

# Eosinophilic Lung Diseases

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## KEYWORDS

- Eosinophil • Eosinophilic pneumonia • Interstitial lung disease
- Churg-Strauss syndrome • Aspergillus

## KEY POINTS

- Eosinophilic lung diseases may present as eosinophilic pneumonia with chronic or acute onset, or as Löffler syndrome.
- The diagnosis of eosinophilic pneumonia is based on characteristic clinical-imaging features and the demonstration of alveolar eosinophilia (>25% eosinophils at bronchoalveolar lavage, and preferably >40%). Lung biopsy is generally not necessary.
- Peripheral blood eosinophilia (>1000/mm<sup>3</sup> and preferably >1500/mm<sup>3</sup>) may be absent at presentation especially in idiopathic acute eosinophilic pneumonia and in patients receiving corticosteroid treatment.
- Idiopathic chronic eosinophilic pneumonia is the most frequent eosinophilic lung disease in Europe and North America. Idiopathic acute eosinophilic pneumonia may be misdiagnosed as severe infectious pneumonia.
- Possible causes of eosinophilia (especially fungus or parasitic infection, drug or toxic exposure) must be thoroughly investigated.
- Clues that should raise the suspicion of allergic bronchopulmonary aspergillosis in asthmatics include poor asthma control, expectoration of mucous plugs, peripheral eosinophilia, serum immunoglobulin E levels greater than 1000 ng/mL, positive skin prick tests to *Aspergillus fumigatus*, and central bronchiectasis, centrilobular nodules, tree-in-bud pattern, and finger-in-glove pattern at chest imaging.
- Extrathoracic manifestations with eosinophilic lung disease suggest the diagnosis of Churg-Strauss syndrome. Cardiac involvement must be investigated systematically especially in the eosinophilic tissular subtype of Churg-Strauss syndrome. Management is adapted to five prognostic factors.

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## INTRODUCTION

### *Definition*

Eosinophilic lung diseases are a group of diffuse parenchymal lung diseases<sup>1,2</sup> characterized by the prominent infiltration by polymorphonuclear eosinophils of the lung interstitium and the alveolar spaces, with conservation of the lung architecture. As a consequence, a common denominator of eosinophilic lung diseases is represented by a dramatic response to systemic corticosteroid therapy and healing without any sequelae in almost all cases, despite frequent impressive impairment of lung function at presentation.

Alveolar eosinophilia is defined by differential cell count greater than 25% (preferably >40%) eosinophils at bronchoalveolar lavage (BAL) and peripheral blood eosinophilia by eosinophil count greater than 1000/mm<sup>3</sup> (preferably >1500/mm<sup>3</sup>).

### *Classification*

Eosinophilic lung disorders may present as acute or chronic pneumonia (ie, with symptoms present for <1 month or >1 month, respectively), or as the transient Löffler syndrome mostly of parasitic origin (**Box 1**). Eosinophilic pneumonia may remain idiopathic or be related to a known cause, especially drug or toxic exposure or fungus infection. They may occur as solitary pulmonary disorders or in the context of systemic conditions, such as Churg-Strauss syndrome (CSS) or the idiopathic hypereosinophilic syndromes.

## PATHOPHYSIOLOGY

### *Recruitment of Eosinophils to the Lung*

The pathobiology of eosinophils is highly relevant for eosinophilic lung diseases, as they represent the major culprit of tissue injury by these cells. Although the mechanisms by which eosinophils participate to disease pathogenesis are not fully

#### **Box 1**

#### **Classification of the eosinophilic pneumonias in clinical practice**

##### *Eosinophilic pneumonias of unknown cause*

Solitary idiopathic eosinophilic pneumonias

    Idiopathic chronic eosinophilic pneumonia

    Idiopathic acute eosinophilic pneumonia

Eosinophilic pneumonia in systemic syndromes

    Churg-Strauss syndrome

    Idiopathic hypereosinophilic syndromes (lymphocytic or myeloproliferative variant)

##### *Eosinophilic pneumonias of known cause*

Allergic bronchopulmonary aspergillosis and related syndromes (including bronchocentric granulomatosis)

Eosinophilic pneumonias of parasitic origin

Eosinophilic pneumonias of other infectious causes

Drug-induced eosinophilic pneumonias

##### *Other pulmonary syndromes with possible usually mild eosinophilia*

Organizing pneumonia, asthma, idiopathic pulmonary fibrosis, Langerhans cell histiocytosis, malignancies, and so forth

understood, blood and tissue eosinophilia have long been identified as major players in immunity against parasites and pathogenesis of allergic diseases.<sup>3</sup> Following differentiation of precursor cells in the bone marrow under the action of several cytokines, including interleukin (IL)-5, IL-3, and granulocyte macrophage colony-stimulating factor (GM-CSF),<sup>4-6</sup> eosinophils are recruited in the blood and tissue, including the lung in response mainly to circulating IL-5 and eotaxin and the C-C chemokine receptor-3, but tissue and blood eosinophilia are not necessarily associated. The importance of IL-5 in eosinophil biology has led to the development of anti-IL-5 antibodies, such as mepolizumab, to selectively target the eosinophil lineage in vivo with potential therapeutic approaches.<sup>7-10</sup>

### ***Eosinophils and Innate Immunity***

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Eosinophils express cell membrane signaling molecules and receptors, including Toll-like receptors and receptors for cytokines, immunoglobulins, and complement,<sup>4-6,11</sup> resulting in interaction with basophils, endothelial cells, macrophages, platelets, fibroblasts, and mast cells that participate to innate immunity. Activated eosinophils release proinflammatory cytokines, arachidonic acid-derived mediators, enzymes, reactive oxygen species, complement proteins, chemokines, chemoattractants, metalloproteases, and other toxic granule proteins, especially cationic protein. Cationic proteins are released by degranulation of activated eosinophils and have a variety of proinflammatory properties, including direct cytotoxicity, up-regulation of chemoattraction, expression of adhesion molecules, regulation of vascular permeability, and contraction of smooth muscle cells.<sup>4-6</sup> Activated, degranulated (hypodense) eosinophils found in the BAL<sup>12,13</sup> and the lung<sup>14</sup> of patients with eosinophilic pneumonias denote the direct effect of eosinophilic cationic proteins. Cardiac damage in the hyper-eosinophilic syndrome or in tropical eosinophilia exemplifies tissue damage by eosinophils mediated by cationic proteins, which induce local thrombosis, necrosis, and eventually fibrosis.<sup>11</sup>

### ***Eosinophils and Acquired Immunity***

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Eosinophils are involved in adaptive immunity against bacteria, viruses, and tumors through interaction with a variety of cell types and especially T lymphocytes.<sup>4-6</sup> Eosinophils present antigens to naive and antigen-primed T helper-2 cells in tissues and to T helper-0 cells in the draining lymph nodes in the context of major histocompatibility complex class II, thereby inducing T-cell development, activation, and migration to sites of inflammation. Eosinophils further secrete IL-4 and IL-13, thereby amplifying the T helper-2 response in the lung. In turn, the recruitment and activation of eosinophils is enhanced by T helper-2 cell-derived cytokines (IL-4, IL-5, and IL-13).

## **IDIOPATHIC CHRONIC EOSINOPHILIC PNEUMONIA**

Individualized as an entity by Carrington and colleagues,<sup>15</sup> idiopathic chronic eosinophilic pneumonia (ICEP) is characterized by a progressive onset of symptoms leading within a few weeks to an infiltrative pulmonary disease with cough, increasing dyspnea, malaise, and weight loss.

### ***Epidemiology and Risk Factors***

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ICEP is the commonest form of eosinophilic pneumonias in nontropical areas where the prevalence of parasitic infection is low. It is, however, a rare disease, representing less than 3% of cases of various interstitial lung diseases.<sup>16</sup> ICEP predominates in

women (2:1 female/male ratio)<sup>17,18</sup> and may affect every age group, with a mean age of 45 years at diagnosis,<sup>17</sup> and no genetic predisposition.

