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# Advances in the Diagnosis and Treatment of Pulmonary Sarcoidosis

Edited by
Marc A. Judson

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Editor

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# Contents

# Preface

I am honored to present the *Journal of Clinical Medicine* Special Issue entitled "Advances in the Diagnosis and Treatment of Pulmonary Sarcoidosis". This publication contains focused reviews of the clinical aspects of pulmonary sarcoidosis that are important to patients and clinicians. These reviews were written by international experts in the field of pulmonary sarcoidosis. The topics that are covered include the symptoms, imaging studies, and pulmonary function findings of pulmonary sarcoidosis. These topics are integral to establishing a diagnosis of pulmonary sarcoidosis, which is discussed in detail. Once a diagnosis of sarcoidosis is established, treatment can be considered. This Special Issue report contains a discussion of the approach to the treatment of granulomatous inflammation in sarcoidosis, and a further report provided a detailed review of how to use these medications to minimize complications and provide adequate dosing. Novel and emerging potential therapy for pulmonary sarcoidosis is also addressed. Serious complications from pulmonary sarcoidosis include the development of pulmonary fibrosis, pulmonary hypertension, and serious infections. These three complications are discussed in detail in separate chapters.

I hope that this Special Issue will provide useful information to those caring for pulmonary sarcoidosis patients that will lessen their disease and improve their quality of life.

I would like to thank all the authors for their uniformly outstanding contributions, as well as the *Journal of Clinical Medicine* and their staff, including Ms. Dorsey Xue and Ms. Heidi Lu. Finally, I wish to thank my wife, Sooyeon Kwon, who makes me believe that all things are possible.

**Marc A. Judson**
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*Editorial*

# Deconstructing Multiorgan Sarcoidosis

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Sarcoidosis is a multisystem granulomatous disease of unknown cause. Although this definition is commonplace throughout the medical literature, the meaning of the word "multisystem" is unclear. Many have assumed that "multisystem" is synonymous with "multiorgan." Accordingly, some have required granulomatous inflammation in at least two organs for the diagnosis of sarcoidosis to be established [1].

However, in terms of clinical practice, multiple organ involvement is not required for the diagnosis of sarcoidosis. In the A Case Control Etiology of Sarcoidosis Study (ACCESS), half of the included cases (366/736) exhibited single-organ involvement [2]. The recent American Thoracic Society sarcoidosis diagnosis practice guidelines [3] mention certain forms of sarcoidosis organ involvement that are so specific for the diagnosis (e.g., lupus pernio) that evidence of additional organ involvement is not required. Criteria have also been developed to establish a clinical diagnosis of cardiac sarcoidosis without evidence of extracardiac disease (isolated cardiac sarcoidosis) [4]. The diagnosis of sarcoidosis usually requires a compatible clinical presentation, histologic evidence of non-caseating granulomatous inflammation, and exclusion of other disorders capable of producing similar histology or clinical features [3]. However, the diagnosis of sarcoidosis is never completely secure, because the diagnostic criteria of "a compatible clinical presentation" and "exclusion of other disorders capable of producing similar histology or clinical features" have not been clearly defined and are left to the arbitrary decision of the clinician [5,6]. Given this situation, single-organ involvement is adequate for the diagnosis of sarcoidosis provided that ample specific features for the diagnosis are also present [4,7], although admittedly this approach is arbitrary and not standardized. The requirement that two organs be involved to establish a diagnosis of sarcoidosis would increase the specificity of the diagnosis, but at the cost of a markedly diminished sensitivity.

Some "two organ purists" might argue that in the case that sarcoidosis is isolated to one organ, there is most likely occult involvement in a second organ that has escaped clinical detection [8]. It is known that biopsies of clinically uninvolved organs in sarcoidosis reveal granulomatous inflammation in 20 percent to more than 50 percent of cases [9–11]. However, I suspect that there are a sizable number of sarcoidosis patients with true isolated single-organ involvement. It is important to recognize that single-organ sarcoidosis may still be a systemic disease. Even when a single organ is involved with sarcoidosis, the disease often demonstrates systemic features including (a) anergy [12]; (b) parasarcoidosis syndromes where systemic symptoms develop from sarcoidosis that are not attributable to granulomatous deposition in a specific organ (e.g., small fiber neuropathy, pain, and fatigue syndromes [13]); and (c) the development of recurrent sarcoidosis in the allograft of sarcoidosis patients who undergo organ transplantation [14].

Understanding the development of multiorgan sarcoidosis may provide key insights into the immunopathogenesis of the disease. The immunopathogenesis of sarcoidosis is thought to involve entry of antigens into the host that are first identified and phagocytized by antigen-presenting cells, such as macrophages and dendritic cells [15]. Although there is significant evidence that forms of sarcoidosis may be autoimmune [16], the prevalent opinion is that antigens derived from exogenous sources are integrally involved in the

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granulomatous process [17]. These antigens are then processed by antigen-presenting cells and presented via human leukocyte antigen (HLA) class II molecules to a restricted set of T-cell receptors, primarily of the CD4+ class [18]. This activity induces polarization of the T cells to a T-helper-1 phenotype with subsequent cellular recruitment, proliferation, and differentiation leading to the sarcoid granuloma [15]. The two most common organs involved in isolated single-organ sarcoidosis are the lung and the skin [19]. Assuming sarcoidosis is instigated at least in part by exogenous antigens, this would suggest that the lung and skin are common "portals of entry" for the antigens involved in the development of sarcoidosis. This hypothesis is in keeping with the fact that the lung and the skin are particularly conductive sites of antigen capture [20] and adaptive immune responses [21].

Assuming that the initial sarcoidosis granuloma forms as a response to an exogenous antigen, the question arises as to how sarcoidosis granulomas develop in additional organs. It is possible that the causative antigens travel to other organs via the bloodstream or lymphatics. However, except possibly for Propionibacterium acnes [22], specific antigens have not been isolated within sarcoid granulomas. This suggests the possibility that sarcoid granulomas develop on the basis of autoimmunity in organs at or beyond the portal of entry site. It has been conjectured that that a foreign antigen itself or the initial granulomatous response at the portal of entry may lead to the exposure of self-peptides such that molecular mimicry occurs [23,24]. In this scenario, exposure of self-peptides promotes autoreactive T cells that can lead to the development of granulomatous inflammation to autoantigens in distant sites. Vimentin has been recognized as a possible autoantigen in sarcoidosis [25].

Possibly, the development on multiorgan sarcoidosis involves a two-hit hypothesis, wherein granulomatous inflammation develops in an isolated organ where the offending antigen is first encountered by the immune system. Development of multiorgan sarcoidosis may require a second process: the development of autoimmunity whereby granulomas can be formed in distant organs.

Discovering the mechanisms responsible for multiorgan sarcoidosis is more than an academic exercise. Breakthroughs in this area may lead to prevention of dissemination of sarcoidosis into vital organs such as the heart and brain. To that end, the immunologic characteristics of isolated sarcoidosis versus multiorgan sarcoidosis should be rigorously explored.

**Conflicts of Interest:** The authors declare no conflict of interest.

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# The Symptoms of Pulmonary Sarcoidosis

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**Abstract:** The aim of this manuscript is to provide a comprehensive review of the etiology, measurement, and treatment of common pulmonary symptoms associated with sarcoidosis. The assessment of symptoms associated with pulmonary sarcoidosis is an important component of disease management. Some symptoms of pulmonary sarcoidosis are sensitive but nonspecific markers of disease activity, and the absence of such symptoms provides evidence that the disease is quiescent. Although quantifiable objective measurements of pulmonary physiology and chest imaging are important in the assessment of pulmonary sarcoidosis, they correlate poorly with the patient's quality of life. Because the symptoms of pulmonary sarcoidosis directly relate to how the patient feels, they are reasonable endpoints in terms of clinical research and individual patient care. Recently, the symptoms of pulmonary sarcoidosis are capable of being quantified via patient-reported outcome measures and electronic devices. We conclude that a thorough assessment of the symptoms associated with pulmonary sarcoidosis improves patient care because it is a useful screen for manifestations of the disease, provides insight into the pathophysiology of manifestations of sarcoidosis, and may assist in optimizing treatment.

**Keywords:** sarcoidosis; pulmonary; symptoms; cough; wheeze; dyspnea

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## 1. Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown cause. The lung is overwhelmingly the most common organ involved, with pulmonary involvement occurring in approximately 90 percent of patients [1–3]. The assessment of pulmonary sarcoidosis involves the measurement of pulmonary physiology [4], chest imaging techniques [4], and the use of biomarkers of disease activity and prognosis [5]. These assessments are labor-intensive, complex, and costly. Although eliciting symptoms of pulmonary sarcoidosis may lack the resolution of more objective assessments, it can be obtained easily and cheaply. Eliciting symptoms does not even require a scheduled visit with a clinician, as this can be performed in real time via electronic devices [6]. Most importantly, symptoms reflect quality-of-life issues of patients, which are a major treatment indication for sarcoidosis [7]. It is problematic to devise a treatment plan for a disease without taking into account how the patient feels. The ascertainment of pulmonary sarcoidosis symptoms can act as a gatekeeper for expensive and time-consuming sophisticated assessments to optimize their appropriate use and avoid their overuse.

As is the case for most diseases, the presence of pulmonary sarcoidosis symptoms is a more sensitive than specific marker of disease activity. The presence of pulmonary sarcoidosis symptoms may also have prognostic significance. This manuscript will review the major symptoms of pulmonary sarcoidosis and will describe their causes, treatment implications, and impacts on clinical outcomes.

## 2. Cough

Cough is an extremely common symptom of pulmonary sarcoidosis. In comparison to controls, an unselected group of pulmonary sarcoidosis patients was shown to have a markedly increased cough frequency and severity [8]. The reported frequency of cough

varies widely across different sarcoidosis populations, and we suspect that this is, in part, related to the heterogeneity of the sarcoidosis cohorts that were analyzed in terms of disease activity, sarcoidosis treatment, and percentage of patients with significant pulmonary involvement. Given those caveats, the prevalence of cough in sarcoidosis patients has been estimated at between 3% and 53% [9]. Cough has been found to be more severe in black sarcoidosis patients than in white ones, and more severe and more prevalent in women with sarcoidosis than in men [9,10]. The severity of cough does not seem to be associated with spirometry, Scadding stage, smoking status, or age [8,10]. In one series of 36 consecutive exacerbations of pulmonary sarcoidosis (defined as worsening pulmonary symptoms, worsening spirometry, and no clinical evidence of an alternative cause of pulmonary worsening other than pulmonary sarcoidosis) [11], cough was present in 88 percent of the patients, and was more common than any other pulmonary symptom including dyspnea, wheeze, and chest pain [11]. Therefore, cough is a sensitive, although not a specific, finding of active pulmonary sarcoidosis, which we define as symptomatic disease caused by the granulomatous inflammation of sarcoidosis. It is problematic to determine if pulmonary sarcoidosis is active. Although chest scan imaging [12], cellular analysis of bronchoalveolar lavage [13], and pulmonary fludeoxyglucose F18 (FDG) uptake on positron emission tomography (PET) scanning [14] are fairly accurate in determining pulmonary sarcoidosis activity, they are expensive and/or invasive. Therefore, the clinical diagnosis of active pulmonary sarcoidosis is often based on less-specific clinical features such as the clinical presentation and presenting of symptoms. In this regard, the absence of cough significantly lowers, but does not eliminate, the possibility of active pulmonary sarcoidosis.

The characteristics of cough are variable in sarcoidosis depending depending on its etiology (vide infra). The cough may be non-productive or productive, and productive cough is more common in those with a high cough frequency [8]. Pulmonary sarcoidosis-related cough is significantly less frequent during sleep [8]. Cough is often chronic in sarcoidosis, with more than one half of pulmonary sarcoidosis patients experiencing a cough of greater than 8 weeks duration; additionally, a significant percentage experience cough for more than one year [8]. Therefore, an acute self-limiting cough syndrome that resolves without sarcoidosis therapy is unlikely to have been caused by active pulmonary sarcoidosis. Patients with pulmonary sarcoidosis who cough often identify environmental triggers including smoky environments, perfumes, and scents [8]. Other sensations related to cough include a tickle sensation or irritation in the throat [8].

Pulmonary sarcoidosis-associated cough is a common reason for patients to seek medical attention [15]. Using the Leicester Cough Questionnaire (LCQ), a patient-reported outcome quality-of-life measure of cough [16], sarcoidosis patients have been found to frequently experience a significant quality-of-life impairment related to cough [8,10,17]. In addition, a significant association has been found between cough-related quality-of-life impairment as measured using the LCQ and general quality-of-life impairment as measured using the short form-36 (SF-36) [17]. These data suggest that worsening cough significantly impacts quality of life in a large proportion of sarcoidosis patients. Quality of life is a major indication for the treatment of sarcoidosis [7]. However, physicians have tended to rely on objective measures such as forced vital capacity (FVC) or radiographic findings as clinical endpoints in pulmonary sarcoidosis [4,18], and the correlation between these endpoints and quality of life is poor [19]. As it has been demonstrated that FVC and radiographic findings do not correlate with the severity of cough in sarcoidosis [8,10] this suggests that the monitoring of cough may be an important clinical endpoint for pulmonary sarcoidosis.

There are numerous potential causes of cough in pulmonary sarcoidosis. Probably the most common mechanisms causing pulmonary sarcoidosis-associated cough are airway irritation and mechanical airway damage caused directly by granulomatous inflammation. Sarcoid granulomas have a predilection for depositing in the airways [20] and the presence of endobronchial sarcoidosis lesions has been associated with cough [21,22]. This airway irritation/mechanical damage may cause an asthma-like syndrome [23] in which afferent nerve fibers are stimulated, thereby inducing cough [15,24]. Bronchial hyperreactivity with

positive methacholine challenge testing is common in pulmonary sarcoidosis [25–27] and supports an asthma-like cough mechanism. However, sarcoidosis does not commonly cause an eosinophilic asthma condition, as serum IgE tends to be lower in sarcoidosis patients than in the general population [28] and levels of exhaled nitric oxide (eNO) are not increased with sarcoidosis [23]. It is also possible that the chronic cough of sarcoidosis is a primary disorder of sensory nerves, as is the case for other chronic cough syndromes [29]. "Cough reflex hypersensitivity" is the term used to describe this entity, and this has been demonstrated in pulmonary sarcoidosis patients using a capsaicin cough challenge test [8]. Airway distortion from fibrotic pulmonary sarcoidosis (Scadding Stage IV) may lead to significant bronchiectasis [30]. As with other forms of bronchiectasis, mucociliary clearance may be impaired, leading to cough which is often productive. Such patients are at increased risk of developing airway and parenchymal lung infection [31]. The acute onset or worsening of cough in these patients may signify an acute bronchitis, pneumonia, or an acute exacerbation of pulmonary sarcoidosis [23]. Sarcoidosis of the upper respiratory tract (SURT) may cause significant nasal sinus, laryngeal, or pharyngeal disease that may cause significant cough and other upper airway symptoms [32]. In addition, as previously mentioned, cough is not a specific symptom of pulmonary sarcoidosis and is a common complaint with a multitude of pulmonary disorders. The clinician should not assume that the development of cough in a pulmonary sarcoidosis patient is directly related to the disease and should include a search for an alternative explanation. A proposed algorithm for the assessment of cough in a pulmonary sarcoidosis patient is shown in Figure 1.

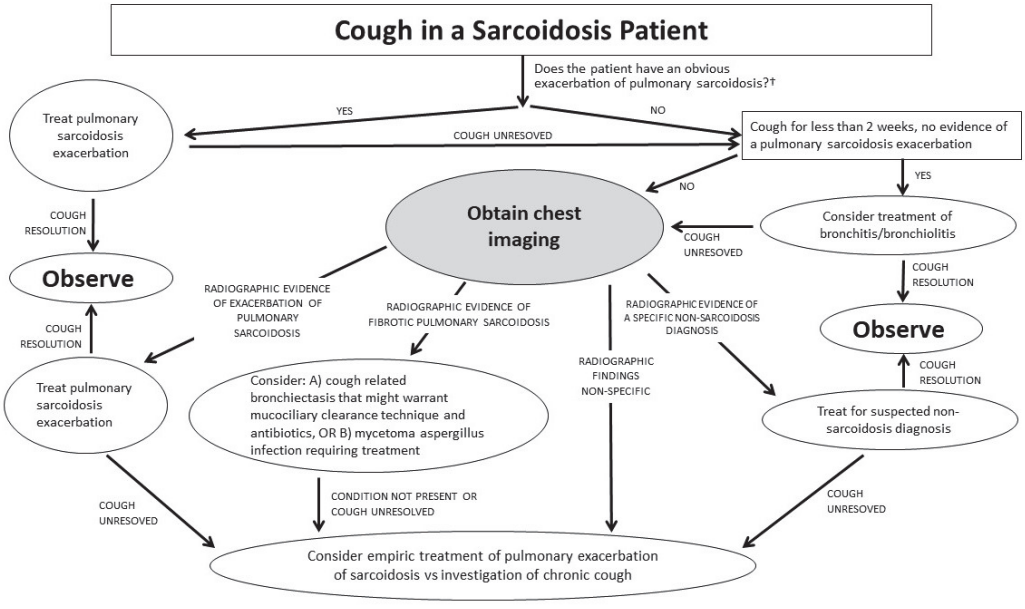


**Figure 1.** Proposed algorithm for the assessment of cough in a pulmonary sarcoidosis patient. †: Examples of such a scenario include (A) concomitant recurrence of sarcoidosis skin lesions or other extrapulmonary manifestations of sarcoidosis; (B) presentation very similar to the initial presentation of pulmonary sarcoidosis.

The measurement of cough is problematic because it is a multidimensional assessment involving both subjective and objective input. Cough frequency can be determined subjectively by the patient, but this method is not very accurate. Cough frequency monitors have been used in clinical trials [8,33]. Recently, smartphone-based artificial intelligence (AI) cough monitoring apps have become available that have the potential to accurately monitor cough frequency in clinical settings [34]. In addition, sound power and sound

energy can now be measured as a non-invasive measure of cough intensity [34]. Although the frequency and intensity of cough may be important to measure in order to assess the effects of therapy, they do not accurately assess the impact of cough on the patient's quality of life. Various health-related quality of life (HRQoL) patient-reported outcome measures (PROMs) of cough have been developed including the aforementioned Leicester Cough Questionnaire [16] (LCQ) and the Cough-specific Quality of Life Questionnaire (CQLQ) [35] both of which are well-validated and have had minimal clinically important differences (MCIDs) determined [33,35]. The LCQ has been used extensively in sarcoidosis [8,10,17]. Because these HRQoL cough PROMs consist of many items that require several minutes for the patient to complete, cough severity can also be assessed via a visual analog scale (VAS). VAS cough scales have been used in previous sarcoidosis trials [8,10] and they have been shown to correlate well with the LCQ in a large sarcoidosis cohort [10].

The treatment of pulmonary sarcoidosis-associated cough depends on its etiology. If cough is a symptom related to active pulmonary sarcoidosis, it usually responds to therapy for that condition, particularly with corticosteroid doses of 20 mg/day of prednisone or less [11]. Very frequently, cough and other pulmonary symptoms related to active pulmonary sarcoidosis respond in a matter of days. Because it is unlikely that sarcoid granulomas will appreciably resolve in this short period of time, it is likely that cough and many other symptoms of acute pulmonary sarcoidosis relate to the airway irritation or asthma-like mechanisms already described in this manuscript. Patients with fibrocystic sarcoidosis often develop cough from fibrosis-induced bronchiectatic airway changes [30] and this often requires bronchodilators and other mucociliary airway clearance techniques. These patients may frequently develop pulmonary infections [31] that require appropriate antimicrobial therapy to control cough. When cough is the most prominent symptom of pulmonary sarcoidosis and the patient does not appear to be experiencing a flare of the disease, inhaled corticosteroids (ICS) may be useful. The recommended doses in this situation are high: 800-1600 mcg/day of inhaled budesonide [36] or 800 mcg/day of inhaled fluticasone [37]. It is unclear if the benefits of ICS for pulmonary sarcoidosis-associated cough are related to a direct effect on granulomatous airway involvement or suppression of airway hyperreactivity. Although a meta-analysis suggests that ICSs are beneficial for pulmonary sarcoidosis-associated cough [38], a subsequent meta-analysis did not clearly show a benefit [39]. Although inhaled bronchodilators have not been extremely useful in chronic pulmonary sarcoidosis [40], they may augment suppression of cough in acute exacerbations of sarcoidosis if asthma-like mechanisms are present. Obviously, cough in pulmonary sarcoidosis patients may have an etiology unrelated to the disease that may require other therapies.

## 3. Wheezing

Wheezing is a very common symptom of pulmonary sarcoidosis. Wheezing was second only to cough as a symptom of acute pulmonary exacerbations of sarcoidosis [11]. Although pulmonary sarcoidosis is often classified as an interstitial lung disease that would be expected to result in restrictive lung physiology, airway obstruction is common in sarcoidosis and may occur via several mechanisms. The failure to appreciate mechanisms of airflow obstruction in pulmonary sarcoidosis frequently results in the disease being misdiagnosed as a highly prevalent obstructive lung disease such as asthma or chronic obstructive pulmonary disease [23].

A major mechanism for airflow obstruction in sarcoidosis is from endobronchial sarcoid granulomas that may narrow, distort, or rarely completely obstruct the airway [41]. Airway involvement in sarcoidosis is common, as random endobronchial biopsies have demonstrated granulomatous inflammation in nearly 60 percent of pulmonary sarcoidosis patients [20]. As mentioned, granulomas may also irritate airways causing bronchospasm by stimulating afferent nerve fibers [8,15,29] or asthma-like mechanisms [23]. As mentioned, the fact that some patients with acute exacerbations of pulmonary sarcoidosis improve after a few days of therapy [42] suggests that bronchospasm, airway nerve fibers, or asthma-like

mechanisms are involved, as this seems too rapid a response to attribute to the resolution of granulomatous inflammation. Endobronchial granulomas may result in significant airway scarring and distortion that often leads to airflow obstruction [12,30]. This is commonly seen in Scadding stage IV fibrocystic sarcoidosis (Figure 2). In fact, these fibrotic pulmonary sarcoidosis patients demonstrate significant airflow obstruction more frequently than all other forms [43]. The airflow obstruction in fibrotic pulmonary sarcoidosis occurs not only in the large airways, but also the small airways which contribute significantly to the pathophysiology [44]. Rare causes of airflow obstruction in pulmonary sarcoidosis include the development of significant bullous disease in fibrotic patients [45] and airway compression from mediastinal lymphadenopathy. Although the latter entity is common radiographically, it usually fails to cause significant airflow obstruction unless the lymph nodes are highly calcified [46]. Table 1 lists the common causes of airflow obstruction in pulmonary sarcoidosis.

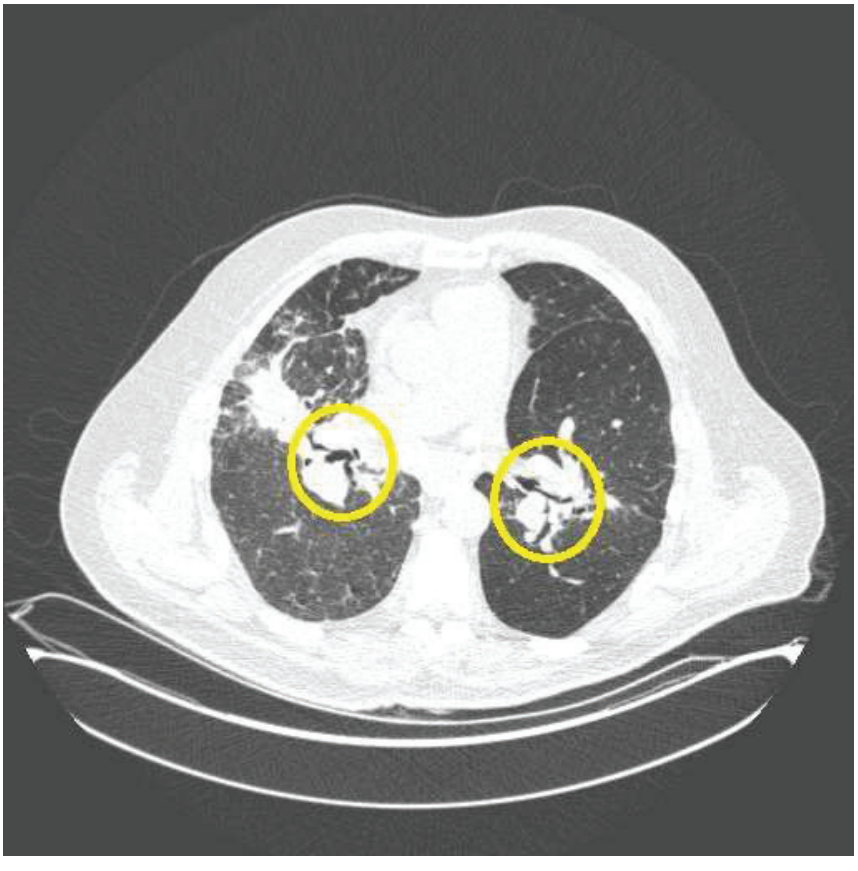

**Figure 2.** Chest CT scan of a patient with fibrotic pulmonary sarcoidosis. Distortion of airways (yellow circles) is common in this condition and is the result of granulomatous-induced airway fibrosis.

Wheezing is problematic to quantify. Although smartphone-based artificial intelligence (AI) monitoring apps have been developed for cough [34], we are unaware that they have been developed to monitor wheezing. Obviously, airflow obstruction, the physiologic basis for wheezing, can be assessed using pulmonary function tests. Still, irrespective of the physiologic abnormalities associated with wheezing or the sound that is generated, wheezing does impact quality of life. We are unaware of specific HRQoL PROMs that address wheezing, although wheezing is a common item in general respiratory disease

HRQoL PROMs [47]. We suspect that there is probably minimal benefit in specifically quantifying the severity of wheezing in pulmonary sarcoidosis, as it is problematic to measure and is usually associated with other clinical manifestations of the disease that are easier to monitor.

**Table 1.** Common causes of airflow obstruction in sarcoidosis (that could induce wheezing).

| Cause | Form of Pulmonary Sarcoidosis |
|---|---|
| Endobronchial deposition of granulomas | Active pulmonary sarcoidosis |
| Cough reflex hypersensitivity granulomatous inflammation of airways | Active pulmonary sarcoidosis |
| Bronchospasm from granulomatous inflammation of airways | Active pulmonary sarcoidosis |
| Airway fibrosis from previous granulomatous inflammation of airways | Fibrotic pulmonary sarcoidosis |
| Development of bullous disease/emphysema * | Fibrotic pulmonary sarcoidosis |
| Airway compression from mediastinal lymphadenopathy *,† | mediastinal lymphadenopathy from sarcoidosis |

* Rare; † This manifestation most commonly occurs in patients with significantly calcified mediastinal lymphadenopathy.

Wheezing is usually not specifically treated in pulmonary sarcoidosis. As wheezing is a manifestation of acute pulmonary exacerbations of sarcoidosis [11], systemic therapy for this condition (often oral corticosteroids initially) is usually effective in alleviating wheezing. Inhaled corticosteroids may be effective as has been described for pulmonary sarcoidosis-associated cough (vide supra). There are almost no clinical data on the use of beta agonist or anticholinergic inhalers in sarcoidosis. One study found that there was an improvement in forced expiratory volume in one second (FEV1) with salmeterol and ipratropium, with the former potentiated by concomitant budesonide inhalation [48]. Certainly, it would be prudent to consider adding a beta agonist inhaler to the standard pulmonary sarcoidosis treatment of a patient with prominent wheezing, although this maneuver has never been subjected to study. Wheezing from airflow obstruction related to endobronchial fibrosis and distortion in fibrotic pulmonary sarcoidosis would not be expected to respond to bronchodilators [49]. As such patients have significant bronchiectasis and retained airway secretions, they may benefit from mucociliary clearance techniques [30].

## 4. Dyspnea

Dyspnea is an extremely common symptom in pulmonary sarcoidosis patients. Dyspnea is more common in pulmonary sarcoidosis patients than in healthy matched controls, with moderate to severe dyspnea being more than 10 times more common (56% versus 4%) in the pulmonary sarcoidosis group [50]. Dyspnea was also the third most frequent symptom of acute exacerbations of pulmonary sarcoidosis behind cough and wheeze [11].

There are numerous causes of dyspnea in pulmonary sarcoidosis patients. These causes include the deposition of sarcoidosis granulomas in the lung, manifestations of fibrotic sarcoidosis, multiple mechanisms that can cause pulmonary hypertension, complications of treatment, manifestations of extrapulmonary sarcoidosis, psychosocial/functional issues, and conditions completely unrelated to sarcoidosis. These mechanisms of dyspnea are listed in Table 2. Obviously, these causes of dyspnea are so diverse that it mandates that the clinician rigorously evaluates the cause of dyspnea in a pulmonary sarcoidosis patient to ensure proper treatment for this symptom. In addition, the cause of dyspnea in a pulmonary sarcoidosis patient may be completely unrelated to the disease, and all of these causes should also be considered.

**Table 2.** Common causes of dyspnea in sarcoidosis.

| Major Category | Mechanism | Mechanism of Dyspnea | Treatment |
|---|---|---|---|
| **Intrathoracic deposition of granulomas** | Intrapulmonary deposition of granulomas in alveoli/interstitium | Decreased lung compliance | Anti-granulomatous therapy |
| | Intrapulmonary deposition of granulomas in airways | Increased airway resistance | Anti-granulomatous therapy |
| | Asthma/bronchospasm | Increased airway resistance | Anti-granulomatous therapy; anti-asthma therapy |
| | Sarcoidosis-associated pleural effusion (deposition of granulomas in the pleura) * | Decreased lung volume, overdistention of respiratory muscles | Anti-granulomatous therapy |
| **Pulmonary fibrosis** | Fibrosis in alveoli/interstitium | Decreased lung compliance | Anti-fibrotic therapy?; Anti-granulomatous therapy? |
| | Fibrosis in airways | Increased airway resistance | Anti-fibrotic therapy?; Anti-granulomatous therapy? |
| **Multiple processes: Intrapulmonary deposition of granulomas, pulmonary fibrosis, hypoxic pulmonary vasoconstriction from parenchymal sarcoidosis** | Pulmonary hypertension | Increased pulmonary vascular resistance, hypoxemia | Pulmonary vasodilators; anti-granulomatous therapy? |
| **Complications of treatment** | Weight gain from corticosteroids | Restrictive ventilatory defect | Weight loss; reduce corticosteroid dose if possible |
| | Pulmonary infection | Immunosuppressive medications | Treat the infectious pathogen; reduce immunosuppression if possible |
| | Respiratory muscle weakness | Corticosteroid myopathy | Reduce corticosteroid dose |
| | Ischemic/hypertensive cardiomyopathy | Corticosteroid-induced hypertension/diabetes | Treatment of hypertension/diabetes and ischemic heart disease; reduce corticosteroid dose if possible |
| **Extrapulmonary sarcoidosis** | Cardiac sarcoidosis | Cardiomyopathy | Anti-granulomatous therapy for cardiac sarcoidosis |
| | Respiratory muscle involvement with sarcoidosis * | Respiratory muscle failure | Anti-granulomatous therapy for respiratory muscle sarcoidosis |
| | Pulmonary embolism | Hypoxemia, increased pulmonary vascular resistance | Anti-granulomatous therapy for respiratory muscle sarcoidosis |
| **Psychological/emotional/ physical state associated with sarcoidosis** | Multiple mechanisms: depression, fatigue, cognitive impairment | Increase in the sensation of dyspnea | Treat the underlying mechanism |
| **Process unrelated to sarcoidosis** | Innumerable mechanisms | Innumerable etiologies | Treat the underlying mechanism |

?: questionable/controversial treatment; *: rare.

Dyspnea is a sensation that may affect or be affected by emotional, psychological, and social states. For this reason, these four conditions cannot be assessed in isolation, and changes in any one of them may affect all the others. The interdependence of these states has been specifically confirmed in sarcoidosis [51–53], and this implies that dyspnea is heavily influenced by non-physiologic factors in pulmonary sarcoidosis.

As dyspnea is a subjective measure, it is typically quantified via a PROM or VAS [54]. It has been clearly shown that the correlation between pulmonary function measurements and dyspnea is poor [19,51]. Therefore, pulmonary function test results cannot be reliably used as a surrogate for dyspnea. Specific dyspnea measures in sarcoidosis have included the Baseline Dyspnea Index (BDI) [51,55], Transitional Dyspnea Index (TDI) [51], the Borg Dyspnea Scale [51,56], and the Modified Medical Research Council (MRC) Dyspnea Scale [51]. The Modified MRC Dyspnea Scale has often been used as an entry criterion in clinical sarcoidosis trials [18]. Although these PROM and VAS measures of dyspnea function well in clinical trials of large cohorts of patients, most have significant variability that make them problematic to use longitudinally in individual patients to assess significant changes in dyspnea over time. Most clinicians do not use these dyspnea measures to make interventions in individual patients but rather to prompt a more thorough evaluation of the patient when dyspnea measures suggest a significant change.

As there are innumerable causes of dyspnea, its treatment is dependent on its specific cause. Although exercise training regimens in sarcoidosis patients have been shown to improve the 6-min walk distance and lessen fatigue, they have no significant effect on dyspnea as measured using the Borg Dyspnea Scale [57]. Inspiratory muscle training in sarcoidosis patients has been demonstrated to significantly reduce dyspnea [58]

**5. Chest Pain**

Chest pain is a common symptom of pulmonary sarcoidosis. Chest pain has been reported as a presenting complaint in 9 percent of sarcoidosis patients [59], in 12 percent of patients experiencing an exacerbation of pulmonary sarcoidosis [11], and in 27 percent of patients with established sarcoidosis [60].

Pulmonary sarcoidosis-associated chest pain is usually pleuritic in character and is most common in the substernal and infrascapular areas [61]. The chest pain is often associated with coughing [61]. The pleuritic character of the pain and its association with cough suggests that it might be caused by cough-induced musculoskeletal irritation of the chest wall [61]. No correlation has been found between pulmonary sarcoidosis-associated chest pain and the following chest imaging features: Scadding chest radiograph stage, location of sarcoidosis-related lung nodules, mediastinal lymph node burden, and location of pleural disease [61]. However, although it is an anecdotal finding, we have identified specific pulmonary sarcoidosis patients with localized pleural disease that correlates well with the location of their pain (Figure 3). We therefore believe that pleural and subpleural sarcoidosis may lead to chest pain on rare occasions.

There are other causes of chest pain associated with sarcoidosis and pulmonary sarcoidosis. As mentioned, chest pain occurs in approximately 10 percent of patients with an exacerbation of sarcoidosis [11]. Patients with sarcoidosis-associated small fiber neuropathy may develop a sensation of numbness and burning in scattered locations, including the chest [62]. Sarcoidosis is associated with pulmonary embolism [63,64], which should be considered in sarcoidosis with the sudden onset of dyspnea and pleuritic chest pain. Rarely, a pneumothorax can occur with pulmonary sarcoidosis from necrosis of subpleural granulomas or rupture of a cystic lesion in a patient with Scadding stage 4 fibrocystic disease [65]. Sarcoidosis-associated pleural effusion is a rare event but may cause chest pain [66].

The treatment of pulmonary sarcoidosis-associated chest pain depends on its etiology. If chest pain develops with an acute pulmonary exacerbation of sarcoidosis, it usually responds to therapy for this condition [11]. The aforementioned common presentation of pulmonary sarcoidosis-associated chest pain with pleuritic substernal or infrascapular pain often responds to non-steroidal anti-inflammatory agents.

There are innumerable alternative causes of chest pain in pulmonary sarcoidosis patients that are unrelated to the disease. The clinician should diligently explore these possibilities and not reflexively assume that the chest pain in pulmonary sarcoidosis is caused by sarcoidosis.

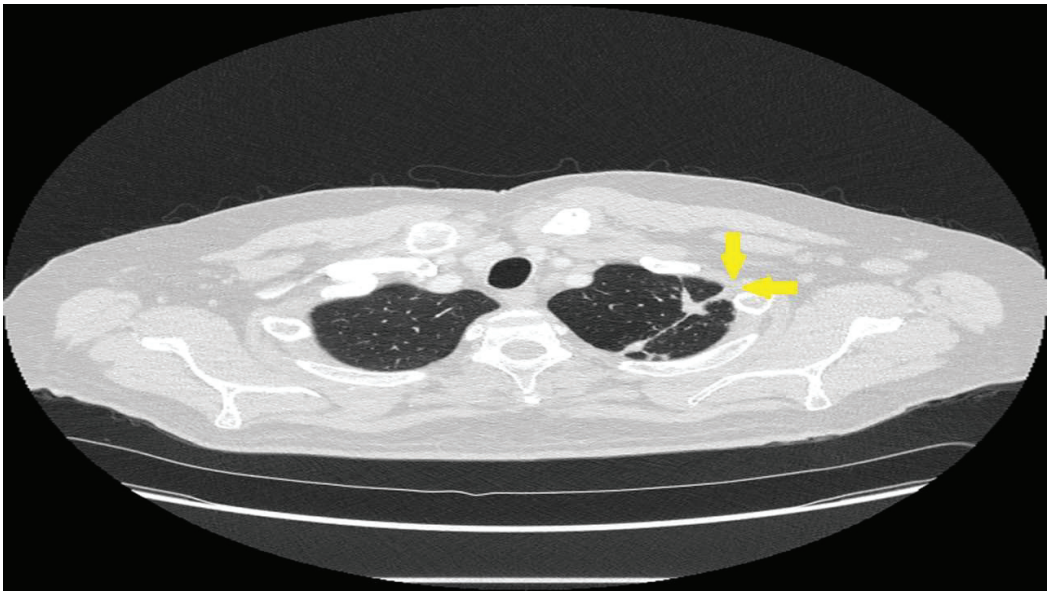

**Figure 3.** Although most chest pain in pulmonary sarcoidosis is unrelated to specific lung lesions, it may be related to pleural lesions on occasion. The CT scan shows an intraparenchymal pulmonary sarcoidosis lesion that extends to the pleura (arrows). This was the exact location of the patient's pleuritic chest pain. The pain responded to anti-sarcoidosis therapy.

