guide practical judgments about the significance or relevance of a given exposure in the diagnostic paradigm.

Clinical Case 1

A 63-year-old man was admitted to another hospital with 1 week of dyspnea, cough, and hypoxemia. CT imaging of the chest (Figs 1A-1C) revealed patchy bilateral ground-glass opacities and air trapping, both diffusely distributed. Following exclusion of infection, corticosteroids were prescribed for nonspecific autoimmune ILD (antinuclear antibody was 1:80). Upon return home, the patient's dyspnea and cough worsened

TABLE 1] Case-Control Studies Identify Exposures and Occupations Associated With Increased Risk for ILD

Study	Disease	Specific Exposure; OR (95% CI)	Occupation/Task; OR or HR (95% CI)
Scott et al,[23] 1990[a]	IPF	Metal dust, 10.97 (2.3-52.4) Wood fires, 12.55 (1.40-114.0) Cows, 10.89 (1.24-96)	...
Hubbard et al,[17] 1996	IPF	Brass dust, 1.97 (1.10-3.52) Lead dust, 5.54 (1.63-18.8) Steel dust, 1.72 (1.09-2.70) Pine wood dust, 3.37 (1.14-9.96)	...
Mullen et al,[19] 1998	Fibrotic ILD	Mold/mildew, 16 (1.62-158) Silica, 11 (1.05-115)	...
Baumgartner et al,[13] 2000[b]	IPF	Metal dust, 2.0 (1.0-4.0) Vegetable/animal dust, 4.7 (2.1-10.4)	Raising livestock, 2.7 (1.3-5.5) Hairdressing, 4.4 (1.2-16.3) Raising birds, 4.7 (1.6-14.1) Stone cutting/polishing, 3.9 (1.2-10.4)
Miyake et al,[18] 2005[a]	IPF	Metal dust, 9.55 (1.68-181.12)	...
Gustafson et al,[15] 2007	IPF	Birch dust, 2.4 (1.18-4.92) Hardwood dust, 2.5 (1.06-5.89)	...
Awadalla et al,[12] 2012[b]	IPF	Men Wood dust or preservatives, 2.71 (1.01-7.37) Birds, 3.49 (1.49-8.19) Cats, 6.38 (1.59-25.56)	Men Chemical/petrochemical industry, 6.47 (1.66-25.1) Carpentry/woodworking, 2.56 (1.02-7.01)
		Women Animal dust, 1.78 (1.01-3.13) Insecticides/pesticides, 8.68 (1.04-72.17) Birds, 3.86 (1.95-7.62) Cats, 8.24 (1.8-37.70)	Women Farming, 3.34 (1.17-10.12) Raising birds, 1.82 (1.03-3.85)
García-Sancho et al,[14] 2011	IPF	Dusts, smokes, gases, or chemicals, 2.8 (1.5-5.5)	
Paolocci et al,[20] 2018	UIP[c]	Metal dust or fumes, 3.8 (1.2-12.2) Organic dust, 2.4 (1.3-4.3)	Metal and steel industry, 4.8 (1.5-15.2) Farmers, vets, and gardeners, 2.73 (1.47-5.1)
Salisbury et al,[21] 2020	FIP	Lead, 2.91 (1.05-8.05) Aluminum smelting, 14.88 (2.67-97.73) Mold, 3.83 (1.78-8.25) Birds, 3.37 (1.53-7.41)	...
Abramson et al,[22] 2020	IPF[b]	Asbestos, 1.37 (1.08-1.74)	
Trout and Harney,[25] 2002	HP	Metal working fluid, 8.1 (1.0-65)	
Cramer et al,[24] 2016	HP	...	Pigeon breeding; HR, 14.36 (8.10-25.44)
Cramer et al,[24] 2016	Non-HP ILD	...	Pigeon breeding; HR, 1.33 (1.05-1.69)

FIP = familial interstitial pneumonia; HP = hypersensitivity pneumonitis, ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.
[a]ORs are matched (by age, sex).
[b]ORs are adjusted for age and cigarette smoking.
[c]Case subjects had UIP on chest CT scanning; control subjects had no lung disease.

despite corticosteroid treatment. Subsequent evaluation in an ILD clinic included a more thorough exposure history and disclosed new down feather comforter use a few weeks prior to hospitalization. Given typical CT features of nonfibrotic HP and a compatible exposure history, the patient was given a moderate-confidence diagnosis of HP, and antigen avoidance was advised.[3] Elimination of feather products from the home resulted