Prior asthma is present in up to two-thirds of the patients.<sup>17,18</sup> About half the patients have a prior history of atopy, consisting in drug allergy, nasal polyposis, urticaria, and/or eczema.<sup>17,18</sup> As opposed to idiopathic acute eosinophilic pneumonia (IAEP), most patients with ICEP are nonsmokers.<sup>17–19</sup> These observations have led to the hypothesis that ICEP may occur predominantly in patients who are prone to develop a T helper-2 instead of T helper-1 response.<sup>20</sup>

### **Clinical Description**

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The onset of ICEP is progressive or subacute, with several weeks or months between the onset of symptoms and the diagnosis.<sup>17,18</sup> Dyspnea present in 60% to 90% of patients is usually moderate and associated with cough (90%), rhinitis or sinusitis (20%), and rarely chest pain or hemoptysis (10% or less).<sup>17,18</sup> In contrast with IAEP, respiratory failure requiring mechanical ventilation is exceptional.<sup>21,22</sup> Wheezes or crackles are found in one-third of patients at auscultation.

Respiratory manifestations are often accompanied by prominent systemic symptoms, with fatigue, malaise, fever, anorexia, night sweats, and weight loss (occasionally severe).<sup>17,18</sup> Although the disease is typically limited to the lungs and airways, mild extrathoracic manifestations (nonabundant pericardial effusion, arthralgia, nonspecific skin manifestations, and altered liver biology tests) are possible<sup>15,17,23</sup> and should systematically prompt further evaluation for CSS.

About 75% of the patients with ICEP experience asthma at some time throughout the course of disease. Asthma frequently precedes the onset of ICEP but occasionally occurs concomitantly with the diagnosis of ICEP (15%).<sup>24</sup> Asthma in ICEP is often severe and can progress to long-term persistent airflow obstruction in approximately 10% of patients despite oral and inhaled corticosteroid therapy.<sup>24</sup> Clinical and functional follow-up of patients is thus necessary even in the absence of recurrence of eosinophilic pneumonia.

### **Chest Imaging**

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The characteristic imaging features of ICEP consist of bilateral alveolar infiltrates with ill-defined margins present on the chest radiograph in almost all cases before initiation of treatment.<sup>15,17,18,25–31</sup> Spontaneous migration of the opacities in approximately a quarter of the cases suggests the diagnosis of either ICEP or cryptogenic organizing pneumonia.<sup>17</sup> A peripheral predominance of the lesions seen in approximately 25% of patients is also evocative of ICEP.<sup>18,27,32,33</sup>

On high-resolution CT (HRCT), confluent consolidations coexist with ground-glass opacities (**Figs. 1** and **2**).<sup>17,26,30</sup> Abnormalities are almost always bilateral<sup>17</sup> and predominate in the upper lobes and subpleural areas.<sup>26</sup> This pattern is sufficiently typical to suggest the diagnosis of ICEP in about 75% of cases in the appropriate setting.<sup>29</sup> Consolidation and ground-glass opacities rapidly decrease in extent and density with corticosteroid therapy.<sup>26</sup> Septal line thickening, band-like opacities parallel to the chest, or mediastinal lymph node enlargement are less characteristic.<sup>17,25</sup> Mild pleural effusions are present in only 10% of cases at HRCT, as opposed to IAEP. Cavitory lesions are exceedingly rare.<sup>17,18,26</sup>

### **Laboratory Findings**

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High-level peripheral blood eosinophilia present in most patients who have not yet received systemic corticosteroids<sup>18</sup> is the key to the diagnosis, with mean values of 5000 to 6000/mm<sup>3</sup> in large series (representing 20%–30% of blood leukocytes).<sup>17</sup>



**Fig. 1.** Chest CT scan of a patient with ICEP, demonstrating peripheral airspace consolidation predominating in the upper lobes.

BAL eosinophilia (25% eosinophils or more at BAL differential cell count) is a major diagnostic feature in ICEP and is found in all patients evaluated before any corticosteroid intake. It is commonly greater than 40%, with a mean of 50% in large series. Sputum eosinophilia may be present.<sup>18</sup> Increase in blood C-reactive protein and total immunoglobulin E level lack specificity.

### **Pathogenesis**

The release in urine of eosinophil-derived neurotoxin<sup>34</sup> and leukotriene E4<sup>35</sup> reflects eosinophilic activation and degranulation in vivo. Similarly, several studies have demonstrated the release of proinflammatory molecules or an increased expression of activation markers by eosinophils from patients with ICEP.<sup>36,37</sup>

Interestingly, clonality of the T-cell receptor-V $\beta$  was reported in the BAL fluid of one patient with ICEP,<sup>38</sup> as well as clonality in the T-cell receptor- $\gamma$  of peripheral blood lymphocytes,<sup>39</sup> similar to that seen in the lymphocytic variant of the idiopathic hyper-eosinophilic syndrome. Further investigation is warranted on the possible role of blood and lung tissue lymphocytes in the pathogenesis of ICEP.



**Fig. 2.** Chest CT of a patient with ICEP, demonstrating alveolar opacities, with dense airspace consolidation and ground-glass opacities.

### **Lung Function**

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Approximately half the patients have an obstructive ventilatory defect, whereas the other half has a restrictive ventilatory defect associated to multiple consolidations at imaging.<sup>17,18</sup> Lung function tests rapidly normalize with treatment in most cases.<sup>18</sup> Mild hypoxemia is present in most patients.<sup>17,18</sup> Carbon monoxide transfer factor is frequently reduced<sup>17,18</sup> and transfer coefficient is reduced in about 25% of cases.<sup>17</sup>

### **Pathology**

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The diagnosis of ICEP only exceptionally requires a lung biopsy, which would not always be contributory especially in patients who already have taken systemic corticosteroids. It is characterized by prominent infiltration of the lung interstitium and the alveolar spaces by eosinophils<sup>15,18</sup> accompanied by a fibrinous exudate, with preservation of the lung architecture. Eosinophilic microabscesses, a nonnecrotizing nongranulomatous vasculitis, and occasional multinucleated giant cells (but no granuloma) can also be found. Some histologic overlap is common with organizing pneumonia.<sup>1</sup> Immunohistochemical and electron microscopic studies have demonstrated eosinophil degranulation within the site of eosinophilic pneumonia.<sup>13,40</sup>

### **Diagnosis**

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The diagnosis of ICEP relies on both characteristic clinical-imaging features and alveolar eosinophilia with or without peripheral blood eosinophilia, with no possible cause identified (**Box 2**). Before the disease can be considered idiopathic, potential causes of eosinophilia must be thoroughly investigated, especially drug intake, exposure to toxics, illicit drugs, and infections with parasites and fungi.

The presence of marked eosinophilia at BAL obviates lung biopsy, especially when exceeding 40% and when BAL eosinophils are more numerous than neutrophils and lymphocytes.<sup>1</sup> Markedly elevated peripheral blood eosinophilia, together with typical clinical radiologic features, also strongly suggests the diagnosis of ICEP. The main pitfall is the lack of blood or BAL eosinophilia in patients already receiving corticosteroid treatment.

### **Treatment and Outcome**

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Although spontaneous resolution can occur, management of ICEP is based on oral corticosteroids, with the goals of inducing remission of disease, reducing the risk of relapse, and minimizing the side effects of corticosteroids. Because relapses (which occur in more than half the patients while decreasing or after stopping corticosteroids) respond very well to resumed corticosteroid treatment, it is the authors' practice to progressively taper with tight control and then to stop corticosteroids to minimize side effects, while informing the patient of the possibility of relapse.