**6. Hemoptysis**

Hemoptysis is a rare symptom of pulmonary sarcoidosis. The most comprehensive review of hemoptysis in pulmonary sarcoidosis was published more than 35 years ago, and found that six percent of 433 sarcoidosis patients developed hemoptysis over the course of their disease [67]. A literature review of 144 cases of sarcoidosis-associated hemoptysis found that the reported incidence of hemoptysis in sarcoidosis varied from 1 to 11 percent [68]. Only 22 percent (31/144) of these patients had a bronchoscopy examination reported, which was normal in one-third of them and in the remainder revealed mucosal thickening, hyperemia, congestion, and/or narrowing of the airways [68]. Interestingly, most of these patients had Scadding stage 1 (bilateral hilar adenopathy without parenchymal opacities) or stage 2 (bilateral hilar adenopathy and parenchymal opacities without fibrosis) chest radiographs. Hemoptysis resolved in most of these cases, with only one death and five recurrences reported.

Hemoptysis may rarely be an initial manifestation of sarcoidosis, with only four percent of 433 patients presenting with this symptom [67]. Scattered reports of hemoptysis at the onset of sarcoidosis suggest that it usually resolves with a course of corticosteroids [68–70]. A biopsy from an endobronchial lesion in one such case revealed "non-caseating granulomas with central necrosis" [68], and we suspect that airway necrosis related to granulomatous inflammation is the most common cause for this presentation. This mechanism is consistent with the fact that hemoptysis at presentation of sarcoidosis usually responds to corticosteroids.

Hemoptysis may occur in patients with Scadding stage 4 fibrocystic sarcoidosis via a number of mechanisms. Sarcoidosis-associated bronchiectasis occurs in up to 50 percent of patients with fibrotic sarcoidosis [30,31]. This bronchiectasis is usually of the traction type, and is most prominent in the central airways (Figure 2) [30,71]. Bronchiectasis in fibrotic sarcoidosis is most likely related to airway fibrosis caused by granulomatous inflammation of the airways [72]. Bronchiectasis may lead to airway infection causing significant hemopt-

ysis [73]. Chronic aspergillus infection including aspergilloma, chronic cavitary pulmonary aspergillosis, and chronic fibrosing aspergillosis commonly occurs with pulmonary sarcoidosis, and almost exclusively in those with fibrocystic disease [30,74]. These patients frequently present with hemoptysis that may be life-threatening (Figure 4) [75]. Although pulmonary hypertension may be seen with any radiographic presentation of sarcoidosis [76], it is most common in those with fibrocystic disease [76]. Pulmonary hypertension may result in significant hemoptysis by causing vascular engorgement and a hemorrhagic diathesis [77]. The management of hemoptysis in fibrocystic sarcoidosis involves rapidly identifying the cause and quickly administering treatment. We have a low threshold for initiating antibiotics empirically for a bronchiectasis-related infection. We also routinely obtain respiratory samples to evaluate for infection. Imaging or microbiologic evidence of aspergillus infection should prompt the obtaining of pulmonary specimens and serologies for the identification of these pathogens. If the fungal disease is localized, bronchial artery embolization is a temporizing procedure that may acutely control the bleeding [78,79], although antifungal agents [74], transcutaneous instillation of antifungals [75], or surgical resection [74] may be required for long-term control. These patients should be evaluated for pulmonary hypertension, as this can not only directly cause hemoptysis [80] but may also exacerbate hemoptysis in patients who have an alternative primary cause of this symptom [75]. Obviously, fibrocystic sarcoidosis patients may develop hemoptysis from numerous other causes that are not associated with this specific form of the disease; these should be searched for and treated.

Other causes of hemoptysis in sarcoidosis include necrotizing sarcoid granulomatosis (NSG), a condition where the granulomas are typically confluent and necrotic [68,81]. The necrosis may be the result of granulomas that deposit around pulmonary vessels that are compressed leading to parenchymal lung infarction and necrosis [82]. Radiographically, NSG often demonstrates multiple pulmonary nodules with cavitation [83]. It is currently unclear as to whether NSG is a specific disease entity or a form of sarcoidosis [82]. The rare entity of sarcoidosis-related pulmonary veno-occlusive disease has also been reported to present with recurrent hemoptysis [84].

Several medical conditions are associated with sarcoidosis that may lead to hemoptysis. Sarcoidosis patients appear to be at a higher risk of pulmonary embolism [63,85,86] and lung cancer [87,88], both of which often present with hemoptysis. Immunosuppressive agents used to treat sarcoidosis may increase the risk of necrotic lung infection that may cause hemoptysis.

Table 3 lists several causes of hemoptysis that are directly or indirectly related to pulmonary sarcoidosis. The clinician should be aware that causes of hemoptysis not related to sarcoidosis may also occur in these patients.

**Table 3.** Causes of hemoptysis in pulmonary sarcoidosis.

| Cause | Form of Sarcoidosis | Mechanism |
| --- | --- | --- |
| Granulomatous airway lesions | Active pulmonary sarcoidosis (granulomatous inflammation) | Granulomatous necrosis of an airway lesion |
| Bronchiectasis | Fibrocystic sarcoidosis | Bronchiectasis from airway fibrosis from previous granulomatous inflammation. Hemoptysis from infectious bronchitis/bronchiectasis |
| Aspergilloma/Chronic aspergillus lung infection | Fibrocystic sarcoidosis | Aspergillus colonization of devitalized lung with subsequent locally invasive disease |
| Pulmonary hypertension | Many forms of sarcoidosis, most commonly fibrocystic disease | Pulmonary hypertension leads to vascular engorgement and a hemorrhagic diathesis that may be exacerbated by infection, granulomatous inflammation |

**Table 3.** *Cont.*

| Cause | Form of Sarcoidosis | Mechanism |
|---|---|---|
| Necrotizing sarcoid granulomatosis | Necrotizing sarcoid granulomatosis—unclear if this is a form of sarcoidosis or a separate disease entity | Parenchymal necrosis |
| Pulmonary embolism | Associated with sarcoidosis epidemiologically | Pulmonary infarction; pulmonary hypertension |
| Lung cancer | Associated with sarcoidosis epidemiologically | Parenchymal/Airway necrosis |
| Pulmonary infection | Associated with immunosuppressive agents used to treat sarcoidosis | Parenchymal/Airway necrosis |
| Hemoptysis not specifically related to sarcoidosis | Not applicable | Not applicable |

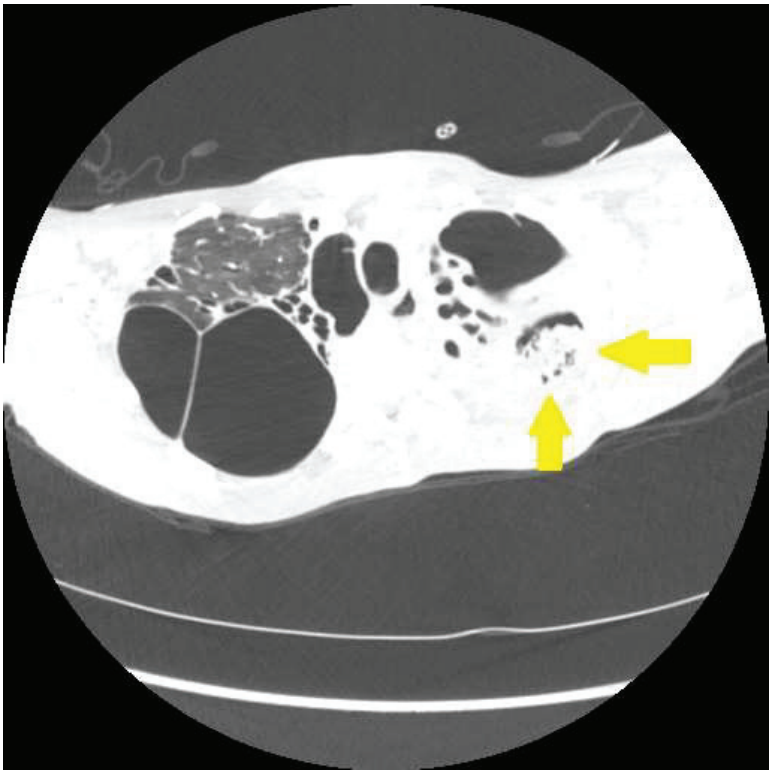

**Figure 4.** Chest CT scan of a fibrocystic pulmonary sarcoidosis patient demonstrating a mycetoma (arrows). These are often associated with significant pleural thickening.

## 7. Pulmonary Sarcoidosis without Pulmonary Symptoms

It has been estimated that 50 [59,89] to 85 [90] percent of pulmonary sarcoidosis patients present without pulmonary symptoms. Some of these patients are diagnosed with pulmonary sarcoidosis fortuitously via chest imaging studies performed for other reasons. Although approximately 50 percent of pulmonary sarcoidosis cases can be discovered in this way via mass population chest radiograph screenings [91], this occurs in less than 10 percent of pulmonary sarcoidosis patients cared for in clinical practices [89,90,92]. Approximately one-quarter of pulmonary sarcoidosis patients present with isolated symptoms

of extrapulmonary organ involvement (e.g., eye symptoms, skin lesions) [89]. Lofgren's syndrome, consisting of bilateral hilar adenopathy on a chest radiograph, erythema nodosum skin lesions, and commonly fever and an ankle periarthritis, [93,94] is a common presentation of sarcoidosis and pulmonary symptoms are often absent. The frequency of Lofgren's syndrome is quite variable throughout the world, being particularly common in Northern Europe and rare in Spain and Japan [95]. In up to 50 percent of cases, pulmonary sarcoidosis may present with constitutional symptoms such as fever, malaise, night sweats, and weight loss that are not attributable to a specific organ [59].

Patients with asymptomatic pulmonary sarcoidosis most commonly have no evidence of parenchymal lung disease on a chest radiograph, with either a normal chest radiograph (Scadding stage 0) or bilateral hilar/mediastinal lymphadenopathy without parenchymal opacities (Scadding stage 1) [96,97]. The spirometry of asymptomatic pulmonary sarcoidosis patients is normal in more than 90 percent of cases [96,97].

The prognosis of asymptomatic pulmonary sarcoidosis is better than that of symptomatic patients. In one series of 660 sarcoidosis patients where 175 (27%) were asymptomatic and at least 145 (83%) of those had pulmonary sarcoidosis, asymptomatic patients less frequently required treatment, developed less organ involvement, and had improved health-related quality of life [98].

## 8. Summary

Although the symptoms associated with pulmonary sarcoidosis are not specific for the disease, they provide important clinical insights. Cough is the most frequent symptom of active pulmonary sarcoidosis, and the lack of cough greatly lowers the probability of an exacerbation of pulmonary sarcoidosis. Wheezing is underappreciated in pulmonary sarcoidosis. It is a very common symptom in acute pulmonary sarcoidosis from the granulomatous involvement of the airways and in chronic sarcoidosis from airway distortion from fibrosis. Chest pain is also an underappreciated symptom of pulmonary sarcoidosis. It is typically pleuritic and usually not associated with the severity of the disease. Hemoptysis is a relatively uncommon initial symptom of pulmonary sarcoidosis that usually responds well to corticosteroids. However, hemoptysis in chronic fibrotic pulmonary sarcoidosis may suggest bronchiectasis, aspergillus infection, or pulmonary hypertension; all of which are serious and potentially life-threatening disease complications. Asymptomatic pulmonary sarcoidosis patients tend to have minimal disease on chest imaging, less often require treatment, and have a better long-term quality of life than symptomatic patients.

The assessment of the symptoms of pulmonary sarcoidosis is easy to obtain and has no cost. We believe that comprehensive knowledge of these symptoms will aid the clinician in identifying and managing various manifestations of the disease. Advances in artificial intelligence may allow for more accurate monitoring of these symptoms that may significantly improve patient management.

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# Imaging of Pulmonary Sarcoidosis—A Review

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**Abstract:** Sarcoidosis is the classic multisystem granulomatous disease. First reported as a disorder of the skin, it is now clear that, in the overwhelming majority of patients with sarcoidosis, the lungs will bear the brunt of the disease. This review explores some of the key concepts in the imaging of pulmonary sarcoidosis: the wide array of typical (and some of the less common) findings on high-resolution computed tomography (HRCT) are reviewed and, with this, the concept of morphologic/HRCT phenotypes is discussed. The pathophysiologic insights provided by HRCT through studies where morphologic abnormalities and pulmonary function tests are compared are evaluated. Finally, this review outlines the important contribution of HRCT to disease monitoring and prognostication.

**Keywords:** thoracic; pulmonary; sarcoidosis; imaging

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## 1. Introduction

Sarcoidosis, the archetypal granulomatous disease, was first reported in the 19th century by the physician Jonathan Hutchinson [1]. For a while thereafter, sarcoidosis was considered a disorder of the skin. However, the multisystem nature of sarcoidosis was soon realised, and it also became clear that the lungs bear the brunt in most patients [2–4]. The cardinal diagnostic finding on histopathologic examination is the non-necrotising or non-caseating epithelioid cell granuloma [5,6]. Yet, despite the commonality of pathologic features, it is also widely known that patterns of functional impairment, responses to treatment and prognosis can vary considerably from patient to patient [7–10]. Indeed, because of this, it has been posited that sarcoidosis might simply be a convenient 'umbrella' capturing what, in essence, are multiple different granulomatous diseases.

Imaging tests play a role not only in diagnosis but also in management and follow-up. In the review that follows, we consider the common and some atypical patterns of lung involvement in sarcoidosis. We also discuss the potential place of computed tomography (CT) in 'staging', quantification of disease extent (leading to discussions on prognostication) and clinical monitoring in sarcoidosis.

## 2. Imaging in Sarcoidosis—General Principles

Kuznitsky and Bittorf first reported the plain chest radiographic (CXR) abnormalities in sarcoidosis early in the first half of the 20th century [11]. Attempts to better characterise CXR appearances, first proposed by Wurm [12], were later modified by Scadding [13]. In Scadding's modification, CXR abnormalities are stratified based on the presence or absence of intra-thoracic nodal enlargement and parenchymal disease. Despite the simplicity, the clinical utility of this CXR staging system has been questioned: linkages with functional tests [14,15] and patient-reported disease severity [16] are, at best, weak. The imperfect interobserver agreement further limits the value of CXR staging [17]. Finally, it is worth

emphasising that even the use of the term staging is misleading; in contrast to malignant disease, there is no predictable, stepwise progression from 'lower' to 'higher' stages in sarcoidosis [18].

### 2.1. Imaging in Sarcoidosis: Plain CXR vs. High-Resolution Computed Tomography

The last two decades have seen significant advances in imaging technologies. Yet, the plain CXR, computed tomography (CT) and, specifically, high-resolution CT (HRCT), remain the mainstays of imaging tests for interstitial lung disease. Plain CXR has the benefits of relative technical simplicity, high spatial resolution, reasonably low cost and a limited radiation burden. Against this, contrast resolution in CXR is lower than in CT, and anatomical superimposition on CXR images also hampers diagnostic interpretation.

The advent of HRCT was a major step forward in the diagnosis of diffuse interstitial lung diseases (DILDs): compared with standard CT images, spatial resolution and image quality, in general, were enhanced by reducing section thickness [19–21] and the use of a dedicated high-spatial-frequency ('bone') reconstruction algorithm [22]. The diagnostic potential of HRCT was realised in the pivotal study by Mathieson and co-workers in which three experienced, blinded observers independently reviewed CXRs and HRCT studies in 118 patients with DILDs [23]. The key findings were not only that observers were more than twice as confident in formulating a diagnosis with HRCT (23% versus 49%) but also that, when confident, the HRCT diagnosis was almost always correct. The advent of spiral volumetric and, subsequently, multidetector computed tomography scanning has facilitated the rapid (single breath-hold) acquisition of volumetric thin-section datasets yielding further improvements in image quality [24,25]. Volumetric—as opposed to interspaced—thin-section CT of the lungs is now the norm in most imaging departments. The reader should note that for the purposes of the current review, the abbreviation CT will be used to refer to volumetric HRCT acquisitions.

### 2.2. Imaging in Pulmonary Sarcoidosis: Other Imaging Modalities

Plain CXR and CT are almost always the first imaging tests requested in patients with suspected or established lung disease. In specific clinical scenarios, other imaging tests are brought to bear. Positron emission tomography (PET) using a radioactive tracer (most commonly radio-labelled fluorodeoxyglucose [$^{18}$FDG]), is coupled with CT to pinpoint the foci of metabolically 'active' disease. Accordingly, in pulmonary sarcoidosis, $^{18}$FDG-PET/CT may be used to assess the presence and extent of active inflammation [26]. Indeed, diffusely increased PET avidity in lung parenchyma has been correlated with a significant decrease in diffusion capacity for carbon monoxide in sarcoidosis (Dlco) [27]. Away from the lungs, PET/CT has a more established role in the detection and monitoring of cardiac sarcoidosis, with a reported sensitivity and specificity of 89% and 78%, respectively [28,29]. PET/CT also has a potential role in detecting occult extra-thoracic disease in sarcoidosis [30–32].

Assessment of pulmonary disease with magnetic resonance imaging (MRI) is limited by several factors, including poor signal-to-noise ratio, significant susceptibility artefact at the interfaces between air and soft tissue, and respiratory and cardiac-related motion artefacts during long scanning times [33]. Despite technical developments in MRI, such as ultrashort echo times and parallel acquisition methods [34], the spatial resolution does not allow distinction between finer morphological features, for instance, differentiating reticulation from honeycombing [35]. As with PET/CT, MRI is more often utilised in the detection of cardiac sarcoidosis, with 95% and 85% sensitivity and specificity, respectively [36], and it is also sensitive, but not particularly specific, for neurosarcoidosis [37].

## 3. CT Detection and Diagnosis of Sarcoidosis

### 3.1. Intra-Thoracic Nodal Enlargement

Enlargement of mediastinal and hilar lymph nodes is a hallmark of sarcoidosis, reported on CT in up to 84–97% of cases [38–41], and most commonly involving stations 4R, 7, 11L and 11R [40]; the classical Garland's triad of bilateral hilar and right paratracheal

nodal enlargement will be known to most readers [42]. Not surprisingly, the distribution and extent of nodal enlargement are best evaluated on CT [43]. On the whole, symmetrical hilar nodal enlargement most often points to a diagnosis of sarcoidosis and away from lymphoma, other malignancies and tuberculosis (TB); in TB, calcification is more often unilateral and along predictable lymphatic drainage pathways [44]. Necrosis of lymph nodes is recognised in sarcoidosis but should prompt a search for an alternative aetiology, such as TB [39]. Nodal calcification, present in 44–53% of patients, also tends to be bilateral and may have a focal pattern (as opposed to complete, asymmetrical nodal calcification which is more commonly observed in TB) [41,44]; so-called 'egg-shell' calcification is also reported [45]. An interesting variant is seen in some patients wherein the calcification has a more ill-defined or 'icing sugar' quality [44] (Figure 1).

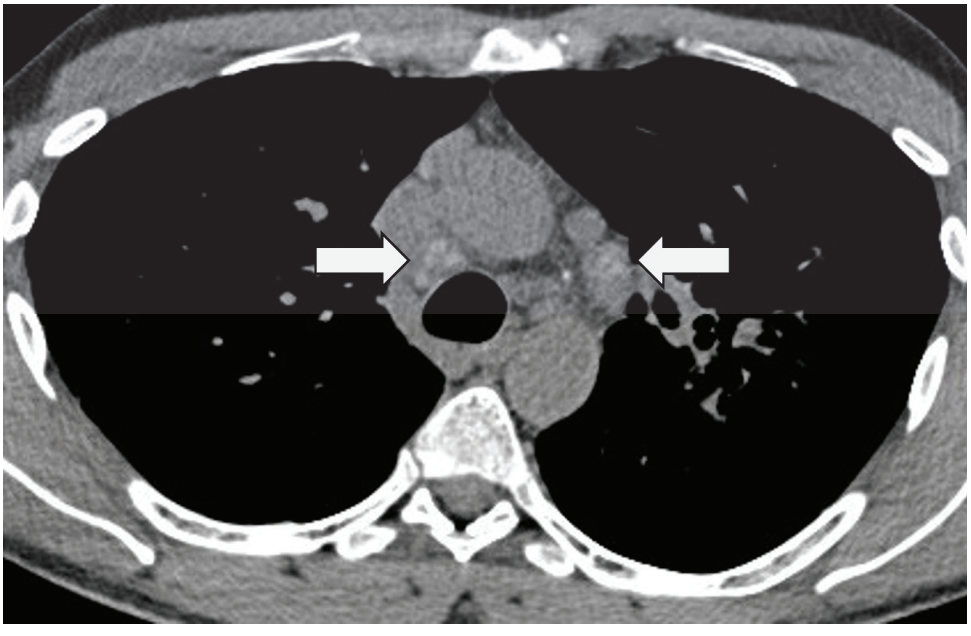

**Figure 1.** Axial CT in a patient with sarcoidosis. Images at a level below the aortic arch demonstrating classical 'icing sugar' calcification in mediastinal lymph nodes (arrows).

Precise localisation of intra-thoracic lymph nodes on CT may facilitate the planning of endobronchial ultrasound-guided biopsy, a minimally invasive technique that can provide a more definitive diagnosis in ambiguous clinico-radiological presentations [46].

### *3.2. Nodules*

Lung nodules on CT are the most widely recognised and common CT manifestations of sarcoidosis [7,47,48]. In a small series of 45 patients with suspected or known sarcoidosis, nodules were present in 80% [7]. In a larger study of 95 patients by Remy-Jardin et al., a nodular pattern was present in 93% [49]. In the classical case, bronchocentric micronodules (measuring 1–3 mm in diameter), are seen in the mid and upper zones. Lung nodules, corresponding to aggregates of microscopic epithelioid granulomata [50], may be diffusely distributed throughout the lungs or, less frequently, localised to one or several focal areas. The predilection for the axial interstitium (i.e., surrounding bronchovascular bundles), accounts for the readily recognisable thickened, irregular perihilar and peribronchovascular appearance [48] (Figure 2). Irregular or nodular thickening of interlobular septa—mimicking lymphangitis carcinomatosa—is recognised but is rarely a dominant feature [51–53].

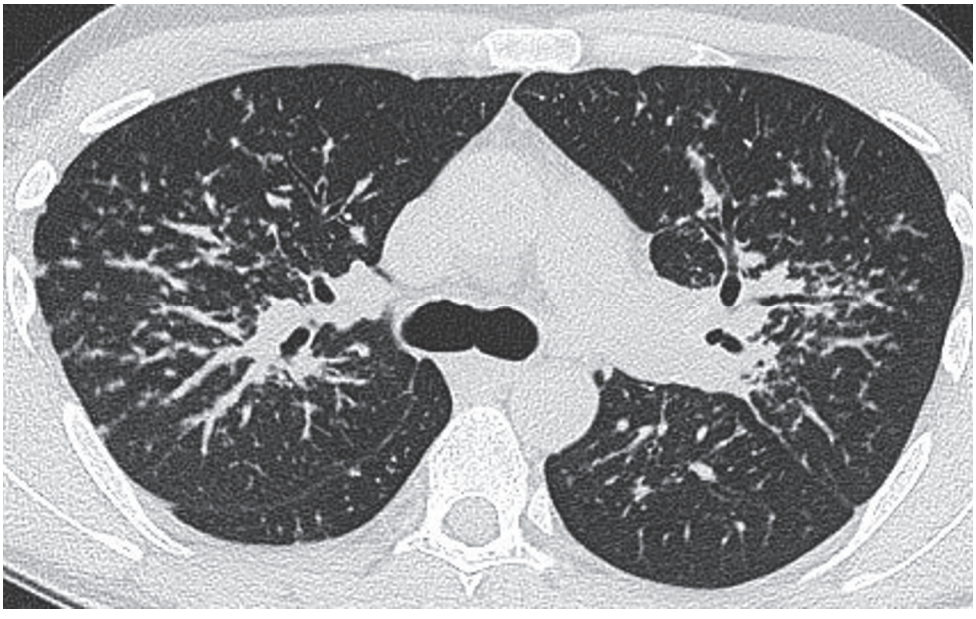

**Figure 2.** CT at the level of the carina in the same patient as in Figure 1. There is a roughly symmetrical bronchocentric micronodular infiltrate. More centrally, there is dense parenchymal opacification caused by conglomeration of nodules around the bronchovascular structures.

Nodules along the subpleural surfaces (including the fissures) give rise to a characteristic beaded appearance [54]. Less often, centrilobular or branching nodularity is seen but this is usually in conjunction with a dominant pattern of bronchovascular nodules [55,56]. Extensive nodularity in a random distribution is present in some patients and, for obvious reasons, the distinction from disseminated TB or malignancy then not only becomes important but also difficult, often mandating histopathologic/microbiologic confirmation [57].

### *3.3. Masses and Consolidation*

On occasion, granulomata coalesce to form larger nodules or masses, sometimes manifesting as a pattern of consolidation [48,49]. Nodules measuring over 1 cm in maximum diameter have been reported in 15–53% of patients; these nodules tend to have irregular margins and predominate in the mid and upper zones [50,58–60]. Despite the occasional presence of air bronchograms (giving the impression of airspace involvement), the large nodules and appearance of 'consolidation' are a consequence of conglomerated granulomata and/or interstitial thickening as opposed to filling of the alveoli [50,61].

Clustering of micronodules around a larger central nodule gives rise to the so-called 'galaxy sign' [62], (Figure 3) reportedly seen in nearly one-third of patients [63], but not pathognomonic for sarcoidosis [64].

### *3.4. Ground-Glass Opacification*

The reported prevalence of ground-glass opacification on CT in sarcoidosis is highly variable, ranging from 16 to 42%, with most instances of this pattern occurring in conjunction with other more common CT features [7,47,49]. Indeed, in the recent multinational Delphi study of recognisable CT phenotypes in sarcoidosis, there was no consensus, among a large body of experts, as to the existence of a predominant pattern of ground-glass opacification [65]. When present in sarcoidosis, ground-glass opacities most commonly reflect multiple microscopic granulomata [50].

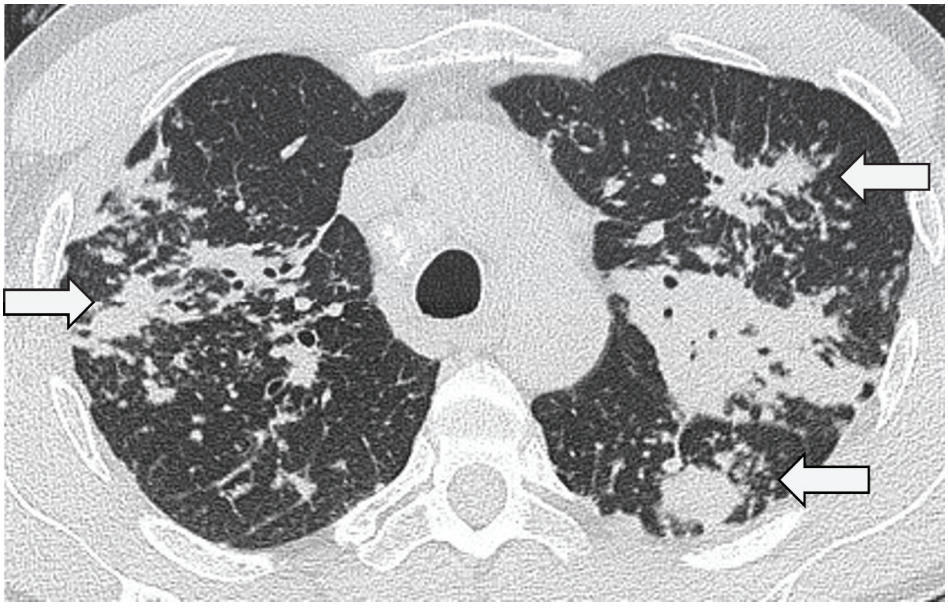

**Figure 3.** Nodular sarcoidosis in a 46-year-old male patient. CT at the level of the aortic arch showing large nodules with surrounding micronodules (the 'galaxy sign') in both upper lobes (arrows).

*3.5. Airway Disease*

Airway involvement in sarcoidosis is more prevalent on CT than generally appreciated; the putative pathogenetic mechanisms of airway disease include inflammation, constriction related to surrounding fibrosis and, in some cases, extrinsic compression. Non-specific and mild bronchial wall thickening may be seen in nearly two-thirds of patients and correlates with the presence of bronchial granulomata, erythema and oedema on endoscopy, evolving to fibrotic bronchial stenosis in up to 14% [66,67]. In addition, the formation of granulomata along the axial interstitium of the bronchovascular bundles may lead to extrinsic airway narrowing. In fibrotic sarcoidosis, the airways may be distorted and abnormally dilated by surrounding retractile fibrosis (i.e., traction bronchiectasis) (Figure 4a,b).

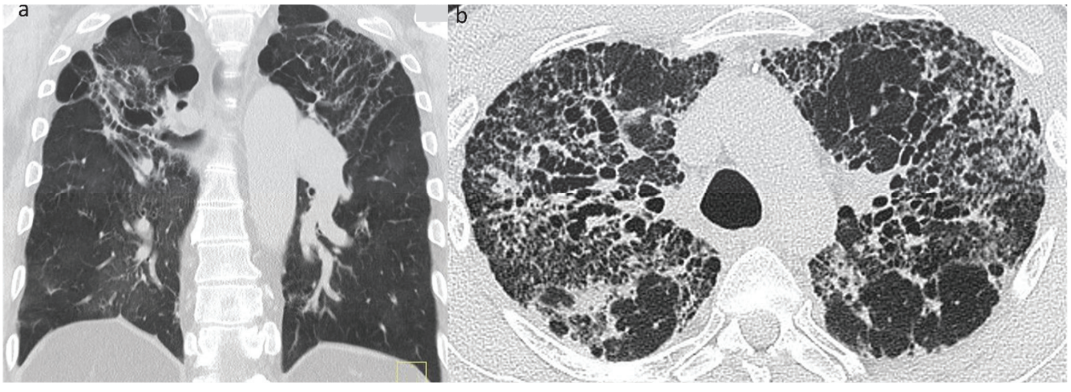


**Figure 4.** (**a**,**b**) Bilateral upper zone fibrosis with volume loss in two patients with sarcoidosis: (**a**) striking peri-bronchovascular fibrosis with retractile airway dilatation (i.e., traction bronchiectasis) and (**b**) CT through the upper lobes in a 64-yr-old male patient. Again, note the marked bronchocentric reticulation with severe traction bronchiectasis, which is particularly severe on the right.

Involvement of the small airways is a surprisingly common finding on CT in sarcoidosis: subtle mosaicism—reflecting obliterative bronchiolitis—is often visible and enhanced on images obtained at end-expiration [68]. Limited involvement of less than 25% of the lung is likely to be clinically insignificant, but air trapping is reported on expiratory phase CT in the majority of patients [7,69–71] (Figure 5).

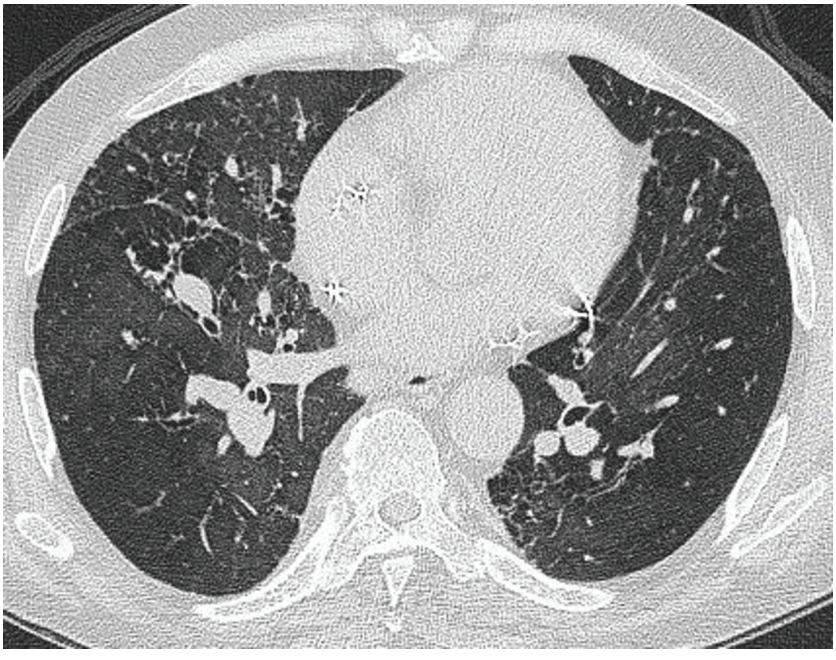

**Figure 5.** Small airway disease in sarcoidosis. Image through the lower zones shows a subtle but definite mosaic attenuation pattern; there is a reduction in the number/calibre of vessels within the lucent lung.

*3.6. Pulmonary Fibrosis*

Pulmonary fibrosis develops in 20–30% of patients [13,72]. The typical CT manifestations include coarse linear opacities, bronchocentric reticulation causing volume loss in the upper lobes and classical posterior retraction of the central bronchovascular structures [48,58] (Figure 6). Encasement of the bronchovascular bundles with conglomerate fibrosis masses may occur, with bronchial distortion and traction bronchiectasis/bronchiolectasis [10,47,73]. Honeycombing is seen in a significant minority and, in contrast to idiopathic pulmonary fibrosis (IPF), has a predilection for the mid-to-upper zones [10,74]. That said, in some patients, sarcoidosis does appear to masquerade as IPF on CT with basal predominant reticulation, ground-glass opacification and interlobular septal thickening [75]. In a recent study by Collins et al., 25 patients with combined sarcoidosis and IPF were reviewed [76]. Interestingly, the diagnosis of sarcoidosis was made, on average, a decade earlier than IPF; in 68%, sarcoidosis had been diagnosed on histopathologic examination at the time of IPF diagnosis. More importantly, survival in patients with combined disease was comparable to patients with classical IPF. Reports such as this raise the question of whether patients with combined disease represent a novel sarcoid phenotype or simply reflect a chance association (i.e., with IPF developing in patients with established sarcoidosis) [77].

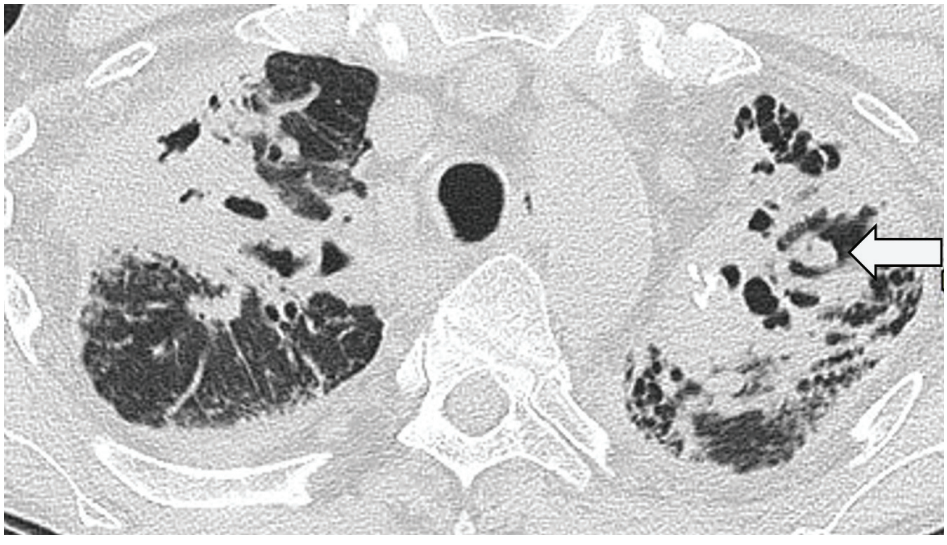

**Figure 6.** CT through the upper zones in a 61-year-old patient with pulmonary sarcoidosis. There is extensive disease with bronchocentric fibrosis manifest as a pattern of the consolidated lung. Note that in the left upper lobe, there is evidence of cavitation with a small aspergilloma (arrow).

## 4. Uncommon CT Manifestations and Complications in Pulmonary Sarcoidosis

### *4.1. Cavitation*

Cavitation in sarcoidosis is uncommon and seen in ~10% of patients with advanced disease [78]. Primary cavitary sarcoidosis is estimated to affect around 2% and, again, tends to occur in patients with severe, 'active' sarcoidosis [79]. Superimposed infection (particularly with fungi or mycobacterial species) should always be considered in this context.

