The respiratory tract and juvenile rheumatic diseases

Vinicius Domingues1, Marta Cristine Félix Rodrigues2, Christianne Costa Diniz3, Rozana Gasparello de Almeida4, Flavio Roberto Sztajnbok5

ABSTRACT
Respiratory tract disorders in the juvenile rheumatic diseases are not infrequent and can have different clinical features when compared with those in the adult diseases. The purpose of this review article is to show the main manifestations of the respiratory tract, with an emphasis on lung involvement, in the most frequent juvenile rheumatic diseases.

Keywords: lung, rheumatic diseases, child, respiratory tract.

INTRODUCTION
Respiratory tract impairment in the pediatric patient with rheumatic diseases can occur at any level, the most frequent manifestation being pleuropulmonary involvement, which usually occurs as a manifestation of primary disease, and, less frequently, as an adverse effect of the medicamentous treatment. Through a literature review using the bibliographic research databases LILACS and MEDLINE, this article aimed at providing a practical review about the subject.

RHEUMATIC FEVER
Pleuropulmonary manifestations in the acute phase of rheumatic fever (RF) are rare. Rheumatic pneumonia and pleurisy are pleuropulmonary manifestations that show large parahilar opacities, which modify rapidly, in addition to interlobar or interalveolar trabecular thickening. Pleural effusion, when present, is usually serofibrinous. One wonders whether that rheumatic pneumonitis would not be a manifestation resulting from signs of heart failure, since chest X-ray can reveal signs of pulmonary congestion secondary to severe carditis. There are a few reports about pulmonary edema, usually unilateral, associated with severe mitral regurgitation, with or without ruptured chordae tendineae.1-3

JUVENILE IDIOPATHIC ARTHRITIS
Systemic juvenile idiopathic arthritis (JIA) is the subtype most frequently associated with airway manifestations, which occur in up to two thirds of the cases, usually in a mildly symptomatic form and associated with pericarditis or other signs of disease activity.4 Clinically the patient can have tachypnea, pleural fremitus, and rales. Chest X-ray can show pleuritis, with or
without pleural effusion. Some patients with the polyarticular subtype can develop interstitial pneumonitis and bronchiolitis obliterans. There are a few reports of patients with primary pulmonary hypertension, diffuse interstitial fibrosis of the pulmonary parenchyma associated with the presence of intraalveolar and interstitial granulomas, pneumomediastinum, and pulmonary hemosiderosis.

**JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS**

The severity of the pulmonary manifestations of juvenile systemic lupus erythematosus (JSLE) varies from mild pleuritic pain to pulmonary hemorrhage. They are less frequent in the pediatric than in the adult population, and can appear in the beginning or during disease course. Chest pain is the most frequent manifestation, can be of musculoskeletal origin or present as a pleuritic type pain, with or without pleural fremitus on auscultation and pleural effusion on chest X-ray. The pleural effusion can be uni- or bilateral, and auto-antibodies can be present. The complement C3 and C4 fractions are usually decreased and the protein concentration is low. Small asymptomatic effusions resolve with the use of non-steroidal anti-inflammatory drugs.

An infectious etiology has been suggested to acute pneumonitis with pulmonary infiltrate in JSLE patients. Bacterial or viral pneumonia, secondary to the use of immunosuppressive drugs, should always be ruled out. However, the clinical syndrome of acute lupus pneumonitis related to disease activity has been reported and can occur in approximately 10% of the cases. It is clinically characterized by fever, dyspnea, cough, occasional hemoptysis, predominantly basal interstitial-alveolar infiltrates, hypoxemia, and pleural effusion in half of the cases. The prognosis of acute lupus pneumonitis is very poor, with mortality in up to 80% of the cases, when treatment onset is not early. Chronic pneumonitis is infrequent and behaves as pulmonary fibrosis. The most common complaint is dry cough, followed by dyspnea, and recurrent pleuritic pain.

Interstitial lung disease (ILD) is less frequent than in adults. A study with children with JSLE reported spirometric alterations in 37% of the patients, with a predominance of the restrictive pattern, while alterations in the carbon monoxide lung diffusion capacity occurred in 26% of the cases. That study has also shown that a correlation between the findings of spirometry and high-resolution computed tomography, present in 8% of the patients, and disease activity seems not to exist.