#### **Box 2**

##### **Diagnostic criteria for ICEP**

1. Diffuse pulmonary alveolar consolidation with air bronchogram and/or ground-glass opacities at chest imaging, especially with peripheral predominance
2. Eosinophilia at BAL differential cell count  $\geq 40\%$  (or peripheral blood eosinophils  $\geq 1000/\text{mm}^3$ )
3. Respiratory symptoms present for at least 2 to 4 weeks
4. Absence of other known causes of eosinophilic lung disease (especially exposure to drug susceptible to induce pulmonary eosinophilia).

Although there are no established dose and duration of systemic corticosteroids in ICEP,<sup>17,19,32,41,42</sup> we usually use an initial dose of 0.5 mg/kg/d of oral prednisone for 2 weeks, followed by 0.25 mg/kg/d for 2 weeks, then corticosteroids are progressively reduced over a total duration of about 6 months and stopped.<sup>1</sup> ICEP responds dramatically to corticosteroids, with clinical improvement within 2 days,<sup>18,19,43</sup> and clearing of chest opacities within 1 week.<sup>17,18</sup> Relapses are usually treated with a dose of 20 mg/d of prednisone. Most patients need corticosteroids for 6 to 12 months.<sup>17</sup> Whether inhaled corticosteroids may be useful in nonasthmatic patients with ICEP is unknown.

At last follow-up, almost all patients are asymptomatic with a normal chest radiograph.<sup>17</sup> Death from ICEP is exceedingly rare. The main potential morbidity is related to adverse events of oral corticosteroids. Persistent airflow obstruction may develop in some patients despite bronchodilators and inhaled corticosteroids and often oral low-dose corticosteroids.<sup>42</sup> Therefore, long-term clinical and functional follow-up of patients is necessary.

## IDIOPATHIC ACUTE EOSINOPHILIC PNEUMONIA

IAEP, the most dramatic of eosinophilic pneumonias, mimics infectious pneumonia or acute respiratory distress syndrome in previously healthy individuals. It differs from ICEP by its acute onset, the severity of hypoxemia, the usual lack of increased blood eosinophils at the onset of disease in contrast with a frank eosinophilia in BAL fluid, and the absence of relapse after recovery. It was first described by Badesch and colleagues<sup>44</sup> and later individualized by Allen and colleagues,<sup>45</sup> with characteristics confirmed in later series.<sup>43,46–56</sup>

### *Epidemiology and Risk Factors*

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IAEP occurs acutely in previously healthy young adults (without a history of asthma), with a mean age of about 30 years, and with male predominance.<sup>44,45,48,55,56</sup> Two-thirds of patients are smokers. The triggering role of various respiratory exposures has been well established, with the responsibility of a recent initiation of tobacco smoking (in a case-control study in militaries deployed in or near Iraq<sup>56</sup>), a recent change in smoking habits,<sup>57</sup> and restarting to smoke (rechallenge).<sup>37,55,57–64</sup> IAEP can occur within days after the initiation of smoking large quantities of cigarettes (or cigars). Patients should be informed about the responsibility of tobacco in the disease process and should be strongly encouraged to quit. Less frequently, short-term passive (massive) smoking may be sufficient to induce IAEP.<sup>57,65</sup> In addition, IAEP can develop a few days after environmental exposures to various inhaled contaminants,<sup>1</sup> suggesting triggering by nonspecific injurious agents. Whether this condition should be termed idiopathic in cases clearly related to tobacco smoking or other exposures is debatable.

### *Clinical Description*

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IAEP is very frequently misdiagnosed as community-acquired pneumonia, with acute onset of dyspnea (100% of patients), fever usually moderate (100%), cough (80%–100%), and thoracic pain (50%–70%) mostly pleuritic, sometimes with myalgias (30%–50%) or abdominal complaints (25%).<sup>48,55–57,66</sup> The delay between the first symptoms and hospital admission is typically less than 7 days,<sup>48,55</sup> but a duration of up to 1 month is possible.<sup>55</sup> Tachypnea, tachycardia, and crackles are present in most patients. Acute respiratory failure is frequent and admission to the intensive care unit and mechanical ventilation is often required.<sup>55,56</sup>

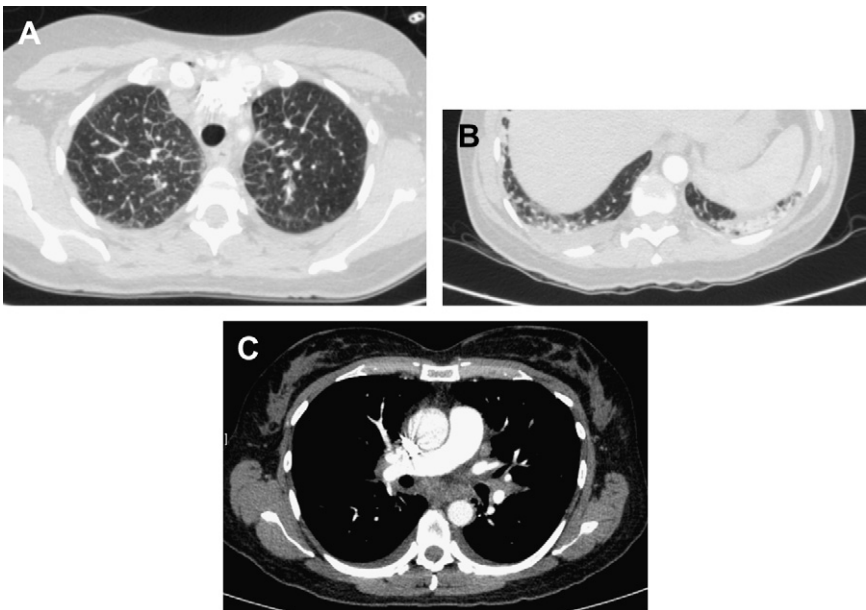
### Chest Imaging

The chest radiograph shows bilateral infiltrates, with mixed alveolar and interstitial opacities, especially Kerley lines.<sup>48,49,54</sup> The coexistence on the chest radiograph areas of airspace consolidation, interlobular thickening, and pleural effusion can suggest the diagnosis.<sup>54,55</sup> These are better identified at chest HRCT, demonstrating the typical combination of poorly defined nodules of ground-glass attenuation (100%), interlobular septal thickening (90%), bilateral pleural effusion (76%), and airspace consolidation (55%) (**Fig. 3**).<sup>67</sup> Thickening of bronchovascular bundles, lymph node enlargement, and centrilobular nodules may also be seen.

### Laboratory Findings

Blood eosinophil count is normal at presentation in most cases of IAEP.<sup>48,56</sup> This feature differs from all other eosinophilic lung diseases and can contribute to misdiagnosing IAEP as infectious pneumonia. The eosinophil count may rise to high values within days after presentation.<sup>43,48,55,56</sup> This finding is very evocative of IAEP. Given the usual lack of initial blood eosinophilia, BAL eosinophilia is the key to the diagnosis of IAEP, with 37% to 54% of eosinophils on average.<sup>48,55,56</sup> BAL bacterial cultures are sterile. BAL eosinophilia usually resolves with corticosteroid therapy but may persist for several weeks.<sup>68</sup> When performed, thoracentesis may show nonspecific pleural eosinophilia.

Several biomarkers have been found elevated in serum, urine, and BAL of patients with IAEP, especially IL-5, IL-18, and vascular endothelial growth factor; however, these are have no diagnostic value. The measurement of the serum levels of CCL17/TARC and KL6 (Krebs von den Lungen-6) might be useful in discriminating IAEP from other causes of acute lung injury.<sup>69</sup>



**Fig. 3.** Chest CT scan of a patient with acute eosinophilic pneumonia due to nitrofurantoin intake, showing (A) interlobular thickening in the upper areas of the lungs, (B) mild airspace consolidation in the lung bases, and (C) nonabundant bilateral pleural effusion and mediastinal lymphadenopathy. (A, B) Lung parenchymal windows. (C) Mediastinal window.