### *4.2. Fungal Colonisation*

Fungal colonisation, most commonly with *Aspergillus* species, complicates between 3 and 12% of sarcoidosis cases with fibrocavitary (or fibrobullous) disease [80]. The radiologic manifestation might be in the form of a simple aspergilloma within a densely fibrotic lung, within a pre-existing bulla or grossly ectatic airway [81,82] (Figure 7). Serological and biochemical markers may be of value in diagnosis [83,84]. In a minority of patients, untreated fungal colonisation will lead, over time, to chronic and extensive fibrotic destruction [81].

### *4.3. Pleural Disease*

Although generally considered rare, Szwarcberg et al. found that in a study of 61 patients with sarcoidosis, 41% had evidence of pleural involvement, predominantly in the form of pleural thickening, and that this was associated with restrictive pulmonary dysfunction [85]. However, it is possible that inward retraction of the pleura and extrathoracic soft tissue in the context of fibrotic pulmonary sarcoidosis might mimic pleural thickening, and interstitial fibrosis also accounts for restrictive functional abnormality in some cases. Pleural effusions are observed in under 10% of sarcoidosis patients [85,86]; reports of pneumothorax are limited to case reports in the literature and are mostly accounted for as a complication of bullous disease [87–90].

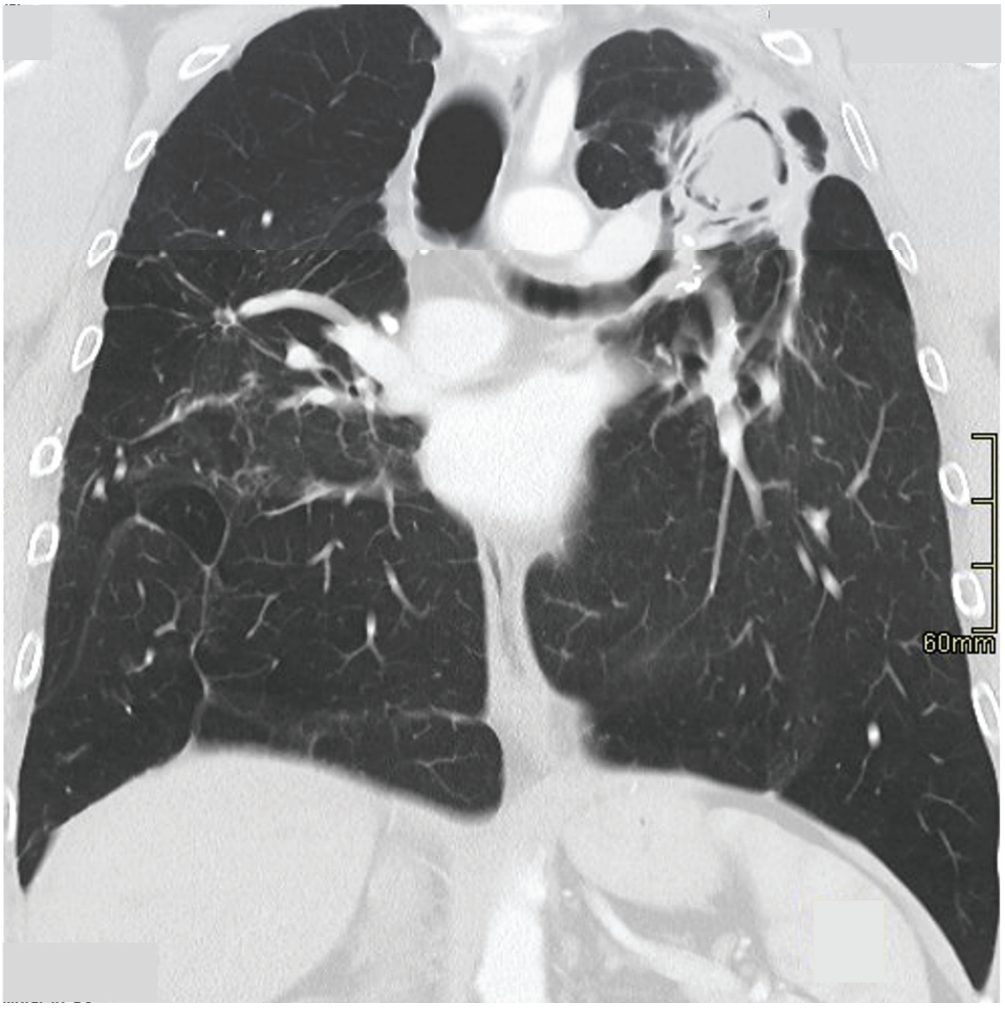


**Figure 7.** Coronal reconstruction of fibrocavitary disease in sarcoidosis; there is a large cavity in the left upper zone containing fungal material.

*4.4. Pulmonary Hypertension*

Pulmonary hypertension (PH), defined as mean pulmonary pressures above 20 mmHg [91], affects between 5.7 and 12% of sarcoidosis patients and is associated with significantly reduced pulmonary function [92–94]. While predominantly affecting those with CXR Stage IV disease, sarcoidosis-associated PH (SAPH) is not limited to patients with fibrosis [95]. The pathophysiology of SAPH is multifactorial, including granulomatous involvement of the vessel walls, vasoconstriction due to fibrosis and venous occlusion secondary to lymphatic granulomas [96,97]. PH may also follow left heart disease in patients with cardiac sarcoidosis.

Mean pulmonary artery diameter measurement (MPAD) of more than 29 mm or a ratio of the diameter relative to the ascending aorta greater than 1 is suggestive of raised pulmonary pressures (greater than 25 mmHg) and should be considered in decisions concerning the need for formal assessment for PH [98]. Another feature suggestive of PH on CT is a segmental artery-to-bronchus ratio greater than 1 in three of four lobes [99]. In a small study by Nunes et al., septal lines were more frequently seen in patients with fibrotic

sarcoidosis and PH than in those with fibrotic sarcoidosis without PH [100]. While CT may prompt further workup, the absence of the described features does not exclude PH in patients with sarcoidosis.

### 4.5. Halo/Reversed-Halo Sign

The 'halo sign' on CT comprising a central nodule (or consolidation) with surrounding ground glass opacification—also found in other pathologies (Including angioinvasive aspergillosis and hypervascular metastases [101–103])—is an infrequent manifestation in sarcoidosis, corresponding to aggregates of macrophages in the alveolar spaces surrounding sarcoid granulomata [104]. A variant of this sign, the 'reversed halo' or 'atoll' sign (once touted as a highly specific sign for organising pneumonia [105]), is also recognised in sarcoidosis, albeit rarely [106,107].

## 5. Disease Monitoring in Pulmonary Sarcoidosis

In any disease, monitoring seeks to identify patients with severe and/or progressive disease which is almost inevitably associated with poorer outcomes [108–110]. With regard to sarcoidosis—and, for that matter, any other interstitial lung disease (ILD)—it is also worth stressing that monitoring disease behaviour where previously only a provisional or 'working' diagnosis was possible, might confirm the initial suspicion or, at least, suggest diagnostic alternatives. As highlighted previously, one of the bigger challenges in sarcoidosis is the heterogeneous nature of sarcoidosis: in many patients, complete resolution occurs (or, at least, there is stabilization without treatment) whereas others face inexorable deterioration culminating in end-stage fibrosis [111,112]. Indeed, the notion of sarcoidosis as a 'benign' disorder is questionable, particularly given a recent large registry review [113]. Hambly and co-authors showed that just under one-third of 92 patients with sarcoidosis fulfilled the criteria for progression (as per the INBUILD trial parameters [114]). That said, in contrast with IPF, fibrotic hypersensitivity pneumonitis, ILDs related to connective tissue disease and even unclassifiable ILDs, the intrinsic likelihood of progression in sarcoidosis is lower. In sarcoidosis, this has implications not only for monitoring but also for the setting of satisfactory 'thresholds' by which progression is to be judged.

For most pulmonologists, establishing progression will be a three-pronged exercise: firstly, a symptomatic assessment, second, evaluation of serial changes in pulmonary function tests (PFTs) and, finally, review of imaging tests (principally CXR and CT). In this respect, it is worth stressing that while each might provide a clue, none is sufficiently sensitive or specific in isolation. Another key challenge for the pulmonologist is determining what constitutes significant change. A detailed critique of the advantages and limitations of clinical assessment and PFTs is not the focus of the present article. Suffice it to say that determining progression on the basis of patient-reported symptoms is not straightforward. For instance, worsening breathlessness, while being indicative of progression in some might, equally, be the harbinger of pulmonary hypertension or a consequence of infection associated with treatment. In contrast to symptomatic assessment, PFTs have the benefit of greater objectivity. Yet, here too, there are important considerations: for instance, minor serial changes in forced vital capacity (FVC), of $\leq$10%, in the absence of a decline in Dlco should be interpreted with caution. Another consideration is that the estimation of Dlco, an important physiologic marker of interstitial lung disease, is not consistent across laboratories, making the evaluation of serial change based on Dlco measurement more difficult.

Plain CXR and CT are the cornerstones of imaging assessment in sarcoidosis. The limitations of CXR have been discussed briefly above and the diagnostic advantage of CT is clear. Against this, it is worth emphasizing that the detection of a real change (for instance, in the patterns or extent of disease) on CXR is still clinically meaningful, especially so where serial changes in symptoms or function are equivocal. Admittedly, the exact place or utility of CT in monitoring disease has not been defined. Suffice it to say that any programme of monitoring sarcoidosis should probably also include a 'baseline' CT against

which change might be judged even though, as it stands, no national or international guidelines recommend CT for this purpose. The latter situation may change following the publication recently of the Delphi-based position statement showing high-level agreement among experts on the need for baseline CT in patients with sarcoidosis and evidence of interstitial lung disease [65].

CT monitoring in sarcoidosis serves a number of purposes (Table 1). In some patients, the main issue will be to assess reversibility: in 'classical' nodular sarcoidosis, for instance, significant or even complete resolution might be expected. By contrast, with predominant upper zone bronchocentric fibrosis and volume loss, the prospects for improvement are likely to be lower. Other indications for requesting serial CT will be to assess the response to treatment and to identify those who progress despite management. With regard to the latter, the evaluation of progression on CT can be difficult and this is compounded by inter-/intra-observer variation and observer experience, to say nothing of the technical challenges of CT interpretation (e.g., variation between CT scanners, scan-to-scan differences in inspiratory effort, etc). Deciding what constitutes a significant change in CT also warrants brief discussion—minor differences in the overall CT extent of the abnormal lung are best disregarded, particularly in the absence of major symptomatic and/or functional decline. Another point to remember is that progression should not solely be defined by an increase in extent; a change in the pattern(s) of disease—for example, an increase in the severity of traction bronchiectasis over time (for the same overall extent of abnormality)—can also indicate that disease has progressed.

**Table 1.** Principal reasons for CT monitoring in pulmonary sarcoidosis.

| **Principal Reasons for CT Monitoring in Pulmonary Sarcoidosis** |
| --- |
| To chart disease behaviour in patients with an initial 'low confidence, provisional' diagnosis of sarcoidosis in whom integration with serial PFTs and clinical features may modify diagnostic likelihoods. |
| To ascertain the likelihood of reversibility at baseline and/or during the natural course of the disease. |
| For the assessment of treatment response (including drug trials in sarcoidosis). |
| Prognostication based on the presence/absence of CT features (e.g., disease extent, traction bronchiectasis/bronchiolectasis and honeycombing). |

## 6. CT Phenotypes in Sarcoidosis

There are few (if any) disorders of the lung with such a plethora of possible imaging manifestations. Added to this and given the considerable variability in functional parameters, natural history, treatment response or outcomes, it is tempting to speculate that the diagnostic label 'sarcoidosis' might simply refer to a multiplicity of entirely different diseases. With this background, a recent multinational study sought consensus from sarcoidosis experts on the existence of distinct morphological CT subtypes or 'phenotypes' of pulmonary sarcoidosis [65]. A total of 146 expert radiologists and pulmonologists from 28 countries took part in a Delphi study. Over two rounds—with 'consensus' defined as $\geq$70% agreement among observers—the study investigators achieved agreement on seven CT phenotypes comprising combinations of CT signs and patterns in sarcoidosis, broadly divided into 'non-fibrotic' and 'likely to be fibrotic' subtypes (Table 2). Further work in the field is certainly required to define the prevalence of different phenotypes (including those for which no consensus was reached), observer agreement for their recognition of CT and the physiological/prognostic impact, if any, of CT subtypes. However, studies of the type listed above might pave the way for a 'new' classification of sarcoidosis based on CT morphology which, in contrast with histopathologic features, may link more closely with observed physiologic and/or prognostic differences in sarcoidosis.

**Table 2.** CT phenotypes in sarcoidosis based on the expert opinion of pulmonologists and thoracic radiologists [65].

| CT Phenotype | Description |
|---|---|
| Non-fibrotic | Micronodular—peri-bronchovascular, peri-fissural and/or subpleural predilection, predominantly in the mid/upper zones, with or without a minority component of larger nodules with surrounding micronodules (i.e., 'galaxy sign'), architectural distortion or volume loss |
| | Nodular (>3 mm but <3 cm)—peri-bronchovascular, peri-fissural and/or subpleural predilection, predominantly in the mid/upper zones, with or without a minority component of larger nodules with surrounding micronodules (i.e., 'galaxy sign'), architectural distortion or volume loss |
| | Nodular (>3 mm but <3 cm)—random distribution |
| | Consolidation as the dominant or sole pattern |
| Likely to be fibrotic | Bronchocentric reticulation without cavitation and/or fibro-bullous destruction and with or without dense parenchymal opacification and/or a minority component of other CT abnormalities (e.g., delicate bands of 'loose' reticulation; enlarged peripheral pulmonary arteries, central pulmonary artery enlargement or a mosaic attenuation pattern) |
| | Bronchocentric reticulation with cavitation and/or fibro-bullous destruction and with or without dense parenchymal opacification and/or a minority component of other CT abnormalities (e.g., delicate bands of 'loose' reticulation; enlarged peripheral pulmonary arteries, central pulmonary artery enlargement or a mosaic attenuation pattern) |
| | Bronchocentric masses ('progressive massive fibrosis [PMF]-lookalike') with or without a minority component of other CT abnormalities (e.g., delicate bands of 'loose' reticulation; enlarged peripheral pulmonary arteries, central pulmonary artery enlargement or a mosaic attenuation pattern) |

## 7. Disease Quantification and Prognostication in Sarcoidosis

### *7.1. Morphological–Functional Relationships in Sarcoidosis*

In pulmonary sarcoidosis, pulmonary function tests (PFTs) may be entirely normal, but airflow obstructive, restrictive and mixed defects are widespread [8]. Not surprisingly, severe restrictive ventilatory defects are usually associated with extensive fibrosis [110,115,116]. However, an obstructive defect, which is not typically associated with fibrotic ILDs other than sarcoidosis, is also relatively common, even in patients with advanced fibrosis [15]. Diffusion capacity (Dlco) is reduced in as many as two-thirds of patients with sarcoidosis [117], variably reflecting interstitial disease and pulmonary vasculopathy [118].

The ability to characterize and quantify specific lung abnormalities on CT and relate these to functional indices or outcomes has provided unique pathophysiologic insights into many DILDs [119–127]. Similar structure–function studies have been undertaken in sarcoidosis. For instance, lung nodules in pulmonary sarcoidosis, for the most part, appear to be functionally 'silent' [7,49,128,129]. There are more intriguing linkages between a CT reticular pattern and functional tests in sarcoidosis: in the study by Hansell et al., reticulation was the dominant independent determinant of functional impairment, especially airflow obstruction [7]. Moreover, an unexpected finding was that the extent of reticulation was associated with indices of obstruction—more often than not, a CT reticular pattern implies lung fibrosis which would cause functional restriction. It should be stated that, in this same study, the extent of decreased attenuation (as part of a CT mosaic pattern) on expiratory imaging also correlated with obstructive impairment but the relationship was less strong than for reticulation [7].

In many patients with pulmonary sarcoidosis, a combination of CT patterns and signs co-exist. For instance, Abehsera et al. identified three patterns of fibrotic sarcoidosis based on the predominant lesions with very good interobserver agreement [10]. Pulmonary restriction with a low diffusion capacity was mostly associated with the honeycomb pattern, whereas obstructive indices were more often linked to bronchial distortion. Those with a linear pattern generally had less severe functional impairment, except in cases of 'distorted septal reticulation', which correlated with pulmonary hypertension, perhaps as a consequence of venous occlusion because of septal fibrosis [10].

### 7.2. Reversible, Irreversible and Progressive Disease in Sarcoidosis

Of the variety of CT patterns reported in sarcoidosis, nodular infiltrates are most likely to improve or resolve at follow-up [41]. Additionally, peribronchovascular thickening, consolidation and ground-glass opacification also have the potential to resolve completely [41,49,130], particularly with treatment [49] (Figure 8a,b). While linear opacities may clear, Murdoch and co-workers found an increased likelihood of progression over time and more so than with other morphologic features [41]. The natural history of ground-glass opacities is more difficult to predict and this CT pattern is a poor predictor of both disease activity and prognosis [41,49]. In part, this might be due to the non-specificity of CT ground-glass opacification which might indicate 'active' (and therefore potentially reversible) granulomatous inflammation or irreversible fine fibrosis below the limits of CT resolution [50]. CT abnormalities tending to indicate irreversible disease include reticulation, architectural distortion, honeycombing and traction bronchiectasis/bronchiolectasis. However, while some patients inevitably progress despite treatment, relative stability over time is more common in sarcoidosis-related ILD than in overtly progressive fibrotic DILDs [108].

While risk factors such as black race and female sex have been associated with higher rates of fibrotic pulmonary sarcoidosis [131,132], there are no formal, large-scale studies that have identified reliable morphological predictors on CT. This may relate to the high prevalence of asymptomatic disease [133] and the fact that patients are rarely observed to progress from one recognisable 'stage' to another. In the authors' experience, fibrotic sarcoidosis often presents with imaging features that appear disproportionately severe when compared to symptoms and functional profiles.

### 7.3. Factors Contributing to and Predictors of Mortality in Sarcoidosis

Overall, the outlook for patients with pulmonary sarcoidosis is reasonably good with a mortality rate of 0.5–4.8% [134]. Lung fibrosis in sarcoidosis is a harbinger of ventilatory impairment leading to respiratory failure and death [109,135]. A study by Nardi et al., focussing on a subgroup of 142 patients with fibrotic pulmonary sarcoidosis, reported mortality as high as 11.3% with a mean age at death of just 55.2 years [110]. Pulmonary hypertension is an important independent predictor of mortality and, in the context of sarcoidosis, has a 5-year survival rate of only 55% [109,136,137]. The prevalence of sarcoidosis-associated pulmonary hypertension is higher in those with fibrosis but correlates poorly with the extent of abnormality on CT; moreover, nearly one-third of SAPH cases have no evidence of fibrosis on CT [95,100,136].

The utility of CT coupled with physiologic indices (including the composite physiological index (CPI) which was first developed in IPF [119]), has been explored as a 'staging' system to predict mortality in sarcoidosis [138]. In this system, a CPI threshold of 40 units was combined with the mean pulmonary artery to ascending aortic diameter ratio and an extent of fibrosis of more than 20% to form an algorithm which was significantly more predictive of outcome than any variable taken alone.

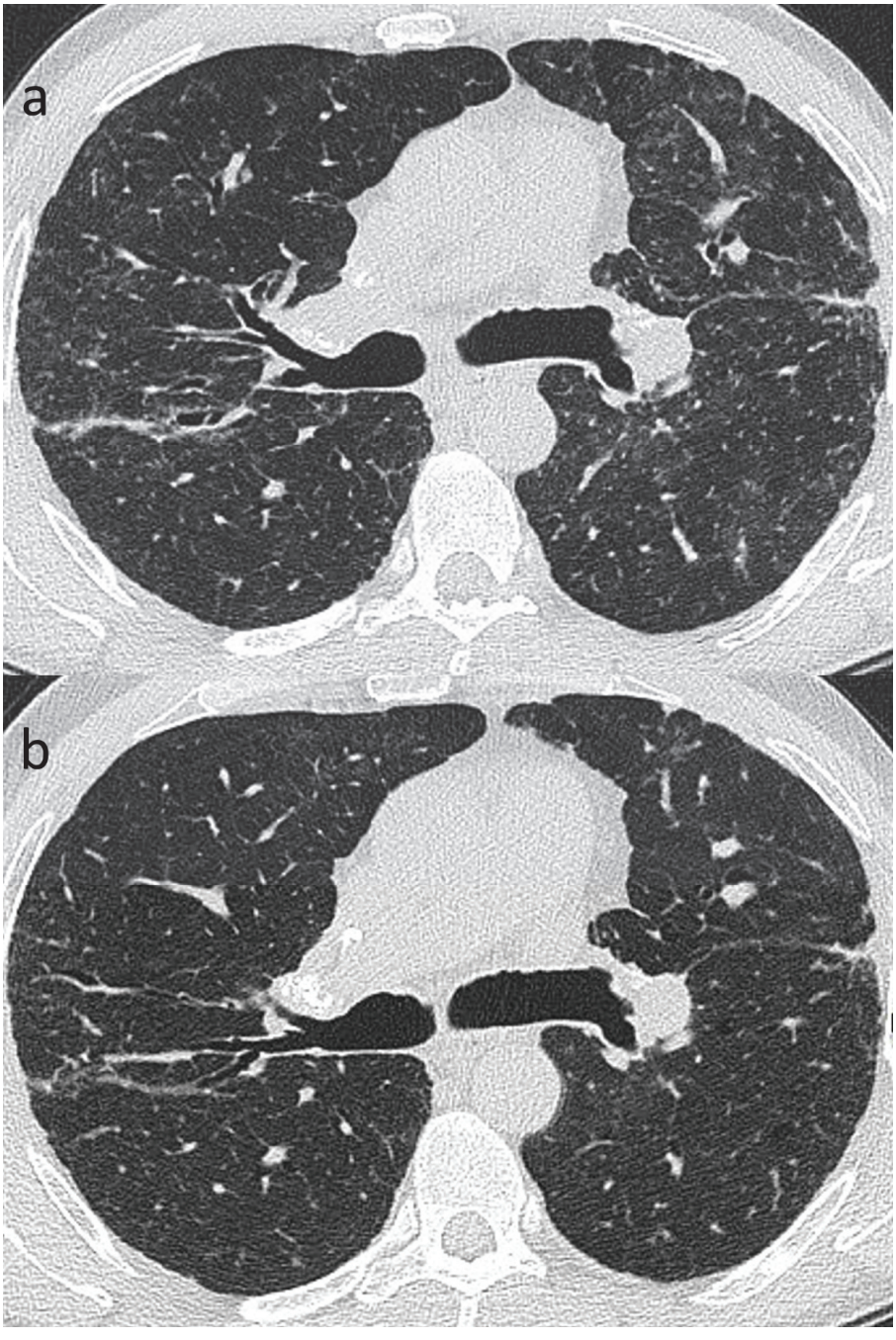


**Figure 8.** (**a**,**b**): Reversible disease in sarcoidosis. Targeted images of the left mid-zone showing the resolution of multiple random micronodules over time in (**a**) 2015 and (**b**) 2017.

**8. Summary**

Imaging tests have an established place in the management of sarcoidosis. In patients with 'classical' appearances—either on CXR or CT—experienced radiologists will

frequently offer a confident radiological diagnosis. In this regard, because of superior contrast resolution and the absence of anatomical superimposition, CT outperforms CXR. CT appearances in sarcoidosis vary considerably although expert opinion suggests that, among the apparently myriad different morphologic manifestations, there are recognisable CT phenotypes. Quantitative studies in which morphological abnormalities on CT are related to functional indices have provided unique insights into the pathophysiology of sarcoidosis and these have been discussed in the present review. Finally, the important role of CT in monitoring sarcoidosis has been presented.

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**Informed Consent Statement:** All images have been obtained from the patient population of the Royal Brompton Hospital, London. There is a policy at this institution that all anonymised images can be used for research purposes.

**Data Availability Statement:** No new data were created or analyzed in this study. Data sharing is not applicable to this article.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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# Pulmonary Function in Pulmonary Sarcoidosis

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**Abstract:** The pulmonary function test (PFT) has been widely used in sarcoidosis. It may vary due to the severity, extent, and the presence of complications of the disease. Although the PFT of most sarcoidosis patients is normal, there are still 10–30% of cases who may experience a decrease in the PFT, with a progressive involvement of lungs. Restrictive ventilatory impairment due to parenchymal involvement has been commonly reported, and an obstructive pattern can also be present related to airway involvement. The PFT may influence treatment decisions. A diffusing capacity for carbon monoxide (DLCO) < 60% as well as a forced vital capacity (FVC) < 70% portends clinically significant pulmonary sarcoidosis pathology and warrants treatment. During follow-up, a 5% decline in FVC from baseline or a 10% decline in DLCO has been considered significant and reflects the disease progression. FVC has been recommended as the favored objective endpoint for monitoring the response to therapy, and an improvement in predicted FVC percentage of more than 5% is considered effective.

**Keywords:** sarcoidosis; pulmonary function; diagnosis

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## 1. Introduction

Sarcoidosis is a systemic granulomatous disorder of unknown etiology that may affect almost every body organ. The most commonly involved organs remain the lung and mediastinal lymph nodes. The diagnosis of it depends on a compatible clinical and imaging feature, histologic evidence of non-necrotizing epithelial granuloma, and exclusion of alternative causes of granulomatous diseases [1]. Clinicians have been involved with the disease activity and severity of sarcoidosis through clinical symptoms, radiological imaging, the pulmonary function test (PFT), and blood tests. The PFT plays an important role in the initial workup, diagnosis, and treatment monitoring, as well as follow-up of the disease. It is sensitive for detecting pulmonary parenchymal changes, airway obstruction, and pulmonary hypertension in sarcoidosis. In this review, we evaluated the evidence published in this area to summarize the role of the PFT in initial and follow-up evaluation, the correlation of the PFT with radiological findings, disease severity, and the scoring system for sarcoidosis, as well as the influence of the PFT in treatment.

## 2. Methods

The PubMed database was searched for the period from January 2012 to December 2022 using the terms: "Sarcoidosis[title]". The inclusion criteria included: (1) the article was about pulmonary sarcoidosis rather than other organs' sarcoidosis; and (2) the article contained the content of the FPT. The exclusion criteria included: (1) the article was written in languages other than English; (2) case reports, study designs, comments or letters; (3) animal or laboratory studies; and (4) the full text was unavailable. According to the inclusion and exclusion criteria, there were 45 articles selected by investigators. An

additional 39 articles were found by searching the reference lists of previously selected articles.

## 3. Results

### 3.1. PFT in the Initial and Follow-up Evaluation of Sarcoidosis

The PFT, as well as radiographic and laboratory biomarkers tests, is useful for initial assessment in sarcoidosis diagnosis [2]. The American Thoracic Society (ATS), European Respiratory Society (ERS), and World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG) guidelines recommend a series of preliminary examinations, including the PFT, for all patients with sarcoidosis [2]. Among the PFT parameters, forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and diffusing capacity for carbon monoxide (DLCO) are necessary for assessing lung involvement in clinical practice. FVC is the most important parameter for monitoring diseases and is often used as the primary endpoint in clinical trials of sarcoidosis [3]. The FEV1/FVC ratio may be effective in identifying most sarcoidosis patients with airway obstruction [4]. DLCO appears to be more sensitive in detecting pulmonary fibrosis than FVC, and it can be used to indicate pulmonary hypertension [5,6]. However, DLCO is not as effective as FVC as a treatment indicator or a primary research endpoint due to its high variability.

The PFT in sarcoidosis patients may vary due to the severity, extent, and the presence of complications of the disease. Most sarcoidosis patients have a normal PFT, whereas 10–30% of cases may experience a decrease in the PFT, with progressive involvement of the lungs and progress to chronic disease [7]. An impaired PFT at the onset of sarcoidosis has been implicated in poor prognosis in the long term. A value of FVC < 80% was associated with persistence of activity, while a vital capacity (VC) of <1.5 L implied a high risk of mortality [8,9]. Viskum et al. found that patients with a FEV1 lower than or equal to 50% predicted had 4.2-fold increase in mortality rate compared with those with a FEV1 exceeding 80% predicted [10]. Any PFT pattern can be seen in patients with sarcoidosis, such as a restrictive ventilatory defect (RVD), an obstructive ventilatory defect (OVD), reduced DLCO, or mixed ventilatory defects. The most prevalent pattern of PFT abnormality was an RVD due to parenchymal involvement, which occurred in about 45% of the patients [11]. An obstructive pattern can also be present and may be related to airway involvement caused by external compression of mediastinal disease, granulomatous tissue, or peri-bronchial fibrosis [12,13]. In the stage IV sarcoidosis group, spirometry and DLCO are almost always abnormal. An RVD was observed in approximately two-thirds of cases, while an OVD was observed in one-third. Mixed defects were present in 20% of patients, and a decrease in DLCO was observed in 90% of patients [14].

The clinical course of sarcoidosis is usually evaluated and tracked with objective clinical outcome measures, including radiographic findings and a PFT [15]. The PFT is the gold standard indicator in evaluating pulmonary parenchymal progression and treatment response. Despite the lack of consensus on follow-up times, it is recommended to conduct an assessment at least every 3 to 6 months in the first 2 years, and yearly for the next 3 to 5 years; thereafter, no further follow-up is required unless recurrence or new symptoms occur [2]. The PFT reflects the effectiveness of treatment. Out of various pulmonary function parameters, FVC is routinely used to assess the response to therapy due to its high reproducibility [16]. Changes in FVC during follow-up are important, and a significant reduction in FVC is an indication for therapy. An absolute change of 5% in FVC is considered significant, and has been proposed as one of the criteria for exacerbation of sarcoidosis [3,17]. Meanwhile, an absolute improvement of FVC > 5% is considered as a positive response to treatment [18]. The FEV1 is related to the severity of airway obstruction. The FEV1 and FEV1/FVC decrease can be seen in sarcoidosis patients with bronchial distortion, peripheral lymph node compression of the airway, or endobronchial involvement [12,19]. After successful therapy, improvement in the FEV1 may be seen in these cases.

### 3.2. Correlation between PFT and Chest Imaging in Sarcoidosis

X-ray is the most common radiologic technique for assessing pulmonary involvement in sarcoidosis. There are differences in PFT parameters of sarcoidosis patients at different imaging stages [20]. The PFT is impaired in approximately 20% of sarcoidosis patients with stage I, but in 40–80% of stage II to IV patients, with parenchymal involvement [21]. Stage I disease was associated with mild PFT abnormalities, which were better than those of stages II and III, whereas patients at stage IV had the worst pulmonary function and 75% of them died from respiratory complications including pulmonary hypertension and chronic respiratory failure [14,22–24]. However, the initial Scadding stage was not well correlated with changes in pulmonary function or subsequent clinical recovery, apart from stages 0 and 4, which were related to great and poor prognosis, respectively [25,26]. A study from the United Kingdom conducted serial chest X-rays (CXR) and simultaneous PFT tests in 354 patients with sarcoidosis, and found that the PFT data of 50% patients were inconsistent with the chest X-ray data, which suggested that disease extent on chest radiography was more appropriate for routine monitoring of sarcoidosis than the X-ray Scadding stage [27].

High-resolution computed tomography (HRCT) is an accurate modality to identify mediastinal lymphadenopathy and subtle pulmonary parenchymal changes. In clinical practice, it is widely used for the initial evaluation of sarcoidosis and monitoring of disease progression. Compared with CXR stages, HRCT findings of sarcoidosis have a better correlation with the severity of PFT changes [23,28]. PFT parameters were negatively correlated with CT scores of consolidation pattern and ground-glass opacities. There were obvious correlations between lung consolidation imaging scores and FVC, FEV1, and FEV1/FVC, while the ground-glass opacity scores were significantly related to DLCO [22,29]. As for micronodules, whether lung function is affected depends on the amount of micronodules and the extent of lung involvement. It was suggested that the higher the number of micronodules is, the lower the spirometric values are [29]. If micronodule patterns occur in a very limited lung area, PFT parameters will not be affected [22]. The main CT features of pulmonary fibrosis included honeycombing patterns, diffuse linear patterns, and bronchial distortion. Honeycombing patterns are usually associated with restrictive dysfunction and decreased DLCO. Patients with bronchial distortion often experience a lower FEV1 and FEV1/FVC. Linear patterns generally only cause slight functional damage [28]. Figure 1 shows the CT images of three sarcoidosis patients with different pulmonary dysfunctions.

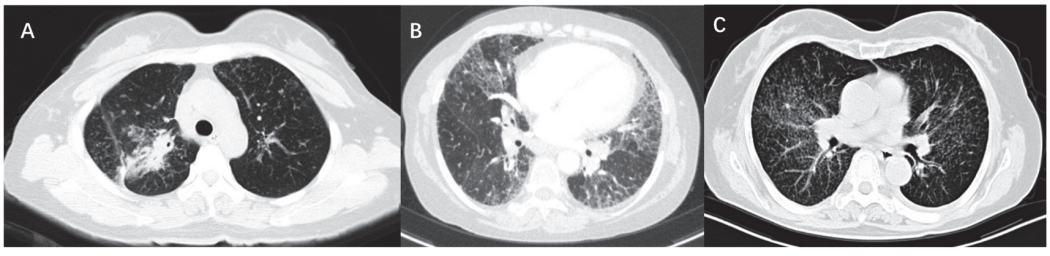


**Figure 1.** CT images of three patients with sarcoidosis. (**A**) Shows consolidation on CT scan and the PFT is characterized by restrictive ventilation dysfunction, with an FVC of 67.9% predicted and FEV1 of 61% predicted. (**B**) Shows fibrosis and bronchial distortion on CT scan and the PFT is characterized by restrictive ventilation dysfunction and decreased diffusion function, with an FVC of 44.4% predicted, FEV1 of 52.0% predicted, and DLCO of 50.9% predicted. (**C**) Shows multiple micronodules on CT scan and the PFT is characterized by mixed ventilation dysfunction, with an FVC of 71.3% predicted, FEV1 of 62.3% predicted, FEV1/FVC of 69.46%, and normal DLCO.

Airflow limitation was observed in patients with thickening of bronchovascular bundles (BVBs), air trapping, and reticular shadow [12,30,31]. Handa et al. conducted a

prospective, observational study, and found that 8.8% (20/228) of the sarcoidosis subjects had airflow limitation, and chest radiographic stage IV, higher age, smoking, and thickened BVB were independently associated with a lower FEV1/FVC [12]. Hansell et al. evaluated CT scans of 45 patients with semi-quantitative scoring for five CT patterns. The range of the reticular pattern is closely correlated with airflow obstruction severity. The larger the extent of the reticular pattern is, the lower the values of FEV1 and FEV1/FVC are [30]. Another study considered that air trapping patterns on HRCT were related to PFT parameters in patients with pulmonary sarcoidosis. In that study, 20/21 patients had air trapping patterns. The extent of air trapping patterns was negatively related to the percentage of predicted residual volume (RV) to total lung capacity (TLC), and the percentage of predicted maximal mid-expiratory flow rate between 25 and 75% to VC [31].

Fluorodeoxyglucose positron emission tomography (FDG-PET) is a useful tool to evaluate inflammatory activity. The metabolic activity of pulmonary parenchyma displayed by FDG-PET was associated with PFT parameters and may represent an impaired pulmonary function [32–34]. In a study, pulmonary PET positive patients had lower DLCO and FVC compared with pulmonary PET negative patients, and PET positivity was observed in all patients with decreased lung function parameters of DLCO < 45% or FVC < 50% [32]. Patients with active pulmonary PET and impaired lung function may have a positive response to treatment. Keijsers et al. found that patients with parenchymal metabolic activity imaged by PET had an obvious increase in lung function of VC, FEV1 and DLCO after treatment, while PET negative subjects showed no change in PFT parameters [35]. Meanwhile, the maximum standardized uptake value (SUVmax) of PET at baseline can predict clinical improvement in pulmonary function after treatment. A prospective open-label trial was performed to evaluate infliximab efficacy in sarcoidosis patients whose symptoms were refractory to conventional treatment in a clinical setting. After 26-week therapy, infliximab significantly improved FVC (6.6% predicted) in refractory sarcoidosis patients with positive 18F-FDG PET [36]. A similar conclusion was reached in another study, which correlated 18F-FDG PET during infliximab treatment with standard sarcoidosis activity parameters, and concluded that the reduction in the SUVmax in pulmonary parenchyma was related to the improvement of VC [37].

### *3.3. Evaluation of Severe Sarcoidosis*

Severe sarcoidosis may lead to significant disability or reduced life expectancy. Pulmonary fibrosis, impaired lung function, extensive disease on HRCT, and pulmonary hypertension are related to poor clinical outcomes in sarcoidosis patients [38]. Most sarcoidosis patients go into remission spontaneously or after treatment, but up to 20% of patients will develop pulmonary fibrosis [39]. Cough, dyspnea after exercise, and hypoxemia are common clinical symptoms. The most common abnormalities of the PFT in sarcoidosis patients with pulmonary fibrosis are an RVD and a decrease in diffusion capacity, while airflow obstruction caused by central airway fibrosis can also be seen [28,39]. An extension of pulmonary fibrosis greater than 20% on CT is associated with poor survival [5,40]. Therefore, the best strategy is to identify those patients who will develop pulmonary fibrosis early and prevent them from developing advanced diseases by focusing on the progression of respiratory symptoms and changes in PFT parameters, mainly the deterioration of FVC and DLCO.