Acute pulmonary hemorrhage, clinically translated as the presence of acute hemoptysis and accompanied by a high mortality rate (85%), can occur in JSLE. The clinical and radiological presentation, histopathological findings, and natural history of acute pulmonary hemorrhage are indistinguishable from those observed in acute lupus pneumonitis, suggesting that both entities belong to the same spectrum of lupus pulmonary disease.

Pulmonary arterial hypertension (PAH) in JSLE is being more frequently recognized and described. The clinical manifestations include dyspnea, chest pain, dry cough, asthenia, lower limb edema, and palpitation. Diagnosis is established by use of Doppler echocardiography. When neither the diagnosis is clear nor secondary causes, such as chronic primary thromboembolism, have been ruled out, right cardiac catheterization and pulmonary angiography should be requested.

Diaphragmatic dysfunction or “shrinking lung syndrome”, characterized by dyspnea and pleuritic pain with radiological findings of lung volume reduction with basilar atelectasis, has been reported in JSLE. Myositis, as a cause of diaphragmatic elevation, has been reported in approximately 13% of patients on chest X-ray. The diaphragmatic function can be studied by use of ultrasound, phrenic nerve stimulation, or diaphragmatic electroneuromyography.

**ANTIPHOSPHOLIPID ANTIBODY SYNDROME**

In children, antiphospholipid antibody syndrome (APS) is rare and have different characteristics from those of the adults, such as the frequent lack of risk factors (smoking, contraceptive use, atherosclerosis) and the higher incidence of infection as a predisposing factor. The related thrombotic events are deep venous thrombosis in lower limbs, pulmonary embolism, and thrombotic complications of the central nervous system. The APS has already been described as a thromboembolic phenomenon in children. In a multicenter study with 121 patients with primary and secondary APS, no pulmonary involvement was reported. In patients with JSLE and secondary APS, diagnosis and treatment can be challenging, because pulmonary hemorrhage can be a catastrophic manifestation of the syndrome.

**SJÖGREN’S SYNDROME**

Sjögren's syndrome (SjS) is rare in children, and the diagnostic criteria used for adults are less sensitive in that age group. The presence of anti-Ro/SS-A antibodies is related to a higher frequency of extra-glandular manifestations, mainly interstitial lung disease, with altered respiratory function tests (small airway obstruction). In primary SjS, the most commonly found
pulmonary manifestations are cough, hoarseness, and ILD manifestations. In its secondary form, the underlying disease prevails, and no difference has been reported in the manifestations in children. Xerotrachea and “dry” bronchitis are more commonly observed in adults. The involvement of upper airways leads to symptoms related to the nose, facial sinuses, and posterior larynx. Dry cough can be mistaken for respiratory allergy, asthma, or bronchitis for a long time. Because of its rare occurrence in children, most studies about its pulmonary manifestations refer only to adults.

JUVENILE DERMATOMYOSITIS

In juvenile dermatomyositis (JDM) and juvenile polymyositis (JPM), pulmonary alterations can occur as part of the disease or be due to adverse effects related to the drugs used in the treatment. Interstitial lung disease (ILD) can occur in both diseases equally, affecting up to 40% of the patients, and can precede the diagnosis of myositis. Its presence is a determinant of poor prognosis, with high mortality rates. The presence of the Anti-Jo1 antibody is described as a marker of its presence, but studies have shown its association with a better prognosis and better therapeutic response. A possible new serum marker for ILD, named KL-6, has been recently described and consists of a glycoprotein produced by type II pneumocytes, and acts as a chemotactic factor for fibroblasts. Spontaneous pneumothorax and pneumomediastinum have been reported as one of the ILD complications. Cases of PAH have been reported. Pulmonary function tests show a restrictive pattern with decreased diffusion capacity.