### Lung Function

Because most patients fulfill diagnostic criteria for acute lung injury (including a  $P_{aO_2}$ /fraction of inspired oxygen [ $F_{iO_2}$ ]  $\leq 300$  mmHg) or for acute respiratory distress syndrome ( $P_{aO_2}/F_{iO_2} \leq 200$  mmHg), arterial blood gas is warranted to evaluate hypoxemia, which is often severe owing to right-to-left shunting. Performed only in the less severe cases, lung function tests may show a mild restrictive ventilatory defect, reduced carbon monoxide transfer capacity, and increased alveolar-arterial oxygen gradient of  $P_{O_2}$ .

### Pathology

The lung biopsy shows acute and organizing diffuse alveolar damage together with interstitial alveolar and bronchiolar infiltration by eosinophils, intra-alveolar eosinophils, and interstitial edema.<sup>66</sup> Damage to the basal lamina is more pronounced than in ICEP.

### Diagnosis

The lung biopsy is seldom necessary to ascertain the diagnosis of IAEP, which is established on clinical, radiological, and BAL findings (**Box 3**).<sup>1</sup> Alveolar eosinophilia at BAL and negative BAL cultures virtually exclude infectious pneumonia. Some patients with moderate disease severity may not fit established criteria.<sup>70</sup> The main characteristics that differ between IAEP and ICEP are listed in **Table 1**.

As in all eosinophilic lung diseases, a careful search for a potential cause of eosinophilia is mandatory. Potential causes include infectious agents, parasites, red spiders,<sup>71</sup> and illicit<sup>72,73</sup> and over-the-counter drugs, especially in the most severe cases or in cases of poor response to therapy. The etiologic enquiry is particularly important in IAEP because a similar presentation can be caused by drugs and infections, especially fungi<sup>74–78</sup> or viruses.<sup>79</sup> IAEP must be distinguished from AEP occurring after allogeneic hematopoietic stem cell transplantation<sup>80</sup> or in the context of acquired immunodeficiency virus infection.<sup>81</sup>

### Treatment and Outcome

Most patients receive systemic corticosteroids for 2 to 4 weeks, with a starting dose of oral prednisone or intravenous methylprednisolone of 1 to 2 mg/kg/d. Extrapulmonary organ failure or shock is the exception; only a couple of lethal cases have been reported.<sup>56,82</sup> Extracorporeal membrane oxygenation has been used occasionally.<sup>72</sup>

#### Box 3

##### Diagnostic criteria for IAEP

1. Acute onset with febrile respiratory manifestations ( $\leq 1$  month, and especially  $\leq 7$  days duration before medical examination)
2. Bilateral diffuse infiltrates on imaging
3.  $P_{aO_2}$  on room air  $\leq 60$  mmHg (8 kPa), or  $P_{aO_2}/F_{iO_2} \leq 300$  mmHg (40 kPa), or oxygen saturation on room air  $< 90\%$
4. Lung eosinophilia, with  $\geq 25\%$  eosinophils at BAL differential cell count (or eosinophilic pneumonia at lung biopsy when done)
5. Absence of determined cause of acute eosinophilic pneumonia (including infection or exposure to drugs known to induce pulmonary eosinophilia). Recent onset of tobacco smoking or exposure to inhaled dusts may be present.

	ICEP	IAEP
Onset	>2–4 wk	<1 mo
History of asthma	Yes	No
Smoking history	10% of smokers	2/3 of smokers, often recent initiation
Respiratory failure	No	Usual
Initial blood eosinophilia	Yes	No (delayed)
BAL eosinophilia	>25%	>25%
Chest imaging	Homogeneous peripheral airspace consolidation	Bilateral patchy areas of ground glass attenuation, airspace consolidation, interlobular septal thickening, bilateral pleural effusion
Relapse	Yes	No

Complete clinical recovery occurs rapidly on corticosteroid treatment. Parenchymal infiltrates and pleural effusions resolve within less than 1 month<sup>48,54,55</sup> and pulmonary function normalizes.<sup>48,55</sup> In contrast with ICEP, IAEP does not relapse.

## CSS

### Definition

CSS is a small-vessel vasculitis defined as an eosinophil-rich and granulomatous inflammation involving the respiratory tract and associated with asthma and eosinophilia. This eponymous syndrome was described by J. Churg and L. Strauss, in 1951, mainly from autopsied cases.<sup>6</sup> In the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis,<sup>66</sup> CSS was included in the group of small vessel vasculitides and defined as an eosinophil-rich and granulomatous inflammation involving the respiratory tract, as a necrotizing vasculitis affecting small to medium-sized vessels, and as associated with asthma and eosinophilia. However, the coexistence of all three lesions on a biopsy is rare and the diagnosis is now more frequently made on the clinical presentation. In about 40% of cases, CSS is associated with antineutrophil cytoplasmic antibodies (ANCA). The terminology of eosinophilic granulomatosis with polyangiitis has been recently proposed to replace the eponymous terminology.

### Epidemiology and Risk Factors

CSS occurs at a mean age from 38 to 49 years at the onset of vasculitis, with no gender predominance.<sup>83–86</sup> The incidence has been estimated to 0.5 to 6.8 cases per million inhabitants per year, and the prevalence to 10.7 to 13 cases per million inhabitants.<sup>87</sup>

Allergy can be evidenced by specific serum IgE with corresponding clinical history in less than one-third of patients.<sup>88</sup> When present, allergy in CSS mainly consists of perennial allergies especially to *Dermatophagoides*, with seasonal allergies less frequent than in control asthmatics.<sup>88</sup> Familial CSS is an exception,<sup>89</sup> and genetic predisposition has been linked to the major histopathology complex DRB4 allele.<sup>90</sup>

The pathogenesis of CSS is largely unknown.<sup>87</sup> Several triggering or adjuvant factors have been suspected to play a role in CSS, which would result from an excessive inflammatory response to antigens,<sup>1,87,91</sup> including infectious agents (*Aspergillus*, *Candida*, *Ascaris*, *Actinomyces*), bird exposure, cocaine, drugs (sulfonamides used

together with antiserum, diflunisal, macrolides, diphenylhydantoin, and recently omalizumab<sup>92–97</sup>), as well as allergic hyposensitizations and vaccinations.<sup>98</sup>

The possible link between leukotriene-receptor antagonists (montelukast, zafirku-kast, and pranlukast) and the development of CSS is controversial.<sup>99–103</sup> There is increasing consideration that CSS may be mostly due to the flare of smoldering pre-existing disease because of reducing oral or inhaled corticosteroids instead of to a direct effect of these drugs on the vasculitis pathogenesis.<sup>87,102</sup> However, in individual cases, CSS may occur following montelukast treatment in the absence of pre-existing disease, may recur on rechallenge with leukotriene receptor antagonists, or may remit on withdrawal of this treatment without modifying other treatments.<sup>99,101,103</sup> The authors avoid leukotriene-receptor antagonists in asthmatics with eosinophilia and/or extrapulmonary manifestations compatible with smoldering CSS.

### **Clinical Description**

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The natural course of CSS has been described to follow three phases<sup>84</sup>: rhinosinusitis and asthma, blood and tissue eosinophilia, and eventually systemic vasculitis. These can significantly overlap in time.

