Highlights of the Brazilian Thoracic Association Guidelines for Interstitial Lung Diseases*

Destaques das Diretrizes de Doenças Pulmonares Intersticiais da Sociedade Brasileira de Pneumologia e Tisiologia

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Abstract

Interstitial lung diseases (ILDs) are heterogeneous disorders, involving a large number of conditions, the approach to which continues to pose an enormous challenge for pulmonologists. The 2012 Brazilian Thoracic Association ILD Guidelines were established in order to provide Brazilian pulmonologists with an instrument that can facilitate the management of patients with ILDs, standardizing the criteria used for the diagnosis of different conditions and offering guidance on the best treatment in various situations. The objective of this article was to briefly describe the highlights of those guidelines.

Keywords: Lung diseases, interstitial; Guidelines as topic; Brazil.

Resumo

As doenças pulmonares intersticiais (DPIs) são afecções heterogêneas, envolvendo um elevado número de condições, cuja abordagem ainda é um grande desafio para o pneumologista. As Diretrizes de DPIs da Sociedade Brasileira de Pneumologia e Tisiologia, publicadas em 2012, foram estabelecidas com o intuito de fornecer aos pneumologistas brasileiros um instrumento que possa facilitar a abordagem dos pacientes com DPIs, padronizando-se os critérios utilizados para a definição diagnóstica das diferentes condições, além de orientar sobre o melhor tratamento nas diferentes situações. Esse artigo teve como objetivo descrever resumidamente os principais destaques dessas diretrizes.

Descritores: Doenças pulmonares intersticiais; Guias como assunto; Brasil.

*Study carried out by the Interstitial Disease Committee, Brazilian Thoracic Association, Brasília, Brazil.

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Financial support: None.
Submitted: 4 May 2012. Accepted, after review: 11 June 2012.

Introduction

Interstitial lung diseases (ILDs) are heterogeneous disorders, involving a large number of conditions, the approach to which continues to pose an enormous challenge for pulmonologists. In view of similarities in presentation, various forms of bronchiolitis are included in this group, as are alveolar filling disorders and pulmonary vasculitis.

The diagnosis of ILD is often delayed, largely because of a lack of knowledge on the part of health professionals and because of a lack of local resources. The prognosis and treatment of ILDs vary. In addition, no pharmacological treatment can change the course of certain ILDs. One of the major factors limiting the care provided to ILD patients in Brazil is the small number of health facilities with an appropriate multidisciplinary team, given that it is essential that expert pulmonologists, radiologists, and pathologists participate in the evaluation of patients with ILDs. In this context, the Brazilian Thoracic Association (BTA) Guidelines for ILDs were established in order to provide Brazilian pulmonologists with an instrument that can facilitate the management of patients with ILDs, standardizing the criteria used for the diagnosis of various pathologies and offering guidance on the best treatment in various situations. The objective of the present article was to briefly describe the highlights of the 2012 BTA Guidelines for ILDs.

Methods

One group of Brazilian experts with recognized experience in the treatment of ILDs was convened to develop ILD guidelines. An updated review of the major articles on ILD was carried out by searching the Medline, SciELO, and LILACS databases. An attempt was made to find the best available evidence, and the review was supported by the opinion of the expert panel. After all of the material was delivered, a final review was performed by all of the authors. The highlights of the 2012 BTA Guidelines for ILDs are herein divided into topics.

Classification of ILDs

A classification of ILDs was established in order to group the diseases by clinical, radiological, and histological criteria; to facilitate communication among health professionals; to facilitate the development of epidemiological registries and clinical trials; and, first and foremost, to improve patient management. Figure 1 shows the ILD classification, the highlights of which are as follows:

- the inclusion of smoking-related diseases, including smoking-associated fibrosis and combined pulmonary fibrosis and emphysema[1-3]
- the inclusion of bronchiolocentric interstitial pneumonia in the group of idiopathic interstitial pneumonias[4,5]
- the creation of a group of lymphoid diseases, characterized by lymphocyte proliferation[6]

Noninvasive diagnostic tests

In addition to detailed clinical examination and careful occupational history taking, emphasis was placed on noninvasive diagnostic tests, including chest X-ray, chest CT, pulmonary function tests, and exercise tests, the highlights of which are summarized below.