Weakness of the respiratory muscles, which occurs in 4% to 8% of the patients with JDM/JPM, is present in more severe cases. The most affected muscles are the diaphragm, intercostal, and accessory muscles. The consequence of that involvement can vary from mild-to-moderate dyspnea, with an image of atelectasis on chest X-ray, to clear pulmonary insufficiency. Several studies have shown that that impairment is frequently underestimated. Hypercapnia due to diaphragm weakness has been reported.

Infection is one of the potentially lethal complications of myopathies. The responsible factors are as follows: weakness of the respiratory muscles, leading to ineffective cough, atelectasis, and predisposition to bacterial pneumonia; esophageal dysmotility, leading to aspiration pneumonia; and the pathogenesis of the disease itself, with T and B cell lymphopenia, generating an increased risk of opportunistic infection.

SCLERODERMA

The major organs involved in systemic sclerosis (SSc) are the gastrointestinal tract and lungs. Pulmonary complications, either isolated or associated, are the major causes of death, and are listed in Table 1.

Table 1

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<th>Major pulmonary complications of scleroderma</th>
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<tr>
<td>§ interstitial fibrosis</td>
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<td>§ pulmonary arterial hypertension</td>
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<td>§ pleural effusions</td>
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<td>§ spontaneous pneumothorax secondary to the rupture of subpleural blebs</td>
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<td>§ bronchiectasis</td>
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<td>§ restriction of the thoracic cage secondary to skin and subcutaneous tissue stiffness</td>
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<td>§ diaphragmatic dysfunction</td>
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<td>§ chronic aspiration pneumonitis secondary to esophageal dysmotility</td>
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<td>§ pneumonitis associated with drugs used in the treatment, such as methotrexate</td>
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<td>§ pulmonary neoplasia</td>
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The most common pulmonary manifestation of SSc is interstitial fibrosis, less frequent in children than in adults. The worst prognosis of SSc is directly related to the severity of PAH and coexistence of ILD. Pulmonary involvement can be diagnosed in patients without cardiopulmonary symptoms by use of a combination of non-invasive tests for screening and invasive tests for confirmation. Early detection and therapeutic intervention in PAH and ILD delay the appearance of complications and reduce mortality in SSc.

The usefulness of assessing the presence of antibodies as risk or protective factors for the different pulmonary manifestations of scleroderma is lower in juvenile SSc as compared with that in the adult disease, because those antibodies are less frequently found in the younger age group.

VASCUITIS

In this heterogeneous group of diseases, some can progress with pulmonary vasculitis, mainly those affecting small vessels, such as arterioles, venules, and capillaries.

Wegener’s granulomatosis

Necrotizing granulomatous vasculitis of small vessels, rare in the pediatric group, can affect the lower and upper respiratory tracts. The isolated involvement of the upper airway is rare, but, when associated with other symptoms, is considered the second most frequent manifestation, and usually causes the...
patient to see a doctor, because it resembles infections, such as otitis, sinusitis, mastoiditis, chondritis, or pneumonia. Such manifestations can lead to permanent damages, such as nasal septal perforation with saddle nose deformity, chronic sinusitis, chronic otitis with facial nerve lesion and facial paralysis, conduction deafness, subglottic and tracheobronchial stenoses, complications that can be found in up to 50% of the children with that disease. The patient can have rhinorrhea, purulent and/or bloody nasal discharge, dryness of the nasal mucosa with formation of crusts and pustules, nasal ulcers, epistaxis, otitis media, sinusitis, hemoptysis, dyspnea, chest pain of the pleuritic type, and signs of upper airway and larynx obstruction, such as stridor and hoarseness.

Fever is frequently found due to secondary infection. Akikusa et al. have reported a case series in which 80% of the patients progressed with pulmonary involvement, 44% had pulmonary hemorrhage and 20% respiratory failure. Massive pulmonary hemorrhage is the most life-threatening manifestation. The patient can have hemoptisis due not only to pulmonary capillaritis, but also to pulmonary embolism and deep vein thrombosis. A multicenter study involving North-American and Canadian centers of pediatric rheumatology has reported that the most frequent initial clinical manifestations were as follows: constitutional symptoms (89.2% of the patients); pulmonary symptoms (80%); and upper airway (80%) and renal (75.4%) involvements. The pulmonary signs and symptoms that stood out the most were as follows: shortness of breath; chronic cough; hemoptysis; alveolar hemorrhage; nodules; abnormal pulmonary function tests; fixed pulmonary infiltrates; pleurisy; and oxygen dependence. The pulmonary involvement was severe enough to require oxygen therapy or mechanical prosthesis in almost 25% of the patients. Regarding the upper airways, the following occurred: nasal involvement; sinusitis; otitis; mastoiditis; subglottic stenosis; alteration of the hearing acuity; and oral ulcers.