Asthma is present in all patients with CSS. It is generally severe and becomes rapidly corticoiddependent, occurring at a mean age of about 35 to 50 years,<sup>84,86,104–107</sup> preceding the onset of the vasculitis by 3 to 6 years (ranging from 0–9 years).<sup>83–86,107,108</sup> Often severe, asthma may attenuate after the onset of the vasculitis<sup>84,108</sup>; however, this likely reflects the effect of systemic corticosteroids.<sup>109,110</sup> Other pulmonary manifestations of CSS consist in eosinophilic pneumonia, often similar to ICEP in presentation.<sup>1</sup>

Chronic rhinitis, present in about 75% of cases, is the most frequent extrathoracic manifestation. However, nasal and sinus manifestations lack specificity, consisting in chronic paraseptal sinusitis, crusty rhinitis, nasal obstruction, and nasal polyposis, often with eosinophilic infiltration at histopathology.<sup>84,86,111–114</sup> Septal nasal perforation does not occur as it does with granulomatosis with polyangiitis (Wegener syndrome).

General symptoms present in two-thirds of patients (eg, asthenia, weight loss, fever, arthralgias, and/or myalgias) often herald the onset of the vasculitis or its relapse. Any organ system can be affected by the systemic disease through eosinophilic infiltration and/or granulomatous vasculitis.<sup>87,115</sup> Heart and kidney involvement are frequently insidious and must be systematically investigated because of potential morbidity and mortality. Skin and gastrointestinal manifestations are also frequent.<sup>87,115</sup>

Cardiac involvement, although often asymptomatic, can lead to chronic cardiac failure requiring heart transplantation or sudden death.<sup>84–86,107,108,116,117</sup> It results from eosinophilic myocarditis or, much less commonly, from coronary arteritis.<sup>118</sup> Therefore, any patient with suspected CSS should undergo a strict cardiac evaluation with ECG, echocardiography, N-terminal pro-brain natriuretic peptide, and serum level of troponin I. MRI of the heart is currently the investigation preferred by most investigators to detect cardiac involvement.<sup>117,119,120</sup> MRI<sup>117,120,121</sup> and echocardiography<sup>120,122</sup> frequently detect cardiac abnormalities in asymptomatic patients, the clinical significance of which is unknown. Patients with CSS are at greater risk of venous thromboembolic events.<sup>92</sup>

### **Chest Imaging**

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Chest imaging abnormalities in patients with CSS are twofold:

- Pulmonary infiltrates (50%–70%) corresponding to eosinophilic pneumonia consist of ill-defined opacities, sometimes migratory, with peripheral predominance or random distribution, and density varying from ground-glass opacities

to airspace consolidation (**Fig. 4**).<sup>84,86,108,123–127</sup> These abnormalities rapidly disappear with corticosteroid therapy.

- Airways abnormalities include centrilobular nodules, bronchial wall thickening, and bronchiectasis.<sup>1,29,31,125</sup>

Interlobular septal thickening, hilar or mediastinal lymphadenopathy, pleural effusion, or pericardial effusion may also be seen.<sup>31,124,125,127,128</sup> When present, pleural effusion should lead to consider cardiomyopathy as a possible cause.

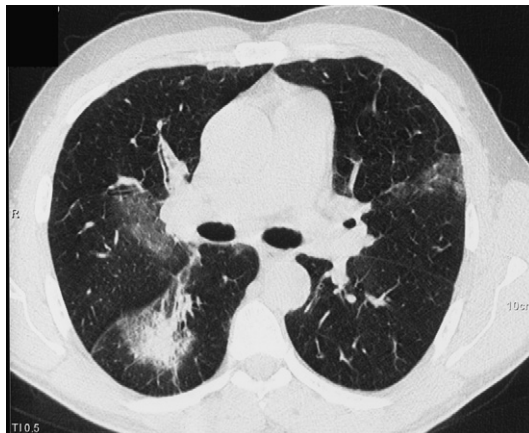
### Laboratory Findings

Peripheral blood eosinophilia is a major feature of CSS, with mean values generally between 5 and 20,000/mm<sup>3</sup> at diagnosis.<sup>84,86,108</sup> Blood eosinophilia usually parallels the vasculitis activity. BAL eosinophilia (sometimes >60%) is found in most cases.<sup>129</sup> Serum IgE levels and C-reactive protein levels are increased. High levels of urinary eosinophil-derived neurotoxin representing eosinophil degranulation in vivo reflect disease activity.<sup>130</sup> Serum IgG4 levels<sup>131</sup> and CCL17/TARC<sup>132</sup> may correlate with disease activity.

ANCA, reported in about 40% of patients, are mainly perinuclear-ANCA with myeloperoxidase (MPO) specificity.<sup>85,133,134</sup> Thus, absence of ANCA does not exclude the diagnosis of CSS. No correlation was found in most studies between the titer of ANCA and the activity of disease. However, the clinical presentation and especially extrathoracic manifestations differ between ANCA-positive and ANCA-negative patients,<sup>133,134</sup> suggesting two clinical and pathophysiologic subtypes of CSS (**Table 2**).<sup>135</sup> Interestingly, the disease subtypes of CSS may have a genetic predisposition.<sup>90,136</sup>

### Lung Function

Airflow obstruction is present in 70% of patients at diagnosis despite inhaled bronchodilator and corticosteroid therapy prescribed for asthma.<sup>109</sup> Improvement in lung function is obtained with oral corticosteroid therapy given for the systemic disease; however, mild airflow obstruction may persist.<sup>109,110</sup> Long-term oral corticosteroids are required for asthma in most patients despite inhaled therapy.<sup>84,86,109</sup> In patients with long-term follow-up, persistent airflow obstruction may be present in about



**Fig. 4.** Chest CT scan of a patient with CSS, showing areas of ground glass attenuation and of airspace consolidation.

**Table 2**  
**Distinct subtypes of Churg-Strauss syndrome**

	Vasculitic Phenotype	Eosinophilic Tissular Disease Phenotype
Respective frequency	~40%	~60%
ANCA	Present (mostly perinuclear-ANCA with anti-MPO specificity)	Absent
Predominant manifestations	Glomerular renal disease Peripheral neuropathy Purpura Biopsy-proven vasculitis	Cardiac involvement (eosinophilic myocarditis) Eosinophilic pneumonia Fever

Data from Sablé-Fourtassou R, Cohen P, Mahr A, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 2005;143:632–8; and Sinico RA, Di Toma L, Maggiore U, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum* 2005;52:2926–35.

40% of patients, in whom a transient sustained increase in the daily dose of oral corticosteroids may partially improve the lung function and restore some response to beta-2-agonists.<sup>109</sup>

### Pathology

Because the diagnosis is now made earlier in the course of disease and based on clinical features, a lung biopsy is seldom necessary to confirm CSS. When a biopsy is performed (of skin, nerve, or muscle, in most cases<sup>86</sup>), the pathologic lesions<sup>137,138</sup> rarely comprise all the characteristic features on a single biopsy, including a vasculitis (necrotizing or not, involving mainly the medium-sized pulmonary arteries) and a granulomatous eosinophilic tissular infiltration (with palisading histiocytes and giant cells).

### Diagnosis

In most patients, the diagnosis of CSS is currently based on clinical features. A pathologic diagnosis of CSS is not mandatory in patients with characteristic clinical features and marked eosinophilia; however, histology of vasculitis and presence of ANCAs further corroborate the diagnosis. Although the diagnosis is straightforward in patients with sub acute or chronic eosinophilic pneumonia and true vasculitis with positive ANCA, it may be more difficult in those with asthma, blood eosinophilia, and mild extrathoracic manifestations. Smoldering CSS may be suppressed by corticosteroid treatment of asthma, with disease flare on treatment tapering. Patients may present the so-called forms frustes of CSS<sup>106,139,140</sup> without overt vasculitis involving several organs. Diagnostic difficulties thus largely depend on the stage of disease, yet it is crucial that this diagnosis be established before severe organ involvement (especially renal or cardiac) is present.