Patients with ILD can have normal chest X-rays. Therefore, the ILD guidelines emphasize the importance of examining chest X-rays for lung volumes, disease pattern, and disease distribution, as well as for extrapulmonary findings. In addition, it is essential that all previous X-rays be reviewed to determine whether the disease has progressed or become stable.[7] Chest HRCT, which should be performed during inhalation and exhalation, is described as playing a crucial role in the differential diagnosis of ILDs. In addition, when associated with the clinical and functional profile, chest HRCT findings can play a decisive role in the diagnosis of ILD. In patients with ILD, the most common HRCT patterns are the septal, reticular, cystic, nodular, ground-glass, and consolidation patterns.[8-10]

The guidelines describe the major functional changes observed in patients with ILD. The pattern that is classically associated with ILDs is a restrictive pattern, with decreased DLCO. Determination of DLCO is the most sensitive test, DLOC being often the first to be affected in ILD patients. Reductions in SpO_2 can be observed at rest and during exercise.[11-13] Cardiopulmonary exercise testing and the six-minute walk test are the main methods for evaluating ILD patients during exercise. However, we should bear in mind that exercise limitation has a multifactorial origin,

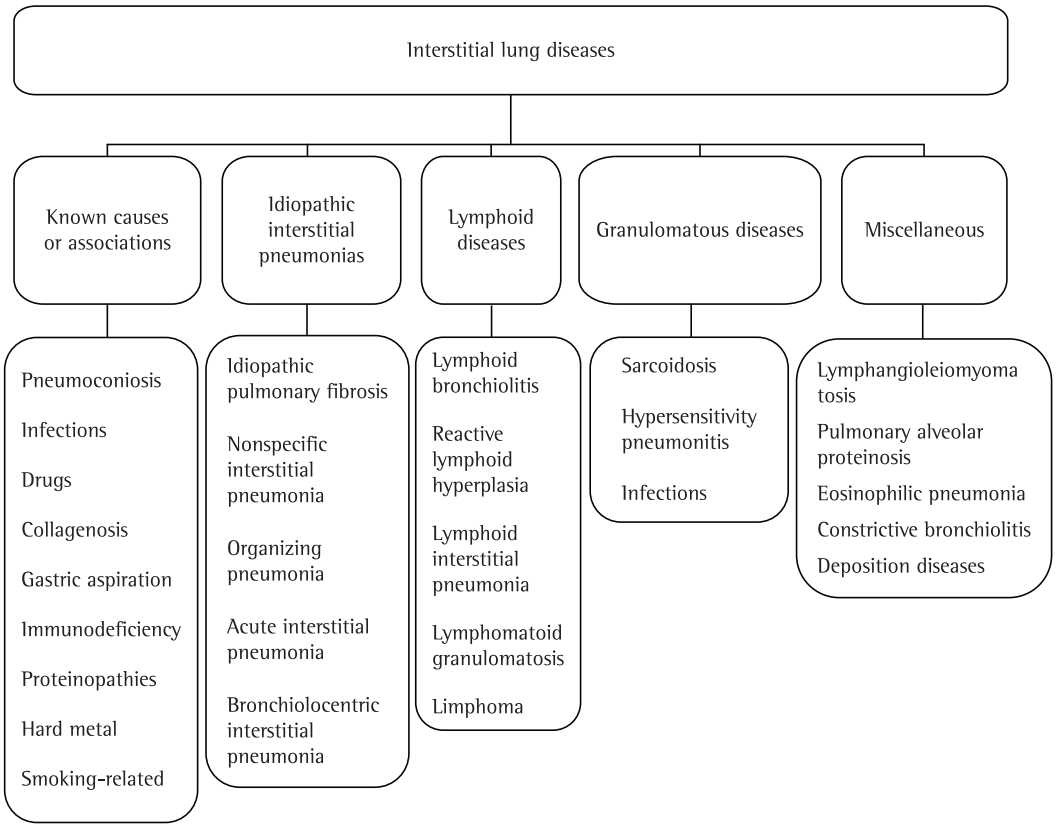

Figure 1 - Interstitial lung disease classification used in the Brazilian Thoracic Association Guidelines for Interstitial Lung Diseases.

including ventilatory, cardiovascular, and peripheral factors. In ILD patients, the main objectives of functional evaluation at rest and during exercise include detecting airflow limitation in a timely manner and facilitating the differential diagnosis, as well as determining disease severity, treatment response, and prognosis.[12,13] Other tests can be performed on the basis of clinical suspicion.

Invasive diagnostic tests

The invasive diagnostic tests recommended in the ILD guidelines include BAL, transbronchial biopsy (TBB), and surgical biopsy. The guidelines emphasize that it is essential to correlate invasive test results with clinical and radiological findings, as well as with ancillary test results. Ideally, such correlations should be established by a multidisciplinary team including pulmonologists, radiologists, and pathologists.