Chest X-ray can be normal or reveal pulmonary alterations, such as atelectasis, nodules, cavitary lesions, pulmonary infiltrates/opacifications, and pleural opacifications, which can be confirmed by use of computed tomography. A tomographic study with 18 children has revealed the presence of nodules in 90% of the cases, ground-glass opacification in 52%, and airway opacification in 45% of the cases. Laboratory tests are unspecific, except for the presence of anti-neutrophilic cytoplasmic antibodies (central pattern, known as c-ANCA), which, is highly specific for the diagnosis of Wegener’s granulomatosis. The biopsy of nasal sinuses shows the typical presence of granulomatous necrosis and chronic inflammation.

**Churg-Strauss syndrome**
Granulomatous vasculitis that progresses with important peripheral eosinophilia, transient pulmonary infiltrate, severe asthma, sinusitis, mono- or polyneuropathy, cutaneous lesions, and extravascular eosinophilia. Chest X-ray can show transient pulmonary infiltrate, bilateral nodular or interstitial infiltrate, bilateral hilar lymphadenopathy, and pleural effusion. Zwerina et al., in a systematic literature review, collected 33 cases of the Churg-Strauss syndrome in children and reported that, in that age group, cardiopulmonary manifestations were more frequent than in adults. Although asthma and sinusitis had similar frequencies, transient pulmonary infiltrates were more frequent in the pediatric age group, affecting 88% of the patients (as compared to 59% of adults), while pleural effusion occurred in 12% of the patients.

**Henoch-Schönlein purpura**
Henoch-Schönlein purpura is the most common vasculitis in children, and comprises cutaneous, gastrointestinal, articular, renal, and systemic manifestations. It is a leukocytoclastic vasculitis of small vessels, characterized by IgA immune complex deposition. It is usually preceded by an upper airway infection. It can rarely progress to pulmonary hemorrhage and interstitial pneumonitis.

**Microscopic polyangiitis**
Microscopic polyangiitis is a non-granulomatous necrotizing vasculitis extremely rare in the pediatric group, and is considered a lung-kidney syndrome. It affects small-sized vessels, and its main characteristic is the development of rapidly progressive glomerulonephritis and alveolar hemorrhage. Patients with pulmonary impairment can have hemoptysis, pleurisy, dyspnea, and bronchospasm. Only a few cases have been reported in the pediatric age group, with constitutional and pulmonary manifestations, ranging from focal infiltrates to massive pulmonary hemorrhage and hemoptysis secondary to alveolar capillaritis. High levels of the p-ANCA (peripheral pattern) and c-ANCA antibodies can be seen.

**Kawasaki disease**
This necrotizing vasculitis of unknown etiology affects small and medium-sized vessels, is relatively common in children, and can have a severe complication, the appearance of coronary aneurysms. At the initial phase of the disease, the patient can have airway manifestations, such as cough, coryza, and hoarseness, suggestive of an upper airway infection. Pneumonitis...
due to vasculitis in the pulmonary vessels or secondary to cardiovascular involvement (myocarditis and endocarditis) can occur. Chest X-ray can show a transient infiltrate in the acute phase of the disease. Some children can reactivate their BCG vaccination scars, with intensification of the exanthem around them, of unknown cause.41

Takayasu arteritis
Although of unknown etiology, in some parts of the world, it seems to be related to tuberculosis. It affects mainly the aorta and its major branches, and, in approximately 50% of the patients, the pulmonary arteries can be involved, although the symptoms related to pulmonary arteritis are less frequent. The pulmonary involvement can lead to chest pain, hemoptysis, pulmonary hypertension, and dyspnea.42