The diagnostic criteria proposed by Lanham and colleagues<sup>84</sup> include (1) asthma, (2) eosinophilia exceeding  $1.5 \times 10^9/L$ , and (3) systemic vasculitis of two or more extrapulmonary organs (**Box 4**). Classification criteria have been established by the American College of Rheumatology.<sup>141</sup> The presence of ANCA deserves to be considered a major diagnostic criterion when present.

### Treatment and Outcome

Corticosteroids remain the mainstay of treatment of CSS, with oral prednisone initiated at a dose of 1 mg/kg/d for 3 to 4 weeks, then tapered progressively to reach

**Box 4****Diagnostic and classification criteria of CSS***Lanham and colleagues*<sup>84</sup>

- Asthma
- Eosinophilia
- Evidence of vasculitis (clinical) involving at least two organs

*American College of Rheumatology*<sup>139</sup>

- Asthma
- Eosinophilia greater than 10%
- Mononeuropathy or polyneuropathy
- Pulmonary infiltrates, nonfixed
- Paranasal sinus abnormality
- Extravascular eosinophil infiltration on biopsy findings

Diagnosis is probable when four of the six criteria are present (sensitivity 85%, specificity 99.7%). These are classification criteria that may be used when the diagnosis of systemic vasculitis has been established by histopathology.

*Chapel Hill Consensus conference*<sup>142</sup>

- Eosinophil-rich and granulomatous inflammation involving the respiratory tract
- Necrotizing vasculitis affecting small-to-medium-size vessels
- Asthma
- Eosinophilia

*Diagnostic criteria used by the authors*

1. Asthma
2. Peripheral blood eosinophilia greater than 1500/mm<sup>3</sup> and/or alveolar eosinophilia greater than 25%
3. Extrapulmonary clinical manifestations of disease (other than rhinosinusitis), with at least one of the following:
  - Systemic manifestation typical of the disease: mononeuritis multiplex, cardiomyopathy confidently attributed to the eosinophilic disorder, or palpable purpura;
  - Any extrapulmonary manifestation with histopathological evidence of vasculitis as demonstrated especially by skin, muscle, or nerve biopsy
  - Any extrapulmonary manifestation with evidence of ANCA with anti-MPO or antiproteinase 3 specificity.

When a single extrarespiratory manifestation attributable to the systemic disease is present, disease may be called *forme fruste* of CSS.

5 to 10 mg/d at 12 months of therapy.<sup>87</sup> An initial methylprednisolone bolus (15 mg/kg/d for 1–3 days) is useful in the most severe cases. Cyclophosphamide therapy (0.6–0.7 g/m<sup>2</sup> intravenously at days 1, 15, and 30; then every 3 weeks) should be added to corticosteroids to induce remission in patients with manifestations that could result in mortality or severe morbidity,<sup>143</sup> including one or more of the following criteria: age over 65 years; cardiac symptoms; gastrointestinal involvement; renal insufficiency with serum creatinine greater than 150 µg/L; and absence of ear, nose and throat

manifestation.<sup>143</sup> Subcutaneous interferon alpha, high-dose intravenous immunoglobulins, plasma exchange, and cyclosporine have been used successfully in a few cases refractory to corticosteroids.<sup>2</sup>

Once remission has been achieved, prolonged maintenance therapy is necessary to prevent relapses. Patients without poor prognosis criteria are generally treated by corticosteroids alone; the possible benefit of azathioprine to maintain remission in this setting (especially in patients who relapse despite 20 mg/d of prednisone or more) is currently evaluated. In patients with poor prognosis criteria, maintenance therapy for 18 to 24 months (after remission has been obtained using cyclophosphamide) is generally based on azathioprine, which has a favorable risk-to-benefit ratio.<sup>87</sup> Of note, rituximab, which is increasingly used in ANCA-associated vasculitis, can induce bronchospasm in this setting,<sup>144</sup> and should not be used routinely in patients with CSS.<sup>87</sup>

Interesting preliminary results have been obtained using the anti-IL5 antibody mepolizumab.<sup>10,145,146</sup> It is likely that strategies aiming at controlling the eosinophil cell line may become part of the treatment strategy in eosinophilic lung diseases and, especially, CSS in coming years.<sup>147</sup>

Despite strict management, about a quarter of CSS patients experience at least one relapse (generally with peripheral eosinophilia), which should be distinguished from severe asthma exacerbations. The 5-year overall survival in CSS is currently between 95% and 100%.<sup>143,148,149</sup> Most deaths during the first year of treatment are due to cardiac involvement,<sup>150</sup> whereas treatment-related side effects, difficult asthma, and persistent airflow obstruction later cause significant morbidity.<sup>109,149</sup>

## ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

### *Epidemiology and Pathogenesis*

Allergic bronchopulmonary aspergillosis (ABPA) occurs in 1% to 2% of asthmatic adults and in up to 7% to 10% of patients with cystic fibrosis,<sup>151,152</sup> but is exceptional in other contexts. However, isolated cases have been discussed in patients with chronic obstructive pulmonary disease and in peculiar occupational situations (eg, in workers in the bagasse-containing sites in sugar-cane mills<sup>153</sup>). ABPA may be associated with allergic *Aspergillus* sinusitis,<sup>154</sup> a sinusal equivalent of ABPA, resulting in a syndrome called sinobronchial allergic aspergillosis.<sup>155</sup>

ABPA is secondary to a complex chronic immune and inflammatory reaction in the bronchi and the surrounding parenchyma in response to the presence of *Aspergillus* growing in mucous plugs in the airways of asthmatics, progressively resulting in damage to bronchial and pulmonary tissue and impairment of the mucociliary clearance.<sup>156</sup> Both viscid mucus and exposure to fungus spores are necessary for this condition to develop. The immunologic response of the host includes, but is not restricted to, type I hypersensitivity mediated by IgE antibodies and type III hypersensitivity with the participation of IgG and IgA antibodies and of exaggerated Th2 CD4+ T-cell-mediated immune response. Excessive B-cell response and immunoglobulin production in response to circulating IL-4 seem to play a central role.<sup>156</sup>

Genetic predisposition has been demonstrated, especially with an increased prevalence of heterozygotic cystic fibrosis transmembrane conductance regulator gene mutations in non-cystic fibrosis patients with ABPA<sup>157</sup>; polymorphism within the IL-4 receptor alpha-chain gene, the IL-10 promoter, and surfactant protein A genes<sup>158–160</sup>; and association with HLA DR2/5 subtypes<sup>161–163</sup>; and familial cases have rarely been reported.<sup>164</sup> ABPA may, therefore, result from an abnormal host immune response to *Aspergillus* antigens in the setting of predisposing genetic factors.<sup>156</sup>

### **Clinical Description**

Most patients with ABPA experience chronic cough, dyspnea, expectoration of brown or tan sputum plugs, low-grade fever, and chronic rhinitis with chronic evolution and repeated flares (exacerbations).<sup>156,165</sup> Sputum production may be abundant in patients with bronchiectasis, with sputum cultures often positive for *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus fumigatus*, and/or non-tuberculous mycobacteria.<sup>166</sup>

Five stages of ABPA have been described: acute, remission, recurrent exacerbations, corticosteroid dependent asthma, and fibrotic end stage. ABPA may progress to chronic respiratory failure. However, patients do not necessarily progress from one stage to another. Pulmonary infiltrates or peripheral blood eosinophilia may only be present during the acute phase or recurrent exacerbations of the disease.