Sarcoidosis-associated pulmonary hypertension (SAPH), a late complication of sarcoidosis, is most common in stage IV or advanced disease, but can also occur in the condition of relatively normal lung function and preserved parenchymal architecture. Approximately 5–6% of pulmonary sarcoidosis patients will develop SAPH, and it is a predictor of a worse outcome with a five-year survival rate of 55% [41,42]. Patients with SAPH usually have an advanced chest radiographic stage and decreased pulmonary function. DLCO is useful in evaluating suspected pulmonary hypertension. Pulmonary hypertension (PH) should be suspected when DLCO is reduced or the symptoms of unexplained dyspnea are persistent, especially when DLCO decreases disproportionately compared

with pulmonary volumes, with a FVC/DLCO ratio > 1.6 [43–46]. In a 6-minute walk test (6MWT), DLCO levels < 60% and oxygen saturation (SpO2) < 90% were independently related to the presence of PH, and the level of potential PH increased sevenfold [15,47]. A screening echocardiogram is recommended in these situations. In an international registry study of SAPH patients, the factors related to reduced transplant-free survival have been analyzed with long-term follow-up. Reduced DLCO < 35% predicted and a 6-minute walk distance < 300 m at registration have been considered as powerful predictors of decreased survival [48].

### 3.4. Scoring System for Sarcoidosis

Several comprehensive scoring methods have been developed to assess the severity of pulmonary sarcoidosis and guide treatment. Wells and his colleagues designed a composite physiological index (CPI), which is a weighted index of pulmonary function variables, and is related to the extent of disease on HRCT in idiopathic pulmonary fibrosis (IPF), and they confirmed that a CPI can predict mortality more than any single pulmonary function variable in IPF [49]. The calculation formula for the CPI is as follows: $91.0 - (0.65 \times$ percent predicted DLCO$) - (0.53 \times$ percent predicted FVC$) + (0.34 \times$ percent predicted FEV1). Combining CPI (< or >40) and HRCT variables, including the main pulmonary artery diameter to ascending aorta diameter ratio (MPAD/AAD) (< or >1) and the extent of fibrosis (< or >20%), Walsh et al. established a clinical staging system for rapid risk prediction of sarcoidosis, which was considered more accurate than any single variable alone [5].

The sarcoidosis treatment score (STS) system has been developed to assess treatment efficacy based on multiple factors of pulmonary sarcoidosis. This STS system integrates six variables, including 5% of absolute FVC change, 10% of absolute DLCO change, HRCT variations, King's sarcoidosis questionnaire, the fatigue assessment scale, and changes of daily glucocorticoid dose [50,51]. Each positive change is scored 1 point, while negative change is scored $-1$ point, with a total score of $-6$ to 6 points. A score of $\geq 3/6$ is considered as Response (R), a score of 2/6 points is considered as Partial Response (PR), while a score of $\leq 1/6$ is considered Non-Response (NR). The components of the STS have a good correlation, with 5% of absolute change in predicted FVC and 10% of absolute change in predicted DLCO [51]. Recently, this STS system has been successfully validated as a primary study endpoint in a multicenter clinical trial [52].

Pulmonary function parameters can also be applied to clinical phenotype identification. A cluster analysis has been studied to phenotype sarcoidosis subjects with slight or severe manifestation [53]. Six phenotypes of sarcoidosis were produced by this cluster analysis. Clusters 1, 2, and 3 had a normal PFT, and cluster 1 was in Scadding stages 2/3, cluster 2 in stages 0/1, and cluster 3 between stages 0/1 and 2/3. Compared with clusters 1, 2, and 3, patients in clusters 4, 5, and 6 had at least one reduced PFT parameter, and needed more therapy. Poorer lung function performances in severe phenotype clusters 4, 5, and 6 were presented as an obstructive type with Scadding stages 2/3, restrictive type with stages 2/3, and mixed types with stage 4, respectively. It is a clinically useful way for clinicians to identify patients with more slight or more severe conditions.

### 3.5. The 6-Minute Walk Distance (6MWD) and Cardiopulmonary Exercise Testing (CPET)

The 6MWD is a simple indicator for measuring pulmonary and cardiac status of patients with sarcoidosis, and it is useful for evaluating exercise tolerance and oxygen demand. It has been confirmed that the 6MWD decreases in some patients with pulmonary sarcoidosis. The 6MWD is most commonly used in the initial assessment, and it is also often used as one of the secondary endpoint indicators in clinical trials of sarcoidosis and as a predictive indicator of the patient survival rate.

In a prospective study with 142 patients, Baughman and his colleagues assessed the role of the 6MWD in impairment and prognosis of disease, and found that 73 (51%) patients had a 6MWD < 400 m and 32 (22%) patients had a 6MWD < 300 m. Meanwhile, they found

that the active ingredients of the St George's Respiratory Questionnaire (SGRQ), FVC, as well as minimum oxygen saturation were independent predictors of 6MWD [54]. In another observational study, Pescaru et al. found that patients with sarcoidosis had reduced exercise capacity assessed by the 6MWD compared with healthy controls, and observed there was obvious associations between the 6MWD and PFT parameters, including FEV1, FVC and DLCO [55].

The 6MWT has been usually tested as one of the secondary endpoints in sarcoidosis therapy clinical research. The 6MWD improved from 227 m to 240 m after six months' treatment in some patients with SAPH [56]. In another retrospective study of patients with SAPH, the 6MWD increased by 59 m ($p = 0.032$) after specific therapies [57]. This was also confirmed in patients with pulmonary sarcoidosis. A randomized and double-blind study found the 6MWD significantly improved in an infliximab treatment group compared with the placebo group (+8 versus −34.1) [58]. However, the 6MWD is considered to be influenced by several factors involving other lung diseases, cardiac diseases, or muscle involvement, which makes it difficult to identify the reasons for a decrease in the 6MWD and monitor therapy response in some cases [59].

The CPET has been considered as a useful tool for assessing exercise tolerance, and it offers added value in detecting impaired PFT in pulmonary sarcoidosis patients [60]. A comparative study found CT findings were correlated with a significant amount of variance in CPET parameters [61]. Compared with the 6MWT, the CPET shows no obvious difference in parameters of HR and SPO2. It could be used as a suitable method in pulmonary sarcoidosis patients, except those with advanced stages [62].

### *3.6. Decision Making and Evaluation of Treatment*

The PFT may influence treatment decisions. Most sarcoidosis patients do not require treatment when they have no obvious symptoms, normal PFT parameters, or a high possibility of remission. A cohort study demonstrated that oral glucocorticoids, disease-modifying antirheumatic agents (DMARDs), or biologic agents were required only in 104/311 of pulmonary sarcoidosis cases [63]. However, an obvious and rapid decline in PFT parameters indicated active granulomatous inflammation and progressive disease that might lead to worse outcomes if left untreated. The statements of ATS/ERS/WASOG suggest that systemic treatment in time is necessary for sarcoidosis cases with obvious symptoms, progressive decline of lung function, and persistent pulmonary infiltrate [2]. FVC is the greatest PFT parameter for treatment decisions for pulmonary sarcoidosis, while DLCO provides useful information when the value is significantly lower in percent predicted. At diagnosis, FVC < 70% and DLCO < 60% portend clinically significant pulmonary sarcoidosis pathology, which warrants treatment [15,64]. During follow-up, development of symptoms or an objective loss of pulmonary function reflects the progression of the disease. Treatments should be considered when FVC significantly decreases by 5% from baseline or DLCO decreases by 10% [17].

Of the PFT parameters, FVC is recommended as a favored objective indicator for evaluating the response to therapy [3]. The commonly approved treatment goal is to improve the predicted FVC percentage by more than 5% [3,18,51]. Table 1 shows the information about FVC improvement after treatment in several clinical studies.

**Table 1.** Forced vital capacity (FVC) as a measure of clinical outcomes in sarcoidosis.

| First Author (Ref.) | Year | Treatment | Duration | Improvement in FVC % Pred | Improvement in FVC (L) |
|---|---|---|---|---|---|
| Anne Pietinalho [65] | 1999 | oral prednisolone + inhaled budesonide | 3 months + 15 months | 11.4% | 0.15 L |
| RM du Bois [66] | 1999 | inhaled fluticasone propionate | 6 months | Not Reported | 0.08 L |
| Anne Pietinalho [67] | 2002 | oral prednisolone + inhaled budesonide | 3 months + 15 months | Not Reported | 0.33 L |
| Robert P Baughman [68] | 2006 | intravenous infusions of infliximab | 24 weeks | 2.5% | Not Reported |
| Adriane D M Vorselaars [36] | 2015 | intravenous infusions of infliximab | 26 weeks | 6.6% | Not Reported |
| Caroline E. Broos [69] | 2018 | oral prednisone | 1 months | 11.8% | Not Reported |
| Caroline E. Broos [70] | 2018 | oral prednisone | 12 months | 9.6% | Not Reported |

Oral glucocorticoids are the first-line therapeutic approach for sarcoidosis patients [2,71]. The therapeutic dose was usually initiated with 0.5–1 mg/kg of prednisone, tapered slowly by 10 mg per 4 weeks, to 5–10 mg/day maintenance. Generally, treatment could be stopped after 6 to 12 months if patients' symptoms and PFT parameters improved, while the period of treatment needed to be extended to 24 months in refractory disease [72]. Randomized controlled trials have showed that glucocorticoid treatment could improve FVC and DLCO in stage II and III sarcoidosis patients compared with those on placebo. However, no benefit was observed in the glucocorticoid treatment of asymptomatic stage I sarcoidosis subjects, and there was evidence to suggest therapy with glucocorticoids could result in a higher possibility of relapse [67,73]. In a meta-analysis of clinical trials of corticosteroid treatment in sarcoidosis patients, a significant difference in FVC of 4.2% and DLCO of 5.7% of predicted values was observed compared with untreated patients [74]. A multicenter, prospective and observational study in the Netherlands demonstrated that the improvement in FVC occurred within one month after prednisone therapy initiation in newly treated sarcoidosis patients, with an improvement in predicted FVC of 11.8% [69]. Similar results were obtained in another study. An increase of 7.4% predicted FVC at 3 months and 9.6% predicted at 12 months were seen after prednisone therapy, and the improvement in FVC mainly occurred in the first 1–3 months of treatment [70].

Methotrexate (MTX) is a preferred second-line medication for sarcoidosis patients [75]. According to the ATS/ERS/WASOG statements, the addition of MTX was suggested to improve pulmonary function or quality of life if glucocorticoids were ineffective or led to unacceptable side effects [71]. Various studies have found that MTX is associated with improved lung function and may help with steroid sparing [76–80]. Lower and Baughman performed a non-randomized clinical study on patients with chronic symptomatic sarcoidosis to determine the efficacy and safety of methotrexate. The authors found that 35 out of 50 patients (70%) showed an improvement in FVC of greater than 10% after at least 2 years of MTX treatment [79]. Azathioprine (AZA) is used as an alternative second-line medication in the treatment of sarcoidosis, but there is no randomized controlled study assessing its efficacy and safety in sarcoidosis. An international retrospective study has been conducted to evaluate MTX and AZA as a second-line treatment. The results showed that both agents had similar effects, with an obvious improvement in the PFT in 70% of patients and steroid-sparing capacity, while patients in the AZA treatment group had a higher infection rate [77]. Mycophenolate mofetil (MMF) may be beneficial for some patients with sarcoidosis, but research results are controversial. In a retrospective study from Switzerland, Brill found that MMF treatment could decrease the maintenance dose of corticosteroids to under 10 mg/day, and improved the lung function, with a median FVC change of +8.5% [81]. However, another retrospective study from the United States

demonstrated there was no statistically significant change in PFT measurements before and after MMF treatment [82].

Biologic agents are considered as the third-line treatment for patients with refractory diseases or those who cannot tolerate glucocorticoids and other immunosuppressants [64,71]. Infliximab is a humanized monoclonal antibody that neutralizes TNF-α, and has the most robust data for the treatment of sarcoidosis. In a randomized controlled study including 138 cases with chronic pulmonary sarcoidosis, intravenous infusions of infliximab were compared with placebo, and it was found that the predicted FVC in the infliximab treatment group increased by 2.5% at 24 weeks, while the placebo group did not improve [68]. Similar results were noted in a prospective study. Patients with refractory FDG-PET-positive pulmonary sarcoidosis had a 6.6% increase in predicted FVC after being given infliximab treatment at 26 weeks [36].

## 4. Conclusions

The PFT is a widely available and useful method for evaluating and managing sarcoidosis. The review of available data suggested the baseline PFT could provide an estimate of disease severity, and a series of PFTs provide valuable information for monitoring disease progression as well as assessing the response to treatment. DLCO < 60% as well as FVC < 70% portends clinically significant pulmonary sarcoidosis pathology, which warrants treatment. During follow-up, a 5% decline in FVC from baseline or a 10% decline in DLCO is considered significant and reflects the disease progression. The improvement in the predicted FVC percentage by more than 5% is considered effective to therapy. In the future, the STS as a key endpoint should be widely used and further optimized in a sarcoidosis clinical study.

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# Establishing a Diagnosis of Pulmonary Sarcoidosis

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**Abstract:** Pulmonary sarcoidosis is the most prevalent manifestation of sarcoidosis and the commonest diagnosis in clinics for ILD. Due to the lack of a simple and reliable test, making the diagnosis is often challenging. There are three criteria that must always be considered: (1) compatible clinical presentation; (2) evidence of granuloma formation (usually non-caseating); and (3) exclusion of alternative causes of granulomatous disease. There are various tools available for diagnosis, amongst which serum biomarkers like sACE and sIL-2R, HRCT, BAL, EBUS/EUS and sometimes bronchoscopic or surgical lung biopsy are most contributive. However, the degree of invasiveness of the applied test and associated risk to the patient must be weighed against management consequences. In specific situations (e.g., presentation as Löfgren's syndrome) or when there is high suspicion based on HRCT in the context of supportive clinical findings, it might be justifiable to decide on a "working diagnosis of sarcoidosis" and to refrain from further invasive procedures for the patient. This should, however, preferably be agreed upon after discussion in an experienced multidisciplinary team and requires close follow-up of the patient. In general, it is advisable to always maintain a healthy dose of skepticism when making the diagnosis of sarcoidosis, especially when the clinical course of disease gives rise to this.

**Keywords:** pulmonary sarcoidosis; diagnosis; working diagnosis; multidisciplinary team discussion

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## 1. Introduction

Pulmonary sarcoidosis is the most common manifestation of sarcoidosis and the most frequent established diagnosis in the group of interstitial lung diseases (ILD). Clinically, suspicion usually arises through finding of intrathoracic lymph node enlargement and/or diffuse nodular lung disease. Although HRCT is the cornerstone for diagnosis, its imaging findings are currently not considered diagnostically sufficient. Sarcoidosis has many lookalikes and currently remains a diagnosis by exclusion. Moreover, so far, no international agreement on the diagnostic approach has been brought about. Furthermore, usability and availability of diagnostic tools vary around the word. All in all, this makes establishing a diagnosis challenging.

## 2. Aim of Article

The aim of the article is to give an overview of the diagnostic criteria, differential diagnosis, clinical presentations, and approach to the diagnosis of sarcoidosis. Secondly, the value of the currently available tools for diagnosis is discussed. Further, the value of multidisciplinary team discussion and the concept of likelihood and working diagnosis are discussed. Finally, the reader is provided with a diagnostic algorithm based on the recent literature and experience of the author, along with future perspectives.

## 3. Definition of Disease

Sarcoidosis is defined as multisystem immune-mediated disease of unknown cause, pathologically characterized by non-caseating granuloma formation in various organs or tissues throughout the body. It commonly affects young and middle-aged adults and

usually presents with bilateral hilar lymphadenopathy and/or pulmonary infiltration but can also manifest with ocular manifestations or skin lesions, and the liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved [1,2].

## 4. Diagnostic Criteria

Three major criteria must be met to make a diagnosis of sarcoidosis: (1) a compatible clinical presentation; (2) findings of non-caseating granulomatous inflammation in one or more tissue samples; and (3) the exclusion of alternative causes of granulomatous disease or diseases capable of producing a similar clinical picture [2]. Recently, a multidisciplinary international panel of experts in sarcoidosis constructed clinically important questions related to diagnostic testing for sarcoidosis and performed systematic review of the evidence [3]. One strong recommendation, thirteen conditional recommendations, and one best-practice statement were formulated, of which the majority relate to screening for extrapulmonary disease in patients with an established diagnosis of sarcoidosis. A summary of the recommendations related to lymph node sampling in patients suspected of pulmonary sarcoidosis is provided in Table 1. Unfortunately, all evidence was of very low quality.

**Table 1.** Summary of current evidence-based recommendations on lymph node biopsy in patients suspected of sarcoidosis and presenting with mediastinal and/or hilar lymphadenopathy.

| Clinical Context | Recommendation | Level of Evidence | Remark Experts |
|---|---|---|---|
| In patients for whom there is a high clinical suspicion for sarcoidosis (e.g., Löfgren's syndrome, lupus pernio, or Heerfordt's syndrome) | Lymph nodes sampling is not suggested (conditional recommendation) | Very low-quality evidence | Patients who do not undergo lymph node sampling require clinical follow-up |
| For patients presenting with asymptomatic, bilateral hilar lymphadenopathy | | | No recommendations for or against obtaining a lymph node sample can be made |
| For patients with suspected sarcoidosis and mediastinal and/or hilar lymphadenopathy for whom it has been determined that tissue sampling is necessary * | Endobronchial ultrasound (EBUS)-guided lymph node sampling, rather than mediastinoscopy, as the initial mediastinal and/or hilar lymph node sampling procedure is suggested (conditional recommendation) | Very low-quality evidence | |

Adapted from Crouser et al. [3]. * Criteria are (1) the desired diagnostic certainty, especially when an alternative diagnosis is reasonably possible; (2) the consideration of possible immunosuppressive treatment; and (3) when there is lack of skin and/or peripheral lymph node findings for a less risky and less invasive method of tissue sampling.

## 5. Challenges in Diagnosis

A number of challenges in accomplishing a diagnosis of sarcoidosis are to be addressed.

First, there is significant heterogeneity in manifestations of the disease, which are often referred to as clinical phenotypes. There are not only various types of pulmonary involvement but also many extrapulmonary manifestations, and on top of that, many combinations of both are possible in sarcoidosis.

The GenPhenReSa (Genotype–Phenotype Relationship in Sarcoidosis) project, a European multicenter study, was designed to map in detail multi-organ involvement in over 2000 European sarcoidosis patients. The study found five distinct clusters according to predominant organ involvement: (1) abdominal organ involvement, (2) ocular–cardiac–cutaneous–central nervous system disease involvement, (3) musculoskeletal–cutaneous involvement, (4) pulmonary and intrathoracic lymph node involvement, and (5) extrapulmonary involvement [4]. Not surprisingly, lung involvement was 100% in cluster 4 (largest, represented 64% of patients) but also high (>90%) in clusters 1–3. Cluster 5 (6% of patients) showed only around 10%

lung involvement. These data not only show the dominance of pulmonary involvement in sarcoidosis but also illustrate well the heterogeneity that challenges daily clinical practice.

Secondly, the defined multisystemic nature of the disease is clinically not always evident. It is well recognized from daily practice in specialized centers that isolated single-organ involvement may occur, especially in cardiac sarcoidosis. Also, other single-organ manifestations with strong suggestion of sarcoidosis may sometimes manifest without clinical evidence of a second organ's involvement, leading to fundamental discussion about whether the diagnosis of sarcoidosis is acceptable [5,6].

Thirdly, the diagnosis of sarcoidosis needs exclusion of other causes of granulomatous disease such as tuberculosis, fungal infections, and organic and inorganic exposure-related ILDs such as hypersensitivity pneumonitis and berylliosis. Also, there are other rare diseases that might need consideration in proper context. Differential diagnosis of sarcoidosis is further discussed elsewhere. It should be noted that the likelihood of certain differential diagnosis of (pulmonary) sarcoidosis will differ around the world.

Finally, the diagnosis of sarcoidosis can never be 100% sure: It is a diagnosis of exclusion, and this cannot be accomplished with complete confidence. The diagnosis requires clinic-radiographic findings compatible with sarcoidosis, histologic or cytological confirmation of granulomatous inflammation, exclusion of known causes of granulomatous disease, and presence of disease in at least two organs or tissues. The end result of the diagnostic evaluation for sarcoidosis is neither a definitive diagnosis nor an exclusion of the diagnosis but rather a confident likelihood of the disease. In this light, a recent BTS clinical statement on pulmonary sarcoidosis raised the issue that decisions made by individual patients to decline bronchoscopy when there is a highly probable but not definite clinical diagnosis should be supported in most cases, with careful subsequent monitoring [7].

**6. Clinical Presentation**

Onset and type of symptoms of pulmonary sarcoidosis can vary largely. Most patients will manifest with gradual onset (symptoms present over months, sometimes years; can be progressive but not necessarily). Symptoms can be respiratory (e.g., ongoing cough or dyspnea on exertion) but also non-respiratory or combinations (e.g., fatigue, which can be the dominant-presenting symptom in pulmonary sarcoidosis). Because the presenting symptoms of sarcoidosis are not specific for the disease, the primary care physician is usually the first health care provider to assess the patient. If a patient with respiratory symptoms does not improve on (empirical) treatment for more common diseases like bronchitis, asthma, or chronic obstructive disease, it is usually through chest imaging, revealing signs of lymph adenopathy and/or diffuse lung disease, that referral to a medical specialist will takes place [8,9]. Also, a probably substantial but not specifiable proportion of sarcoidosis will remain asymptomatic and might only be found by chance, e.g., during medical examination or by self-referral body-screening services. The presenting symptoms of sarcoidosis will be discussed elsewhere in this issue.

Although most patients will manifest with gradual onset, a small subgroup of patients will present with symptoms of acute/subacute onset. These symptoms can be either directly related to sarcoidosis or indirectly, i.e., due to secondary complications. A well-known acute clinical manifestation of pulmonary sarcoidosis is Löfgren's syndrome. Besides acute onset of disease, most commonly with fever, this syndrome is characterized by bilateral hilar lymphadenopathy, erythema nodosum, and/or ankle arthritis or marked periarticular inflammation of the ankles [10]. Another rare subtype of sarcoidosis, usually with acute presentation, is uveoparotid fever, also known as Heerfordt(–Waldenstrom)'s syndrome. This syndrome is charactered by a combination of facial palsy, parotid gland enlargement, and uveitis and is associated with low-grade fever [11]. In the majority of cases, hilar lymph node and/or lung involvement of sarcoidosis are also observed [12].

Occasionally, acute presentations can be caused by complications related to pulmonary sarcoidosis, such as pneumothorax, pneumonia, or pulmonary embolism [13]. These

complications are, however, extremely rare and not regarded a characteristic course and onset of the disease.

## 7. Differential Diagnosis

After presentation of a patient with symptoms and/or signs on imaging that could be compatible with pulmonary sarcoidosis, various other diagnoses need to be considered, especially infectious diseases and malignancy like lymphomas. The differential diagnosis will therefore depend on the level of clinical suspicion and other contextual information (like age, smoking history, family history, travel history, etc.) and will usually become narrowed during the course of the diagnostic process. Other diseases should also be excluded that may give the impression of sarcoidosis but are non-granulomatous, such as lymphomas, other malignancies, and immune-mediated conditions like IgG4-related disease or auto-inflammatory syndromes like VEXAS syndrome, the latter being increasingly recognized as a novel entity [14].

When evidence of granulomatous inflammation is found, the differential diagnosis can be categorized into granulomatous disorders of either infectious or noninfectious origin. Table 2 provides a schema of these diagnoses in relation to the site of thoracic involvement. Infectious granulomas are often associated with necrosis, whereas typical sarcoid granulomas are not; i.e., they are non-caseating. However, it is important to note that presence or absence of necrosis in a biopsy is of relative importance. In a recent large-cohort study, it was shown that both presence or absence of necrosis in a biopsy specimen are possible in sarcoidosis [15].

Differential diagnosis of sarcoidosis requires customization, taking into account not only the individual's clinical history and presentation but also risk factors, and can depend on geographic situation. Of note, due to migration and the increase of human travel activity over the past decades, infectious causes of granulomatous lung disease that used to be tied to certain continents can now also show up elsewhere (e.g., histoplasmosis in the Netherlands) [16,17].

Finally, as the diagnosis of sarcoidosis is never fully secure, it is advisable to always maintain a healthy degree of skepticism that an alternative diagnosis has been overlooked, especially when the clinical course of the disease gives rise to this [18].

**Table 2.** Differential diagnoses of pulmonary sarcoidosis, related to site of thoracic involvement.

| Site of Thoracic Involvement | Infectious Granulomatous Diseases | Non-Infectious Granulomatous Diseases |
|---|---|---|
| Lung parenchyma | Tuberculosis | Hypersensitivity pneumonitis (many causal antigens) |
| | NTM infections | Chemical induced granulomatosis (e.g., beryllium, aluminum, zirconium, silica, and talc) |
| | Histoplasmosis (very rare in Europe) | Drug-induced granulomatosis (e.g., TNF-alpha antagonists, immune checkpoint inhibitors, targeted therapies, and interferons) |
| | Parasitic infections (very rare, e.g., leishmaniosis, paragonimiasis, and schistosomiasis), occurring mainly in endemic countries | Aspiration pneumonia with foreign body granulomatosis |
| | Viral infections (very rare, e.g., varicella zoster and cytomegalovirus), mainly in immunocompromised patients) | Vasculitis, CTD, and inflammatory disease (e.g., GPA, EGPA, NSG, ILD in Sjogren's syndrome, and Crohn's disease) |
| | Other infections (very rare, e.g., Whipple's disease, cryptococcosis, coccidioidomycosis, and mucormycosis), mainly in immunocompromised patients | Immune deficiency granulomatosis (e.g., granulomatous-associated CVID and CGD) |

**Table 2.** *Cont.*

| Site of Thoracic Involvement | Infectious Granulomatous Diseases | Non-Infectious Granulomatous Diseases |
|---|---|---|
| | | Genetic disorders: Blau syndrome |
| | | Malignancy-associated granulomatosis (e.g., cancer and lymphoma) |
| | | Other proliferative disorders (e.g., LCH, ECD, and lymphomatoid granulomatosis) |
| Thoracic lymph nodes | Tuberculosis | Sarcoid-like reaction (especially occurring in linkage to malignancies but also in rare occasions of hypersensitivity pneumonitis and CTD such as Sjogren's syndrome) |
| | NTM infections | Chemical-induced granulomatosis (e.g., beryllium, aluminum, zirconium, silica, and talc) |
| | Histoplasmosis (very rare in Europe) | Drug-induced granulomatosis (e.g., TNF-alpha antagonists, immune checkpoint inhibitors, targeted therapies, and interferons) |
| | Other infections (very rare, e.g., Whipple's disease and fungal infections) | Immune deficiency granulomatosis (e.g., granulomatous-associated CVID and CGD) |
| | | Malignancy-associated granulomatosis (e.g., cancer and lymphoma) |

Definition of abbreviations: CGD, chronic granulomatous disease; CTD, connective tissue disease; CVID, common variable immune deficiency; ECD, Erdheim–Chester disease; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; ILD, interstitial lung disease; LCH, Langerhans cell histiocytosis; NSG, necrotizing sarcoid granulomatosis; NTM, nontuberculous mycobacteria; TNF, tumor necrosis factor. The differential diagnosis should be prioritized on the basis of the individual's clinical history and presentation and can depend on geographic location.

## 8. Tools for Diagnosis

In patients suspected of pulmonary sarcoidosis, various tools are available to secure the diagnosis of sarcoidosis. None of the tests can be regarded as diagnostic proof alone. The extension and the nature of the tests will depend on the degree of ambiguity of the clinical presentation. Usually, a combination of tests lead to sufficient confidence that sarcoidosis may be diagnosed.

The first step is an assessment of epidemiological factors, notably the incidence of sarcoidosis and of alternative diagnoses in the region/country and exposure to risk factors (e.g., infectious, occupational, and environmental agents). Also, exposure to drugs taken for therapeutic or recreational purposes must be addressed. Family history is of importance, as approximately 10% of sarcoidosis patients report familial occurrence [19].

Subsequent investigations usually include (chest-)imaging, serum biomarkers, bronchoscopy with or without bronchoalveolar lavage, endo sonography, and/or pathologic evaluation of biopsy tissue. Each of these tests are discussed below with focus on their diagnostic value. Of note, to support clinicians as to the probability of sarcoidosis, especially in situations where biopsies might not be easy to perform, it might also be helpful to use clinical scores that support the likelihood of sarcoidosis in front of a compatible presentation [20,21].

### *8.1. Chest Imaging*

The discovery of electromagnetic radiation and subsequently that of chest radiography made the early pioneers of sarcoidosis aware that the disease was much more than a skin, eye, and joint disease and that lungs and/or intrathoracic lymph nodes were the prime manifestation of the disease [22].

Based on chest radiography, thoracic sarcoidosis has classically been staged in four groups [23,24]. Stage I involves bilateral hilar lymph node enlargement (BHL); stage II

shows BHL and pulmonary infiltration; in stage III only, pulmonary infiltration is found; and in stage IV, features of fibrosis, often with distortion of macroscopic lung architecture and calcifications, are demonstrated.

Although the staging has some prognostic significance (stage I: high likelihood of spontaneous resolution; stage II: spontaneous resolution possible; stage III: spontaneous resolution in rare cases; stage IV: permanent organ damage), it has many limitations. First, interobserver variability is poor, especially between stages with parenchymal involvement. Second, the stages suggest a relationship between disease severity and/or the order in which sarcoidosis may evolve. However, this is far from true, as a patient with stage I might seem to have mild disease but instead can suffer from severe cardiac involvement. Furthermore, although stage I on a chest radiograph is associated with high probability of resolution of intrathoracic lymphadenopathy after 1–2 years, the disease may nevertheless still evolve to progressive sarcoidosis in a minority of patients. Thus, instead of *stage*, the term radiographic *type* is more appropriate for use here [1].

Currently, HRCT is regarded as the most valuable tool for the diagnosis of pulmonary sarcoidosis. With this technique, characteristic features can be visualized, such as "beading" along fissures (Figure 1) and a peri-lymphatic micronodular pattern that, in combination with symmetrical nodal involvement and supportive clinical findings (see also Table 5 later on in this article), make sarcoidosis very likely [25]. Also, signs of fibrosis and different patterns of fibrosis can be identified more consistently on HRCT than on chest radiograph, including bronchial distortion, linear pattern, and cystic lung disease, which can be accompanied by honeycombing [26]. In addition, HRCT contributes in two other conditions. Firstly, HRCT is essential for establishing a confident diagnosis of progressive fibrosis in advanced pulmonary sarcoidosis, which may occur in approximately 15% of patients with advanced disease [27]. Also, HRCT can be useful for diagnosis of possible complications in pulmonary sarcoidosis, such as aspergilloma and pulmonary hypertension (by measuring pulmonary artery diameter) [28].

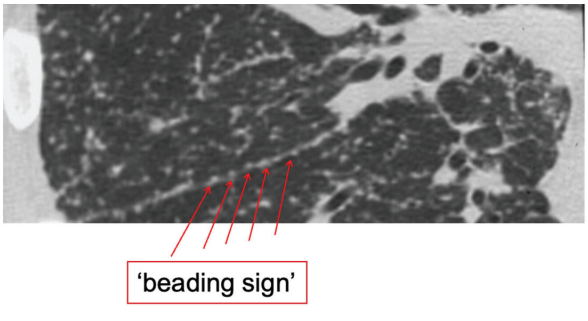


**Figure 1.** "Beading" along a fissure of the right lung in a patient with pulmonary sarcoidosis. Image source: Dr. H.W. van Es (Dept of Radiology, St. Antonius Hospital, Nieuwegein, The Netherlands).

Imaging of pulmonary sarcoidosis is further discussed elsewhere in this issue.

### *8.2. Nuclear Imaging*

Simultaneous uptake of (67)gallium ($^{67}$Ga) in the salivary and lacrimal glands (panda sign) and intrathoracic lymph nodes (lambda sign) has shown to represent distinctive nuclear imaging patterns that are highly specific for sarcoidosis. In the 1990s, the combination of both panda and lambda sign or panda sign in combination with bilateral symmetrical hilar lymphadenopathy on chest X-ray has been suggested to obviate the need for invasive diagnostic procedures [29,30].

Today however, the use of $^{67}$Ga scanning in diagnostic evaluation of sarcoidosis has been outperformed by fluor-18-deoxyglucose (FDG) positron emission tomography (PET) scanning. It has been shown that FDG-PET is more sensitive than $^{67}$Ga imaging in the

assessment of sarcoidosis activity. Furthermore, FDG-PET has demonstrated a very good inter observer agreement in contrast to $^{67}$Ga imaging [31]. Of note, the radiation dose is significantly higher for $^{67}$Ga imaging than for FDG-PET. In $^{67}$Ga imaging, the radiation dose is 18.5 mSv compared to 5.6–7.6 mSv for FDG-PET, depending on the patient's weight [31].

It is not recommended to apply FDG-PET routinely in the diagnostic work-up of sarcoidosis, but in selected cases, it can be useful in identifying sites for biopsy or in differentiating extinguished fibrotic lesions from treatable inflammatory disease.

### *8.3. Serum Biomarkers*

Recent evaluation of the diagnostic value of different serum biomarkers in sarcoidosis has revealed the best performance of serum angiotensin converting enzyme (sACE), soluble IL-2 (sIL-2R) receptor, and chitotriosidase (CTO). These markers stand out as the most useful diagnostic tools, with significant sensitivity and specificity, although none functions alone as a gold-standard biomarker [32]. The same markers also have significant value as monitoring tools after establishing a diagnosis, as change correlates with lung function improvement during methotrexate therapy [33]. A summary of test characteristics is given in Table 3. Of note, ACE diagnostic test performance can be significantly improved by performing genotype correction [34,35]. Further, none of the biomarkers mentioned is currently recommended for differential diagnosis by itself, although it seems plausible that a combination of different biomarkers might further improve sensitivity and specificity and become the standard of care in the future, but this needs further investigation [36].

**Table 3.** Serum biomarkers for diagnosing sarcoidosis.

| Biomarker as a Diagnostic Tool | Sensitivity, % | Specificity, % | First Author [Ref.] |
|---|---|---|---|
| sACE | 20–90.5 | 47–89.9 | Nguyen, Eurelings, Uysal, Csongrádi, Lopes, and Ungprasert |
| sIL-2R | 47–94.4 | 90.4 | Nguyen, Eurelings, Keijsers, Schimmelpennink, and Miyata |
| CTO | 82.5–88.6 | 70–92.8 | Popevic, Enyedi, and Bargagli |

Definition of abbreviations: sACE, serum ACE; sIL-2R, soluble IL-2 receptor; CTO, chitotriosidase. Adapted Table 2 from Korenromp I.H.E., Maier L.A., Jan C. Grutters J.C. Sarcoidosis: Serum and Imaging Biomarkers. In *Sarcoidosis (ERS Monograph)*; Bonella, F., Culver, D.A., Israël-Biet, D., Eds.; European Respiratory Society: Sheffield, UK, 2022; pp. 107–121 (https://doi.org/10.1183/2312508X.10031720), reproduced with permission of the © ERS 2023 [32].

### *8.4. Bronchoscopy*

Bronchoscopy can reveal endobronchial lesions due to the mucosal involvement of sarcoidosis. These lesions are typically referred to as "cobble stone lesions" and reveal a high likelihood of finding granulomas upon biopsy.

Also, in the absence of visual lesions, there is chance of finding granulomas in random biopsies taken from the endobronchial mucosa of patients suspected of pulmonary sarcoidosis [37]. Even when the mucosa appears normal, biopsy of tissue at the first and secondary carinas is still positive in about 20–30% of patients [38].

Bronchoalveolar lavage (BAL) is a useful and safe procedure that is widely applied in the diagnostic evaluation of pulmonary sarcoidosis. Cytologic evaluation of BAL fluid shows lymphocytic alveolitis in 90% of patients and therefore contributes to the likelihood of diagnosis [39]. Also, a CD4/CD8 ratio >3.5 is generally regarded as supportive for the diagnosis [40]. However, no single feature in BAL is diagnostic proof of sarcoidosis. Only in an appropriate clinical setting does a CD4/CD8 ratio >3.5 provide a likely diagnosis of sarcoidosis with a specificity of 94% [2]. Additionally, relatively novel studies show that lower CD103 expression on CD4+ lymphocytes and markers identifying Th17.1 cells might have diagnostic value, but data are limited, and further studies are needed before clinical recommendations can be made [41].

Finally, the last important role of BAL to be mentioned is, of course, narrowing the differential diagnosis, e.g., by excluding (opportunistic) infections.

### 8.5. Endo Sonography

In most centers, endo sonography will by now have replaced mediastinoscopy as the standard procedure for intrathoracic nodal sampling in the diagnosis of pulmonary sarcoidosis. The latest guidelines justify the preference of endobronchial ultrasound (EBUS)-guided lymph node sampling (87% yield) over mediastinoscopy (98% yield) because it is safer for the patient and usually better tolerated [3]. Also, costs are generally lower for procedures such as EBUS that are performed in an endoscopy room compared with an operating room. International recommendations related to lymph node sampling in patients suspected of pulmonary sarcoidosis are given in Table 1.