The ILD guidelines emphasize certain aspects of BAL in the evaluation of ILD patients, including the appearance and cellular profile of the BAL fluid, as well as the presence of neoplastic cells, together with screening for infectious agents and cytopathic effects. A BAL is most important and most likely to aid in diagnosis in cases of diseases that present with ground-glass opacities, consolidations, and nodules on HRCT, such as sarcoidosis, hypersensitivity pneumonitis (HP), pulmonary alveolar proteinosis (PAP), alveolar hemorrhage, acute diffuse lung disease, eosinophilic lung disease, and infection.[14,15]

Regarding biopsies, the ILD guidelines emphasize that the decision of whether to perform TBB or surgical biopsy in ILD patients should take into account the clinical evaluation, including patient age, occupational history, and functional status, as well as the location and CT features of the lesions. The yield of TBB is higher than is that of BAL in cases of diseases that present with ground-glass opacities, consolidations,

and nodules on HRCT, especially when there is bronchiolar and peribronchiolar involvement.[16,17]

Surgical biopsies can be performed by conventional limited thoracotomy (open lung biopsy) or by video-assisted thoracoscopy, with similar yields in ILD patients.[18] The choice of biopsy site should be guided by HRCT, and areas of honeycombing should be avoided.[19] Terminal lung, severe pulmonary dysfunction, (relative) pulmonary hypertension, and high cardiovascular risk are contraindications to the procedure.[20] Surgical biopsy should not be performed when there is a typical clinical and radiological profile, when the diagnosis is established by BAL or TBB, or when there is stable fibrosing disease with minimal repercussions.

Idiopathic pulmonary fibrosis

The diagnostic criteria for idiopathic pulmonary fibrosis (IPF), which are primarily based on recently published international guidelines, are presented, HRCT being given greater weight and surgical biopsy being dispensed with if the HRCT findings are characteristic of usual interstitial pneumonia (UIP). When biopsy is performed, it is recommended that a multidisciplinary team including pulmonologists, radiologists, and pathologists discuss the diagnostic approach.[21]

Various therapeutic studies were reviewed, and most showed disappointing results. No pharmacological treatment has proven effective in changing the course of IPF. Treatment is limited to palliative care, management of comorbidities, early referral for lung transplantation, and inclusion in randomized trials of new drugs. Although drugs such as pirfenidone, tyrosine kinase inhibitors, and N-acetylcysteine have been reported to have favorable prospects, results from ongoing studies are awaited.[21-24]

Nonspecific interstitial pneumonia

Regarding nonspecific interstitial pneumonia (NSIP), the guidelines emphasize the following[25-27]:

- the two different forms of presentation of NSIP (i.e., fibrotic NSIP and cellular NSIP), according to the predominance of fibrosis or inflammation
- the need for thorough screening for underlying diseases, especially connective tissue diseases (CTDs), HP, and drug exposure
- a better response to corticosteroids and immunosuppressants when compared with that of UIP

Organizing pneumonia

In addition to a definition of organizing pneumonia (OP), the ILD guidelines present the major forms of OP, namely primary OP (cryptogenic OP) and secondary OP, and their most common causes, as well as the most important radiological patterns (i.e., consolidations, mass/nodule, and reticular opacities).[28-30] Furthermore, the guidelines describe the most commonly used diagnostic options and emphasize the favorable response to corticosteroids in most cases, despite the possibility of recurrence.[28,31]

Sarcoidosis

The ILD guidelines describe the concept of sarcoidosis and recommend that etiologies for granulomatous tissue inflammation be ruled out. The guidelines also describe the diagnostic criteria for sarcoidosis; the disease is diagnosed on the basis of clinical, radiological, and histological findings, and tissue confirmation is not always necessary.[32]

The ILD guidelines emphasize that TBB is the primary method for diagnosing pulmonary sarcoidosis, transesophageal endoscopic ultrasound-guided and endobronchial ultrasound-guided fine-needle aspiration of lymph nodes being described as promising tests.[33,34] Ophthalmologic examination, cardiac evaluation, pulmonary function testing, chest X-ray, HRCT, blood workup, serum biochemistry, assessment of calcium metabolism, PPD testing, and urinalysis are recommended for all patients who have recently been diagnosed with sarcoidosis.

With regard to the treatment of sarcoidosis, the ILD guidelines state that spontaneous remission can occur, treatment being required in the following cases: presence of symptoms; significant systemic involvement (neurological involvement, myocardial involvement, or hypercalcemia); and pulmonary involvement with significant dysfunction or disease progression after a period of observation. In addition, the guidelines recommend that corticosteroids be used as the treatment of choice in most patients, the use of non-steroidal anti-inflammatory drugs, such as methotrexate (second-line treatment),

azathioprine, leflunomide, TNF-α antagonists, and antimalarials, being reserved for special cases, such as those in which treatment with non-steroidal anti-inflammatory drugs fails and those in which there are significant steroid-related adverse effects.[32,35]

HP

The most common exposures associated with HP are described in the ILD guidelines.[36] In addition, the diagnostic criteria for HP are defined, more weight being given to CT patterns suggestive of HP and to the possibility of confirming the diagnosis by BAL and TBB.[37] With regard to treatment, the guidelines emphasize the need for withdrawal from exposure; corticosteroids, which determine a better response mainly in the acute and subacute phases can be used.[37]

CTDs

The ILD guidelines state that the CTDs that are most prevalent in ILD patients are progressive systemic sclerosis, polymyositis/dermatomyositis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and mixed connective tissue disease. The predominant patterns are NSIP and UIP; less common patterns include OP, bronchiolitis, and lymphocytic interstitial pneumonia.[38,39] The guidelines emphasize the need to be on the alert for extrapulmonary involvement, including respiratory muscle involvement and esophageal abnormalities, which can lead to pulmonary complications. In the initial routine evaluation and in the follow-up of CTD patients with pulmonary involvement, HRCT and full pulmonary function testing, with determination of DLCO, are recommended, as is assessment of respiratory muscle strength, in the presence of disease with possible muscle involvement.[40]

With regard to treatment, the possibility of periodic observation, without starting the patient on any medication, should always be considered, as should the possibility of referral for lung transplantation in advanced cases. When there is a need for treatment, initial options include a low-dose combination of cyclophosphamide and prednisone in cases of progressive systemic sclerosis and a corticosteroid with or without an immunosuppressant in cases of polymyositis/dermatomyositis.[41,42]