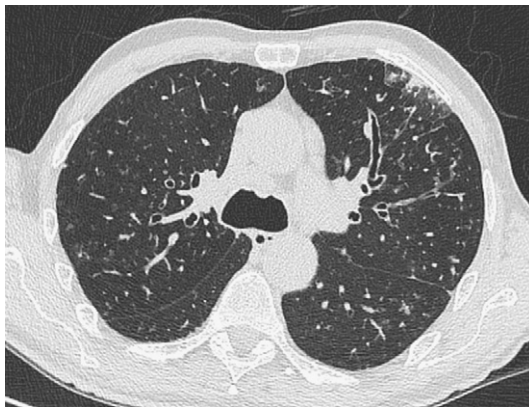
### **Chest Imaging**

The imaging findings comprise prominent bronchial features with central bronchiectasis (including in the upper lobes), bronchial wall thickening, mucous plugging (mucoïd impaction) with finger-in-glove pattern in about a quarter of patients,<sup>167,168</sup> ground-glass attenuation, and airspace consolidation.<sup>29,169–171</sup> The finger-in-glove sign corresponds to bronchial mucous impaction radiating from the hilum to the periphery.<sup>170</sup> Bronchiectases are most commonly cylindrical and suggest ABPA in asthmatics. HRCT direct signs of bronchiolitis resulting from extensive bronchiolar mucous impaction are also common in ABPA, with centrilobular nodules and tree-in-bud pattern (**Fig. 5**).<sup>169,171</sup> Overall, imaging abnormalities are evocative enough to suggest the diagnosis of ABPA in the appropriate context.<sup>29</sup>

Eosinophilic pneumonia is rare in ABPA, occurring especially during the early course of the disease. Consolidation should be differentiated from segmental or lobar atelectasis caused by mucous plugging.<sup>165</sup>

### **Laboratory Findings**

Elevated blood eosinophils especially greater than 1000/mm<sup>3</sup> or elevated serum levels of total IgE levels should raise the suspicion of ABPA in asthmatics, as well as recurring infiltrates and central bronchiectasis.<sup>156</sup>



**Fig. 5.** Chest CT scan of a patient with allergic bronchopulmonary aspergillosis, showing proximal cylindrical bronchiectasis, bronchial wall thickening, centrilobular nodules, tree-in-bud pattern, and mild airspace subpleural consolidation.



Skin prick testing, and serum IgE and IgG (precipitin) reactions to *Aspergillus fumigatus* corroborate the diagnosis. In addition, total and *Aspergillus*-specific IgE levels generally increase during exacerbations of ABPA although they are not reliable markers of disease activity.<sup>172</sup> Fungal mycelia can be found at direct examination of sputum plugs. Whether antibodies specific for recombinant *Aspergillus* allergens (especially *Asp f4* and *Asp f6*) may contribute to diagnosis and help to differentiate ABPA from *Aspergillus*-sensitive asthma or eosinophilic asthma remains to be further investigated.

### Pathology

A lung biopsy is not needed; however, limited resection is occasionally performed because of chronic pulmonary consolidation. Typical pathologic findings comprise bronchiectasis filled with mucous or mucopurulent plugs, granulomatous inflammation of the bronchiolar wall, peribronchiolar chronic eosinophilic infiltrates with areas of eosinophilic pneumonia, exudative bronchiolitis, and fungal hyphae or mucous impaction of bronchi.<sup>173</sup>

### Diagnosis

The current primary diagnostic criteria are listed (**Box 5**). In patients with ABPA, typical proximal bronchiectasis may be absent; such cases are designated ABPA-seropositive.<sup>174</sup> The diagnosis of allergic bronchopulmonary syndromes associated with yeasts or fungi other than *Aspergillus fumigatus*<sup>1</sup> is particularly challenging.

#### Box 5

##### Minimal essential diagnostic criteria of ABPA

###### *Patients with asthma and central bronchiectasis*

1. Asthma
2. Central bronchiectasis (inner two-thirds of chest CT field)
3. Immediate cutaneous reactivity to *Aspergillus*
4. Total serum IgE concentration >417 kU/L (1000 ng/mL)
5. Elevated serum IgE-*A fumigatus* and/or IgG-*A fumigatus* (infiltrates on chest radiograph and serum precipitating antibodies to *A fumigatus* may be present but are not minimal essential diagnostic criteria)

###### *Patients with asthma (ABPA-seropositive)*

Patients with the above criteria 1, 3, 4, and 5 (infiltrates on chest radiograph may be present but are not a minimal essential diagnostic criteria)

###### *Patients with cystic fibrosis*

1. Clinical deterioration (increased cough, wheezing, exercise intolerance, increase sputum, and decrease in pulmonary function)
2. Immediate cutaneous reactivity to *Aspergillus* or presence of IgE-*A fumigatus*
3. Total serum IgE concentration  $\geq 1000$  kU/L
4. Precipitating antibodies to *A fumigatus* or serum IgG-*A fumigatus*
5. Abnormal chest radiograph (infiltrates, mucous plugging, or a change from earlier films)

*Adapted from Greenberger PA. Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 2002;110:685–92.*

### **Treatment and Outcome**

Management of patients with ABPA aims at treating asthma exacerbations and at preventing progression to bronchiectasis and severe fibrotic lung disease while minimizing corticosteroids side effects. The treatment mainly relies on corticosteroids during attacks, with long-term oral corticosteroids maintained only in patients with frequent symptomatic attacks or evidence of progressive lung damage. Treatment of episodes of pulmonary consolidation may prevent the progression of ABPA to the fibrotic end-stage.<sup>175</sup> Inhaled corticosteroids may reduce the need for long-term oral corticosteroids. However, persistent airflow obstruction may develop over the years.

Oral itraconazole reduces the burden of fungal colonization in the lung and has been demonstrated in two randomized trials to be a useful adjunct to corticosteroids.<sup>176,177</sup> Antifungal therapy leads to reduction of the doses of corticosteroids, reduction in sputum production, and frequency of exacerbations (with a trend for functional improvement) and decrease in biomarkers (sputum eosinophils, sputum eosinophil cationic protein levels, serum IgE levels, and serum IgG levels to *A fumigatus*).<sup>176,177</sup> Measuring total serum IgE level may be helpful for monitoring therapy.<sup>156</sup> Itraconazole is generally prescribed for 4 to 8 months. Itraconazole interacts with many medications and may further induce adrenal insufficiency. Experience with voriconazole in ABPA is limited. Treatment with the anti-IgE recombinant antibody omalizumab may be useful in cystic fibrosis patients<sup>178–180</sup> and in asthmatics.<sup>181,182</sup>

## **OTHER EOSINOPHILIC LUNG DISEASES**

### ***Idiopathic Hypereosinophilic Syndromes***

The idiopathic hypereosinophilic syndrome, historically defined as a persistent eosinophilia greater than 1500/mm<sup>3</sup> for longer than 6 months, without a known cause of eosinophilia, and with presumptive signs and symptoms of organ involvement,<sup>183</sup> now encompasses two variants<sup>184,185</sup>:

- The myeloproliferative variant (about 20% of cases) shares common features with chronic myeloproliferative syndromes (including hepatomegaly, splenomegaly, anemia, thrombocythemia, increased serum vitamin B<sub>12</sub> and leukocyte alkaline phosphatase, and circulating leukocyte precursors) and is attributed to a constitutively activated tyrosine kinase fusion protein (*Fip1L1-PDGFR $\alpha$* ) because of an interstitial chromosomal deletion in 4q12.<sup>186</sup>
- The so called lymphocytic variant (about 30% of cases) is a T-cell disorder resulting from the production of chemokines (especially IL-5) by clonal Th2 lymphocytes bearing an aberrant antigenic surface phenotype (such as CD3<sup>-</sup>CD4<sup>+</sup>).<sup>187</sup>

At least half of the cases have neither fusion protein activity nor clonal proliferation of lymphocytes detected and thus they remain presently idiopathic.