Recently, EBUS transbronchial needle aspiration (TBNA) has been compared head-to-head with esophageal endoscopic ultrasound (EUS)-B fine-needle aspiration (FNA) for diagnosing sarcoidosis [42]. The results of this randomized clinical trial, including 358 patients from 14 hospitals in 9 countries, showed a similar granuloma detection rate of mediastinal/hilar nodes in patients suspected of pulmonary sarcoidosis (Scadding stage I/II). The granuloma detection rate was 70% for EBUS-TBNA and 68% for EUS-B-FNA. The authors concluded that both diagnostic tests can be safely and universally used in patients suspected of sarcoidosis [42]. However, EBUS has an additional advantage over EUS, as it allows adding transbronchial biopsy when lymphadenopathy is accompanied by the radiographic findings of parenchymal disease or endobronchial biopsy when mucosal abnormalities are noted and/or BAL during endoscopy, which further increase the diagnostic yield [3].

### 8.6. Peripheral Lung Biopsy

There are different techniques to collect tissue from the peripheral lung parenchyma for the diagnosis of sarcoidosis.

A summary of different lung tissue sampling procedures, including diagnostic yield, is given in Table 4. The choice of method will often also depend on the possibilities and experience within a particular center.

**Table 4.** Different tissue sampling procedures and their diagnostic yield for the diagnosis of pulmonary sarcoidosis.

| Method | Diagnostic Yield | Invasiveness | Granuloma | Lymphatic Pattern | Comments |
|---|---|---|---|---|---|
| Conventional transbronchial biopsy | High (up to 70–80%) | Intermediate/high | Yes | Yes | Sarcoid granulomas and lymphatic pattern may be appreciated; serial sections may be very helpful in highlighting granulomas when absent in the first slides |
| Transbronchial cryobiopsy | Very high (up to 100%) | High (10–15% pneumothorax; occasionally hemorrhagic events) | Yes | Yes | Very helpful in case of negative results from more conventional procedures and to avoid open-lung biopsy |
| Surgical lung biopsy | Very high (100%) | Very high (patients should be carefully selected); non-intubated, "awake" biopsy reduces complications | Yes | Yes | Limited to very challenging cases when transbronchial procedures failed to demonstrate granulomas (i.e., chronic form with hyaline sclerosis replacing granulomas and mimicking other ILDs) |

Adapted Table 1 from Rossi G, Farver C. Sarcoidosis: pathological features and differential diagnosis. In *Sarcoidosis (ERS Monograph)*; Bonella, F., Culver, D.A., Israël-Biet, D., Eds.; European Respiratory Society:Sheffield, UK, 2022; pp. 107–121 (https://doi.org/10.1183/2312508X.10031720), reproduced with permission of the © ERS 2023 [37].

Of note, only in very few cases suspected of sarcoidosis will performing surgical lung biopsy for confirmation of the diagnosis be necessary. In such cases, it may be advisable to first weigh the advantages and disadvantages of a surgical lung biopsy in a multidisciplinary discussion, with special attention to the diagnostic added value and therapeutic consequences.

As mentioned above, non-caseating granulomas are the pathological hallmark of sarcoidosis. Typical for sarcoidosis is that the granulomas are well formed, without significant surrounding lymphoid infiltrate. The granulomas are discrete and compact (also called "naked granulomas"). Although this type of granuloma is characteristic for sarcoidosis and sometimes referred to as "sarcoid granuloma", it may also be found in other conditions such as Blau's syndrome, foreign material, drugs, secondary syphilis, common variable immune deficiency, and chronic granulomatous disease [37,43]. Also, sarcoid granulomas typically contain multinucleated giant cells, sometimes containing cytoplasmic inclusions such as asteroid and Hamazaki–Wesenberg and Schaumann bodies [2,44].

The other key feature of sarcoid granulomas is their anatomic distribution. Sarcoid granulomas in the lung are characteristically found along lymphatics, around the bronchovascular bundles, in the interlobular septa, and on the pleural surface. The number of granulomas in each of these locations may vary, but generally, they are more abundant around the bronchovascular bundles. Sarcoid granulomas and/or giant cells may also be found around and sometimes in the wall of pulmonary arteries or veins with a weak-to-absent inflammatory infiltrate and without necrosis of the vessel. The latter pathological finding is, however, not usually clinically associated with pulmonary hypertension or veno-occlusive disease [37].

As finding necrosis in relation to granulomas should always raise high suspicion of an infectious granulomatous disease, the presence of some necrosis in the granulomas of patients with confirmed sarcoidosis has been described in up to 20% of biopsies [15]. Necrotic foci generally consist of small foci of fibrinoid ("rheumatoid-like") necrosis punctuating occasional granulomas, whereas larger areas of fibrinoid, infarct, or suppurative ("GPA-like") necrosis may be rarely seen [45]. When necrosis is particularly prominent, entity-necrotizing sarcoid granulomatosis may be considered. In general, however, the presence of necrosis in granulomas should always raise the possibility of infection, and a diagnosis of necrotizing sarcoid granulomatosis, which is probably an unusual variant of sarcoidosis, should not even be considered until an infection has been unconditionally excluded.

### *8.7. Pulmonary Function Testing*

Pulmonary function testing is also central to the evaluation of patients suspected of sarcoidosis but in whom results are not contributing to diagnosis, although they reveal important information on the severity and/or progression of disease and can determine decisions on invasive diagnostic procedures, as mentioned above. Typically, in pulmonary sarcoidosis, all kinds of abnormal ventilatory patterns are possible, including mixed ventilatory defects, which have recently been reported to occur in approximately 10% of patients [46]. Also, it is important to note that pulmonary functions tests may not reflect disease activity or symptom burden. Pulmonary function in sarcoidosis is further discussed elsewhere in this issue.

## 9. Diagnostic Approach

An algorithm for the diagnostic approach in pulmonary sarcoidosis is given in Figure 2. It consists of a multistep process that usually starts with the clinical suspicion based on chest imaging. In some cases, the disease can be diagnosed clinically, without performing a tissue biopsy (left side of the figure), especially when there is no need for systemic treatment. Otherwise, cytologic or histologic evidence of granulomatous inflammation and exclusion of alternative causes are required for a confident diagnosis, ideally after multidisciplinary team discussion. In both cases, compliance to the diagnostic criterium on the exclusion of

alternative causes of granulomatous disease such as tuberculosis or fungal infection and using the appropriate methods are of utmost importance.

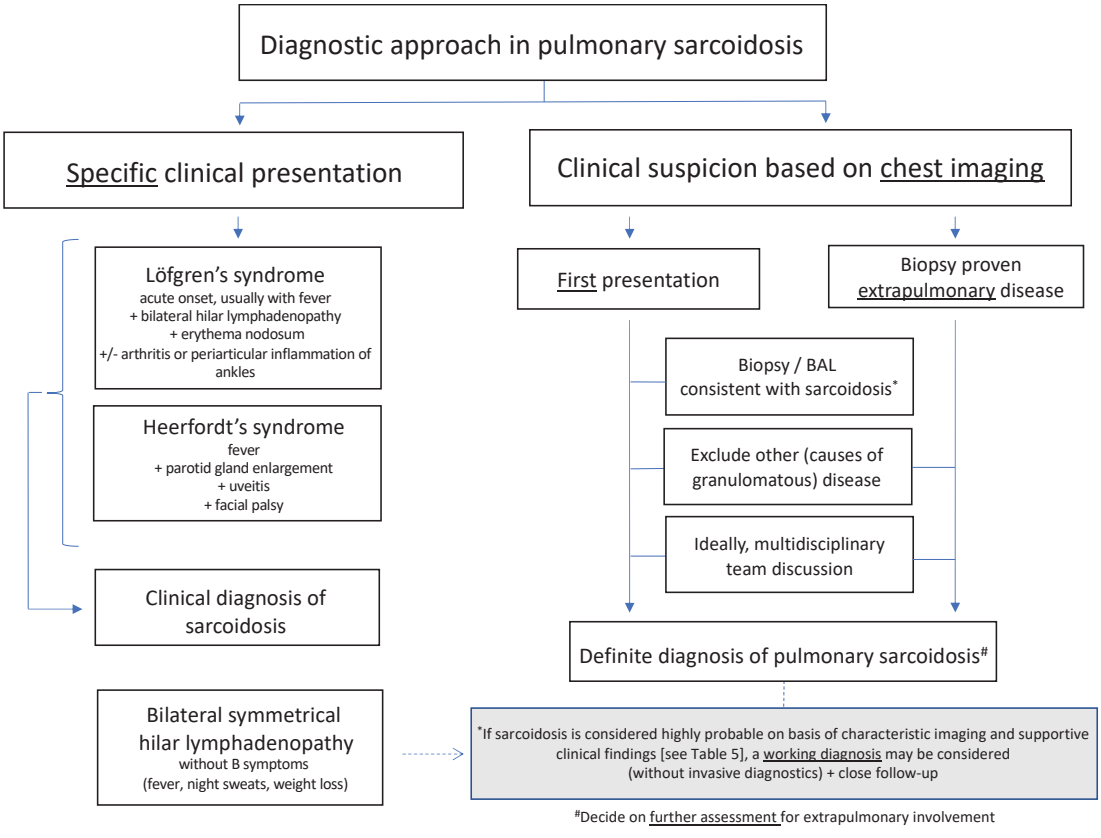


**Figure 2.** Algorithm for the diagnostic approach in pulmonary sarcoidosis.

In case sarcoidosis is regarded highly probable on the basis of collected clinical data, including supportive findings such as elevated serum ACE and/or sIL2R and others (Table 5), it is not uncommon, especially in centers with expertise in sarcoidosis, to decide on a "working diagnosis of sarcoidosis" and to refrain from further invasive diagnostic procedures for the patient, especially when patients are not threatened by organ failure or organ damage due to sarcoidosis and when indication to start immunosuppressive therapy is absent at that time, or the patient is frail. A working diagnosis should preferably be agreed upon after discussion in MDT [7].

The ultimate goal of the diagnostic process is to rule out all diagnoses other than sarcoidosis that are consistent with the clinical situation. In some patients, a definite diagnosis may require the continuous gathering of information during follow-up. After diagnosis, a healthy degree of skepticism remains indispensable, especially in the case of an unexpected course of disease during follow-up. In that situation, additional investigations might be needed with reconsideration of the diagnosis.

**Table 5.** Supportive and not-supportive clinical findings for likelihood of pulmonary sarcoidosis.

| Clinical Data | Supportive | Not Supportive |
|---|---|---|
| Demographics | African American | Age < 18 years; >80 years |
| | Northern European | |
| Medical history | Family history of sarcoidosis | |
| | Non-smoker | |
| | History of unexplained fatigue and/or pain | |
| | Symptoms involving two or more organs | |
| | Specific combinations, e.g., lung and eyes; lung and skin | |
| | History of kidney stones | |
| Extrapulmonary disease potentially related to sarcoidosis | Uveitis, erythema nodosum (small fiber), neuropathy, etc. | |
| Disease course | | Rapid progressive (diffuse) lung disease (days to few week) +/− respiratory failure |
| Laboratory results | Increased serum sACE | |
| | Increased sIL-2R | |
| | Increased CTO | |
| | Lymphopenia | |
| | Increased serum calcium | |
| | Hypercalciuria | |
| | Decreased 25-hydroxyvitamin D/increased 1,25-hydroxyvitamin D | |
| BAL findings | Lymphocytosis | |
| | Increased CD4+/CD8+ ratio | |
| | Decreased CD103+CD4+/CD4+ ratio | |

Definition of abbreviations: sACE, serum ACE; sIL-2R, soluble IL-2 receptor; CTO, chitotriosidase; BAL, bronchoalveolar lavage.

## 10. Multidisciplinary Team

As sarcoidosis is defined as multisystem disease, it would be plausible to involve clinicians of other disciplines than pulmonology in the diagnostic process. The value of multidisciplinary team (MDT) discussion has already been scientifically illustrated and evaluated in ILD [47] and subsequently implemented particularly in the diagnostic guidelines of idiopathic pulmonary fibrosis [48–50]. In addition, MDT discussion in diagnosis of connective tissue disease–ILD (CTD-ILD) has been recommended [51]. However, until now, the literature is still lacking in recommendations for the particular case of sarcoidosis.

Nevertheless, many clinicians working in the field of sarcoidosis find an MDT discussion to be of added value, providing a momentum for intra- and interdisciplinary-supported diagnosis or generating new diagnostic considerations. Additionally, MDT discussion may next contribute to peer support for complex treatment decisions, which is especially important in the absence of guidelines with high-quality evidence recommendations. The implementation of MDT discussion in care pathways for sarcoidosis is therefore an important criterium for the evaluation of patient-centered care for sarcoidosis in expert centers across Europe (https://health.ec.europa.eu/european-reference-networks/overview/evaluation-european-reference-networks_en, accessed on 17 September 2023).

In the author's ILD center of excellence, all patients that are referred with (suspicion of) sarcoidosis receive a standard work-up for diagnosis according to the local care path-

way for sarcoidosis, including MDT discussion, depending on the type of major organ involvement (Figure 3).

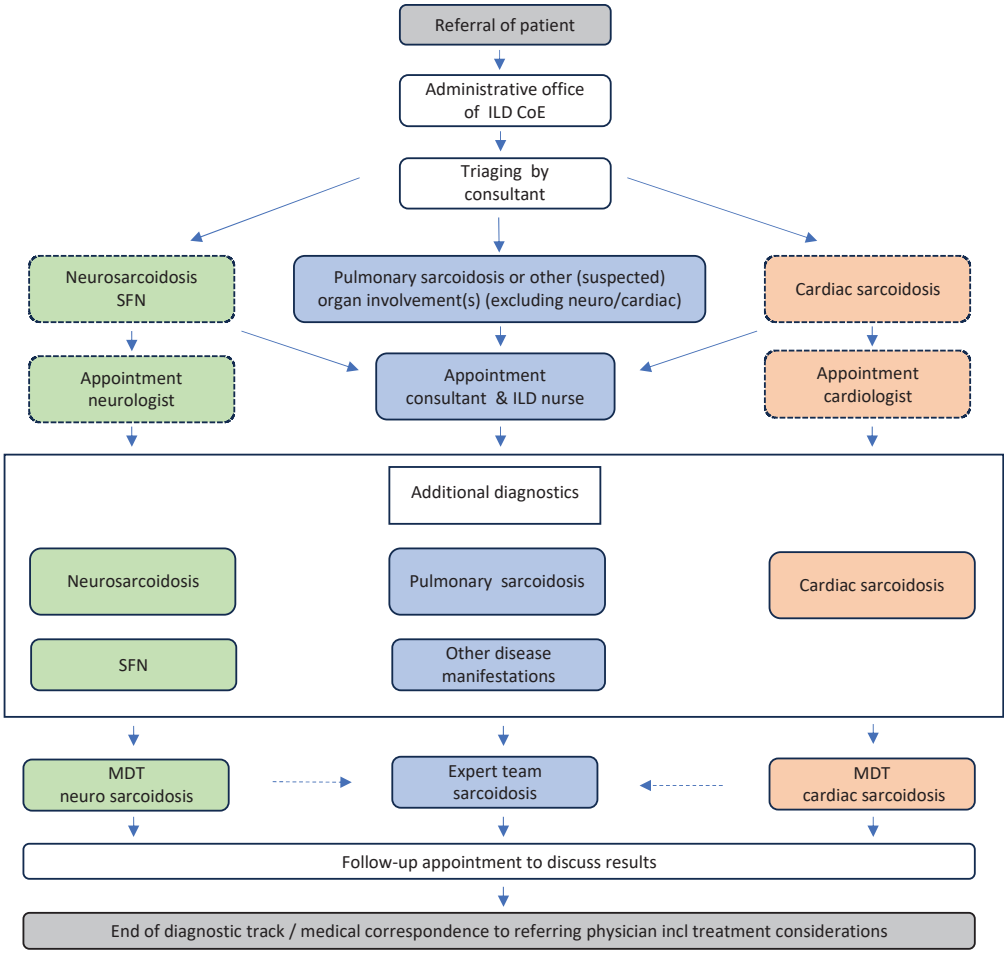


**Figure 3.** Module of the care pathway for sarcoidosis showing the diagnostic track of (suspected) patient referred to St. Antonius ILD and Sarcoidosis Center of Excellence Nieuwegein, The Netherlands. Definition of abbreviations: CoE, center of excellence; ILD, interstitial lung diseases; MDT, multidisciplinary team; SFN, small fiber neuropathy.

Nonetheless, in general, not all patients have the opportunity to consult a center specialized in ILD. It is, however, the author's experience that offering MDT conferences (either virtual or as a review service) for external patients can play a valuable role in the diagnostic decision and care of these patients. In this way, centers of excellence facilitate greater and more rapid access to sarcoidosis expertise.

## 11. Perspective

With ongoing advances in biomolecular technology and the development of artificial intelligence, it is likely that novel diagnostic tools will appear. With no doubt, these will change the methods of diagnosing sarcoidosis in the near future.

Interesting new developments in the field of chest imaging have recently been published. Photon-counting CT (ultra-HRCT) has been shown to improve image quality for

visualization of certain ILD features, such as traction bronchiolectasis and micro-nodules. This technical advance not only results in lower radiation exposure but may also enhance the diagnosis and prognosis of pulmonary sarcoidosis and ILD in the near future [52].

An intriguing example of the potential of omics in establishing a diagnosis of sarcoidosis was recently found in the eNose study (SpiroNose) [53]. Based on analysis of exhaled breath patterns, the eNose technology significantly differentiated sarcoidosis patients from healthy controls as well as from patients with hypersensitivity pneumonitis. Further research is warranted to understand and prove the value of this non-invasive novel technology.

Finally, also research of new and especially combinations of biomarkers is regarded as a promising direction in the field of diagnosis and management of sarcoidosis and might lead to an improved standard of care in the future [36].

## 12. Concluding Remarks

The diagnosis of pulmonary sarcoidosis requires sufficient knowledge and experience with the disease, a sharp clinical eye, and a healthy dose of suspicion. Unfortunately, until now, no single, simple diagnostic test has been available. A systematic and multidisciplinary approach, preferably implemented in a local care pathway for sarcoidosis and including MDT discussion, currently provides the best guarantee for establishing the right diagnosis. In this context, based on ATS and BTS recommendations, increased specificity of CT features, and/or cases of acute presentation with specific symptoms, it might also be justifiable to refrain from further invasive procedures and follow-up for the patient.

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# Treatment of Granulomatous Inflammation in Pulmonary Sarcoidosis

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**Abstract:** The management of pulmonary sarcoidosis is a complex interplay of disease characteristics, the impact of medications, and patient preferences. Foremost, it is important to weigh the risk of anti-granulomatous treatment with the benefits of lung preservation and improvement in quality of life. Because of its high spontaneous resolution rate, pulmonary sarcoidosis should only be treated in cases of significant symptoms due to granulomatous inflammation, lung function decline, or substantial inflammation on imaging that can lead to irreversible fibrosis. The longstanding basis of treatment has historically been corticosteroid therapy for the control of granulomatous inflammation. However, several corticosteroid-sparing options have increasing evidence for use in refractory disease, inability to taper steroids to an acceptable dose, or in those with toxicity to corticosteroids. Treatment of sarcoidosis should be individualized for each patient due to the heterogeneity of the clinical course, comorbid conditions, response to therapy, and tolerance of medication side effects.

**Keywords:** granuloma; treatment; immunosuppression; corticosteroids; sarcoidosis

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## 1. Introduction

Sarcoidosis is a multi-system disease of granulomatous inflammation that affects the lungs in the vast majority of those afflicted. Spontaneous resolution occurs in over half of patients, but the rest can develop chronic symptoms, progressive organ dysfunction, or a waxing and waning course. Treatment of inflammation is the basis of therapy; however, management decisions are often complex due to the variability of clinical course, differing patient responses to therapies, and uncertainty regarding the dose and duration of medications. In the current concept of sarcoidosis management, treatment is suppressive rather than curative. Herein, the mechanisms of anti-granulomatous therapy for sarcoidosis, practical clinical applications, and future directions of sarcoidosis management are reviewed.

## 2. Pathophysiology

The hallmark of sarcoidosis is the formation of nonnecrotizing granulomas. The amplified immune response is presumably due to an environmental antigen in a genetically predisposed individual. The concept of an inciting exposure is supported epidemiologically by the association of a higher incidence of sarcoidosis with occupational (e.g., firefighters, agricultural jobs, and Navy personnel) and environmental exposures (e.g., insecticides and mold/mildew exposures), as well as case cluster events such as the World Trade Center collapse [1–3]. Familial clusters of sarcoidosis, the identification of gene variants associated with disease development, and differences in prevalence rates globally suggest a genetic component [4,5]. Genome-wide association (GWA) scans of both familial and sporadic sarcoidosis incident cases have identified numerous chromosomal regions, particularly in the major histocompatibility complex (MHC) locus, contributing to sarcoidosis risk; however, no single gene has been identified as a main contributor [6]. Gene-environment interactions influencing phenotype have further been noted, such as the DRB1*11:01 gene

interaction with mold and musty odors in the development of pulmonary sarcoidosis [7]. Ideally, definitive treatment of sarcoidosis would involve the removal of the antigen to cease the inflammatory response and cure the disease. However, it is possible that the antigen will remain unknown or differ for each specific case. Until the antigens are identified, current treatment strategies target the steps of the cascade that initiates and perpetuates granulomatous inflammation.

The granuloma of sarcoidosis is a tightly formed conglomeration of macrophages and multinucleated giant cells, surrounded by a well-formed ring of CD4+ T cells interspersed with CD8+ T cells and an occasional B-cell [8]. The initiation of the immune response is thought to be due to the presentation of the antigen via the MHC complex, which triggers the production of numerous cytokines and chemokines, which then attract cells of the adaptive immune response. Dendritic cells likely play an important role in the presentation of antigen and continued immune response, although there are few studies establishing the exact role of these cells [9]. The abundance of current data indicates that sarcoidosis is a highly polarized Th1 response with a predominance of CD4+ lymphocytes and fewer CD8+ lymphocytes producing interferon-gamma [10]. Activated lymphocytes, macrophages, and mononuclear cells then migrate to the site of granulomatous inflammation in a process driven by the amplification of oligoclonal T-cells, forming granulomas (Figure 1). The cells within the granulomas in the lungs appear to be the result of both in situ proliferation and redistribution of cells from peripheral blood. Importantly, the cells involved in this immune response, as well as many of the upregulated cytokines, are targeted by current therapies with the goal of breaking the immunologic cycle of activation. Dysfunction of regulatory T-cells ("T regs") and immune 'exhaustion' with failure to clear an antigenic agent may also play a role in the lack of immune resolution, which has opened discussion regarding alternative future medication targets [11].

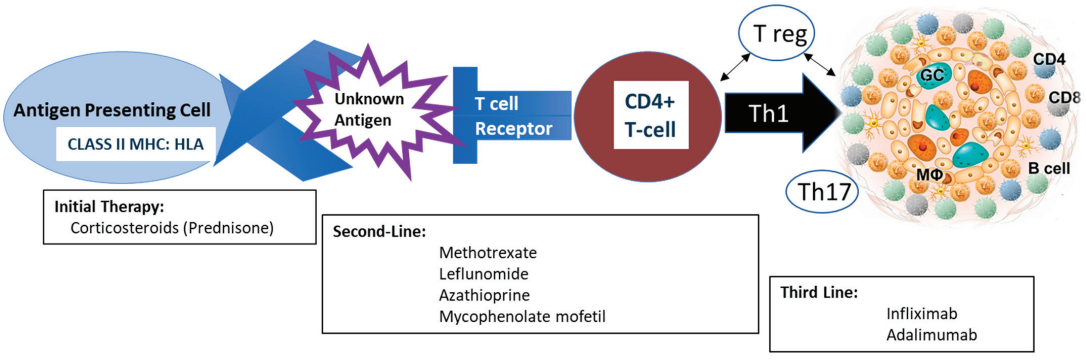


**Figure 1.** Pathophysiology of granulomatous inflammation in sarcoidosis and medications utilized in treatment. The granuloma of sarcoidosis is a tightly formed conglomeration of macrophages (Mθ) and multinucleated giant cells (GC), surrounded by a well-formed ring of CD4+ T cells interspersed with CD8+ T cells and rare B cells. Initiation of the immune response is thought to be due to the presentation of an unknown antigen that triggers the production of numerous cytokines and chemokines, which then attract cells of the adaptive immune response, resulting in a highly polarized Th1 response. Activated lymphocytes, macrophages, and mononuclear cells then migrate to the lung, forming granulomas. Both regulatory T cells and TH17 responses are also involved, although less well-delineated than the Th1 response.

### 3. When to Treat

Because over half of patients will spontaneously resolve, treatment is not indicated for patients with asymptomatic disease. For example, in patients with pulmonary sarcoidosis, mediastinal and hilar lymphadenopathy is rarely symptomatic and is not usually an indication to treat. In many cases, a period of close monitoring is warranted prior to

the initiation of therapy to determine the disease course. In the setting of progressive disease, which is determined by lung function decline, significant symptoms, or worsening radiographic findings, treatment is indicated to preserve lung function and improve quality of life [12]. Patients with mild symptoms may be monitored unless radiographic findings suggest imminent danger of organ dysfunction (e.g., computed tomography (CT) findings of moderate to severe parenchymal lung disease). More prominent symptoms often include dyspnea, cough, fatigue, and atypical chest pain. Objective and subjective assessments may not always correlate, making patient-centered discussions regarding risks and benefits important prior to the initiation of anti-inflammatory therapy. Similarly, even concurrent objective measurements such as pulmonary function and the severity of CT chest imaging may not correlate, complicating disease assessment [13]. Thus, the decision to treat is rarely straight-forward. Ultimately, the goals of anti-inflammatory treatment are two-fold: 1. To alleviate debilitating symptoms that impair quality of life; and 2. To preserve organ function and prevent fibrosis by decreasing repetitive inflammation, tissue injury, and aberrant healing. The benefits of treatment must outweigh the likely toxicity of medications.

## 4. Medications Targeting Granulomatous Inflammation

*Corticosteroids:* Corticosteroids have long been the basis of first-line treatment for sarcoidosis, as they are very effective at immune suppression [14,15]. Corticosteroids act to repress many genes responsible for the cytokine cascade that perpetuates the Th1 inflammatory response, including those responsible for the production of interleukin (IL)-1 and TNF-α [16]. In cases of progressive lung dysfunction and significant symptoms, corticosteroids have been shown to improve biomarkers, symptoms, chest X-ray scores, and spirometry in the short term (up to two years) [17]. Data beyond that are lacking, particularly regarding mortality benefits or modifications of the natural history. The exact immunosuppressive treatment regimen to prevent fibrosis is unknown, and initial treatment considerations are similar for non-fibrotic sarcoidosis and for fibrotic pulmonary sarcoidosis with concurrent inflammation. Establishing long-term efficacy is difficult as corticosteroid therapy is the standard of care, and withholding treatment or the use of placebo in cases of organ damage is deemed unethical by most treating physicians. Whether a stepwise approach to medications or more aggressive initial therapy is superior warrants further study.

Prednisone is the most commonly used corticosteroid for the treatment of sarcoidosis. Prednisone is metabolized rapidly in the body to prednisolone, which is responsible for the anti-inflammatory effects. Patients with severe liver disease may have impaired this process, affecting drug efficacy. The initial recommended dose for pulmonary sarcoidosis is 20 to 40 mg per day, with the goal of tapering down to the lowest dose that provides the maximum benefit and minimizes the side effects [12]. Prednisone is readily bioavailable for most patients and rapidly absorbed, although because of the metabolism via the cytochrome P450 3A4 pathway, drug interactions should be considered in the dosing decision. Varying tapering schedules have been proposed, but there are no standardized guides. Exact dosing regimens differ, in part, due to the variability in severity and clinical course for each individual patient.

For pulmonary sarcoidosis and most other manifestations, the estimated dose of 20 to 40 mg is a reasonable dosing range for efficacy. A Delphi study of treating physicians showed consensus among experts that doses above 40 mg provide no additional benefit [18]. Similarly, a study on the treatment of cardiac sarcoidosis in Japanese patients showed those who were treated with higher doses of corticosteroids (greater than 40 mg per day) compared to lower doses (less than 30 mg per day) had higher morbidity and mortality, with no additional clinical benefit [19]. In a longer-term follow-up study of patients with pulmonary sarcoidosis, the initial starting dose of prednisone was not associated with greater improvement in lung function, although the side effect of weight gain was significant in those starting at higher doses [20]. It is important to note, however, that higher initiating doses may be necessary in cases of severe extrapulmonary involvement with life-threatening or organ-threatening manifestations such as neurologic demise or blindness.

The tapering of corticosteroids can be individualized based on response. In pulmonary sarcoidosis, the lung function improvement is seen within the first month of treatment and maximized by three months, arguing for early re-evaluation after treatment initiation [21]. A few proposed tapering regimens have been published, but there are no head-to-head studies. Conceptually, corticosteroid dosing includes a higher-dose initiation phase, decreasing the dose to a tolerable maintenance dosage of 7.5 mg to 15 mg per day, then tapering off therapy. A Delphi consensus suggests that sarcoidosis experts generally agree that maintenance doses above 10 mg per day are not acceptable [18]. Treatment duration averages around one year, although a large British series reported long-term success after five years (as determined by improved lung function) with an eighteen-month tapering regimen [22], whereas others have proposed shorter durations of even six months in some patients with favorable clinical courses [23].

Unfortunately, despite the efficacy of corticosteroids for immunosuppression, long-term use has significant toxicity that is dose- and duration-dependent and may even affect outcomes adversely. A large meta-analysis of mortality in sarcoidosis showed that patients treated in referral centers were seven times more likely to receive corticosteroids and had a higher mortality rate (4.8%) compared to those from population-based centers (0.5%), which could not be accounted for by stage of disease or ethnicity [24]. Higher cumulative doses are associated with poor quality of life and increased emergency room visits in patients with sarcoidosis [25]. Even cumulative low doses or periodic dosing have been shown to have adverse effects for many chronic inflammatory diseases [26,27]. For the duration often needed to treat sarcoidosis, clinicians must be aware of side effects that can complicate management (Table 1). Furthermore, many of the side effects of prednisone, or symptoms due to the withdrawal of prednisone, can mimic nonspecific symptoms of sarcoidosis, such as weakness, fatigue, and dyspnea, confounding management decisions. For these reasons, clinicians often consider corticosteroid-sparing options to alleviate the burden of disease.

**Table 1.** Management of common side effects and toxicity of corticosteroid use in sarcoidosis.

| Corticosteroid Toxicity | Clinical Considerations |
|---|---|
| Suppression of the hypothalamic-pituitary-adrenal axis | • Close attention to the tapering of corticosteroids.<br>• Differentiation of withdrawal symptoms versus sarcoidosis. |
| Increased susceptibility to infection | • Evaluation of new cough, sputum, and dyspnea to differentiate from sarcoidosis.<br>• Administer vaccines prior to immunosuppression.<br>• At high doses, *Pneumocystis jirovecci* prophylaxis. |
| Weight gain | • Counseling on appetite side effects, dietary management, and exercise program. |
| Ocular complications: cataracts, glaucoma | • Routine eye exams. |
| Impaired bone density | • Consider concurrent bisphosphonates, bone density scans, and exercise. |
| Steroid-induced myopathy | • Consider continued tapering of the dose and an exercise program. |
| Dermatologic effects: skin thinning, bruising, acne, Cushingoid features | • Consider a dermatology referral.<br>• Wean corticosteroids to the lowest possible dose. |
| Fluid retention | • Caution in heart failure.<br>• May need the diuretic dose adjusted. |
| Hypertension | • Blood pressure monitoring. |
| Gastric irritation and ulcer disease | • Consider concurrent acid-suppression therapy. |
| Hyperglycemia | • Caution in diabetes: monitor blood glucose closely. |
| Insomnia, Dysthymia, and Psychosis | • Counsel the patient about potential psychiatric and neurologic effects. |

Of note, inhaled corticosteroids are occasionally used in the treatment of pulmonary sarcoidosis, despite the lack of positive randomized controlled trials (RCTs) [28]. Inflammation frequently affects the airways of patients with sarcoidosis, and inhaled methods have few side effects with theoretical benefit, making them an attractive option for clinicians. Older pilot studies suggested a benefit [29–31], but most subsequent RCTs failed to show objective effects, although many of these patients were concurrently treated with oral therapy [32,33]. One study from the Dutch Study Group on Pulmonary Sarcoidosis did find an improvement in symptoms (cough) and inspiratory vital capacity, but no change in serum ACE, diffusing capacity, or chest imaging [34]. Future studies are needed to delineate the anti-inflammatory effect of inhaled therapy and the exact type of patient who may benefit.

*Corticosteroid-Sparing Medications*: The long-term use of corticosteroids is still the standard treatment for sarcoidosis. This contrasts with the treatment of other autoinflammatory and autoimmune diseases, including rheumatoid arthritis and inflammatory bowel disease, where the early use of a steroid-sparing agent is well established. This may be due to the paucity of clinical trials with these agents in sarcoidosis. A systematic review from 2010 summarized immunosuppressive and cytotoxic therapy for pulmonary sarcoidosis and concluded that the current body of evidence supporting the use of cytotoxic therapies is limited [35]. However, increasing data from the last decade supports the role of corticosteroid-sparing agents in many cases of chronic or progressive sarcoidosis. Certain older medications, such as cyclosporine, chloroquine, and cyclophosphamide, have fallen out of favor due to their severe side effects and are not currently recommended for sarcoidosis in general. Some therapies are more organ-specific, such as hydroxychloroquine. It is useful for skin involvement or hypercalcemia, but it does not seem to be as effective for lung involvement. On the other hand, there are efficacious and well-tolerated drugs that are employed in the treatment of pulmonary sarcoidosis to minimize the toxicity of long-term corticosteroid use. Additionally, it can be argued that, in cases with poor prognostic factors or severe organ risk, aggressive treatment and early control of inflammation may be of value in improving outcomes [36].

The timing of second-line agents is debatable and can be affected by several factors, including comorbid conditions, cost, patient preference, tolerance of side effects, and the characteristics of the inflammatory response itself. Generally, indications for a steroid-sparing agent include refractory disease, inability to taper corticosteroids, or intolerance/toxicity to corticosteroid therapy [15]. Interestingly, corticosteroid resistance in patients with sarcoidosis has been associated with exaggerated TNF-α release by alveolar macrophages, arguing for the potential use of alternative therapies (such as a TNF antagonist) to augment response and decrease steroid dose [37]. As noted above, most clinicians feel that corticosteroids above 10 mg per day for any phenotype would be an acceptable reason to initiate a second-line agent [18]. Given the long half-lives of many of the corticosteroid-sparing options, tapering corticosteroids is reasonable 1 to 2 months after the initiation of the second-line agent. In ideal situations, corticosteroids can be tapered off completely and replaced; however, in some cases, dual therapy is necessary for the best effect. Future studies are warranted to determine the efficacy of up-front monotherapy with a corticosteroid-sparing medication, combination therapy with corticosteroids, and as a replacement agent, as is often seen in other diseases such as rheumatoid arthritis or inflammatory bowel disease [38,39].

Methotrexate is the most recommended corticosteroid-sparing medication, supported by studies showing improvement in forced vital capacity and symptoms when used as a steroid-sparing agent [15,40,41]. Methotrexate is an anti-metabolite with a myriad of actions upon the immune response via folate antagonism and through adenosine pathways that suppress inflammatory cytokine production by monocytes and macrophages [42]. Its efficacy is not universal (55–80%), however, and may depend on pharmacogenetic profiles or dose-limiting side effects [42,43]. Generally, dosing ranges from 7.5 mg to 15 mg per week, depending on age, weight, and renal function, but higher doses, such as 20 to 25 mg per week, can be used at times if there is an inadequate response [40]. It can take up to six

months for full efficacy. Methotrexate is usually started at a low dose and increased every 2 to 4 weeks to the goal dose. It can be used subcutaneously in the same doses in patients with gastrointestinal side effects or concern for absorption. Folic acid is used in conjunction with methotrexate to reduce toxicity from gastrointestinal distress, transaminitis, and mouth ulcerations to help maintain compliance [44]. Regular testing of liver function, blood counts (to assess for neutropenia), and renal function should be carried out while on methotrexate. Rare cases of pulmonary toxicity can occur and should be considered with an unexplained worsening of lung infiltrates and symptoms. Methotrexate is being studied as a first-line agent compared with prednisone in an ongoing clinical study [45].

Azathioprine, an inhibitor of purine and protein synthesis in lymphocytes, likely has equal efficacy to methotrexate as a second-line agent in terms of lung function improvement and the ability to taper steroids [46–48]. However, in a large retrospective cohort, a potential for increased risk of infection was seen in patients treated with azathioprine as compared to methotrexate [46]. The ideal dose for sarcoidosis is not known but is usually started at 50 mg per day and titrated up to effect in a 1 to 2 mg/kg/day dosing range, with a maximum dosage of 200 mg/day. Complete blood counts and liver function are monitored regularly.

Leflunomide, another anti-metabolite that inhibits dividing lymphocytes and promotes the T-reg response, has shown efficacy in case series. It can be used as an alternative to, or in combination with, methotrexate [49,50]. In one larger series of 76 patients with progressive sarcoidosis or those who failed other second-line agents, effects were seen in forced vital capacity and in extrapulmonary disease [49]. Leflunomide has the same monitoring requirements as methotrexate due to similar side effects, including liver toxicity, GI distress, pulmonary toxicity, and peripheral neuropathy. Dosing is 20 mg/day, although 10 mg/day doses can be trialed during initiation if tolerance is a concern. If toxicity is of immediate concern, cholestyramine can be used to bind and remove the drug from the body more rapidly.

