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Archives of Environmental & Occupational Health

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/vaeh20

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To cite this article: Rafael E. de la Hoz & Kerri A. Johannson (2023) World Trade Center Health Program best practices for the diagnosis and treatment of fibrosing interstitial lung diseases, Archives of Environmental & Occupational Health, 78:4, 232-235, DOI: 10.1080/19338244.2023.2166007

To link to this article: https://doi.org/10.1080/19338244.2023.2166007

ARCHIVES OF ENVIRONMENTAL & OCCUPATIONAL HEALTH
2023, VOL. 78, NO. 4, 232–235
https://doi.org/10.1080/19338244.2023.2166007

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BRIEF REPORT

World Trade Center Health Program best practices for the diagnosis and treatment of fibrosing interstitial lung diseases

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ABSTRACT

Interstitial lung diseases (ILDs) are a diverse set of related conditions with multiple etiologies, in addition to a group where the cause is unknown. There is concern for a potential association of WTC-related exposures with ILD, but the disease range has not differed from what is observed in the general population, and active investigations to study that association are ongoing. Although these diseases are very diverse, some are extremely rare, and they often are disabling and have a poor prognosis, evidence-based guidelines for their diagnosis, management and long-term monitoring have emerged and will evolve as knowledge and therapeutic options increase. This brief article summarizes pertinent issues of diagnosis and management of ILDs, applicable to the diverse group of ILDs that have been observed in the WTC Health Program covered population.

KEYWORDS

Interstitial lung disease; occupational lung disease; sarcoidosis; smoke inhalation injury; World Trade Center Attack; 2001

Introduction

"Interstitial Lung Disease" (ILD) is an umbrella term for a large and heterogeneous group of disease entities,[1] that are frequently inflammatory and/or fibrotic in nature. Many ILDs are chronic and progressive, diffusely involving the lung interstitium. Some ILDs are causally associated with specific etiologies, including environmental, occupational, and iatrogenic exposures, and neoplastic and connective tissue diseases. However, a subset of ILDs is idiopathic, with risk factors but no clear causal relationship with exposures. The ILDs are associated with a high burden of symptoms, morbidity and early mortality and, while antifibrotic agents seem to benefit some patients by slowing the rate of lung function decline, there is presently no cure for fibrotic ILD other than lung transplantation. While many classifications include sarcoidosis as an ILD and the disease is covered by the WTC Health Program, the disease does not involve the lungs in many patients, its treatment differs substantially from the other fibrosing ILDs when it does.[1,2] This document will thus focus on the so-called fibrosing or fibrotic ILDs. After a 30-year interval, updated guidelines for the diagnosis[3] and treatment[4] of sarcoidosis became recently available.

Occupational exposures have long been known to cause ILD, with asbestos fibers, Cobalt-tungsten carbide alloy (hard metal), coal mine dust and crystalline silica among the best-known examples. The majority of occupational ILDs have long latency periods (often decades) between exposures and disease manifestations. The largest systematic review and meta-analysis to date reported that occupational exposure to vapors, gases, dusts and fumes may account for 26% of idiopathic pulmonary fibrosis (IPF) cases.[5] Little is known about the dust, gases and fumes present at the WTC disaster site and surrounding areas in 2001 and 2002, but they have been presumed to have a potential to cause or contribute to ILD development.[6] The true epidemiology of ILD is difficult to estimate, because of limitations in the ascertainment of the diagnoses in research studies. No study has thus far established a causal link between WTC exposures and pathologically and/or clinically ascertained ILDs, but further investigations are needed and ongoing. Some ILDs, such as IPF, are associated with tobacco smoking, and can in fact coexist with chronic obstructive pulmonary disease (so-called combined pulmonary fibrosis and emphysema).[7]

The ILDs observed in the WTC Health Program covered cohorts include the most common types and

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clinical presentations observed in the general population, such as IPF, nonspecific interstitial pneumonia (NSIP), fibrotic hypersensitivity pneumonitis (HP), fibrosing sarcoidosis, connective-tissue disease associated ILD (CTD-ILD), etc. Given this, we chose the Canadian Thoracic Society position statements on fibrotic ILDs,[2,8,9] because they met the quality requirements for this best evidence-based clinical practice article series,[10] and because they sought to provide diagnostic and treatment frameworks for all fibrosing ILDs.

Diagnosis

The diagnosis of ILD2 requires a thorough assessment of symptoms, potential past and present toxic, occupational and environmental exposures, medications, comorbidities, and their treatment (e.g., cancer chemotherapy), family history of ILD, a complete physical examination and complete pulmonary function tests. Other recommendations include: (1) high resolution chest computed tomography (HRCT), usually without contrast (unless there is a diagnostic indication) and with consideration of paired expiratory and prone imaging; (2) collagen vascular disease markers, taking into account pretest probabilities. With this information, the case should be reviewed at a multidisciplinary discussion (MDD), where available, including expert pulmonologists, radiologists and pathologists, and sometimes thoracic surgeons and rheumatologists. Given the complexity and challenges of establishing an accurate ILD diagnosis, the breadth of the diagnosis of ILD, and the markedly reduced use of open lung biopsies, establishing an accurate diagnosis frequently requires MDD.[11] MDD is intended as an often-iterative process, that re-reviews cases as additional information becomes available, and should take place before a patient is considered for surgical lung biopsy and before initiating disease-specific pharmacotherapy.