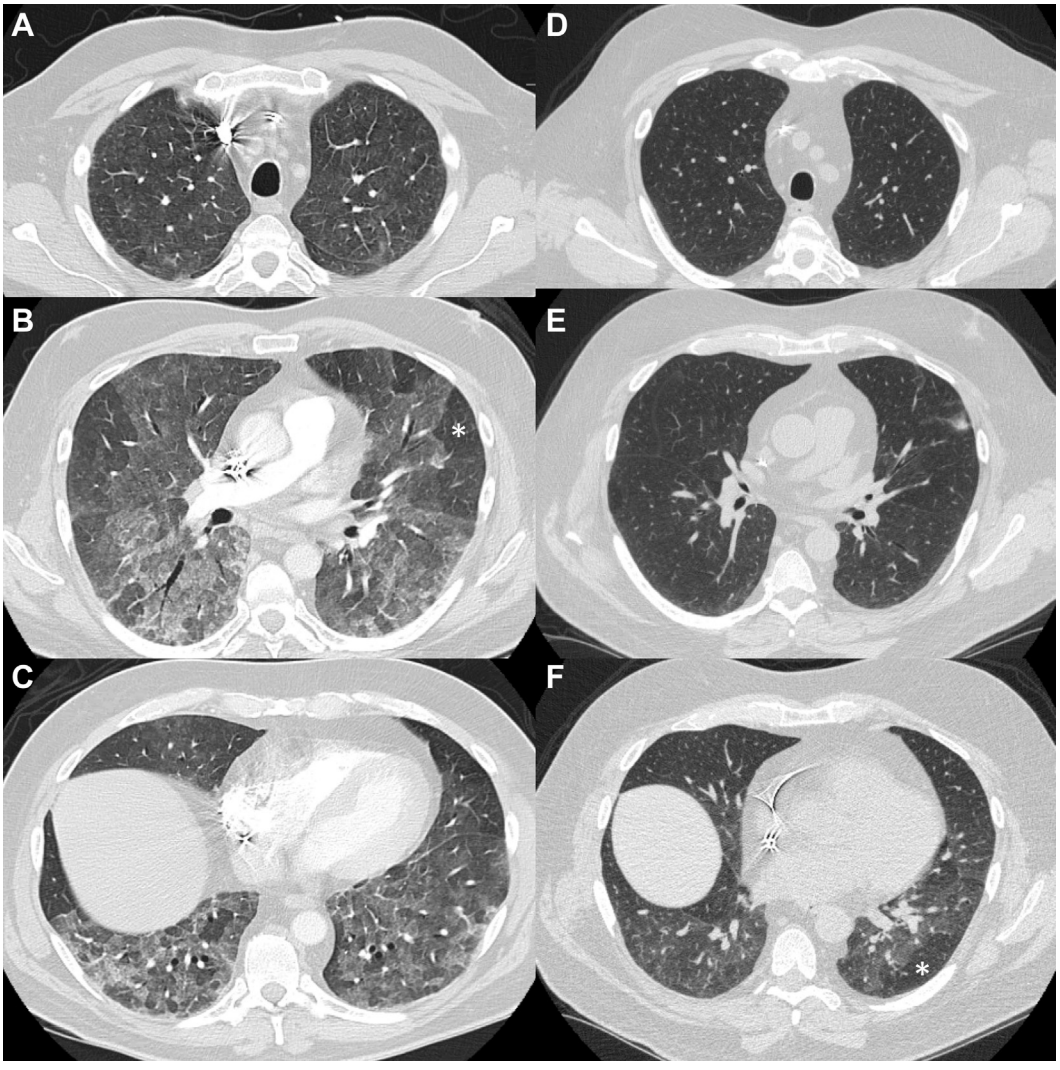

Figure 1 – *A-F, Chest imaging in Case 1 prior to and following antigen remediation and treatment. A-C, CT angiography chest images from the Case 1 patient at the time of ED presentation show diffusely distributed, bilateral, patchy ground-glass opacities. There are also some areas of relatively normal lung and some areas of hyperlucency (an example is indicated by the white asterisk) in the lower lobes. D-E, Inspiratory high-resolution CT images taken 3.5 months later show interval improvement following antigen avoidance and corticosteroid treatment. F, Expiratory CT images at 3.5 months show mild residual air trapping with hyperlucency (an example is indicated by the white asterisk).*

in sustained clinical improvement during corticosteroid tapering. Follow-up chest CT imaging showed improvement in radiologic abnormalities (Figs 1D-1E), although mild air trapping remained (Fig 1F).