Mycophenolate mofetil, converted to mycophenolic acid upon ingestion, is another useful second-line agent that has been shown to be of benefit in several case series, mostly via its steroid-sparing effect [51,52]. Lung function improvement was not as obvious, although a greater effect was seen in patients who were intolerant rather than refractory to other therapies [51]. Mycophenolate mofetil inhibits purine nucleotide synthesis in lymphocytes, disrupts proliferation, and decreases the production of autoantibodies by B cells. Notably, mycophenolate tends to have a better tolerability profile than most other options for second-line treatment, but monitoring for leukopenia is still advised. Dosing ranges from 500 mg twice daily to 1500 mg twice daily, and an enterically coated option is available for patients with gastrointestinal side effects.

Third-line therapies are used in cases where patients are refractory to second-line agents or intolerant of all options. In one large referral center, 15% of patients received at least one third-line agent [53]. Third-line agents include the TNF antagonists infliximab and adalimumab. Infliximab, a chimeric monoclonal antibody given by intravenous (IV) infusion, have the strongest data supporting its use in pulmonary sarcoidosis [54–57]. Because of the large role that TNF-α plays in the proliferation of granulomatous inflammation, impeding the action of the cytokine would suggest a beneficial effect in the treatment of sarcoidosis. A double-blind RCT in 138 patients with chronic pulmonary sarcoidosis showed that treatment with infliximab increased FVC by 2.5%, whereas the placebo group did not improve lung function [54]. Further analysis showed benefits in surrogate measures such as measured serum cytokines and reticular opacities on chest X-rays. Although the improvement in lung function was statistically significant, its clinical impact was debated. However, increasing data from large case series supports its beneficial use in pulmonary sarcoidosis, particularly the imaging findings in pulmonary disease [56]. Dosing of infliximab is 5 mg/kg IV at weeks 0, 2 and every 4–8 weeks thereafter [58]. Low-dose corticosteroids or methotrexate are often co-administered to prevent antibody formation, albeit with an undetermined increased long-term risk of malignancy when combination therapy is used [59]. Adalimumab is a fully human monoclonal antibody to TNF-α. Its effect has particularly

been noted in extrapulmonary disease (e.g., skin and ocular involvement), but small case series show effects in pulmonary disease and in those who have developed intolerance to infliximab [60–65]. The effects seen in current trials of anti-TNF therapy may be muted by the fact that most enrolled patients have been refractory to other agents. Adalimumab is a subcutaneous administration of 40 mg every two weeks, but the dose can vary depending on response. Interestingly, anti-TNF therapy can cause a sarcoid-like reaction, which can complicate management in rare cases [66]. Current limited data suggest similar efficacy with biosimilars for the TNF antagonists (with possible cost benefits), but further evaluation is necessary as clinical data for these drugs accumulates [67,68]. In the long term, the most common reasons for drug discontinuation for infliximab and adalimumab include allergic reactions, infections, insurance denial, and loss/lack of efficacy [53]. In less than 10% of patients, the drug is discontinued because remission is achieved [53].

Of note, pentoxifylline is an older oral medication that inhibits the production of TNF-$\alpha$ from macrophages. It is not commonly used, but some limited data suggests that it may have a mild steroid-sparing effect when used in conjunction with corticosteroids [69,70]. Etanercept, a TNF receptor antagonist, was shown to be ineffective for sarcoidosis, as were other biologics such as golimumab (anti-TNF) and ustekinumab (an antibody to IL-21/IL-23) [71,72].

*Other Therapies with Limited Data*: As insights into the pathophysiology of granulomatous inflammation emerge, both new and re-purposed drugs are being evaluated for use in pulmonary sarcoidosis. B-cells are known to be present in the periphery of the granuloma and may play a role in granulomatous inflammation or altered immune homeostasis that leads to non-resolving disease. For this reason, rituximab, an anti-CD20 monoclonal antibody that depletes B cells, has been proposed as an option in refractory disease. In a small prospective study of ten patients with refractory disease, seven patients responded to therapy either by a 5% increase in FVC or improvement in walk distance by at least 30 m [73]. However, two deaths in the group (likely related to progressive sarcoidosis) and concern about infection risk dampen excitement around the use of rituximab, except in rarer cases of severe refractory disease. Other drugs that have potential include the Janus kinase (JAK) inhibitor tofacitinib, which has shown both a steroid-sparing effect and improvement in imaging biomarkers in two small series that included pulmonary evaluation [74–76]. Similarly, tocilizumab, an anti-IL-6 antibody, showed a significant response in a series of four patients who were refractory to alternative medications [77]. Transdermal nicotine is also under current study based upon data from a RCT of thirteen patients showing nicotine treatment normalized toll-like receptor (TLR) 2 and 9 responses and increased the T regulatory response in patients with pulmonary sarcoidosis [78]. The potential immunomodulating effect is also supported by epidemiologic data showing that smoking is a protective factor in the development of sarcoidosis [1]. Repository corticotropin injection has garnered interest, with an early small RCT showing improvements in pulmonary function, quality of life parameters, imaging, and a steroid-sparing effect in patients with chronic sarcoidosis [79]. A more recent study was unable to reproduce these improvements statistically but was able to show a faster steroid-tapering effect than standard of care [80]. As with many past clinical trials, controversy exists over the true efficacy of many medications, as limitations of sample size and inclusion criteria often hamper drug development in this disease. These and other potential immune modulating agents approved for other rheumatologic and inflammatory diseases may be candidates for larger clinical studies to determine efficacy and target populations.

A novel biologic drug, efzofitimod, has recently been tested in a safety and tolerability study in 37 patients with pulmonary sarcoidosis [81]. Efzofitimod binds to the neuropilin-2 receptor protein and modulates the immune cells in the granulomatous reaction, decreasing inflammation and fibrosis in preclinical studies. Results showed no difference in adverse events compared to placebo, a subtle improved steroid-sparing effect, and statistically significant improvement in patient-reported outcomes (Sarcoidosis Assessment Tool, King's

Sarcoidosis Questionnaire (KSQ), Fatigue Assessment Scale, KSQ general health) at the higher dose range [82].

## 5. Clinical Considerations in the Choice of Corticosteroid-Sparing Therapies

In deciding on a corticosteroid-sparing agent, it is also important to consider alcohol use, fertility concerns, and the presence of extrapulmonary involvement. Comorbid conditions such as liver or kidney dysfunction may also sway the choice or dosage of therapy. Other comorbidities, such as uncontrolled diabetes, hypertension, or obesity, may preclude the use of corticosteroids in some cases. Medication interactions, even with commonly used drugs such as antibiotics and anticoagulants, can be extensive with the use of corticosteroid-sparing medications and should be reviewed prior to initiation and when any new drug is prescribed. For example, methotrexate is contraindicated with concurrent alcohol use and should not be used by those desiring pregnancy or with inadequate birth control. Methotrexate should also be avoided in those with significant liver disease, a low glomerular filtration rate (less than 30 mL/min), and may need dose adjustment for those with mildly impaired renal function. Infliximab should only be used with great caution after consultation with a cardiologist in patients with heart failure.

When initiating any type of anti-granulomatous therapy, detailed preparation and counseling of the patient are important to manage and alleviate toxicity. Prior to therapy, evaluation for hepatitis, tuberculosis, endemic fungi, and HIV should be considered. Vaccinations should be given, if possible, prior to therapy and updated periodically per guideline recommendations [83]. Medications may be held during times of infection or perioperatively. *Pneumocystis jirovecii* prophylaxis should be considered for patients on higher-dose corticosteroids for a prolonged period, particularly if combined with a steroid-sparing agent. Routine lab assessments, including complete blood counts and comprehensive metabolic panels specific to each drug, should be obtained and monitored closely for drug toxicity [84–86]. Shared decision-making with a patient and clinician is important to incorporate compliance barriers (both external and internal), risk acceptance, and patient preferences into the choice of drug. In the setting of progressive fibrotic lung disease despite anti-granulomatous therapy, clinicians may consider anti-fibrotic medication (not further discussed within this review) and should be referred for lung transplant evaluation if no other contraindications exist [87,88]. Additionally, it is important to address other aspects of care associated with sarcoidosis, including depression, anxiety, pain, and fatigue, which are not treated with anti-granulomatous therapy (Figure 2).

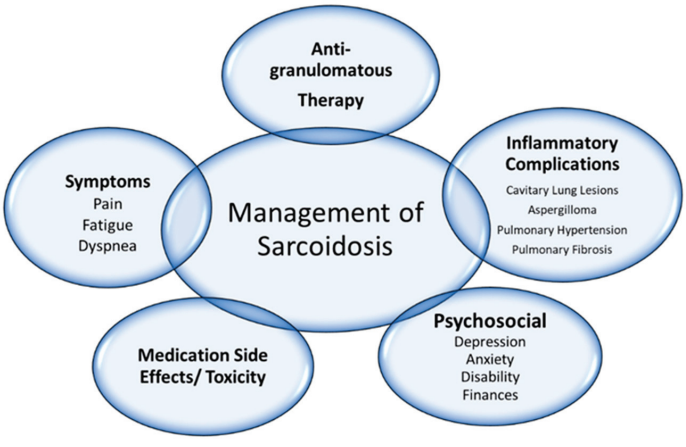


**Figure 2.** Complexity of management in pulmonary sarcoidosis. The treatment of a patient with sarcoidosis requires consideration of several aspects of care, not only treatment of granulomatous inflammation.

Pharmacogenetics may also play a role in the efficacy and tolerability of treatment options for sarcoidosis. Glucocorticoid receptor gene polymorphisms may affect sensitivity and response to glucocorticoids, thereby affecting dosing. Similarly, the lack of response to methotrexate in up to one-third of patients may be influenced by several potential polymorphisms in genes that are involved in the metabolism of methotrexate [89]. However, given the complexity of methotrexate genetics and metabolism, genetics are not used in the clinical realm for this medication. Azathioprine metabolism is also affected by mutations in the gene coding for thiopurine S-methyltransferase (TPMT), increasing the risk of toxicity, particularly in leukopenia [90]. TPMT enzyme activity with phenotyping can be measured in clinical practice. For infliximab, TNF-$\alpha$ polymorphisms within the TNF-$\alpha$ G-308A gene have been shown to predict response [91].

**6. Relapses**

Current recommendations to treat for approximately a year are based on a high relapse rate associated with shorter courses of therapy. A 'relapse' of sarcoidosis is based upon a significant need to increase systemic anti-inflammatory medications and worsen dyspnea, chest imaging, and pulmonary function [92], with chronic sarcoidosis cases having higher rates of relapse. Most relapses are seen within six months of cessation of therapy, but approximately 20% of relapses occur after one year, indicating the need for long-term monitoring after treatment [93]. It is unclear if this relapse rate is affected by the type of initial therapy. Some prior data have suggested a higher relapse rate in those treated only with corticosteroids [93]; how this varies with different combinations of immunomodulating therapies is unknown. In one study of advanced sarcoidosis cases requiring third-line therapies, approximately half of patients had to discontinue drugs, and 50–93% had recurrences requiring re-initiation of therapy [53]. Treatment of relapses mimics the original successful doses, although one study suggested that lower dosing regiments may be just as effective for relapses [94]. Alternatively, relapses often indicate a prolonged, chronic course, broaching the benefits of an early corticosteroid-sparing agent in longer-term management [95]. Predicting relapses is difficult, although recent data have suggested that high Fluorodeoxyglucose (FDG)-PET uptake in the lung is associated with relapse after cessation of therapy, including after corticosteroids and infliximab [96,97]. Similarly, high levels of soluble interleukin-2 receptor (sIL-2R) have also been associated with relapse after treatment with infliximab, making it an intriguing marker of prognosis once a medication has been stopped [96].

**7. Biomarkers in the Management of Therapy**

Biomarkers have been an active area of study in sarcoidosis management, although standardized diagnostic and prognostic markers are still lacking. Advanced imaging techniques have shown promise in the past decade that may be useful in the prognosis and evaluation of treatment efficacy. FDG-PET/CT scans have been used to evaluate granulomatous inflammation and can be used to identify sites of reversible activity as well as clinical response. Positive uptake in FDG-PET is seen in patients with radiographic stages 2 and 3 sarcoidosis, whereas negative uptake is common in stages 0, 1, and 4 [98]. Its use has been suggested as a potential marker to differentiate the presence of potential reversible inflammatory disease-requiring therapy or irreversible fibrosis in those with advanced lung disease, but its use in this manner is controversial [99,100]. Because the clinical utility and cost-effectiveness of FDG-PET remain unclear, it is not routinely used in the diagnosis and management of pulmonary sarcoidosis. However, it could potentially be useful in combination with other biomarkers in difficult cases.

Serum biomarkers are also potentially useful in treatment assessment [101]. Angiotensin-converting enzyme does modestly correlate with parenchymal burden in the lung. High levels of ACE and sIL-2, another biomarker of the Th1 inflammatory cascade, are associated with improvement in lung function after six months of treatment with methotrexate [102]. Subtyping of bronchoalveolar lavage cells could also be informative for pulmonary sarcoidosis,

as the cells are a direct window to the lung microenvironment. Higher neutrophil counts have been linked to a lower response to therapy [103]. More recently, the presence of Th17 cells has been associated with the development of chronic sarcoidosis, and the ratio of Th1 cells and T cells also holds promise in prognostication [104,105].

Genomics has also been revealing in both diagnostic and prognostic biomarker evaluation. A recent meta-analysis of transcriptome-wide association studies of tissue developed a prediction classifier using gene expression profiles that could discern sarcoidosis from healthy controls in the lymph nodes [106]. Similarly, based on the evaluation of candidate genes identified in genomic analysis, plasma biomarkers extracellular nicotinamide phosphoribosyl transferase (eNAMPT) and angiopoietin-2 (ANG-2) have also been associated with complicated phenotypes and pulmonary fibrosis [107]. The finding of certain genes and proteins associated with fibrosis or the discernment of progressive phenotypes may, in the future, be an intriguing way to determine the need for and type of treatment.

Early work in the field of artificial intelligence also holds promise for future prognostic and management biomarkers, although it is currently predominately focused on diagnosis [108]. Radiomics, the interpretation of imaging characteristics not seen by the human eye, has been able to help differentiate sarcoidosis from malignancy and other granulomatous diseases. Certain measures have been correlated to pulmonary function testing, which is notable given the historical discrepancy in pulmonary function and qualitative imaging [109]. Machine and deep learning methodologies have also been used to create a decision tool for the diagnosis of sarcoidosis from imaging data and to help differentiate pulmonary sarcoidosis from tuberculosis [110,111]. As further validation of these techniques evolves, their application as novel outcome measures and prognostic biomarkers holds great promise, particularly as larger datasets incorporate serum, tissue, imaging, and clinical data.

## 8. Summary

Management of pulmonary sarcoidosis is a complex interplay of disease characteristics, the impact of medications, and patient preferences (Figure 2). First, it is important to weigh the need for anti-granulomatous treatment with the risks of toxicity that each treatment entails. Pulmonary sarcoidosis should be treated in cases of significant symptoms, lung function decline, or progressive pulmonary inflammation that poses a risk to the lung. The basis of treatment is corticosteroid therapy for initial control of granulomatous inflammation, but corticosteroid-sparing agents can be initiated in cases of refractory disease or toxicity to corticosteroids. Each case of sarcoidosis will have an individualized plan due to the heterogeneity of the clinical course, response to therapy, and tolerance of medication side effects.

## 9. Future Directions

Future directions in anti-granulomatous treatment in pulmonary sarcoidosis include clinical trials based on careful phenotyping to establish the long-term efficacy of anti-inflammatory medications and whether these therapies prevent pulmonary fibrosis. Additionally, trials of dual therapy, duration and dosing of therapy, or steroid-sparing monotherapy would aid in diminishing the corticosteroid side effect profile and establishing standardized treatment guidelines. Head-to-head trials of anti-metabolites may also reveal the order and choice of medications, and novel formulations of repurposed drugs that minimize toxicity would be helpful. The development of home monitoring devices, such as reliable spirometry or symptom reporting tools, could also aid in accelerated steroid-tapering.

In this manner, there is much work to be carried out in clinical trial development for pulmonary sarcoidosis to enroll the necessary population and develop better outcomes that show the important effects of drug therapy. New methods within radiomics, genomics, and proteomics, possibly aided by artificial intelligence, could help with more accurate phenotyping of patients. Additionally, novel drug development based on emerging knowledge of the pathophysiology of disease that will diminish the toxicity of treatment could

revolutionize treatment paradigms. Ultimately, the discovery of the cause of sarcoidosis will lead to the cure and prevention of disease in the future.

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# Clinical Pharmacology in Sarcoidosis: How to Use and Monitor Sarcoidosis Medications

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**Abstract:** When sarcoidosis needs treatment, pharmacotherapy is usually required. Although glucocorticoids work reliably and relatively quickly for sarcoidosis, these drugs are associated with numerous significant side effects. Such side effects are common in sarcoidosis patients, as the disease frequently has a chronic course and glucocorticoid treatment courses are often prolonged. For these reasons, corticosteroid-sparing and corticosteroid-replacing therapies are often required for sarcoidosis. Unfortunately, many healthcare providers who care for sarcoidosis patients are not familiar with the use of these agents. In this manuscript, we provide a review of the pharmacotherapy of sarcoidosis. We discuss the mechanism of action, dosing, side-effect profile, approach to monitoring and patient counselling concerning glucocorticoids, and the common alternative drugs recommended for use in the recent European Respiratory Society (Lausanne, Switzerland) Sarcoidosis Treatment Guidelines. We also discuss the use of these agents in special situations including hepatic insufficiency, renal insufficiency, pregnancy, breastfeeding, vaccination, and drug–drug interactions. It is hoped that this manuscript will provide valuable practical guidance to clinicians who care for sarcoidosis patients.

**Keywords:** sarcoidosis; pharmacotherapy; corticosteroid; biologics; DMARD

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## 1. Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown cause. Sarcoidosis is usually treated with pharmacotherapy. The treatment of sarcoidosis is nuanced because the disease outcome varies from an asymptomatic state to a life-threatening disease, therapeutic agents are associated with significant toxicity, the prognosis of the disease is problematic to predict, and the effectiveness of specific drugs is dependent upon the specific organs involved. All these issues are discussed in detail in the recent European Respiratory Society (ERS) Clinical Practice Sarcoidosis Treatment Guidelines [1].

The ERS guidelines review the indications for numerous drugs used for the treatment of sarcoidosis. Many healthcare providers who care for sarcoidosis patients are not familiar with the use of these agents. Many are primary care physicians or subspecialists such as pulmonologists, ophthalmologists, and dermatologists who are unaccustomed to using many of these drugs in their routine practice. In this manuscript, we review characteristics of the pharmacologic agents that are most often used for the treatment of sarcoidosis. We will focus on the proper use and monitoring of these pharmacologic agents in clinical practice.

## 2. Glucocorticoids

### 2.1. Mechanism of Action

There are numerous mechanisms responsible for the anti-inflammatory effects of glucocorticoids including its inhibitory effects on a vast number of mediators such as tumor necrosis factor alpha (TNFa), various interleukins (IL), endothelial leukocyte adhesion molecule 1 (ELAM-1), and intercellular adhesion molecule 1 (ICAM-1), which are impaired by glucocorticoids [2].

### 2.2. General Treatment Indications for Glucocorticoids in Sarcoidosis

Glucocorticoids are considered the drug of choice for most forms of sarcoidosis [3]. These drugs are recommended as first-line agents for pulmonary, skin, cardiac, and neurologic sarcoidosis in the European Respiratory Society (ERS) Clinical Practice Sarcoidosis Treatment Guidelines [1]. However, because of the myriad of potential side effects from glucocorticoids, several other drugs are considered for the treatment of sarcoidosis for their glucocorticoid-sparing or glucocorticoid-replacing effects [3].

### 2.3. Dosing

Glucocorticoid dosing in sarcoidosis is not standardized. For symptomatic pulmonary sarcoidosis, the recent European Respiratory Society (ERS) Sarcoidosis Treatment Guidelines recommend an initial daily prednisone dose of 20 mg. However, glucocorticoid dosing in sarcoidosis varies based on the severity of disease, the organ involved, the risk of glucocorticoid side effects, the risk of leaving sarcoidosis partially treated or untreated, and the efficacy of concomitant corticosteroid-sparing medications. Various glucocorticoid preparations and potencies are listed in Table 1.

**Table 1.** Frequently used glucocorticoids and their comparative potency.

| Compounds | Anti-Inflammatory Potency | Equivalent Dose (mg) |
|---|---|---|
| Cortisone | 0.8 | 25 |
| Hydrocortisone | 1 | 20 |
| Prednisolone | 4 | 5 |
| Prednisone | 4 | 5 |
| Methylprednisolone | 5 | 4 |
| Triamcinolone | 5 | 4 |
| Betamethasone | 25 | 0.75 |
| Dexamethasone | 25 | 0.75 |

From references [2,4].

Although glucocorticoids are primarily metabolized in the liver as they are substrates for CYP3A4, hepatic dose adjustment is not required. Renal dose adjustment is also not required.

### 2.4. Side Effects and Monitoring

Glucocorticoids have numerous side effects such as gastritis, weight gain, hypertension, fluid retention, hyperglycemia, skin atrophy, impaired wound healing, osteoporosis, depression, mood change, adrenocortical insufficiency (when glucocorticoids are tapered or withdrawn), Cushing syndrome, decreased growth in children, myopathy, glaucoma, cataract, and an increased risk of infection. The risk for developing these side effects is dependent upon individual patient factors such as comorbidities. Clinicians may alter glucocorticoid regimens based on individual patient risks. Glucocorticoid side effects are also dose dependent, and it is recommended to use the smallest dose for the shortest duration possible. In the case of sarcoidosis, which is often a chronic condition, glucocorticoid-

sparing agents should be considered in patients requiring glucocorticoid therapy for more than a few months [5,6].

Some glucocorticoid side effects can be detected by eliciting symptoms from the patient such as gastrointestinal discomfort or mood change. However, many glucocorticoid side effects may not be detected at an early stage because they do not result in appreciable symptoms; therefore, patients receiving glucocorticoids must be monitored for the development of potential side effects while they are asymptomatic. The developments of weight gain, hypertension, hyperlipidemia, and diabetes (components of the metabolic syndrome) are serious glucocorticoid complications for which the patient should regularly be evaluated. Side effects that the patient cannot easily perceive, such as osteoporosis and eye disease, need to be regularly monitored. Table 2 lists parameters that should be assessed at the initiation of glucocorticoid therapy as well as those that should be monitored during therapy.

**Table 2.** Prednisone monitoring parameters.

| Monitoring Parameter | Monitoring Time Frame | Reference |
|---|---|---|
| Body weight | Baseline, frequently. | [6] |
| Height | Baseline, annually. | [6,7] |
| Blood pressure | Baseline, frequently. | [5,6] |
| HbA1C | Baseline, every 3~6 months. | [6] |
| Blood glucose | Baseline, frequently. | [6] |
| CBC | Baseline, frequently. | [6] |
| Lipid profile | Baseline, one month after initiation of glucocorticoid therapy, then every 6–12 months. | [5,6,8] |
| Bone-mineral density | Baseline, every 1–2 years. | [7] |
| Fracture history | Baseline, then at routine follow up visits. | [6] |
| Joint pain | Baseline, then at routine follow up visits. | [6,9] |
| Infection | Baseline, then at routine follow up visits. | [5,6] |
| Eye exam | Baseline, then annually or as recommended by an ophthalmologist. | [5,6] |
| Healthy lifestyle inventory and education | Baseline documentation of patient's lifestyle and awareness. After initial counseling, reinforce healthy lifestyle choices at routine follow up visits. | [6] |
| Perceived fatigue | Baseline, then at routine follow up visits. | [6,10] |
| Adrenal insufficiency | Measure serum cortisol or perform an ACTH stimulation test in patients with symptoms of adrenal insufficiency (or withdrawal) who have been tapered to a low dose or off corticosteroids. | [6] |
| Anginal symptoms (cardiovascular events) | Baseline, at routine follow up visits, educate the patient concerning these symptoms. | [6,11] |

ACTH: adrenocorticotropic hormone.

The American College of Rheumatology guidelines recommend osteoporosis monitoring for all adults initiating glucocorticoid therapy or continuing glucocorticoid therapy ≥2.5 mg/day for more than three months. [7] An initial fracture-risk assessment using the clinical fracture-risk factor assessment (FRAX®, https://frax.shef.ac.uk/FRAX/tool.aspx, accessed on 20 November 2023) is strongly recommended for all such patients, including for those who have never had a fracture-risk assessment or have been previously treated for osteoporosis. FRAX® estimates the fracture risk based on many factors including alcohol use, smoking history, hypogonadism, history of prior fractures, body weight, height, parental history of hip fracture, fall history, rheumatoid arthritis, thyroid disease, hyperparathyroidism, malabsorption, chronic liver disease, inflammatory bowel disease, and height loss. Treatment recommendations for loss of bone density are based on the FRAX® score. If available, bone-mineral density (BMD) testing with vertebral-fracture assessment (VFA) or spinal x-ray is recommended as soon as possible after starting glucocorticoid therapy as a baseline measurement, and then every 1–2 years thereafter while continuing a glucocorticoid regimen [7].

### *2.5. Drug Interactions*

Concomitant use of glucocorticoids and fluoroquinolones increases the risk of tendonitis and tendon rupture [12]. There are inconsistent reports regarding drug interaction between glucocorticoids and antacids; while some studies reported that concomitant antacid use may decrease glucocorticoid's bioavailability by 40–75%, [13,14] others reported no change in bioavailability [15,16]. Careful monitoring of the international normalized ratio (INR) is required with concomitant use of warfarin and glucocorticoids, as glucocorticoids may increase the INR [17].

Glucocorticoids are metabolized in the liver via the CYP450 3A4 enzyme (CYP3A4). Therefore, concomitant use of CYP3A4 inhibitor(s) or inducer(s) may change glucocorticoid metabolism: CYP3A4 inhibitors may decrease glucocorticoid metabolism leading to increased anti-inflammatory effectiveness with an increased risk of side effects. Conversely, CYP3A4 inducers can increase prednisone metabolism, which can lead to diminished glucocorticoid effectiveness (Table 3). The effects of CYP3A4 inhibitors and inducers on glucocorticoid potency and side effects are often clinically significant [18–20].

**Table 3.** Examples of CYP3A4 inhibitors and inducers.

| **CYP450 3A4 Inhibitors** | | **CYP450 3A4 Inducers** | |
|---|---|---|---|
| **INCREASED GLUCOCORTICOID EFFECTIVENESS INCREASED GLUCOCORTICOID SIDE EFFECT RISK** | | **DECREASED GLUCOCORTICOID EFFECTIVENESS DECREASED GLUCOCORTICOID SIDE EFFECT RISK** | |
| **Moderate Effect** | **Strong Effect** | **Moderate Effect** | **Strong Effect** |
| Diltiazem | Clarithromycin | Rifapentine | Phenobarbital |
| Verapamil | Erythromycin | Rifabutin | Phenytoin |
| Erythromycin | Itraconazole | Efavirenz | Fosphenytoin |
| Fluconazole | Ketoconazole | Bosentan | Primidone |
| Isavuconazole | Voriconazole | | Rifampicin |
| Cyclosporine | Posaconazole | | Rifampin |
| Dronedarone | Ritonavir | | Carbamazepine |
| | Indinavir | | Eslicarbazepine |
| | Darunavir | | Lumacaftor |
| | Nelfinavir | | Lumacaftor-ivacaftor |
| | Saquinavir | | |

*2.6. Special Situations*

*Pregnancy*: Because sarcoidosis frequently occurs in women of childbearing age, glucocorticoid use during pregnancy is a clinically relevant issue. Prednisone and methylprednisolone are non-fluorinated glucocorticoids and are therefore the preferred oral glucocorticoids during pregnancy because the placental barrier limits its transport to the fetus, while fluorinated glucocorticoids such as dexamethasone and betamethasone can readily cross the placenta [21]. Conflicting data have been reported regarding the associations between systemic glucocorticoid use during the first trimester of pregnancy and the development of cleft lip and palate as well as low birth rate [22,23]. These associations appear to be influenced by the glucocorticoid dose, duration of use, frequency, and indication for use [23–25]. The general recommendation for glucocorticoid use during pregnancy is to use prednisone at the lowest effective dose for shortest duration possible, and to avoid high doses, particularly during the first trimester [24,26].

*Breastfeeding*: Mothers should be counselled that glucocorticoids are present in breast milk. Although glucocorticoids are generally well tolerated by the child receiving breast milk from mothers using standard glucocorticoid doses, it is recommended to monitor the infant for adverse events such as growth suppression. The European Respiratory Society/Thoracic Society of Australia and New Zealand (ERS/TSANZ) task force team recommended waiting 3–4 h after a prednisone dose to begin breastfeeding to minimize the potential glucocorticoid exposure to the breastfeeding child [27]. Based on prednisone's half-life, approximately 87–94% of the drug is eliminated from mother's plasma by this time.

*Osteoporosis*: For the prevention and treatment of glucocorticoid-induced osteoporosis, the American College of Rheumatology guidelines suggest specific recommendations for adults who are taking a prednisone equivalent of $\geq$2.5 mg daily for >3 months, based on the individual patient's level of risk: low risk, moderate, high, and very high risk, respectively [7]. These levels of risk are based on the glucocorticoid dose, dual-energy X-ray absorptiometry (DEXA) T score and Z score, FRAX® score, and a prior history of osteoporosis-related fracture. Specific details can be found in the 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis [7].

*Pneumocystis jirovecii pneumonia (PJP) prophylaxis: PJP* Prophylaxis with trimethoprim and sulfamethoxazole (TMP/SMX) is often used in patients receiving high-dose glucocorticoid therapy. Although there is no consensus on a specific glucocorticoid dose that requires TMP/SMX for PJP prophylaxis, most reports recommend PJP prophylaxis in patients receiving a prednisone equivalent $\geq$20~30 mg daily [28–30]. In clinical practice, PJP prophylaxis with TMP/SMX is generally not used in sarcoidosis patients unless they are receiving concomitant immunosuppressive medication.

*Glucocorticoid interaction with the QuantiFERON test:* The QuantiFERON test is an interferon gamma (IFN-$\gamma$) release assay (IGRAs) that measures an immunologic response to TB antigen exposure [31]. This test involves a positive control tube to measure IFN-$\gamma$ release in blood in response to a non-specific lymphocyte activator, i.e., phytohemagglutinin [32]. High doses of glucocorticoids ($\geq$20 mg/day of prednisone equivalent) and other immunosuppressants often cause an inadequate IFN-$\gamma$ release in the phytohemagglutinin-stimulated tube, which leads to an "indeterminate" QuantiFERON test result. If an indeterminate QuantiFERON test result is obtained while the patient is receiving high-dose glucocorticoids, then a repeat QuantiFERON test is recommended after tapering glucocorticoids to <20 mg of daily prednisone [33,34]. Because of this potential effect of high-dose glucocorticoids on the QuantiFERON test result, it is prudent to perform this test prior to initiating high-dose corticosteroids in patients with severe sarcoidosis who are thought likely to be prescribed biologic therapy that requires prior latent tuberculosis (TB) infection screening.

*Vaccination*: Influenza vaccine can be administered while patients are receiving glucocorticoids at any dose. Other non-live-attenuated vaccines are recommended when the prednisone equivalent dose is <20 mg daily. However, for prednisone equivalent doses of ≥ 20 mg daily, other non-live-attenuated vaccines are recommended to be deferred until the glucocorticoid dose is tapered to <20 mg prednisone daily equivalent. For live-attenuated vaccines, glucocorticoids are recommended to be held from four weeks before until four weeks after vaccination. For patients receiving a lower dose of glucocorticoids (<20 mg prednisone equivalent), glucocorticoid therapy may be continued while the patient receives a live-attenuated vaccine [35]. The following glucocorticoid regimens may be continued while receiving a live vaccine: short-term use of glucocorticoid <14 days, low-to-moderate dose prednisone (defined as <20 mg/day or <2 mg/kg/day for a child), long-term but alternate day glucocorticoids, daily use of topical glucocorticoids, inhaled corticosteroids, and localized glucocorticoid injections into joints [36].

The Centers for Disease Control and Prevention (CDC), in January 2022, updated their recommendation on Shingrix® Recombinant Zoster Vaccine (RZV) such that all individuals ≥19 years old who have an immunocompromised condition or who will imminently receive immunocompromised medication are eligible for RZV administration [37]. This recommendation applies not only to glucocorticoids but also to all other immunosuppressants that are discussed in this review.

### *2.7. Counseling Points for a Patient Receiving Glucocorticoid(s)*

- Take glucocorticoids with food to prevent gastrointestinal discomfort.
- Take glucocorticoids in the morning time to minimize insomnia.
- Educate the patient concerning potential glucocorticoid side effects including hyperglycemia, osteoporosis, adrenocortical insufficiency, weight gain, fluid retention, hypertension, mood change, myopathy, glaucoma, cataract, and infections.
- Contact the healthcare provider if an infection occurs, or if an invasive procedure is planned that may increase the risk of infection. Glucocorticoids may have to be held temporarily in this instance.
- Encourage vaccination prior to initiating glucocorticoids, as vaccination is a highly effective infection mitigation strategy.
- Patients receiving glucocorticoids or another immunosuppressive medication are eligible for RZV, Shingrix® (GlaxoSmithKline, Durham, NC, USA).

## 3. Methotrexate

Methotrexate (MTX) is a disease modifying anti-rheumatic drug (DMARD) that is effective for many rheumatologic and inflammatory conditions, including sarcoidosis. Originally, MTX was used for childhood leukemia in the 1940s. Placebo-controlled clinical trials in the 1980s demonstrated MTX's effectiveness for the treatment of rheumatoid arthritis [38–41], which currently is the first-line therapy [42].

### *3.1. Mechanism of Action*

MTX's therapeutic effectiveness is achieved by inhibiting the enzyme dihydrofolate reductase (DHFR). DHFR reduces dihydrofolate to tetrahydrofolate, which is necessary during DNA synthesis.

### *3.2. General Treatment Indications for Methotrexate in Sarcoidosis*

MTX is regarded as a second-line agent for sarcoidosis. MTX is specifically recommended as a second-line agent for pulmonary, skin, cardiac, and neurologic sarcoidosis in the European Respiratory Society (ERS) Clinical Practice Sarcoidosis Treatment Guidelines [1]. The drug is often effective as a glucocorticoid-sparing agent and, in approximately 25% of cases, as a glucocorticoid-replacing agent [43]. Because of drug accumulation with renal insufficiency (vide infra), MTX is not recommended for the treatment of renal sarcoidosis [44].

### 3.3. Dosing

Various MTX dosing regimens have been used for different medical conditions. We will review the clinical approach concerning the most recent and generally accepted low-dose MTX regimens for the treatment of sarcoidosis. Higher doses of MTX regimen for oncology will not be discussed in this review.

It is important to immediately stress that patients should be specifically counselled to take MTX once weekly, and not daily. Dosing error is one of the major causes of MTX overdose [45]. The usual MTX dose for the treatment of sarcoidosis is between 5 mg and 25 mg, with this total dose given once per week. The usual starting dose ranges from 5 mg to 12.5 mg, and then can be titrated up by 2.5~5 mg every 1–2 weeks to reach the desired target dose. Dosing above 25 mg per week has minimal additional benefit and is not routinely recommended [46].

The oral bioavailability of MTX is significantly reduced with oral doses of $\geq$15 mg per week, as there is a plateau of absorption above that dose [47]. Therefore, when an oral MTX dose above 15 mg weekly is needed, a split oral dosing strategy can be used to increase bioavailability: administer half of the weekly oral dose in the morning, and the remaining half in the evening on the same day (12 h apart). A split dose of oral MTX regimen is conditionally recommended over switching to an alternative DMARD(s) for patients not tolerating oral weekly MTX per 2021 ACR rheumatoid arthritis guidelines [42]. This approach can be extrapolated for the treatment of sarcoidosis. We acknowledge that practice varies geographically and that guidelines from other regions may not explicitly comment on the split dosing recommendation.

MTX can be administered by the subcutaneous route. Subcutaneous administration bypasses the gastrointestinal (GI) tract such that patients who have GI side effects may better tolerate the drug. Subcutaneous administration of MTX also results in improved drug bioavailability compared to the oral route. The issues of inadequate oral bioavailability for MTX doses above 15 mg can also be avoided by administering MTX by subcutaneous injection [47–49]. The oral-to-subcutaneous dose conversion is 1:1.

MTX is hepatically metabolized to polyglutamate MTX, which is an active metabolite. Because polyglutamate MTX is excreted renally, individuals with compromised renal function may have a high risk of side effects from accumulation of this metabolite. Therefore, when the estimated glomerular filtration rate (eGFR) is <50~60 mL/min, the MTX dose needs to be reduced appropriately (Table 4) [50]. MTX is contraindicated in patients receiving hemodialysis and peritoneal dialysis [51]. MTX is also contraindicated in patients with a chronic pleural effusion, which acts as a drug sanctuary and increases the risk of side effects [52].