Hypocomplementemic urticarial vasculitis
This is a leukocytoclastic vasculitis of unknown etiology, characterized by the presence of recurring urticarial, purpuric, or erythema multiforme-like lesions that usually last 24 to 72 hours. Some patients have facial and laryngeal angioedema, progressing with stridor and dyspnea. Pulmonary involvement can occur in 30% of the cases, with cough, dyspnea, and hemoptysis.43

Goodpasture syndrome
Rarely found in children and adolescents, the syndrome is characterized by pulmonary hemorrhage and proliferative glomerulonephritis associated with the presence of anti-glomerular basement membrane antibodies. Patients complain of dyspnea, chest pain, bronchospasm, and hemoptysis, accompanied by systemic symptoms, such as fever, tremor, and severe sweating.35,36

Behçet’s disease
The disease affects vessels of any size, both arterial and venous. The most affected arteries are the carotid, pulmonary, aorta, iliac, and popliteal arteries. Involvement of the pulmonary artery usually occurs in the large proximal branches, which can lead to hemoptysis, due to a fistula between the artery and the bronchi, and to venous obstruction. The following can also be observed: pulmonary infarction; hemorrhage; pleural effusion; pulmonary arteritis or venulitis; bronchial stenosis; airway obstructive disease; chronic bronchitis; and fibrosis. Imaging exams can show well-defined or reticular-nodular opacities, and pulmonary volume loss. In addition, rupture of pulmonary arterial aneurysms can occur, causing hemoptysis, areas of hemorrhage, pneumonia, deep venous thrombosis, and embolism.35,36

Relapsing polychondritis
Relapsing polychondritis is a systemic inflammatory disease affecting the structure and, consequently, the function of cartilages, sense organs, and the cardiovascular, renal, and nervous systems. The patient can have the following: auricular chondritis; nasal chondritis with saddle nose deformity; involvement of the tracheobronchial tree with tracheal and/or laryngeal chondritis; aorta lesions; inflammatory polyarthritis due to synovial involvement; costochondritis; neurosensory hearing loss; vestibular dysfunction vertigo; and eye inflammation, such as conjunctivitis, keratitis, episcleritis, and uveitis. Chest X-ray can show the presence of tracheal stricture, opacities secondary to pneumonia or obstruction-induced atelectasis, increased pulmonary vascularization, or pulmonary edema. Lateral cervical X-ray can show tracheal or laryngeal cartilage calcifications. Computed tomography and specially magnetic resonance imaging allow better assessment of the lesions and distinction between inflammation and fibrosis. The pulmonary function tests can show various degrees of inspiratory and/or expiratory obstruction.35,36

AUTOINFLAMMATORY DISEASES
Autoinflammatory diseases, also known as periodic fever syndromes, are caused by innate inherited or acquired immunity disorders. They are multisystem diseases characterized by recurring episodes of fever and systemic inflammation in the absence of infection and with no antibody production. They can affect the skin, eyes, joints, serous surfaces, and other inner organs. The following hereditary syndromes have pleuropulmonary manifestations: familial Mediterranean fever (FMF); tumor necrosis factor receptor-associated periodic syndrome (TRAPS); hyperimmunoglobulinemia D and periodic fever syndrome (HIDS); cryopyrin-associated periodic syndromes (CAPS); NOD2-associated pediatric granulomatous arthritides (Blau syndrome and early-onset sarcoidosis).

The manifestations of autoinflammatory diseases in the respiratory tract are characterized by acute and recurring inflammation episodes, in which self-limited sterile pleuritis, the most frequent manifestation, and severe pulmonary vasculitis can be found. A chronic course, usually a complication of non-controlled inflammation, can occur in pulmonary amyloidosis and neoplasias.
Pleuritis

The FMF usually manifests during childhood with recurring attacks that can be spontaneous or triggered by stress, immunization, or menstruation. The attacks last three to four days, and high fever and serositis are the major manifestations. Sterile pleuritis is the second most frequent serositis after peritonitis, and the third most common clinical manifestation after peritonitis and arthralgia. Pleuritic chest pain occurs in approximately 40% of the cases, is usually unilateral, and can be isolated or associated with peritonitis. The respiratory movements cause pain, the respiratory sounds can be reduced in the most severe cases, and the chest X-ray can show a small pleural effusion or pleural thickening in recurring cases.