Clinical Case 2

A 64-year-old man was diagnosed with IPF 4 years ago when chest CT imaging (Figs 2A-2B) and transbronchial lung cryobiopsy results showed compatible findings. The biopsy specimen showed alveolar parenchyma with temporally and spatially heterogeneous interstitial fibrosis with fibroblast foci, without granulomas, chronic inflammation, or airway-centeredness of the ILD. The patient had stable disease for approximately 3.5 years, at which time he developed worsening cough, dyspnea, and hypoxia, with significant decline in FVC. An updated chest CT scan (Figs 2C-2D) revealed progressive fibrosis without new abnormality. The patient had recently moved to a new home and noticed black discoloration of several home air filters, CPAP filters, and oxygen system filters (Figs 2E-2F). Given concern for possible mold exposure contributing to disease progression, the home was inspected. No mold was identified, but dust was identified in the air ducts, possibly sourced from refuse burning at a nearby construction site. Remediation was performed, but, unfortunately, disease progression continued.

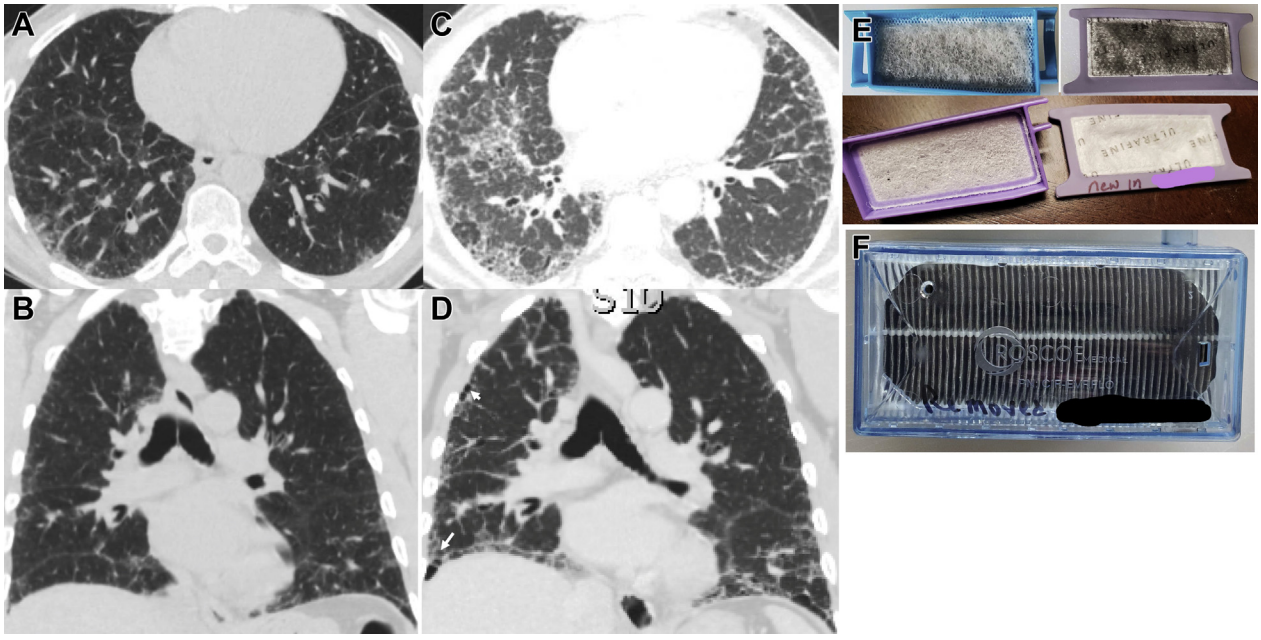

Figure 2 – *A-F, Chest imaging and filter discoloration in Case 2. Chest CT images from the Case 2 patient at the time of diagnosis of idiopathic pulmonary fibrosis and following progression of symptoms. A-B, Axial and coronal images taken at diagnosis show reticular fibrosis, with mild traction bronchiectasis, with peripheral and basilar predominance. C-D, Axial and coronal images taken following worsening of clinical symptoms, showing progression of mixed ground-glass and reticular fibrosis, and development of honeycombing (white arrows). E, Black discoloration of CPAP filters (top) compared with new filters (bottom). F, Oxygen system filters that were noted to be blackened during exchanges.*