Clinical manifestations of the idiopathic hypereosinophilic syndrome are dominated by fatigue, weight loss, and nonrespiratory involvement, especially targeting the skin, mucosa, heart, and nervous system.<sup>185</sup> In older series, respiratory manifestations present in up to 40% of patients were nonspecific and included cough, dyspnea, and patchy ground-glass attenuation, consolidation, and small nodules at chest imaging.<sup>183</sup> However, more recent studies in which the idiopathic hypereosinophilic syndromes were diagnosed according to current above standards indicate that respiratory manifestations may be generally of mild severity, rarely with eosinophilic pneumonia.<sup>188</sup>

### ***Eosinophilic Pneumonias in Parasitic Diseases***

Although it is the main cause of eosinophilic pneumonia in the world, parasitic infection is rare in Europe and North America. Clinical manifestations are nonspecific and presentation is rarely as typical as that of ICEP or IAEP.<sup>1,189</sup> Infection with the nematode *Ascaris lumbricoides* mainly causes Löfller syndrome (transient mild eosinophilic pneumonia) during the migration of the larvae through the lung, with transient cough, wheezing, fever, high blood eosinophilia, and pulmonary infiltrates. Visceral larva migrans syndrome caused by *Toxocara canis* occurs throughout the world. It causes fever, seizures, fatigue, blood eosinophilia, and transient pulmonary manifestations (cough, dyspnea, wheezes or crackles at pulmonary auscultation, and pulmonary infiltrates on chest radiograph). Infection with *Strongyloides stercoralis* may cause severe disease, affecting all organs (hyperinfection syndrome), especially in immunocompromised patients. Tropical pulmonary eosinophilia is caused by the filarial parasites *Wuchereria bancrofti* and *Brugia malayi*.<sup>1</sup>

### ***Drug-Induced Eosinophilic Pneumonias***

Drugs taken in the weeks or days before an eosinophilic disease must be thoroughly investigated. The possible association of pleural effusion and extrapulmonary manifestations, especially cutaneous rash, may be a clue for the diagnosis of drug-induced eosinophilic pneumonia.<sup>1</sup> Eosinophilic pneumonia has been reported in association with many drugs ([www.pneumotox.com](http://www.pneumotox.com)), but causality has been confidently established in fewer than 20.<sup>91</sup> Most drugs frequently causing eosinophilic pneumonias are antibiotics and nonsteroidal antiinflammatory drugs (**Box 6**).<sup>91</sup> Presentation may be similar to that of ICEP, or have an acute onset similar to IAEP, especially with minocycline<sup>190</sup> or nitrofurantoin (see **Fig. 3**).<sup>191</sup> Acute eosinophilic pneumonia may occur in the context of drug rash with eosinophilia and systemic symptoms (Dress syndrome).<sup>192</sup>

### ***Toxics***

The eosinophilia-myalgia syndrome that developed in 1989 in the United States was linked to impurities in L-tryptophan preparations in genetically-susceptible hosts.<sup>193–195</sup> One new case has been recently reported in a patient who had been taking L-tryptophan for 3 weeks as well as other dietary supplements.<sup>196</sup>

The toxic-oil syndrome, which affected about 20,000 people in Spain in 1981,<sup>197</sup> is a scleroderma-like disorder characterized in the acute phase by diffuse parenchymal lung disease and possibly respiratory failure with interstitial-alveolar pattern on chest imaging and blood eosinophilia.

Eosinophilic lung disease of varying presentation may be due to illicit drugs, especially cocaine or heroin but also cannabis.<sup>72,73</sup>

#### **Box 6**

##### **Drugs commonly causing eosinophilic pneumonia**

Antiinflammatory drugs and related drugs: acetylsalicylic acid, diclofenac, ibuprofen, naproxen, phenylbutazone, piroxicam, sulindac, and tolfenamic acid.

Antibiotics: ethambutol, fenbufen, minocycline, nitrofurantoin, penicillins, pyrimethamine, sulfamides, sulfonamides, and trimetoprim-sulfamethoxazole.

Other drugs: captopril, carbamazepine, and GM-CSF

A more extensive list of drugs reported to cause eosinophilic pneumonia may be found at [www.pneumotox.com](http://www.pneumotox.com) and Ref.<sup>1</sup>

### **Radiation Therapy**

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A condition similar to ICEP has been reported after radiation therapy for breast cancer in women (similar to the syndrome of radiation-induced organizing pneumonia), with a median delay of 3.5 months after completion of radiotherapy.<sup>20,198,199</sup> Relapse can occur after withdrawal of corticosteroid therapy.<sup>20</sup>

### **Miscellaneous**

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ICEP may overlap with, or mimic cryptogenic organizing pneumonia. Eosinophilia may be found in other bronchopulmonary disorders in which eosinophilic pneumonia is not prominent,<sup>1</sup> including the eosinophilic phenotype of asthma, asthma with marked blood eosinophilia (ie,  $>1500/\text{mm}^3$ ) hypereosinophilic asthma, eosinophilic bronchitis (without asthma), bronchocentric granulomatosis, isolated cases of idiopathic interstitial pneumonias (idiopathic pulmonary fibrosis or usual interstitial pneumonia, nonspecific interstitial pneumonia, and desquamative interstitial pneumonia), pulmonary Langerhans cell histiocytosis, and sarcoidosis.

## **PRACTICAL APPROACH TO DIAGNOSIS AND TREATMENT**

The diagnosis of eosinophilic lung diseases relies on characteristic clinical-imaging features and the demonstration of blood and/or alveolar eosinophilia. Lung biopsy is seldom necessary. Peripheral blood eosinophilia may be absent at presentation, especially in IAEP and in patients who have received corticosteroid treatment for even a few hours.

The etiologic diagnosis of eosinophilic lung diseases is of paramount importance because the identification of a potential cause may have practical consequences, especially when the disease is caused by medicinal drugs, illicit drugs, toxics, or infections with parasites or fungi.<sup>1</sup> Laboratory investigations for parasites must take into account the epidemiology of parasites. Biologic investigations for ABPA should be prompted by, but not restricted to, the presence of proximal bronchiectasis in patients with asthma or cystic fibrosis. When no cause is found, the eosinophilic lung disease is considered idiopathic. Systemic eosinophilic diseases such as CSS are suspected in the presence of extrathoracic manifestations. It is only once all known causes of eosinophilia and systemic manifestations have been excluded that idiopathic eosinophilic pneumonias (eg, ICEP and IAEP) may be considered.

Treatment of eosinophilic lung diseases involves oral corticosteroids in most cases, and withdrawal of the offending agent when identified. Cyclophosphamide is necessary in severe cases of CSS. The development of therapies that more specifically target the differentiation, activation, or recruitment of eosinophils to the lungs (with especially anti-IL-5 monoclonal antibodies) will likely complement available therapeutic approaches in the near future.

## **SUMMARY**

The eosinophilic lung diseases are characterized by the prominent infiltration of the lungs by eosinophils. Eosinophilic pneumonia may present with chronic (with symptoms for more than 1 month before the patient seeks medical advice) or acute onset (less than 1 month), or as Löffler syndrome (which is of parasitic origin in most cases). The diagnosis of eosinophilic pneumonia relies on both characteristic clinical-imaging features and the demonstration of alveolar eosinophilia (greater than 25% eosinophils at BAL and, preferably, greater than 40%), with or without markedly elevated peripheral blood eosinophilia (greater than  $1,000/\text{mm}^3$  and preferably greater than  $1,500/\text{mm}^3$ ). Lung biopsy is generally not necessary for the diagnosis of eosinophilic

pneumonia. Peripheral blood eosinophilia may be absent at presentation, especially in IAEP and in patients receiving corticosteroid treatment. IAEP may be misdiagnosed as severe infectious pneumonia. Particular attention should be paid to extrathoracic manifestations that may raise the suspicion of a systemic eosinophilic disease, especially CSS, thus necessitating specific diagnostic investigations. All possible causes of eosinophilia (especially fungus infection or drug or toxic exposure) must be thoroughly investigated before the diagnosis of idiopathic disease is made. Corticosteroids are the cornerstone of treatment of eosinophilic lung diseases.

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