Smoking-related diseases

The major smoking-related ILDs are presented, including respiratory bronchiolitis with ILD, desquamative interstitial pneumonia, pulmonary Langerhans cell histiocytosis, IPF, combined pulmonary fibrosis and emphysema, and the recently described smoking-related pulmonary fibrosis, all of which can often be seen in the same patient.[1,3] Smoking-related ILDs have varied clinical, functional, radiological, and histological presentations, as well as having different prognoses. With regard to treatment, major emphasis is placed on smoking cessation, which can be sufficient to improve the patient's condition.[1,43]

Lymphangioleiomyomatosis

The ILD guidelines describe the diagnostic criteria for lymphangioleiomyomatosis, with an emphasis on the fact that biopsy is not required in all cases.[44] In addition, the guidelines state that, in the presence of CT findings characteristic of lymphangioleiomyomatosis, serum VEGF-D levels constitute an important diagnostic criterion, although determination of VEGF-D levels is a test that is not widely available.[45] The guidelines also state that hormonal blockade (with progesterone or gonadotropin-releasing hormone analogues) can be used in severe or progressive cases (or both).[44,46] Furthermore, the guidelines present promising options for the treatment of lymphangioleiomyomatosis, including the use of doxycycline (a metalloproteinase inhibitor) and, mainly, the use of sirolimus (a mammalian target of rapamycin inhibitor). However, clinical trials are still needed in order to determine the actual role of these medications in the treatment of the disease.[47,48]

PAP

The ILD guidelines describe the major forms of PAP, namely autoimmune PAP (the most common form), secondary PAP, and genetic PAP, and emphasis is placed on the criteria for confirming the diagnosis of the disease, i.e., CT findings characteristic of PAP (crazy-paving pattern), together with BAL and TBB findings, surgical biopsy being rarely required.[49,50] Regarding the therapeutic approach to PAP, the highlights are whole-lung lavage (current

standard treatment) and, as a promising option, the use of subcutaneous or inhaled GM-CSF.[51-53]

Acute diffuse lung disease

The major causes of acute diffuse pulmonary infiltrates include infections, drug-induced pulmonary toxicity, acute interstitial pneumonia, acute interstitial pneumonia associated with CTDs, acute eosinophilic pneumonia, cryptogenic OP, HP, and diffuse alveolar hemorrhage.[54] For the evaluation of patients with acute diffuse pulmonary infiltrate, the most important ancillary tests are HRCT, bronchoscopy with BAL (with cytological and microbiological examination), TBB, and surgical biopsy.[55]

Acute exacerbation of ILD, classically associated with IPF, is defined by the following criteria: previous or concurrent diagnosis of IPF; unexplained development or worsening of dyspnea; HRCT showing a pattern consistent with UIP and new areas of ground-glass opacity, consolidation, or both; reduced oxygenation; and exclusion of infections and other diagnoses. Although the best treatment for acute exacerbation has yet to be defined, the guidelines recommend the use of moderate-dose corticosteroids or corticosteroid pulse therapy, either in isolation or in combination with cyclophosphamide.[56,57]

Pulmonary hypertension

The ILD guidelines emphasize that mathematical formulas can be used in order to predict the presence of ILD-associated pulmonary hypertension, given that echocardiography has significant limitations in identifying pulmonary hypertension in patients with ILD, producing a high number of false-positive and false-negative results. However, right heart catheterization remains the diagnostic method of choice.[58,59] In addition, the guidelines emphasize that there is currently no indication for the use of drugs that have an antiproliferative and vasodilating effect on the pulmonary circulation for the treatment of ILD-associated pulmonary hypertension.

Lung transplantation

The major indications for referral of ILD patients for an evaluation for lung transplantation are presented, as are the contraindications to the procedure. In addition, the guidelines emphasize the need for early referral of patients to lung transplantation centers, especially those patients with idiopathic interstitial pneumonia, given that transplantation is one of the few treatment modalities that have an impact on survival.[60,61]

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