Methods for Environmental Inquiry

Despite robust evidence for association of various environmental exposures with ILD risk, scant evidence specific to ILD guides identification and management of these exposures. In practice, the initial evaluation consists of physician inquiry into potentially harmful exposures within the domestic and/or occupational environment, including exposure duration and timing of exposure relative to symptoms.[1,2] According to a recent expert consensus (ascertained via Delphi methods), onset of symptoms around the time of an exposure and improvement of symptoms with removal from that exposure are key features in determining the clinical significance of a proposed exposure in the development of fibrotic HP.[41] Consensus as to the minimum duration of exposure necessary for development of HP was not attained. Case 1 illustrates the importance of obtaining a thorough exposure history to achieve an accurate ILD diagnosis. It is also important to revisit exposure history over time, as patients with ILD may acquire new or unexpected exposures that contribute to worsening symptoms and/or progression of disease, as in Case 2. In practice, however, obtaining such a history can be difficult, with variation across providers. Standardized tools are needed to improve environmental assessment in ILD.

Exposure Assessment Based on Patient Self-Reporting

Physician inquiry into the plethora of potentially harmful environmental exposures associated with various ILDs can be time-consuming, making development of a standardized questionnaire (to facilitate patient self-reporting of exposures) appealing. In occupational asthma, validated questionnaires exist to elicit job site exposures among health care workers[42,43] and for VGDF exposures.[44,45] Development and validation of exposure questionnaires applicable to asthma involved collaboration among experts in occupational lung disease, epidemiology, industrial hygiene, and survey design.[46] Following question development and selection, questionnaires were tested for language clarity and ease of administration, and then validated by comparison of agreement vs gold standards for exposure identification (eg, industrial hygienist evaluation and job exposure matrices [JEMs]).[43]

Environmental exposure questionnaires administered directly to patients have been used in determining environmental risk factors for the development of IPF in several case-control studies, although no single questionnaire has been validated.[21,47] From a diagnostic standpoint, current HP diagnosis guidelines recognize

TABLE 2] Professional Qualifications for Environmental Evaluation

Profession	Education and Experience	Certification
Industrial hygienist	Bachelor's degree 5 Years of experience	American Board of Industrial Hygiene
Indoor environmental quality consultant	Interval standardized examinations for maintenance of certification 8 Years of field experience	Council of Engineering and Scientific Specialty Boards
Environmental health professionals	Physicians, nurses, public health experts	Nonstandardized training in environmental investigation

that use of questionnaires may be beneficial in obtaining a thorough exposure history and suggest that exposure questionnaire development and validation should be a focus of future research.[3] Recently, there has been progress in developing a questionnaire to determine significant exposures in fibrotic HP.[41] Through review of the literature, a list of inciting exposures was created; it was then narrowed to key items by using the Delphi method to develop a questionnaire, which was then tested for timing and clarity in a small sample of patients.[41] The questionnaire has not yet been validated against a gold standard.

Another tool available to clinicians is the website hpLung.com, which provides a searchable list of exposures linked with HP, along with a tally of the number of cases identified during a literature search.[48] Although potentially useful, it is limited to HP-related exposures and is not itself peer reviewed. In general, diagnostically or prognostically relevant exposures likely vary based on geographic and cultural factors, and any tool based on self-report would need to be adapted.[41,49-53]

JEMs can be a useful alternative or adjunct to subject self-reporting of specific exposures for research purposes, linking specific exposures with risk of disease onset or progression.[54] Construction of a JEM is typically completed by an expert (eg, industrial hygienist) who uses patient-reported information about job title, occupation, industry, and work tasks to assign likelihood of a particular exposure and the intensity of exposure (low, medium, or high) with each job.[55,56] JEM have been developed for occupational COPD and asthma. Further studies have validated these JEM and revealed acceptable sensitivity and specificity.[57,58] Currently, no ILD-specific JEM exists. Sack et al[47] used a JEM developed for occupational VGDF assessment in COPD to determine environmental risk factors for the development of CT-identified high attenuation areas (HAA) of the lung in the Multi-Ethnic Study of Atherosclerosis (MESA) air and lung cohorts. In this study, higher JEM-based exposure scores were associated with a higher percentage of HAA on CT imaging, whereas self-reported exposures were only associated with HAA in those currently working. This study illustrates the need for tools more sensitive than self-reporting in ILD exposure assessment.