Although much more common in FMF, pleuritis can also occur in TRAPS. The inflammatory attacks can last one to four weeks and manifest as fever, abdominal pain, myalgia, exanthema, lymphadenopathy, conjunctivitis, peri orbital edema, and pleuritic pain. Treatment with high doses of corticosteroids and biological agents, such as anti-TNF, are not always effective. The use of IL-1 blockers (anakinra) proved to be effective in some patients.

Pulmonary vasculitis

Familial Mediterranean fever can be associated with other systemic diseases, such as Henoch-Schönlein purpura, polyarteritis nodosa (PAN), and Behçet disease, and, thus, the pulmonary vasculitic manifestations of those diseases can be present. Although the pulmonary involvement is not common in PAN, severe dyspnea, cough, hemoptysis, chest pain, and fever can be clinical manifestations of interstitial pneumonia, interstitial fibrosis, bronchiolitis obliterans, and pulmonary infiltrate.

Amyloidosis

Systemic amyloidosis is one of the most severe manifestations of autoinflammatory diseases, especially of FMF, being due to the tissue deposition of fragments of serum amyloid A. Such deposits are more frequently found in the kidneys, respiratory tract, gastrointestinal tract, adrenal glands, spleen, and testes. Although amyloidosis occurs after a long time of uncontrolled inflammatory disease, sometimes its appearance can precede attacks of fever, a phenomenon related to the persistence of a subclinical inflammation status, even when symptoms lack. The prophylactic treatment with oral colchicine daily in FMF is effective in preventing the attacks and the development of amyloidosis, and should be maintained for the rest of the patient’s life. Controlling inflammation with immunosuppressive therapies or immunobiologic agents can be necessary in refractory cases. In addition, amyloidosis occurs relatively often in CAPS (Muckle-Wells and CINCA/NOMID syndromes) and TRAPS, but is rare in HIDS. Tracheobronchial amyloidosis is the most common form of respiratory tract involvement, and the clinical symptomatology varies according to the location of the amyloid deposits along the tracheobronchial tree.

Neoplasia

Peritoneal and pleural mesotheliomas have already been reported in patients with FMF, and are associated with the recurring inflammatory stimulus of serous membranes.

Pulmonary manifestations of granulomatous autoinflammatory diseases

Pediatric granulomatous arthritis (PGA) is the currently proposed denomination that encompasses two phenotypically identical diseases, the Blau syndrome, of dominant autosomal inheritance, and the early onset sarcoidosis (EOS), a sporadic form of the disease that begins prior to the age of four years. Currently, the finding of the same mutation in the NOD2 gene in both diseases identifies them as a single disease.

Pediatric granulomatous arthritis is characterized by a clinical triad comprising the non-caseous granulomatous infiltration of the skin, synovium, and eyes (exanthema, arthritis, and uveitis). Although rare in PGA, cases of interstitial pneumonitis, bronchial granuloma, and pulmonary thromboembolism have already been reported. The treatment of the associated pulmonary findings comprises the same drugs used in controlling the other manifestations of the disease, such as corticosteroids, immunosuppressive and immunobiologic agents. The use of methotrexate should be avoided due to its pulmonary toxicity.

SARCOIDOSIS

Sarcoidosis is a multisystemic granulomatous disease of unknown etiology, rare in the pediatric age group. From the histopathologic point of view, it manifests as a non-caseous granulomatous infiltrate. It affects mainly the lungs and the lymphatic system, but granulomas can be found in any organ. The disease can have a benign course with spontaneous remission or evolve to a severe form. It usually manifests with bilateral hilar lymphadenopathy, pulmonary infiltrate, and eye or skin lesions, like erythema nodosum. In children
Aged up to four years, it usually manifests as a skin (78%), articular (58%), and ocular (58%) disease, with no specific pulmonary finding.55

MANIFESTATIONS ASSOCIATED WITH THE TREATMENT OF RHEUMATIC DISEASES

The respiratory system does not seem to be a common target of such undesirable effects, except for the frequency of infectious episodes, mainly of the upper airways.