**Table 4.** Methotrexate dose adjustment by eGFR, adopted from Kintzel, 1995 [50].

| CrCl | Methotrexate Dose |
|---|---|
| CrCl > 60 mL/min | No dose adjustment necessary. |
| 46 $\leq$ CrCl < 60 mL/min | 65% of normal dose. |
| 31 $\leq$ CrCl < 45 mL/min | 50% of normal dose. |
| CrCl < 30 mL/min | Avoid use. |

### 3.4. Side Effects and Monitoring

MTX may cause folate deficiency. Folic acid at a dose of 1 mg to 4 mg daily is recommended for patients receive MTX [53]. Folic acid can prevent MTX toxicity without affecting the effectiveness of MTX. In contrast, folinic acid, an active form of folic acid also known as leucovorin, is a reduced folate that can negate the beneficial effects of MTX. Therefore, folic acid can be dosed daily, seven days per week, even on the day of the MTX dose, whereas leucovorin should be administered at least 12 h after MTX use to preserve MTX's therapeutic effect [53].

Leucovorin is a valuable agent to rescue patients from MTX toxicity. Leucovorin may provide a significant benefit in patients who have known methylenetetrahydrofolate reductase (MTHFR) deficiency or in those have developed MTX side effects daily while receiving a high dose of folic acid supplementation (3–4 mg daily) [54].

Although MTX is usually well tolerated, gastrointestinal side effects, fatigue, headaches, and dizziness may occur. MTX is immunosuppressive and increases the risk of infection. Hepatotoxicity may occur. Reductions in blood cell lines due to bone-marrow suppression may develop and may require a reduction of the MTX dose or discontinuing the drug if bone-marrow suppression is severe. Folic acid supplementation can mitigate these MTX toxicities. Therefore, folic acid should be prescribed along with MTX.

Blood labs such as complete blood count (CBC), serum renal function tests, serum liver function tests, and viral hepatitis serologies are recommended prior to initiation of MTX. CBC, renal, and hepatic function tests are required frequently as often as every two to four weeks initially for at least the first two to three months and every three months thereafter [55].

Patients receiving MTX should have their mean corpuscular volume (MCV) monitored, as it may be an early sign of MTX-induced vitamin B12 or folate deficiency. However, a high MCV is not an indication to adjust the MTX dose if the blood cell lines are not significantly reduced. When significant bone-marrow suppression develops, leucovorin rescue therapy and switching to an alternative drug should be considered.

MTX rarely causes interstitial lung disease. A persistent cough and unexplained dyspnea may be the first symptoms of this complication. A baseline chest radiograph is recommended as it may be used for comparison if MTX pulmonary toxicity is eventually considered [56]. If MTX pulmonary toxicity is confirmed, then the drug should be discontinued.

Patients should abstain from alcohol consumption while receiving MTX. The use of broad-spectrum sunscreen is advised, and sun exposure needs to be limited because of photosensitivity.

### 3.5. Drug Interactions

Although trimethoprim-sulfamethoxazole (TMP-SMX) is often used for prophylaxis against pneumocystis jiroveci pneumonia (PJP) in patients who are significantly immunocompromised, it is not recommended to be used in conjunction with MTX. Even with a small dose of MTX, this combination increases the risk of MTX side effects such as bone-marrow suppression [57–61]. TMP-SMX reduces renal excretion of MTX metabolites, and both TMP-SMX and MTX can cause folate deficiency that may potentiate the risk of MTX toxicity [62,63]. Alternative oral agents for PJP prophylaxis include dapsone, [64,65] atovaquone, [64], intravenous and aerosolized pentamidine, [64] or a combination of primaquine and clindamycin [64,66].

Treatment with multiple DMARDs are acceptable for the treatment of some forms of sarcoidosis [1]. However, it is recommended to avoid the concomitant use of MTX and leflunomide because they share similar side effects such that the likelihood of bone-marrow suppression and liver toxicity are significantly increased when these drugs are used concomitantly [67,68]. Drug databases or some institution's medication ordering systems may flag non-steroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors when concomitantly used with MTX. However, this interaction is significant only with a high dose of MTX and is usually not relevant in the case of sarcoidosis treatment ($\leq$25 mg/week).

### 3.6. Special Situations

*Pregnancy and breastfeeding:* MTX is contraindicated in pregnancy and while breastfeeding. Women of child-bearing age should use contraception while they are using MTX. If pregnancy is planned, then MTX should be discontinued three months prior to conception for a woman [69]. In men, although MTX labeling suggests discontinuing MTX prior to attempting pregnancy, clinical data show no such risks that the continued use of MTX is conditionally recommended for men planning to father a child [69–73].

*Swallowing difficulties:* For patients with swallowing difficulties, a parenteral solution preparation (25 mg/mL) of MTX can be used orally with a 1:1 conversion ratio.

*Preexisting hepatic or renal conditions:* Patients with preexisting hepatic and renal conditions who receive MTX should be monitored closely, and alternative treatment agents should be considered.

*Vaccination*: Influenza vaccine and other non-live vaccines can be administered while MTX is used. Although holding MTX for two weeks after vaccination can increase the immunologic response to the vaccine, this is recommended only when the patient's risk of a disease flare is low [35]. For live-attenuated vaccines, MTX is recommended to be held from four weeks prior to the vaccination until four weeks after vaccination [35].

### 3.7. Counseling Points for a Patient Receiving MTX

- Take MTX "one day per week".
- Take folic acid daily seven days per week, including the day of MTX use.
- Use split dosing for weekly MTX doses of >15 mg weekly: "half of the dose in the morning then half of the dose in the evening, 12 h apart, within one day every week".
- MTX takes up to 3~6 months of use with good adherence to reach its steady state of clinical effectiveness. Encourage the patient to take MTX as prescribed despite the drug's initial minimal efficacy.
- Contact the healthcare provider if unexplained cough develops.
- Potential MTX side effects include birth defects, liver toxicity, bone-marrow suppression, photosensitivity (use sunscreen, wear hat and long sleeves), hair loss, mouth ulcer etc.
- Frequent blood test monitoring (CBC, serum liver, and renal function tests) is required while receiving MTX.
- Hold two doses of MTX after receiving an annual influenza vaccination to maximize vaccine efficacy if sarcoidosis symptoms are minimum and the risk of a sarcoidosis exacerbation is low.
- Contact the healthcare provider if an infection occurs, or if an invasive procedure or surgery is planned. MTX may have to be held temporarily in this instance.
- Encourage vaccination prior to initiating MTX, as vaccination is a highly effective infection mitigation strategy.
- With drug-induced immunocompromised condition, the patient is eligible for RZV, Shingrix®.

## 4. Leflunomide

### 4.1. Mechanism of Action

LEF is a prodrug that is converted in the gut and liver to teriflunomide, its active form. This conversion is almost complete such that its original form of LEF is practically undetectable in the serum [74,75]. LEF's pharmacologic effectiveness is achieved by the inhibition of dihydroorotate dehydrogenase (DHODH) in the de novo synthesis of pyrimidines.

### 4.2. General Treatment Indications for Leflunomide in Sarcoidosis

LEF is regarded as a second-line agent for sarcoidosis. LEF is specifically recommended as a second-line agent for pulmonary and cardiac sarcoidosis in the European Respiratory Society (ERS) Clinical Practice Sarcoidosis Treatment Guidelines [1]. LEF has also been used successfully for skin, eye, and sinus sarcoidosis [76].

### 4.3. Dosing

The typical dose of LEF is 10 mg to 20 mg daily. Although some experts have recommended a 100 mg daily loading dose for the initial three days, this can increase the risk of drug toxicity without a substantiated clinical benefit. LEF does not require a dosage adjustment in patients with renal insufficiency.

### 4.4. Side Effects and Monitoring

Toxicities from LEF include teratogenicity, bone-marrow suppression, serious infection, reactivation of latent TB infection, interstitial lung disease, peripheral neuropathy, dermatologic reactions, hypersensitivity reactions, hepatotoxicity, alopecia, gastrointestinal symptoms (nausea, diarrhea, pain, ulcer), headache, hypertension, and dizziness.

Drug monitoring should include surveillance for signs and symptoms of the above-mentioned side effects. CBC and LFT blood tests should be performed at drug initiation, then every 2 to 4 weeks during the first 3–6 months, and then extended to every 2 to 3 months in stable patients [55].

When LEF toxicity is suspected, an accelerated elimination procedure should be performed with charcoal or cholestyramine. The oral administration of activated charcoal powder (in the form of a suspension) is 50 g every 12 h for 11 days. Cholestyramine is administered orally: 8 g three times daily for 11 days. These accelerated elimination procedures effectively block the LEF's active metabolite, teriflunomide, from being recycled through enterohepatic pathways and force its excretion. After one day of the above regimen with cholestyramine or charcoal, teriflunomide concentration can be reduced by approximately 40% [75]. After 11 days of the accelerated elimination procedure, if the teriflunomide plasma concentration is higher than 0.02 mg/L, then the above procedure should be repeated [77]. An alternative accelerated elimination procedure of cholestyramine, 4 g every 6 h for 2 weeks has been recommended by the European Association for the Study of the Liver [78].

### 4.5. Drug Interactions

Because teriflunomide is highly protein bound (99%) [75], there is a theoretical risk that drugs used concomitantly with LEF may be displaced from their protein-bound state, leading to excessive plasma concentrations. Tolbutamide is a highly protein-bound drug where this may occur. Concomitant use of LEF and methotrexate is generally avoided because they have similar toxicities (vide supra, MTX section).

Because LEF is a CYP2C8 inhibitor, serum levels of CYP2C8 substrates such as pioglitazone, repaglinide, rosiglitazone, and selexipag may be increased in patients receiving LEF concomitantly [79–81]. Patients receiving LEF and warfarin concomitantly require close INR monitoring as LEF may potentiate warfarin's effectiveness, increasing the INR [82,83]. Paradoxically, the prescribing information cautioned that the combination of LEF and warfarin may decrease peak INR by 25% without clear explanation of the mechanism [77].

We recommend that providers closely monitor the INR in patients receiving LEF and warfarin concomitantly.

*4.6. Special Situations*

*Pregnancy*: LEF is teratogenic, and therefore it is contraindicated in pregnancy. Pregnancy should be excluded prior to the initiation of LEF. Woman with reproductive potential should be advised to use effective contraception while receiving LEF. If a woman receiving LEF is found to be pregnant, an accelerated elimination procedure (vide supra) is recommended, [84]. No increased rate of birth defects has been observed with paternal exposure of LEF [85].

*Breastfeeding*: Although there is no information available concerning the concentration of LEF or its metabolites in breast milk [85], it is recommended that women not breastfeed while they are receiving the drug. There is a great potential for LEF to accumulate in breast milk because of its enterohepatic circulation. As LEF is an immunosuppressant, there is concern that the nursing baby's immune function and immunization efficacy could be affected if their breastfeeding mother is receiving LEF.

*Renal adjustment*: Unlike MTX, LEF does not require a dose adjustment in patients with compromised renal function; therefore, LEF has a potential advantage over MTX in such patients. In dialysis patients, the terminal clearance half-life of LEF is similar to that of healthy volunteers such that there is no need for a dose adjustment [75,86].

*Hepatic adjustment*: LEF is not recommended in patients with severe hepatic insufficiency or hypoproteinemia. LEF should be discontinued if the serum ALT is >3 times of the upper limit of normal, and an accelerated elimination procedure may be indicated [77].

*Vaccination*: Influenza vaccine and other non-live vaccines can be administered while LEF is used. For live-attenuated vaccines, LEF is recommended to be held from four weeks prior until four weeks after the vaccination [35].

*4.7. Counseling Points for a Patient Receiving LEF*

- Potential side effects include birth defects, liver toxicity, bone-marrow suppression, neuropathy, blood-pressure increase, and hair loss.
- It may take up to 3~6 months of use to reach its steady state of clinical effectiveness. Encourage the patient to take LEF as prescribed with good adherence despite the LEF's initial minimal efficacy.
- Frequent blood-test monitoring is required while receiving LEF.
- Contact the healthcare provider if an infection occurs, or if a procedure or surgery is planned that may increase the risk of infection. LEF may have to be held temporarily in this instance.
- Encourage vaccination prior to initiating LEF, as vaccination is a highly effective infection mitigation strategy.
- With drug-induced immunocompromised condition, the patient is eligible for RZV, Shingrix®.

**5. Azathioprine**

*5.1. Mechanism of Action*

Azathioprine (AZA) is a cytotoxic immunosuppressive agent that inhibits purine nucleic acid metabolism, which ultimately suppresses cellular immunity. AZA is a prodrug of 6-mercaptopurine (6-MP), which is then further metabolized to its major active metabolite, 6-thioguanine (6-TG), which can be directly incorporated into DNA as a thioguanine nucleotide causing DNA damage (Figure 1) [87]. AZA has been used in many areas of medicine including organ transplantation, oncology, and inflammatory conditions including sarcoidosis.

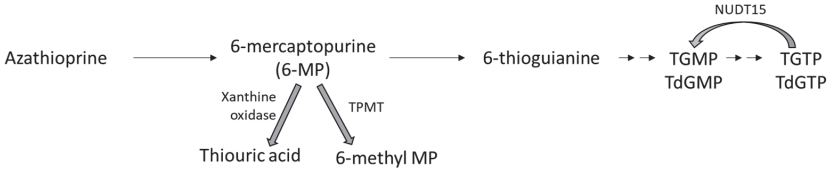


**Figure 1.** Azathioprine metabolism.

TGMP—thioguanine nucleotide monophosphate;
TdGMP—thio-deoxyguanosine monophosphate;
TGTP—thioguanine nucleotide triphosphate;
TdGTP—thio-deoxyguanosine triphosphate;
TPMT—thiopurine methyltransferase;
NUDT15—nucleoside diphosphate-linked moiety X motif 15.

*5.2. General Treatment Indications for Azathioprine in Sarcoidosis*

AZA is regarded as a second-line agent for sarcoidosis. AZA is specifically recommended as a second-line agent for pulmonary, cardiac, and neurologic sarcoidosis in the European Respiratory Society (ERS) Clinical Practice Sarcoidosis Treatment Guidelines [1]. AZA has also been used successfully for eye sarcoidosis [88].

*5.3. Dosing*

For sarcoidosis, the initial AZA dose is usually 25 to 50 mg once daily, which is then increased by 50 mg every two to four weeks as clinically indicated and tolerated. The maximum daily AZA dose for the treatment of sarcoidosis has not been established but it should not exceed 250 mg/day, based on expert consensus [1]. The manufacturer has recommended to use the lower end of the therapeutic dosing range of AZA in patients with kidney impairment but did not supply specific guidance [89]. Some experts have recommended using significantly lower AZA doses in patients with renal impairment [90].

Thiopurine methyltransferase (*TPMT*) and nucleoside diphosphate-linked moiety X motif 15 (*NUDT15*) pharmacogene phenotype testing needs to be performed prior to initiation of AZA [89,91,92]. The test classifies *TPMT* and *NUDT15* phenotypes as "normal metabolizers", "intermediate metabolizers", or "poor metabolizers". Poor and intermediate metabolizers are likely to have an increased concentration of active metabolites of AZA (Figure 1), which can increase drug toxicity. Prescribing information and Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend not using AZA for non-oncologic conditions in patients who are poor *TPMT* and/or *NUDT15* metabolizers. Patients who are intermediate *TPMT* and/or *NUDT15* metabolizers should receive AZA dosing that is 30% to 80% less than the normal [89,92].

*5.4. Side Effects and Monitoring*

The toxic effects of AZA include bone-marrow suppression (leukopenia, anemia, thrombocytopenia), hepatic dysfunction, pancreatitis, nephrotoxicity, lymphoma, fever, gastrointestinal intolerance (nausea, vomiting, and diarrhea), skin rash, and jaundice, particularly in patients who have preexisting hepatic dysfunction, and, rarely, hepatic sinusoidal obstruction syndrome (SOS, also called veno-occlusive disease, VOD). Skin cancer has been reported to be associated with AZA [93].

Baseline CBC, renal, and hepatic-function blood tests should be obtained before initiating AZA. These tests should be monitored every two weeks while doses are being titrated and then every three months thereafter. Clinical signs and symptoms of drug toxicity should be monitored during every visit. Because individuals receiving AZA have a higher risk of non-melanoma skin cancer, close surveillance is recommended [94].

*5.5. Drug Interactions*

Xanthine oxidase inhibitors such as allopurinol and febuxostat increase the risk of AZA toxicity by inhibiting the conversion of 6-MP to inactive metabolites. This can cause the accumulation of 6-MP. Therefore, xanthine oxidase inhibitors are avoided with AZA; alternative immunosuppressives to AZA should be considered in this situation. The concomitant use of AZA with other immunosuppressant drugs such as tumor necrosis alpha inhibitors can increase the risks of infection and malignancy [94].

*5.6. Special Situations*

*Pregnancy and breastfeeding*: AZA is a pregnancy category D drug, meaning there is evidence of fetal risk [95]. The category D status was given to AZA based on studies concerning high-dose AZA treatment of leukemia [96]. However, data from clinical trials and case series suggest that anti-inflammatory doses of AZA are safe with minimal risks in pregnancy and with breastfeeding; therefore, the drug may be used in these situations [68,69,97].

Children whose mothers received AZA while they were in utero were found not to have a decrement in long-term immune function [98]. The concentration of AZA in breast milk is low enough that breastfeeding is acceptable in nursing mothers receiving this drug [99]. Men who are planning to father a child may continue receiving AZA according to the American College of Rheumatology guidelines [69,100].

*Renal impairment*: Patients receiving AZA with a CrCl <30 mL/min or receiving dialysis require a 25% to 50% dose reduction.

*Hepatic impairment*: Although AZA can cause significant hepatotoxicity, there is no standard recommendation for adjusting the AZA dose based on hepatic impairment. When AZA hepatotoxicity occurs, treatment should be paused, and a dose reduction or discontinuation of AZA should be considered. If a patient receiving AZA develops a hepatic sinusoidal obstruction syndrome (SOS; veno-occlusive disease), the drug should be permanently discontinued.

*Combination therapy of AZA with other immunosuppressants*: Because AZA, LEF, and MTX have overlapping side effects of liver toxicity, bone-marrow suppression, and increased risk of infection, patients receiving at least two of these drugs concomitantly need close observation. AZA and tumor necrosis factor alpha inhibitor (TNFi) coadministration may lead to a higher rate of malignancy compared with monotherapy [68].

*Vaccination*: Influenza vaccine and other non-live vaccines can be administered while AZA is used. For live-attenuated vaccines, AZA is recommended to be held from four weeks prior to vaccination until four weeks after vaccination [35].

*5.7. Counseling Points for a Patient Receiving AZA*

- The potential side effects of AZA include liver toxicity and bone-marrow suppression.
- It takes up to 3~6 months of use to reach its steady state of clinical effectiveness. Encourage the patient take AZA as prescribed with good adherence despite the drug's initial minimal efficacy.
- Frequent blood-test monitoring is required while receiving AZA.
- Contact the healthcare provider if an infection occurs, or if a procedure or surgery is planned that may increase the risk of infection. AZA may have to be held temporarily in this instance.
- Encourage vaccination prior to initiating AZA, as vaccination is a highly effective infection-mitigation strategy.
- With a drug-induced immunocompromised condition, the patient is eligible for RZV, Shingrix®.

## 6. Mycophenolate (Mycophenolate Mofetil, Mycophenolate Sodium)

### 6.1. Mechanism of Action

Mycophenolate exhibits its immunosuppressive action by inhibiting inosine 5-monophosphate dehydrogenase (IMPDH), an enzyme involved with de novo purine nucleotides synthesis. This eventually leads to a reduction in lymphocyte proliferation, chemotaxis, and antibody production [101].

### 6.2. General Treatment Indications for Mycophenolate in Sarcoidosis

Mycophenolate is regarded as a second-line agent for sarcoidosis. Mycophenolate is specifically recommended as a second-line agent for pulmonary, cardiac, and neurologic sarcoidosis in the European Respiratory Society (ERS) Clinical Practice Sarcoidosis Treatment Guidelines [1]. MPA has also been used successfully for eye sarcoidosis [102].

### 6.3. Dosing

Mycophenolate is available in two forms: mycophenolate mofetil (MMF) and enteric coated (EC)-mycophenolate sodium. Both are hydrolyzed to the active form, mycophenolic acid (MPA). The usual daily dose of MMF is 500 mg to 3000 mg in divided doses, usually given 1500 mg twice daily. MMF 500 mg is considered equivalent to 360 mg of EC-mycophenolate sodium. MMF is converted to MPA more quickly than EC-mycophenolate sodium, and therefore it is the preferred form of the drug. It is recommended to initiate MMF at a low dose then to up-titrate to the target maintenance dose to minimize GI intolerance. There is a higher incidence of GI side effects with MMF than EC-mycophenolate sodium. Therefore, if a patient experiences GI side effects with MMF, switching to EC-mycophenolate sodium can be considered. A suspension formula (MMF, 200 mg/mL) is available that can be used in patients who have swallowing difficulties. Suspension MMF contains aspartame and is therefore contraindicated in patients with phenylketonuria.

### 6.4. Side Effects and Monitoring

Gastrointestinal complaints are the most common side effects of MMF. Often, this complication is severe enough to result in discontinuation of the drug. Patients receiving MMF are at an increased risk of infection. Due to its teratogenicity, mycophenolate preparations are contraindicated in pregnancy [101,103].

Other adverse reactions to MMF include fever, arthralgia, arthritis, myalgias, increased liver enzymes, anemia, leukopenia, thrombocytopenia, possible reactivation of hepatitis, lymphoproliferative disorders, skin cancers, hypertension, edema, dyslipidemia, renal insufficiency, and John Cunningham (JC) virus-associated progressive multifocal leukoencephalopathy (PML).

CBC, LFT, and serum renal-function tests should be performed at drug initiation, then every two to four weeks until the patient reaches a stable maintenance dose. At that point, these blood tests should be monitored every three months. For those patients with an ANC of $<1.3 \times 10^3$/mcL, MMF therapy should be interrupted, and the maintenance dose should be reduced, or drug discontinuation should be considered [104].

Although some studies showed benefits from monitoring MMF serum levels via therapeutic drug monitoring (TDM), optimal serum levels have not been established [105,106]. Therefore, TDM of MMF is not currently a routine practice.

### 6.5. Drug Interactions

Concomitant use of antacids containing magnesium or aluminum decreases the bioavailability of MMF because of increased gastric pH caused by antacids. It is recommended to take MMF at least 2 h after antacid use. Proton pump inhibitors (PPI), such as omeprazole, pantoprazole, and lansoprazole, may decrease MMF's bioavailability; therefore, careful assessment of the effectiveness of MMF is warranted in this situation. Phosphate binders such as sevelamer also decrease MMF's bioavailability. Doses of these two medications should be separated by >2 h in order to optimize the clinical effect of MMF

therapy [107]. Antibiotics such as aminoglycosides, cephalosporins, fluoroquinolones, and penicillins may interfere with the enterohepatic recirculation of MMF and its metabolites, resulting in a reduction in MMF bioavailability by 30~50% [108,109]. Therefore, patients receiving these antibiotics may require higher doses of MMF [110,111]. Concomitant use of rifampin may decrease MMF bioavailability by >70% [110–112].

*6.6. Special Situations*

*Pregnancy*: MMF is teratogenic and is contraindicated with pregnancy. MMF is incorporated in the Risk Evaluation and Mitigation Strategy (REMS) program required by the Food and Drug Administration (FDA). This program informs doctors, nurses, pharmacists, and patients about the increased risks of taking mycophenolate during pregnancy. The American College of Rheumatology guidelines recommend that women treated with MMF who plan to conceive should stop taking MMF >6 weeks prior. For men who plan to father a child, the ACR conditionally recommends continuing MMF [69], whereas the manufacturer's prescribing information recommends discontinuing mycophenolate at least 90 days before a trial of conception or sperm donation [104]. We recommend conducting an informed shared decision-making process with these men and considering alternative agents to MMF.

*Breastfeeding*: The manufacturer's prescribing information states that no harmful effects have been reported in breastfeeding children based on limited clinical data. Due to lack of sufficient evidence, the American College of Rheumatology guidelines recommend against the use of MMF while breastfeeding [69].

*Renal or hepatic impairment*: The manufacturer does not recommend a MMF dosage adjustment for patients with hepatic dysfunction or renal insufficiency. However, experts have recommended limiting MMF use to a maximum dose of 1 g twice daily if the patient's eGFR is <25 mL/min [113].

*Vaccination*: Influenza vaccine and other non-live vaccines can be administered while MMF is used. For live-attenuated vaccines, mycophenolate is recommended to be held from four weeks prior until four weeks after the vaccination [35].

*6.7. Counseling Points for a Patient Receiving MMF*

- Educate the patient concerning the potential side effects of MMF including gastrointestinal intolerance, liver toxicity, and bone-marrow suppression.
- Educate the patient that MMF takes up to 3~6 months of use to reach its steady state of clinical effectiveness. Encourage the patient take MMF as prescribed with good adherence despite the drug's initial minimal efficacy.
- The 500 mg MMF tablets or capsules may be too big to swallow for some patients. Inform the patient that a smaller size (250 mg) capsule formulation is available. Also, suspension formulation can be considered.
- Frequent blood-test monitoring is required while receiving MMF.
- Contact the healthcare provider if an infection occurs, or if a procedure or surgery is planned that may increase the risk of infection. MMF may have to be held temporarily in this instance.
- Encourage vaccination prior to initiating MMF, as vaccination is a highly effective infection-mitigation strategy.
- With drug-induced immunocompromised condition, the patient is eligible for RZV, Shingrix®.

**7. Hydroxychloroquine**

*7.1. Mechanism of Action*

Hydroxychloroquine (HCQ) is an antimalarial drug with immunosuppressive activity that has been used for many inflammatory diseases including sarcoidosis. The mechanism of action of HCQ is poorly understood. HCQ is thought to increase the pH in lysosomes,

causing suppression of intracellular antigen processing that subsequently leads to decreased T-lymphocyte activation and leukocyte chemotaxis [114,115].

### 7.2. General Treatment Indications for Hydroxychloroquine in Sarcoidosis

HCQ is regarded as a second-line agent for sarcoidosis. HCQ is specifically recommended as a second-line agent for pulmonary, skin, and neurologic sarcoidosis in the European Respiratory Society (ERS) Clinical Practice Sarcoidosis Treatment Guidelines [1]. Despite the European Respiratory Society (ERS), it is the authors' experience that HCQ has inadequate potency to be effective for pulmonary sarcoidosis. Because of the risk of retinopathy from HCQ (vide infra), the drug is not recommended for the treatment of eye sarcoidosis.

### 7.3. Dosing

The usual immunosuppressive dose of HCQ is $\leq$5 mg/kg/day (actual body weight), with a maximum daily dose of 400 mg in two divided doses [116]. No specific adjustment is required for hepatic or renal impairment.

### 7.4. Side Effects and Monitoring

Retinopathy is a common and potentially serious toxicity of HCQ. The risk of HCQ-associated retinopathy is dependent upon the daily dose and the duration of use. At the recommended HCQ dose of $\leq$5 mg/kg/day, the risk of retinopathy is less than 1% during the first five years of use and increases to almost 2% over the subsequent 10 years. However, subsequently, the risk of retinopathy accelerates to 20% after 20 years of HCQ use [116]. Other HCQ side effects include cardiomyopathy [117], hemolysis in those with G6PD deficiency [118], neuropsychiatric manifestations (agitation, anxiety, depression, psychosis, and psychomotor agitation), sleep disorders (hypersomnolence, insomnia, night terrors, and nightmares) [119,120], skin toxicities (exacerbations of psoriasis and dermatitis), gastrointestinal discomfort, and QT prolongation. Hypoglycemia may occur with HCQ use in both diabetic and non-diabetic patients, especially in those receiving concomitant drugs that have hypoglycemic effects [121,122].

Baseline retinopathy screening should include a funduscopic examination within the first year of HCQ use. Visual fields and spectral domain optical coherence tomography (SD-OCT) should be performed if maculopathy is present at baseline [116]. Annual ophthalmology screening is recommended to begin after five years of HCQ use [116]. More frequent ophthalmology evaluations may be warranted if the patient is using HCQ in a high dose range (>5 mg /kg actual body weight), has a diminished estimated glomerular filtration rate (eGFR), or has a history of previous retinal disease. It is recommended that patients receiving HCQ be monitored every 6 to 12 months with the following laboratory tests: CBC, serum liver-function and renal-function tests, and serum glucose.

### 7.5. Drug Interactions

As both tamoxifen and HCQ may cause retinal toxicity, the risk of eye complication increases greatly when both drugs are used concomitantly [123]. Concomitant use of dapsone and HCQ should be prescribed with caution because of a higher risk of hemolytic reactions especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency or methemoglobin reductase deficiency.

With high-dose aspirin (>3 g daily) or other salicylates such as bismuth subsalicylate and salsalate, HCQ may cause hypoglycemia in both diabetic and non-diabetic patients [124,125]. HCQ can increase the blood concentration of digoxin [126]; therefore, careful monitoring is needed when these drugs are given concomitantly. Drugs that prolong the EKG QT-interval, such as ciprofloxacin, norfloxacin, sertraline, escitalopram, trazodone, and IV haloperidol, require regular EKG monitoring of the QT-interval when used concomitantly with HCQ.

*7.6. Special Situations*

Per the manufacturer's prescribing information, HCQ dose adjustment is not required for patients with renal or hepatic insufficiency. However, the American Academy of Ophthalmology identified compromised renal function as one of the risk factors for retinopathy in long-term use patients. Therefore, some clinicians recommend to reduce the daily HCQ dose in patients with a low eGFR [127], although explicit guidance has not been established.

HCQ is safe to continue in women and men planning to have children, throughout pregnancy, and breastfeeding [69].

*Vaccination*: HCQ is considered as non-immunosuppressive by expert opinion that there are no limitations to vaccine administration [35].

*7.7. Counseling Points for a Patient Receiving HCQ*

- Educate the patient concerning potential side effects of HCQ, especially retinal toxicity, gastrointestinal intolerance, liver toxicity, and bone-marrow suppression.
- It takes up to 3~6 months of use to reach its steady state of clinical effectiveness. Encourage the patient to take HCQ as prescribed with good adherence despite the drug's initial minimal efficacy.
- Counsel the patient that ophthalmology evaluations as surveillance for retinopathy is required while receiving HCQ.
- Educate the patient to monitor his/her body weight. Individuals weighing <80 kg (177 pounds) should receive a weight-based daily dose (not to exceed 5 mg/kg/day). Counsel the patient to report to their healthcare provider if significant weight change occurs, as HCQ dose adjustment is needed. Individuals who weigh more than 80 kg should not exceed a daily dose of 400 mg. The maximum dose of HCQ is 400 mg daily, in divided dose, regardless of the patient's weight.
- Educate the patient that a psoriatic rash can develop or worsen while receiving HCQ, and the patient should contact their provider if such a skin reaction occurs.

**8. Tumor Necrosis Factor Alpha Inhibitors (TNFi)**

*8.1. Mechanism of Action*

Tumor necrosis factor alpha (TNFα) is a proinflammatory cytokine involved with coordination of the immune response. There is a sound rationale for this therapy in sarcoidosis, [128] because TNFa is thought to be integrally involved in the development of the sarcoid granuloma [129]. Dysregulation of TNFα production and signaling has been associated with immune-mediated disorders. Therefore, inhibition of TNFα can be an effective strategy for the treatment of sarcoidosis. The recent ERS sarcoidosis treatment guidelines recommend two tumor necrosis alpha inhibitors (TNFi), infliximab (IFX) and adalimumab (ADA), as third-line treatment options [1]. The other three marketed TNFi drugs (etanercept, certolizumab, and golimumab) either failed to demonstrate efficacy for the treatment of sarcoidosis or have not been studied [130,131].

IFX is a chimeric antibody against TNFα, containing both human and murine protein within the bioengineered antibody [132]. ADA, in comparison, is composed of 100% human protein. Fully human antibody has lower immunogenicity.

*8.2. General Treatment Indications for Tumor Necrosis Factor Alpha Inhibitors in Sarcoidosis*

IFX and ADA are regarded as third-line agents for sarcoidosis. Both IFX and ADA are specifically recommended as a third-line agent for pulmonary, skin, cardiac, and neurologic sarcoidosis in the European Respiratory Society (ERS) Clinical Practice Sarcoidosis Treatment Guidelines [1]. IFX is specifically recommended over ADA as a third-line agent for cardiac sarcoidosis. IFX and ADA are also recommended for the treatment of eye sarcoidosis [88]. IFX and ADA are particularly useful agents for the lupus pernio form of skin sarcoidosis, [133] cardiac sarcoidosis, [134] and neurosarcoidosis [135,136].

*8.3. Dosing*

The optimal dosing of TNFi for sarcoidosis is not currently standardized. Based on expert opinion, IFX and its biosimilars are usually dosed at 3–5 mg/kg via intravenous infusion at weeks 0 and 2, then once every 4–6 weeks. ADA is typically dosed at 40 mg subcutaneously every one to two weeks.

Unexpected anaphylactic reaction may occur in both IFX and ADA. Severe infusion reactions can occur with IFX that can be life threatening. Premedication with IV glucocorticoids, acetaminophen, and antihistamines are usually given prior to each IFX infusion.

*8.4. Side Effects and Monitoring*

IFX and ADA are immunosuppressive agents that increase the risk of infection including tuberculosis and hepatitis [137–140]. Prior to the initiation of IFX or ADA, the patient should have documented negative serologies for hepatitis B, hepatitis C, and negative screening for latent tuberculosis by QuantiFERON-GOLD or tuberculosis skin testing.

Both IFX and ADA can potentially develop anti-drug antibodies, but this is more common with IFX than ADA because of the chimeric design of IFX, which includes a murine protein portion. When anti-drug antibodies are formed, the TNFi treatment may become ineffective or can cause adverse reactions such as fever, rash, or bronchospasm [141]. There may be no clinical consequence from developing TNFi anti-drug antibodies; therefore, detection of anti-drug antibody is not a reason to stop the TNFi if the treatment is effective without side effects [141]. To mitigate anti-drug antibody development, concomitant use of methotrexate has been shown to be effective lowering the frequency of this complication [142].

Although the clinical data are inconsistent, TNFi drugs may increase the risk of malignancy, particularly lymphoma [143]. The American College of Rheumatology guidelines recommend that if an individual has history of solid tumor that has been cured for >5 years, then a TNFi agent can be used [55]. TNFi agents are used to treat autoimmune disorders but, paradoxically, the patient may develop autoimmune disorders by using TNFi, with symptoms such as lupus-like syndrome, skin rash, or fever [55,144–149]. TNFi drugs may cause heart failure, demyelinating disease, or worsen these conditions if those conditions were present prior to TNFi use [42,150].

If an infusion reaction occurs during IFX administration, the infusion rate may be reduced, or the infusion may be terminated if it is suspected to be an anaphylaxis event. Warning signs for anaphylaxis (hives or a choking sensation in the throat) that develop during an IFX infusion should be taken seriously and termination of the infusion should be considered.

Other side effects from TNFi include diverticulitis, autoimmune hepatitis, optic neuritis, hematologic symptoms (such as leukopenia, pancytopenia, and thrombocytopenia), headache, confusion, and tremor.

ADA injection-site reactions may occur, but in most cases these reactions have minimal consequences [151]. CBC and LFT is recommended to be obtained every six months while receiving a TNFi to monitor liver function and blood counts.

*8.5. Drug Interactions*

IFX and ADA should not be used with other immunosuppressive biologic medications or Janus Kinase inhibitors (JAKi) due to the profound immunosuppression caused by using these drugs concomitantly. Live vaccines are contraindicated during TNFi use. Drug-database interaction checkers may indicate significant drug interactions between oral DMARDs such as MTX or LEF and TNFi due to a concern of increased infection risks. However, combination therapy with a biologic and oral DMARDs is considered safe and efficacious in clinical practice with routine monitoring.

*8.6. Special Situations*

*Pregnancy:* Both IFX and ADA cross the placenta. However, they can be used during the first two trimesters of the pregnancy. At the third trimester, IFX and ADA are recommended to be discontinued to avoid significant drug concentration in neonate [69].

*Breastfeeding*: IFX and ADA are large protein molecules. It is very unlikely for these TNFi agents to reach appreciable levels in the nursing child's blood stream via oral intake. Therefore, TNFi is considered safe to continue with breastfeeding [69].

*Compromised renal function:* No adjustment is needed for IFX or ADA because of renal dysfunction.

*Compromised hepatic function*: There are no established recommendations for adjusting IFX or ADA in patients with hepatic insufficiency.

IFX may cause elevations of serum liver enzymes, especially in patients with elevated transaminases at baseline or with metabolic dysfunction-associated steatotic liver disease (MASLD, formerly known as non-alcoholic fatty liver disease). Some experts recommend continuing IFX if the serum AST and ALT are elevated but <5 times upper limit of normal (ULN), with frequent LFT monitoring [152]. If AST and ALT are $\geq$5 times ULN then discontinuation of IFX may be considered [153].

*Vaccination*: Annual influenza vaccine and other non-live vaccines can be administered without interruption of IFX or ADA treatment. For live vaccines, the American College of Rheumatology recommends that IFX and ADA be held for one dose before the administration of live vaccine until four weeks after the live vaccine administration [35].