Direct Evaluation of the Home and Workplace

Following detailed physician interview, many patients do not have obvious exposures associated with specific ILDs or that are considered harmful. In some of these cases, there may be a role for environmental evaluation by a trained professional. There are three categories of qualified environmental assessment professionals: industrial hygienists, indoor environmental quality consultants, and environmental health professionals (Table 2).[59-61] Because there is a paucity of data on professional environmental evaluation and remediation as a diagnostic or therapeutic tool applicable to ILD, the subsequent sections review evidence in the setting of domestic and occupational asthma and occupational lung disease (including HP) to describe the potential benefits and pitfalls of such an evaluation.

Exposure Identification: Lessons From Metalworking Fluid-Associated Lung Disease: Some of the most common traditional occupational sources of antigen among individuals with HP in both the United States and the United Kingdom have included farming and raising and/or handling birds.[62,63] Over time, however, the rates of farming- and avian-associated occupational exposures have declined, with an increase in the rate of metalworking fluid-associated HP.[64-67] Metalworking fluids are lubricating fluids with varying ratios of oil and water that are used to reduce friction and prolong the life of machine equipment.[66,67] In 1998, the National Institute for Occupational Safety and Health (NIOSH) set limits on aerosolized metalworking fluid to an average concentration of 0.4 mg/m^3 of thoracic

particulate mass over the course of a 40-h week or a total particulate mass of 0.5 mg/m^3. These limits were set based on epidemiologic data revealing increased risk of development of asthma and decline in pulmonary function at or above these limits, as well as the technical feasibility of detecting such levels.[66,68-70] Thoracic particulate mass, the aerosolized portion of materials able to reach the lower respiratory tract based on particle size, is measured by using a thoracic sampling device fitted with a 10 μm pore and filter that is placed on a worker or in workplace locations of interest.[25] Metalworking fluids are then identified on the filter by using gravimetric or infrared measures. There is evidence that HP can occur below these set relative exposure limits. During an outbreak of HP at an aeronautical plant, the sampled mean total particulate mass was 0.15 mg/m^3, with a range of 0.09 to 0.38 mg/m^3 in all samples taken from source areas affecting 16 patients.[71] A case series from an automotive plant also showed thoracic particulate mass below the NIOSH-recommended limits in 30 patients with respiratory illnesses (six with HP), although the measured levels were not published.[72]

The discrepancy in NIOSH limits and threshold of disease onset may be due to the fact that many cases of metalworking fluid-associated HP result from microbial contamination of the metal working fluid rather than direct sensitization to the particles themselves.[25,64,73] Measurement of bacterial and fungal burden is tested separately during industrial evaluation when metalworking fluid-associated HP is suspected. Samples are taken as several milliliters of bulk fluid obtained from used metal-working sumps and other associated water-based industrial processes, with samples processed and plated for microbial growth.[25,64,71,73,74] Polymerase chain reaction (PCR) amplification of *Mycobacterium* species has also been used.[73] Maintaining bacterial concentrations $< 10^6$ CFUs/mL of metalworking fluid has been suggested, but regulatory agencies have cited insufficient data to set exposure limit standards.[25,66] Microbial air samples have also been taken in some studies using an air sampler in areas of machine use, with samples plated for microbial growth[71]; however, there are no standards for tolerable microbial levels. Comparison with outdoor air samples may be helpful in determining potentially pathogenic species.[71,75] When several microbes grow from bulk samples, antigen extracts were tested against sera of affected workers, measuring specific IgG titers.[64,71,73,74,76] Elevated antibody titers to the same antigen in multiple symptomatic workers have been helpful in identifying the cause of disease, especially when titers are negative or significantly lower in control workers. When a specific antigenic source cannot be identified, qualitative remediation efforts aimed at reducing overall bacterial burden have been pursued.[71,75] For example, one study focused on improvement in ventilation and reduction of aerosolized metalworking fluid and found significantly decreased bacterial concentration in sumps with these efforts, allowing 51% of workers with HP to return to work symptom free within 26 months of the initial outbreak.[75]