Non-hormonal anti-inflammatory drugs rarely have adverse effects associated with the respiratory system. Acetylsalicylic acid and indomethacin have been reported as potentially leading to the appearance of bronchospasm or precipitating an asthma crisis.56

Regarding the synthetic disease-modifying drugs, the major drug associated with adverse effects is methotrexate. Its pulmonary toxicity seems to occur mainly in the first year of drug use. The clinical findings are as follows: acute interstitial pneumonitis; interstitial fibrosis; bronchiolitis obliterans with organized pneumonia; pleuritis; pleural effusion; pulmonary nodules; non-cardiogenic acute edema; and airway hyperreactivity. Adverse effects in adults with rheumatoid arthritis occur in 2% to 7% of those using low doses of methotrexate.57 The use of methotrexate can be associated with pneumonia, mainly opportunistic infections by *Pneumocystis jiroveci*.57 Methotrexate has been widely used for the treatment of several juvenile rheumatic diseases, but studies have shown that its pulmonary toxicity is of little significance in that age group.58,59 Cron *et al.*50 have reported a possible methotrexate-induced pneumonitis in a child with juvenile idiopathic arthritis. Schmuling *et al.*61 have studied the pulmonary function of juvenile idiopathic arthritis patients undergoing long-term treatment with methotrexate and have confirmed its safety. Pulmonary impairment due to sulfasalazine, another drug in this group, has been rarely reported with findings of interstitial pneumonitis, fibrosis, and alveolitis in adults, but not in children.62

The susceptibility to infection of patients receiving corticosteroids seems to relate to the dosage and duration of drug use, in addition to the immunosuppression associated with the underlying disease and the concomitant use of another immunosuppressive agent.55

Cytotoxic drugs can predispose patients to pulmonary infections. Cases of bronchiolitis obliterans with organized pneumonia and interstitial pneumonitis have been recently reported in adults with inflammatory intestinal disease using azathioprine.64

Regarding the class known as biologic agents, the major adverse events relate to an increase in the frequency of infections, mainly in the upper respiratory tract. The TNF plays an important role in the formation and maintenance of granulomas in the immune response. Thus, the use of anti-TNF agents would predispose to the dissemination of agents incarcerated in granulomas, such as mycobacteria and fungi. Data currently available suggest that that class of drugs increases the risk for tuberculosis and that most cases result from the reactivation of a previous infection. The contribution of recent infections, more frequent in children, to that phenomenon is unknown.65 Nevertheless, every child and adolescent undergoing therapy with those drugs should be previously assessed with the tuberculin test and chest X-ray prior to the beginning of treatment, to assess latent tuberculosis or disease.66,67 If active disease is ruled out in patients with a positive tuberculin test, therapy with isoniazid for nine months is recommended as prophylaxis of the progression of the latent infection to disease. In such cases, the beginning of the anti-TNF therapy should be delayed for at least one to two months.65 Thavarajah *et al.*,68 in a literature review, have shown the association of anti-TNF agents with infections (mycobacteria, bacteria, fungi), pulmonary nodules, chronic pneumonitis, and pulmonary fibrosis.

Rituximab, a chimeric anti-CD20 monoclonal antibody, seems to be associated with the increase in viral infections with pulmonary involvement, because it causes a prolonged reduction in the level of serum immunoglobulins, mainly in children.63 Regarding tocilizumab, a recombinant humanized monoclonal antibody that acts as an interleukin-6 receptor antagonist, the reports about pleuropulmonary involvement refer to cases of pneumonia associated with immune alterations caused by the drug. Necrotizing pneumonia and acute bronchitis have been reported, but the major infection site is the upper respiratory tract.69 Keane *et al.*70 have found no evidence in the literature of the association of tuberculosis with other currently used biological agents, such as abatacept and anakinra.
REFERENCES