When a confident diagnosis cannot be achieved despite MDD review of all available information, lung sampling procedures may be recommended. The role of transbronchial biopsy is more prominent for nonfibrotic ILDs and sarcoidosis than for fibrotic ILD, for which surgical lung biopsy should be considered, if there are no contraindications, and it is thought that histopathological data will inform the patient's diagnosis, management and outcome. The value of mineralogic lung studies is established in other areas[12] (and have been described in small case series of WTC exposed individuals[13,14]) but they have not yet been integrated into ILD diagnostic protocols. Transbronchial lung cryobiopsy is an increasingly used approach for histological lung sampling, at centers with expertise using this procedure.

With the widespread use of chest CT, particularly in lung cancer screening, a broad range of interstitial lung abnormalities (ILA) became evident which chest radiographs would easily miss. ILAs are incidentally found nondependent interstitial abnormalities such as ground glass or linear densities, reticular abnormalities, lung distortion, traction bronchiectasis or bronchiolectasis, honeycombing and nonemphysematous cysts affecting at least (an arbitrary) 5% of the volume of any lung zone at a complete or a partial chest CT.[15] These incidentally identified ILAs (also described in the WTC workers[16]) may represent clinically under-recognized disease or may progress to become ILD. If less than 5% of the lung volume is affected, those abnormalities would be considered "minimal", and are less often progressive in nature. If ILA is associated with symptoms, physical findings and/or functional impairment, it may be more appropriately considered an ILD.[15] Quantitative CT approaches to the investigations of ILA are promising, have been investigated in WTC exposed individuals,[17] but are still limited.[18]

Routine monitoring of ILD patients is recommended to occur every 3-6 months,[9] including thorough assessments of symptoms, lung function (FVC and diffusion capacity), functional capacity (6-minute walk test), quality of life, comorbidities, and medication adverse effects. High resolution CT imaging is recommended at baseline assessment, but there is a lack of data to inform frequency of follow-up chest CT, unless there is a clinical indication to evaluate for change. Comorbidities that require particular attention include coronary artery disease, pulmonary vascular disease, hypertension, gastroesophageal reflux disease, and anxiety and depression, while remaining vigilant about pulmonary embolism, lung cancer and obstructive sleep apnea. Disease progression should be assessed using multiple parameters.

Management

The comprehensive management of fibrotic ILD[8] includes smoking cessation, encouraging attainment of ideal body weight, adopting a healthy diet and habits, curtailment of hazardous occupational and environmental exposures, appropriate vaccinations and infection prevention measures, symptom management (such as dyspnea or cough), treatment and/or prevention of disease worsening comorbidities, and supplemental

oxygen and pulmonary rehabilitation when appropriate. ILD is associated with an increased risk of lung cancer,[19] but routine CT-based lung cancer screening is not yet recommended in this patient population. Antifibrotic agents are effective to slow down the progression of progressive fibrotic ILDs with worsening lung function impairment in some patients and some ILD types, and ongoing clinical trials may expand their indications.

Immunosuppressive medications are used for some fibrotic ILDs other than idiopathic pulmonary fibrosis (IPF), when there is underlying inflammation driving disease activity, particularly with CTD -ILDs and HP. As disease progresses, some patients may be eligible for lung transplantation.[20] Optimal timing for referral varies, but a forced vital capacity $<$ 80%, diffusion capacity $<$ 40%, supplemental oxygen requirement, failure to respond to pharmacotherapy, or diagnoses of IPF or fibrotic nonspecific interstitial pneumonitis (NSIP) should lower the threshold for earlier referral and evaluation by lung transplant team.[8] Advanced care planning, palliative and end-of-life care are important parts of comprehensive management of these often disabling and lethal diseases. Medicolegal issues, such as disability assessments, Workers' Compensation claim filing, and registry reporting are important, but vary by individuals and jurisdictions.

Program coverage

Treatment of ILD can be covered by the WTC Health Program. For treatment to be covered, the WTC Health Program member's ILD must be certified administratively. To receive such certification, a WTC Health Program Clinical Center of Excellence (CCE) or Nationwide Provider Network (NPN) physician needs to submit a WTC-3 form (https://www.cdc.gov/wtc/pdfs/Appendix-WTC3.pdf), attesting, among other things, that WTC related exposures were substantially likely to have been a significant factor in aggravating, contributing to, or causing the enrolled WTC member's ILD.

Acknowledgments

The authors acknowledge the comments from the clinicians of the WTC HP Clinical Centers. This review did not involve human subjects research, and was thus exempt from institutional review board review.

Conflict of interest

This work was funded in part by grant U01 OH010401 (RED, PI) from the Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH). The authors have no other relevant financial conflict of interest. The contents of this article are the sole responsibility of the authors and do not necessarily represent the official views of the CDC/NIOSH.

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