As illustrated in metalworking fluid-associated HP, serum testing for antigen-specific IgG antibodies may be helpful in identifying exposure to an antigen known to be associated with HP. However, extrapolation for use in an individual patient (rather than application among a group of coworkers with and without disease), and to situations in which likely culprit exposures are not clearly identified, is difficult.[77] Elevated serum IgG levels to a particular antigen in an individual merely indicate exposure to that antigen at some point in time. Practically, serum IgG testing can be helpful when an exposure is not identified on history. For example, if a patient without self-reported exposure to mold has an elevated serum IgG to *Penicillium* species, environmental evaluation to assess for occult exposure to mold may be pursued.[3] Furthermore, as illustrated with the evaluation of metalworking fluid, there are no well-established or validated exposure thresholds for disease development, which can make interpretation of environmental inspection challenging. Future study is needed to determine and quantify the level of an exposure that is potentially harmful, although this level may vary by individual based on genetics and other cofactors. Antigen avoidance with assessment for clinical improvement over time is proposed as an indirect way of determining the inciting environment. However, the optimal duration of exposure avoidance necessary to observe beneficial effects is unknown and could be particularly difficult among those with fibrotic ILD in which the benefit may be slowing of disease progression rather than objective improvement.[1,2,78]

Exposure Remediation: Lessons From Domestic Asthma: Home evaluation and remediation of triggers have recognized benefits for individuals with asthma. A systematic review documented decreased symptom

burden, improved quality of life, and decreased health-care utilization in children and adolescents with asthma following home-based environmental assessments and interventions.[79,80] Such interventions may also benefit adults with asthma, although the evidence is less robust.[79,81-84] Key studies are detailed in Table 3.[85-87] In children with asthma that is related to household allergens, interventions to nonspecifically reduce allergens (eg, high-efficiency particulate air filter vacuums, education about tobacco smoke and pet avoidance), as well as those targeting specific allergens (eg, pests), reduced symptoms for up to 2 years. Remediation efforts reduced measured (using a thoracic particulate air sampler) household dust allergen and air pollutant levels concurrently with a reduction in asthma symptoms.[88] In one study of children with asthma living in a home with visible mold, residents of the home underwent either education about home cleaning or professional home remediation efforts were provided.[86] Fungal species in dust collected from inside and outside the home were measured by using PCR, and indoor mold was measured visually by an environmental professional. Professional remediation resulted in greater reduction in visible and indoor PCR-measured mold, without reducing mean indoor allergens (eg, dust mite, cockroach); children in the remediation group had significantly fewer days with symptoms and exacerbations. Of note, the investigators in each of these studies had knowledge of allergen testing to target environmental evaluation and remediation efforts. Individuals with ILD may require more in-depth environmental evaluation to determine exposures necessitating remediation.

Professional Environmental Assessment in ILD

Few studies have assessed the use of home evaluation, sampling, and remediation as a diagnostic or therapeutic intervention in HP or other ILDs. One small pilot study focused on the feasibility of identifying a causative antigen in the home and/or workplace in 19 patients with HP using questionnaires, targeted environmental sampling of frequently visited locations, and testing of patient serum against antigens collected from environmental samples.[89] Overall, only seven of 19 patients reacted against environmental samples; however, among the subset of eight subjects suspected to have an accessible culprit antigen following questionnaire administration, seven reacted against environmental samples. Most subjects without reactivity had cessation of ongoing antigen exposure or had completed some remediation efforts prior to study enrollment. Although small, this study suggests that environmental evaluation in HP may be most productive as a diagnostic intervention (to identify/confirm a causative antigen) when conducted early in the disease course and at the time of active exposure. Furthermore, when applied broadly, home evaluation may have limited benefit in antigen identification beyond that of taking a thorough clinical history or use of a standardized questionnaire.

The benefits of home evaluation and remediation as a therapeutic intervention are also not well delineated in

TABLE 3] Selected Randomized Controlled Trials Documenting Benefit of Home Interventions in Asthma

Study	Population	Intervention	Outcomes
Morgan et al,[87] 2004	Children with poorly controlled asthma and documented sensitivity to home allergens	Visual inspection and dust collection All participants receive allergen-impermeable bed covers and HEPA filtration vacuums Child-specific interventions included HEPA air filters and pest control measures	Intervention reduced symptoms at 1- and 2-y follow-up time points
Evans et al,[85] 1999	Children with moderate or severe asthma	Allergen-impermeable bed covers and education about minimizing exposure to tobacco smoke, pets, and pests Social worker-administered global asthma intervention based on the Asthma Risk Assessment Tool	Intervention reduced symptom days and hospitalizations over a 2-y follow-up period
Kercsmar et al,[86] 2006	Children with symptomatic asthma living in a home with visible mold	Control group education about home cleaning and asthma management Intervention group also received home repairs aimed at remediation of water infiltration and mold (eg, HVAC maintenance)	Intervention reduced symptom days and exacerbations over 12 mo of follow-up

HEPA = high-efficiency particulate air; HVAC = heating, ventilation, and air conditioning.

ILDs. In one study evaluating an HP outbreak among workers in a contaminated building, investigators used walk-through evaluation, serum-specific IgG testing, and targeted microbial cultures to identify a contaminated heating, ventilation, and air conditioning system as the source of elevated serum titers to *Aureobasidium pullulans* among multiple affected workers. Remediation of the heating, ventilation, and air conditioning system resulted in improvement in pulmonary function for many of the affected workers, eliminated positive antibody test results, and led to cessation of new cases.[90] Taken together with asthma literature, it is extrapolated that identification and remediation of mold in the homes of individuals with HP (and possibly other ILDs) could have similar benefits. Importantly, these studies focused on patients with acute to subacute symptoms. Short-term benefit of exposure avoidance may be less apparent in a patient with fibrotic ILD. For example, a small study of nine patients with HP and $>$ 1 year of exposure to birds measured lung function prior to and following removal of the bird, and found that only four of the nine subjects experienced improvement of lung function despite negative results on follow-up antigen testing.[91] As illustrated in Case 2, exposure mitigation may not halt fibrotic ILD progression. Rigorous research is needed to understand how to best measure exposure remediation in an environment as well as the effects of exposure remediation interventions on relevant ILD outcomes.

Other Practical Considerations in Exposure Identification and Remediation

Real-world considerations surrounding environmental evaluation and remediation include cost to the patient, both in terms of payment for professional services and interference with livelihood. For instance, a major remediation targeting asthma control averaged $8,358, whereas minor interventions averaged $447.[92] Health and homeowner's insurances in the United States generally do not cover environmental evaluation; the cost is typically borne by the patient and may be prohibitive. Exposures associated with HP, such as avian proteins, can linger in the environment following bird removal, and extensive cleaning of the home can be costly.[93] When the inciting exposure is occupational, some patients may not have other income options. Studies of patients with farmer's lung have found that a majority return to farming following the HP diagnosis due to economic and self-efficacy motives.[94] In cases of avian antigen exposure, patients or family members may have a strong emotional attachment to the birds, and personal costs of rehoming the birds may outweigh a patient's perceived potential benefit.[95] To mitigate these costs, some opt for use of respiratory masks or air filtration systems to reduce exposures, although there is little evidence regarding effectiveness or to guide choice of protective modality.[96-98] It is also important to note that although eliminating exposure to the inciting antigen is typically recommended, limited direct evidence for effectiveness of that practice exists, particularly in the setting of fibrotic disease.[77,99]

Future Directions

Exposures undoubtedly contribute to ILD pathogenesis beyond those classically considered environmental ILDs. Further research is needed to identify the best ways to determine the relevance of specific exposures in the diagnostic paradigm and to optimize remediation interventions for harmful exposures in ILD. Future studies should focus on the feasibility, long-term outcomes, and cost-effectiveness of various domestic remediation strategies in both nonfibrotic and fibrotic ILDs. Furthermore, deeper investigation into genetic factors, biomarkers, and environmental cofactors that may make an individual more susceptible to specific exposures is required, as illustrated in Case 2. Further investigation is also needed in determining whether the type or amount of an exposure alters clinical course or prognosis in HP and other ILDs.[100]

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: B. F. C. reports personal fees from Boehringer Ingelheim Pharmaceuticals, Inc., outside the submitted work. M. L. S. reports grants from the National Institutes of Health, during the conduct of the study; personal fees from Boehringer Ingelheim Pharmaceuticals, Inc.; and personal fees from Orinove, Inc., outside the submitted work. None declared (C. R. C.).

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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