*8.7. Counseling Points for a Patient Receiving TNFi*

- Educate the patient concerning potential TNFi side effects, infections, malignancy, possible onset or worsening of congestive heart failure, or demyelinating diseases such as multiple sclerosis.
- Educate the patient that IFX or ADA may take up to three to six months to reach their steady states of clinical effectiveness. Encourage the patient take these medications as prescribed with good adherence despite the drugs initial minimal efficacy.
- ADA is a subcutaneous injection medication that can be used at home.
- IFX is administered via intravenous infusion at a clinic setting, and it typically takes several hours.
- For ADA, educate the patient on the injection technique. The first injection should be conducted in the presence of a health care professional for patient safety.
- For IFX, educate the patient that (s)he will receive pre-medications per the institution's protocol to prevent an IFX infusion reaction.
- Inform the patient not to compensate for a missed ADA dose with an additional dose. If the patient forgets an ADA injection, the patient should perform that injection as soon as possible and consider that day as the start of a new injection cycle.
- Contact the healthcare provider if an infection occurs, or if a procedure or surgery is planned that may increase the risk of infection. The TNFi agent may have to be held temporarily in this instance.
- Three to six months may take for the medication to build up to reach its maximum effectiveness. Be patient and adhere to the medication.
- The patient should inform the healthcare provider if there is a previous history of tuberculosis, hepatitis B, or hepatitis C infection.
- Emphasize that TNFi drugs are immunosuppressants and encourage vaccine adherence to mitigate risks of vaccine-preventable diseases.
- Live vaccine is contraindicated with TNFi agents.
- With drug-induced immunocompromised conditions, the patient is eligible for RZV, Shingrix®.

## 9. Rituximab

### 9.1. Mechanism of Action

Rituximab (RTX) is a chimeric antibody [154] that has affinity for the CD20 receptor on subpopulations of B cells and thereby leads to their depletion via cell-mediated and complement-dependent cytotoxicity, which promotes their apoptosis [155]. CD20 is only expressed on pre-B cells and mature B cells but not on progenitor (stem) cells or plasma cells [156]. Although sarcoidosis is thought to be a T-cell mediated disease, heightened B-cell activity is also seen in active sarcoidosis, including the development of a polyclonal gammopathy [157].

### 9.2. General Treatment Indications for Rituximab in Sarcoidosis

RTX is regarded as a fourth-line agent/salvage therapy for sarcoidosis. RTX is specifically recommended as a fourth-line agent for pulmonary sarcoidosis in the European Respiratory Society (ERS) Clinical Practice Sarcoidosis Treatment Guidelines [1].

### 9.3. Dosing

The optimal dose of RTX for sarcoidosis has not been established. The usual dose of RTX for autoimmune conditions is 1 g IV at week zero and week two, and this schedule is repeated every six months. However, for sarcoidosis, the decision to repeat this schedule is iterative and based on the treatment response. Because RTX is a chimeric molecule, it has high immunogenicity and pre-medications with IV glucocorticoids, along with oral acetaminophen and antihistamine agents, are typically administered prior to infusion. No dosage adjustment of the RTX dose is needed for hepatic or renal impairment, or dialysis.

### 9.4. Side Effects and Monitoring

Boxed warnings include infusion-related reactions, severe mucocutaneous reactions, progressive multifocal leukoencephalopathy (PML), and tumor lysis syndrome. The following side effects are rare but can be severe: diverticulitis (including bowel perforation), infection-like symptoms (fever, chills), palpitations, dizziness, high or low blood pressure, chest pain, and pulmonary and hepatic toxicity [158].

Prior to RTX administration, patients should be screened serologically for hepatitis B and hepatitis C, and for latent tuberculosis infection via a QuantiFERON-GOLD assay or a tuberculin skin test. Infusion-reaction monitoring is required during RTX administration. As RTX is contraindicated during pregnancy (vide infra), women receiving the drug who have reproductive potential require monitoring of their pregnancy status. PML signs and symptoms (such as hemiparesis, visual field deficits, cognitive impairment, aphasia, and ataxia cranial nerve deficits) also need to be monitored.

### 9.5. Drug Interactions

Combined use with other immunosuppressive biologics should be avoided due to the profound immunosuppression.

### 9.6. Special Situations

*Pregnancy:* The manufacturer recommends effective contraception during therapy and for 12 months following the last RTX dose for women who have reproductive potential. The American College of Rheumatology guidelines recommend that RTX be discontinued if the patient becomes pregnant unless patient is being treated for a life-threatening or organ-threatening situation [69].

*Breastfeeding*: Breastfeeding while receiving RTX is considered acceptable [69].

Compromised renal function: No adjustment is needed.

*Compromised hepatic function*: No adjustment is needed.

*Vaccination*: Because RTX is an anti-CD20 B-cell depleting agent, the therapeutic effect of vaccines can be diminished. If a live vaccine is indicated, it should be given more than six months after the most recent RTX dose, and further RTX doses should be held

for four more weeks after the live vaccine administration. Influenza vaccine and other non-live-attenuated vaccines can be administered in patients who have received RTX. It is recommended to time these vaccinations until just prior to when the next RTX dose is due, then to hold RTX for at least two weeks to enhance vaccine effectiveness [35].

*9.7. Counseling Points for a Patient Receiving RTX*

- Educate the patient concerning potential side effects of RTX.
- RTX is an intravenous infusion medication, which may take several hours to infuse.
- Contact the healthcare provider if an infection occurs while receiving RTX, or if a procedure or surgery is planned that may increase the risk of infection and follow their recommendation.
- Before you receive RTX, inform your provider if you have untreated hepatitis B, hepatitis C, tuberculosis, or previous infections that have been treated.
- Educate the patient that RTX is contraindicated in pregnancy. Pregnancy should be avoided while receiving RTX, and the patient will be monitored for pregnancy while receiving the drug.
- Emphasize that RTX is an immunosuppressant and encourage the patient to receive vaccines.
- Live vaccine is contraindicated with RTX.
- With a drug-induced immunocompromised condition, the patient is eligible for RZV, Shingrix®.
- Counsel the patient concerning PML symptoms such as loss of coordination, loss of language ability, memory loss, vision problems, and progressive weakness in arms and legs.

**10. Repository Corticotropin Injection**

*10.1. Mechanism of Action*

Repository corticotropin injection (RCI) is adrenocorticotropin hormone (ACTH) injected subcutaneously that activates corticotrophin receptors and melanocortin receptors (MCs). RCI activates all five subtypes of melanocortin receptors, MC1 through MC5. MC1 exists on melanocytes and macrophages and stimulates increased pigmentation. MC2 is the ACTH receptor that stimulates adrenal steroidogenesis. The side effects of RCI are therefore, not surprisingly, consistent with those caused by glucocorticoids. MC3 and MC4 are located at the CNS and spinal cord, associated with energy, food intake, and satiety control. MC5 regulates sebogenesis in lymphocytes and exocrine cells [159].

It is unclear if the mechanism of action of RCI works primarily through stimulation of corticotrophin receptors, melanocortin receptors, or both [159,160]. Stimulation of both receptors results in down regulation of several inflammatory cells involved in the formation of the sarcoid granuloma [161]. By using RCI, steroid dosages were reduced by >50% in three clinical trials such that RCI has been referred to as "a steroid sparing agent," [162] although it is unclear if stimulation of corticotrophin receptor results in anti-inflammatory properties and side effects similar to those of glucocorticoids.

*10.2. General Treatment Indications for Repository Corticotropin Injection in Sarcoidosis*

RCI is regarded as a fourth-line agent or salvage therapy for sarcoidosis. RCI is specifically recommended as a fourth-line agent for pulmonary sarcoidosis in the European Respiratory Society (ERS) Clinical Practice Sarcoidosis Treatment Guidelines [1].

*10.3. Dosing*

The manufacturer's prescribing information recommends "individualized dosing" for sarcoidosis, without specific guidance. Per expert opinion, the usual dose of RCI for pulmonary sarcoidosis is 40–80 units twice a week [1]. No dosage adjustment is needed for hepatic or renal impairment.

*10.4. Side Effects and Monitoring*

The side effects of RCI are similar to those from glucocorticoids: infection including hepatitis B or latent TB, adrenal suppression, electrolyte abnormalities, immunosuppression, psychiatric change (mood instability, depression, euphoria, insomnia, irritability, psychosis), fluid retention, hirsutism, hypertension, hyperglycemia, and gastrointestinal toxicities (gastritis, diverticulitis, ulcer, perforation). RCI may also cause cardiovascular complications (atrial fibrillation, heart failure, palpitations), dizziness, fatigue, headache, and malaise. An additional potential side effect from RCI is hyperpigmentation of the skin by MC1 receptor stimulation from the drug.

The monitoring of RCI use is identical to that with glucocorticoids (vide infra). Because RCI is an injectable medication, patients should be monitored for injection-site reactions.

*10.5. Drug Interactions*

RCI virtually shares the same drug interaction with glucocorticoids.

*10.6. Special Situations*

*Pregnancy and breastfeeding:* The manufacturer's prescribing information states that the published literature on systemic corticosteroid use during pregnancy may be relevant for RCI use, suggesting similar concerns. With the current data and level of evidence, we believe that it is reasonable to consider the management of women receiving RCI during pregnancy and while breastfeeding similar to those receiving glucocorticoids.

Compromised renal function: No adjustment is needed.

*Compromised hepatic function*: No adjustment is needed.

*Vaccination*: Live and live-attenuated vaccines are contraindicated for patients receiving "immunosuppressive doses" of RCI per the manufacturer's prescribing information. However, the cut-off of an immunosuppressive dosing level was not specified. RCI specific information regarding vaccination recommendation is scarce.

*10.7. Counseling Points for a Patient Receiving RCI*

- Educate the patient concerning potential side effects of RCI, which are practically the same as glucocorticoids plus increased pigmentation.
- RCI is a subcutaneous injection.
- RCI should be stored in a refrigerator.
- Contact the healthcare provider if an infection occurs, or if a procedure or surgery is planned that may increase the risk of infection. RCI may have to be held temporarily in this instance.
- The patient should inform the healthcare provider if there is a previous history of untreated or previously treated tuberculosis, hepatitis B, or hepatitis C infection.
- Emphasize that RTX is an immunosuppressant and encourage the patient to receive vaccines.
- Live vaccine is contraindicated in patients receiving RCI, per prescribing information.
- With drug-induced immunocompromised conditions, the patient is eligible for RZV, Shingrix®.

**11. Summary**

We have provided an overview of the common pharmacologic agents used for the treatment of sarcoidosis. The dosing, side effects, and monitoring of sarcoidosis drugs are summarized in Table 5. Table 6 summarizes the use of these agents in special situations. Sarcoidosis may require treatment to prevent organ-threatening or life-threatening complications of the disease. However, sarcoidosis is most commonly treated for quality-of-life [163]; in such patients, avoidance of drug side effects and drug-induced adverse events is of paramount importance. We believe that optimal use of these agents will improve sarcoidosis patient care and patient well-being.

**Table 5.** The dosing, side-effects, and contraindications of common sarcoidosis medications.

| Drug | Dosage Form | Dosing | Side Effects | Contraindications per US or Canadian Label | Renal Dose Adjustment Required | Hepatic Dose Adjustment Required | PGx Dose Adjustment Required |
|---|---|---|---|---|---|---|---|
| **Prednisone (FDA approved as "systemic rheumatic disorders")** | Oral | Varies. 5–30 mg daily in single or divided doses. Higher dose may be needed for severe diseases. | gastritis, nausea and other GI effects, osteoporosis, weight gain, diabetes, hypertension, fluid retention, hyperglycemia, skin atrophy, impaired wound healing, depression, mood change, adrenocortical insufficiency with inappropriate tapering, Cushing syndrome, decreased growth in children, myopathy, glaucoma, cataract, risk of infection | Herpes simplex of the eye, measles, or chickenpox (except for short term or emergency), peptic ulcer, diverticulitis, viral or bacterial infections not controlled by anti-infective treatment. | No | No | No |
| **Methotrexate** | Oral, SC | 5-25 mg/week Split dosing for ≥15 mg for oral dosing. Split dosing in not needed for SC. | Mouth sores, bone marrow suppression, hepatotoxicity, nausea and other GI effects, hair loss, pneumonitis, photosensitivity | Pregnancy, severe hepatic insufficiency, alcohol use dialysis, chronic pleural effusion | Yes | Yes | No |
| **Leflunomide** | Oral | 10~20 mg daily | Mouth sores, bone marrow suppression, hepatotoxicity, nausea and other GI effects, hair loss, peripheral neuropathy, increased blood pressure | Pregnancy Severe hepatic insufficiency Alcohol use | No | Yes | No |
| **Hydroxychloroquine** | Oral | 5 mg/kg/day with a maximum of 400 mg daily given in divided doses | Retinopathy, QT prolongation, psoriasis, nausea, and other GI effects | | No | No | No |
| **Azathioprine** | Oral | 50~250 mg daily in divided doses | Bone marrow suppression, nausea and other GI effects, hepatotoxicity | | No (manufacturer) Yes (experts) | No | Yes |
| **Mycophenolate Mofetil** | Oral tablet, capsule, and suspension | Start with 500 mg BID. Max maintenance dose 1500 mg BID. Do so slowly to avoid GI side effects | Bone marrow suppression, nausea and other GI effects, fever, arthralgia, myalgias, liver, hematological, dermatological toxicity, malignancy, hypertension, John-Cunningham (JC) virus associated Progressive Multifocal Leukoencephalopathy (PML) | Pregnancy | No | No | No |
| **Infliximab** | IV | Induction: 3–5 mg/kg at week 0, 2, 6. Maintenance: 3–5 mg/kg every 4–8 weeks after induction. | Serious infection, malignancy, lymphoma, heart failure, demyelinating disease, autoimmune disorder (e.g., lupus-like syndrome, fever), reactivation of latent infections such as Hepatitis B, Tuberculosis, infusion related reactions (e.g., angioedema, bronchospasm) | Severe heart failure | No | No | No |
| **Adalimumab** | SC | 40 mg every week or every other week | Serious infection, malignancy, lymphoma, heart failure, demyelinating disease, autoimmune disorder (e.g., lupus-like syndrome, fever), reactivation of latent infections such as Hepatitis B, Tuberculosis, injection site reaction | Severe heart failure | No | No | No |

**Table 5.** *Cont.*

| Drug | Dosage Form | Dosing | Side Effects | Contraindications per US or Canadian Label | Renal Dose Adjustment Required | Hepatic Dose Adjustment Required | PGx Dose Adjustment Required |
|---|---|---|---|---|---|---|---|
| **Rituximab** | IV | 1 gram two weeks apart (week 0 and 2). Repeat every 6 months if clinically needed. | Serious infection, PML, reactivation of Hepatitis B, infusion related reactions (e.g., angioedema, bronchospasm), flushing, hypertension, edema, pruritis, hematologic side effects (anemia, neutropenia, hypogammaglobulinemia, leucopenia, thrombocytopenia), dyspnea | Severe, active infection, PML, hypersensitivity or anaphylactic reaction to murine proteins | No | No | No |
| **Repository corticotropin injection (FDA approved)** | SC | 40–80 units twice weekly | Same as glucocorticoids<br>Hyperpigmentation | Same as glucocorticoid assumed | No | No | No |

PGx: Pharmacogenomics.

**Table 6.** The use of common sarcoidosis in special situations.

| Drug | Safe to Administer Non-Live Vaccine, Influenza Vaccine | Safe to Administer live or Live-Attenuated Vaccine | Safe to Use during Pregnancy | Safe to Use during Breastfeeding | Drug to be Avoided for Concomitant Use | Cautions |
|---|---|---|---|---|---|---|
| **Prednisone (FDA approved as "systemic rheumatic disorders")** | Yes | Depends on dose | Yes | Yes | | Use steroid sparing agents as possible to avoid long term side effects of glucocorticoids. |
| **Methotrexate** | Yes, hold for 2 weeks after vaccination if possible. | Hold 4 weeks prior and 4 weeks after | No | No | Sulfamethoxazole/ trimethoprim | Folic acid supplement daily (1~4 mg daily) recommended. Leucovorin rescue in case of toxicity. |
| **Leflunomide** | Yes | Hold 4 weeks prior and 4 weeks after | No | No | | Enterohepatic recycling occurs: Accelerated clearance process with cholestyramine or charcoal needed in case of toxicity or unplanned pregnancy |
| **Hydroxychloroquine** | Yes | Yes | Yes | Yes | | Yearly eye exam |
| **Azathioprine** | Yes | Hold 4 weeks prior and 4 weeks after | Yes | Yes | Allopurinol Febuxostat | *TPMT* and/or *NUDT15* deficiency |
| **Mycophenolate Mofetil** | Yes | Hold 4 weeks prior and 4 weeks after | No | No | | Avoid use with azathioprine (↑ risk myelosuppression) Oral suspension formulation useful for patients with swallowing issues |
| **Infliximab** | Yes | Hold 1 dose prior and 4 weeks after | OK 1st and 2nd trimester Hold for 3rd trimester | Yes | Other immunosuppressive biologic DMARD or Janus Kinase inhibitors | Monitor for anaphylaxis, severe infusion reaction. Consider antibody formation if efficacy wanes. |
| **Adalimumab** | Yes | Hold 1 dose prior and 4 weeks after | OK 1st and 2nd trimester Hold for 3rd trimester | Yes | Other immunosuppressive biologic DMARD or Janus Kinase inhibitors | |
| **Rituximab** | Yes | Hold 6 months prior and 4 weeks after | Discontinue at conception unless life or organ threatening condition | Yes | Other immunosuppressive biologic DMARD or Janus Kinase inhibitors | Monitor for anaphylaxis, severe infusion reaction. Consider antibody formation if efficacy wanes. |
| **Repository corticotropin injection (FDA approved)** | No specific recommendationSame as glucocorticoid assumed | No specific recommendation Same as glucocorticoid assumed | No specific recommendation Same as glucocorticoid assumed | No specific recommendationSame as glucocorticoid assumed | No specific recommendation Same as glucocorticoid assumed | Same as glucocorticoid assumed |

DMARD: disease modifying anti-rheumatic drug.

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# Clinical Manifestations and Management of Fibrotic Pulmonary Sarcoidosis

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**Abstract:** Fibrotic pulmonary sarcoidosis represents a distinct and relatively uncommon manifestation within the spectrum of sarcoidosis and has substantial morbidity and mortality. Due to the scarcity of research focused on this specific disease subtype, our current understanding of pathogenesis and optimal management remains constrained. This knowledge gap underscores the need for further investigation into areas such as targeted therapies, lung transplantation, and quality of life of patients with fibrotic pulmonary sarcoidosis. The primary aim of this review is to discuss recent developments within the realm of fibrotic pulmonary sarcoidosis to foster a more comprehensive understanding of the underlying mechanisms, prognosis, and potential treatment modalities.

**Keywords:** pulmonary fibrosis; advanced pulmonary sarcoidosis; sarcoidosis; fibrotic pulmonary sarcoidosis

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## 1. Background

Sarcoidosis is a complex multisystem inflammatory disease characterized by the formation of noncaseating granulomas that predominantly affects the respiratory system [1–3]. While over 60% of sarcoidosis patients have resolution of disease in 2–5 years, the remaining experience chronic disease, including fibrotic change [4]. Sarcoidosis generally exhibits notable demographic disparities, with the highest incidence and prevalence seen in Black patients, particularly among females [5]. A population-based study in the United States found that African Americans with sarcoidosis had a 20% higher rate of pulmonary fibrosis, and African-American women with sarcoidosis had a higher mortality rate at a younger age when contrasted with their Caucasian counterparts [6].

The Scadding staging system is used to assess radiographic stages of pulmonary sarcoidosis, with stage 4 denoting advanced fibrotic changes [7]. Approximately 5.4–19.9% of patients may present with fibrotic disease initially [7,8]. Patients with chronic disease experience increased breathlessness and decreased quality of life as radiographic disease worsens [9]. Advanced pulmonary sarcoidosis (APS) is used to denote the forms of sarcoidosis that cause significant risk of loss of lung function, respiratory failure, or death, and include advanced fibrosis and associated complications as well as pulmonary hypertension [10,11]. Although mortality in sarcoidosis is reported to be less than 5%, mortality in APS ranges from 11–21% [4,11–15]. Most of the poor outcomes attributed to APS are due to fibrotic pulmonary sarcoidosis, an entity that needs to be understood better. In this article, we aim to review recent advances in pathogenesis, clinical presentation, evaluation, and management of fibrotic pulmonary sarcoidosis.

## 2. Pathobiology

### *2.1. Basic Pathophysiology: An Interplay between Genetic and Environmental Factors*

The pathobiology underlying sarcoidosis and its development into fibrotic disease remains a subject of ongoing research. Sarcoidosis is largely believed to result from a

culmination of abnormal immunologic responses following antigen exposure (Figure 1) in a genetically predisposed host. Air pollutants, infectious agents such as mycobacteria and *Cutibacterium acnes*, and exposure to inorganic dust such as silica have been implicated in pulmonary sarcoidosis [16–19]. Genetic factors have been implicated in the susceptibility and manifestation of the disease, such as HLA-DRB1 on chromosome 6, 5q11.2, 1p22, 3p21-14, 11p15, and 17q21 [5,20–22]. Specific alleles of HLA-DRB1 on chromosome 6 may have race-specific associations with varying phenotypes and confer protective effects against disease, while others may be associated with increased disease severity [23,24].

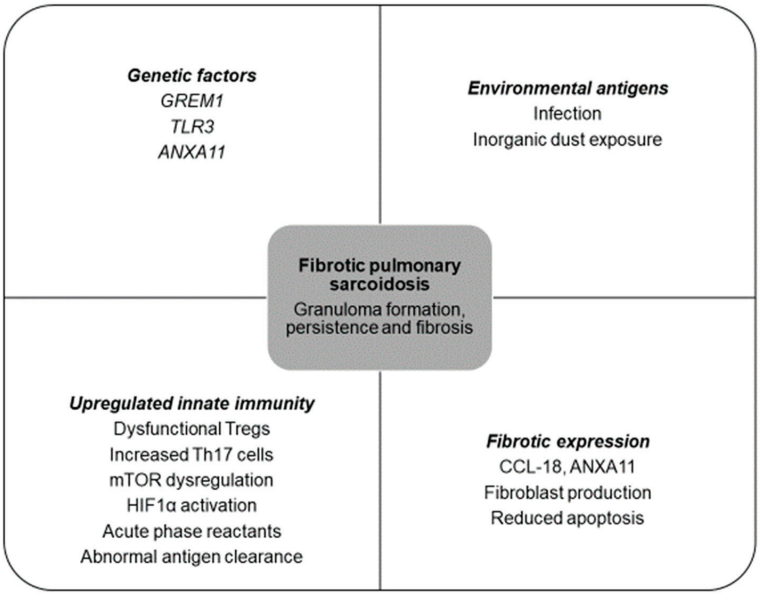


**Figure 1.** Drivers that may be involved in fibrotic pulmonary sarcoidosis. *GREM1*, gremlin 1; *TLR3*, toll-like receptor 3; *ANXA11*, annexin 11; Tregs, T-regulatory cells; Th17, T-helper 17 cells; mTOR, mammalian target of rapamycin complex 1; HIF1α, hypoxia inducible factor 1; CCL-18, C-C motif chemokine ligand 18.

### *2.2. Evolving Knowledge of Pathophysiology in Fibrotic Pulmonary Sarcoidosis*

Several genes have been linked to the pathogenesis of fibrotic disease. *GREM1* on chromosome 15q13-q15 encodes a glycoprotein, gremlin, that inhibits bone morphogenic proteins (BMPs) from the TGF-B family [25]. TGF-B, a cytokine secreted by macrophages, T-lymphocytes, and bronchial epithelial cells, promotes extracellular matrix accumulation and inhibits matrix degradation [26]. A study examining *GREM1* variations among sarcoidosis patients with and without fibrosis on chest radiography revealed that carriers of the *GREM1* CC genotype exhibited elevated gremlin levels and were at a 6.4-fold higher risk of developing fibrosis [27]. Genetic variations of TGF-B3 are notably greater in fibrotic patients, and may be associated with the development of pulmonary fibrosis in sarcoidosis [28].

Fibrotic pulmonary sarcoidosis has also been linked to specific variants, such as caspase recruitment domain 15 (CARD15) 2104T (702W), CARD15 1761G (587R), and C-C chemokine receptor 5 (CCR-5) [29]. Additionally, a promoter variation in prostaglandin-endoperoxide synthase 2 (PTGS2), −765G>C, has been identified as another potential risk factor for fibrotic disease in sarcoidosis. PTGS2 serves as a regulatory enzyme responsible for synthesizing prostaglandin E2, which is known for its antifibrotic properties. Carriers of the −765C allele were found to exhibit increased susceptibility to sarcoidosis, poorer prognosis, and an increased predisposition to fibrotic disease [30].

The pathogenesis of fibrotic pulmonary sarcoidosis remains unclear, but current investigations have identified several potential mechanisms that could elucidate both the fibrotic and inflammatory reactions observed. Pulmonary sarcoidosis is a granulomatous disease characterized by accumulation of lymphocytes and macrophages, inducing granuloma formation. An unknown antigen is first presented to CD4+ T-lymphocytes that trigger T-helper 17 (Th17)-related cytokines, interleukin-17A (IL-17A), regulatory T-cells, and tumor necrosis factor (TNF), a proinflammatory cytokine, to produce granulomas [31]. Granulomas may spontaneously resolve or persist, and may progress to fibrosis via high levels of TNF and mononuclear phagocytes (MNPs) and activation of fibroblasts, myofibroblasts, and collagen formation [32].

Chronic fibrosis is thought to be the culmination of increased Th17 cells and primed monocyte-derived macrophages (toll-like receptor-3 (TLR3) polymorphism, type 1 interferon signaling) responding disproportionately to an insult [33]. In particular, monomorphisms in *TLR3* have been implicated in fibrotic pulmonary sarcoidosis, resulting in reduced TLR3 function in innate immune responses and reduced apoptosis of fibroblasts [33,34]. This response drives production of chemokine ligand 18 (CCL-18), which induces fibrogenesis [33]. CCL-18 is associated with fibrotic pathogenesis in IPF, with increased mortality and fibrotic burden on imaging [35,36]. Another protein, annexin A11 (ANXA11), is a calcium-dependent protein involved in innate immunity and cell apoptosis. A small study found a correlation between a minor allele in the *ANXA11* gene and African Americans with fibrotic pulmonary sarcoidosis, and suggested *ANXA11* polymorphism may lead to persistence of Th1 and Th17 cells, resistance to apoptosis, and persistence of granuloma [24,33].

Increased production of CCL-18 from macrophages attracts activated CD4 T-cells and increases transforming growth factor-beta (TGF-β) secretion, enhancing Th17-mediated inflammation. Th17 expresses IL-17A, a proinflammatory cytokine that drives fibrosis and causes corticosteroid resistance [37]. One study found higher bronchoalveolar lavage (BAL) IL-17 levels in patients with pulmonary sarcoidosis without disease resolution, but this was not studied in patients with or without fibrotic disease [38]. Another acute phase reactant is serum amyloid antigen (SAA), which has been shown to induce Th17 response, chronic inflammation, and fibrosis [39]. It can stimulate the production of Th1-mediated granulomatous inflammation via TNG, IL-10, and IL-18, and has been shown to correlate positively with fibrotic disease in chronic fibrotic sarcoidosis [40,41].

Regulatory T-cells (Tregs) are a specialized subset of CD4+ T-cells involved in immunosuppression via production of inhibitory cytokines such as interleukin-10 (IL-10), inhibitory receptors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and deplete interleukin-2 (IL-2) [42]. Prior studies have found lower numbers of Tregs in BAL and Treg dysfunction in patients with active sarcoidosis [43–45]. In both active and fibrotic sarcoidosis patients compared with IPF patients, a recent study found an imbalance of Tregs and Th17.1 cells in peripheral blood and BAL fluid, with lower frequency of Tregs but high Th17.1 in BAL and higher frequency of Tregs but low Th17.1 in peripheral blood [46]. The authors suggest that an increased proportion of circulating Tregs was associated with fibrotic disease on radiography, and the lung microenvironment may affect immunological pathogenesis of sarcoidosis [46].

Another pathway that may contribute to granuloma formation and Th17 differentiation is a dysregulation of the mammalian target of rapamycin (mTOR) pathway. mTOR regulates autophagy and growth in response to stressors [47]. Defects in mTOR-related pathways may inactivate autophagy, decrease pathogen clearance, and cause granulomatous formation and persistence [48]. In fibrotic pulmonary sarcoidosis, mTOR complex 1 (mTORC1) remains upregulated, impairing antigen clearance and promoting excess granulomatous formation [33,49,50].

Recently, the hypoxia-induced factor 1-alpha (HIF1α) pathway has garnered attention. A recent investigation found that when exposed to hypoxic conditions, monocyte-derived macrophages increase their proinflammatory response and reduce antigen presentation, leading to a reduction in T-cell response [51]. Through the secretion of profibrotic factor

plasminogen activator inhibitor-1 (PAI-1), this process may promote development and persistence of granulomas in active sarcoidosis, reduce fibrinolytic activity, and ultimately contribute to the development of fibrotic disease [51].

## 3. Clinical Manifestations

Prior studies have found that the average age of presentation with fibrotic pulmonary sarcoidosis is in the fourth decade of life [7,12]. Up to 20% of patients can present with fibrotic disease at initial presentation, but chronic disease may develop in 20–25% of patients with a prior diagnosis of sarcoidosis [7,52,53]. Clinical symptoms are nonspecific and include dyspnea (80%), cough (51.4%), hemoptysis (2.8%), sputum production (18.3%), crackles (28.2%), digital clubbing (6.3%), and wheezing (5.6%) [12].

### *3.1. Imaging*

On chest radiography (CXR), Scadding stage 4 is defined by the presence of pulmonary fibrosis, as mentioned above (Figure 2) [7]. Patients may have upper-lobe-predominant linear opacities projecting from the hilum with dilated airways [54]. High-resolution computed tomography (HRCT) gives a more comprehensive understanding of anatomic changes. Three major patterns of fibrotic sarcoidosis can be identified: central bronchial distortion, peripheral upper zone honeycombing, and diffuse hilar linear opacities (Figure 2) [11,55,56]. Fibrocystic opacities may track along the airways from the hilum to peribronchovascular and fissural regions [11]. HRCT may show subpleural honeycombing, fibrocystic lesions larger than traditional honeycombing, paracicatricial emphysema, and development of mycetomas [11,57]. Granulomatous infiltration of the airways will cause airway distortion, airway angulation, and diffuse wall thickening [7,56]. HRCT can also help screen for sarcoidosis-associated pulmonary hypertension by using a ratio of main pulmonary artery diameter/ascending aorta diameter (MPAD/AAD) greater than 1, evaluating for a dilated pulmonary artery greater than 30 mm (Figure 2), and using a ratio of the diameter of the main pulmonary artery/body surface area (MPA/BSA) greater than 16 [3,11,58].

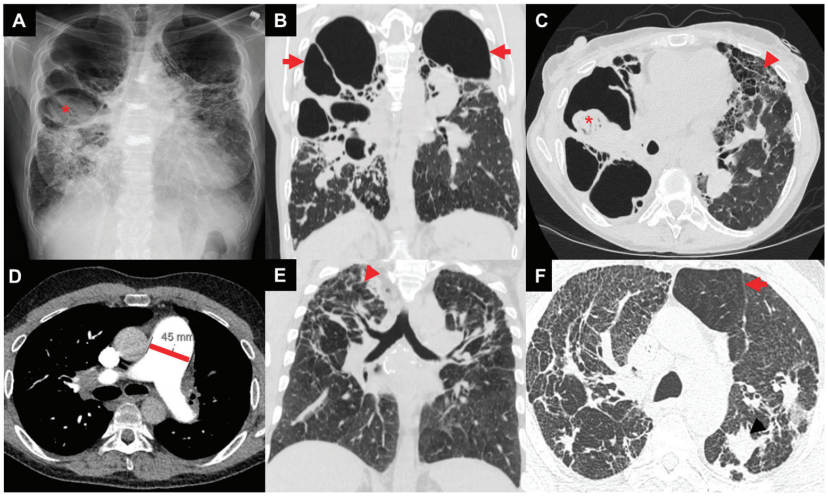


**Figure 2.** Images of three patients with advanced pulmonary sarcoidosis: patient 1 with biapical cavities and mycetoma (asterisk) on chest X-ray (**A**), large biapical bronchiectatic cavities (arrows) on coronal image of CT chest (**B**), right apical mycetoma (asterisk) and extensive left-sided upper-zone predominant fibrosis (arrow head) of anterior lung on axial image of CT chest (**C**); patient 2 with enlarged pulmonary artery diameter (45 mm) on axial image of CT chest (**D**); patient 3 with bilateral irregular reticular and nodular fibrosis (arrow head) on coronal image of CT chest (**E**) with air trapping (arrow) on axial image of CT chest (**F**).

Fluorodeoxyglucose positron emission tomography integrated with computed tomography (FDG-PET/CT) in combination with cardiac MRI is predominantly used for the diagnosis and management of cardiac sarcoidosis [3,59]. In pulmonary sarcoidosis, FDG-PET/CT has exhibited a high sensitivity rate ranging between 94% and 100% in identification of ongoing inflammatory processes (Figure 3) [60,61]. Few studies have investigated its diagnostic use in pulmonary sarcoidosis [62–64]. One retrospective study involving 95 patients, with 85% demonstrating signs of fibrotic disease, found that the severity of pulmonary involvement as assessed by HRCT and lung function parameters was associated with increased FDG uptake at a threshold standardized uptake value (SUVmax) of greater than or equal to 2.5 [63]. Another study assessed the role of FDG-PET/CT in comparison with HRCT to identify sarcoidosis activity, and found a discordance rate of greater than 50% between FDG uptake and pathologic changes on HRCT. The presence of active nodal disease, active parenchymal changes, and disease recurrence in extrapulmonary regions were additional findings noted on FDG-PET/CT not discernible on HRCT [64].

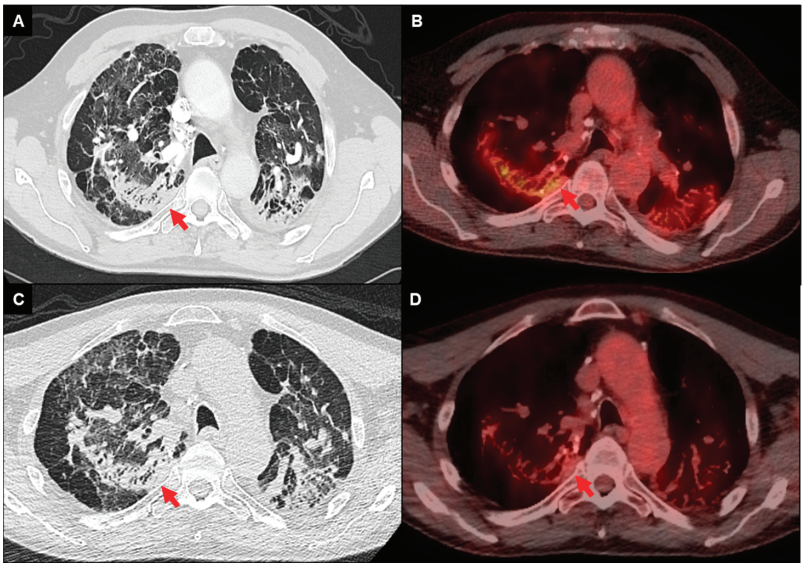


**Figure 3.** FDG-PET/CT imaging of a 68-year-old male with fibrotic pulmonary sarcoidosis on chronic methotrexate with metabolically active infiltrates (arrows) in the right upper lobe and left upper lobe extending into the pleura (**A**,**B**); reduced density and activity on follow-up imaging 12 months after the addition of anti-TNF-alpha inhibitor (**C**,**D**).

In the context of disease activity monitoring, a limited number of studies found that patients who exhibited reductions in SUVmax values following glucocorticoid therapy experienced lower rates of relapse, in contrast to individuals without reduction in SUVmax, who notably had higher relapse rates (Figure 3) [65,66]. To date, there is no SUVmax threshold that is validated to denote disease activity or recommendations for use of FDG-PET/CT in determining anti-inflammatory treatment for fibrotic pulmonary sarcoidosis. Future studies are needed to determine optimal utility of FDG-PET/CT imaging in fibrotic pulmonary sarcoidosis.

### *3.2. Pulmonary Function Testing*

On pulmonary function testing (PFT), fibrotic sarcoidosis presents with varying degrees of gas-exchange, airflow-obstruction, ventilatory-restriction, and mixed defects [12]. One study found associations between HRCT anomalies and pulmonary function testing, revealing a connection between restrictive defects and reduced diffusion capacity with

interstitial fibrosis and subpleural honeycombing, while airflow obstruction correlated with bronchial distortion. Linear opacities without septal changes were found to have the least functional impairment [55]. Patients with fibrotic disease were shown to have a higher prevalence of mixed ventilatory defects, lower diffusion capacity for carbon monoxide, and higher mortality in another study [67]. A recent study characterizing different pulmonary function phenotypes in sarcoidosis found that fibrocystic patterns on chest imaging ($n$ = 22) were more commonly seen in Black individuals, and patients with fibrocystic patterns had a greater degree of restriction and mixed pulmonary function phenotypes than patients with nonfibrotic pulmonary sarcoidosis [68]. The findings of this study emphasize that fibrotic disease is linked to a higher prevalence of restrictive and mixed defects [68]. On 6-min walk tests, individuals with fibrotic sarcoidosis may have reduced walk distance, which has been associated with increased mortality, sarcoidosis-associated pulmonary hypertension, reduced forced vital capacity, and exertional hypoxia [69,70].

### *3.3. Serum Biomarkers*

Inflammatory biomarkers have been proposed as a method to monitor disease activity and treatment response in pulmonary sarcoidosis. These biomarkers have not been studied in the setting of fibrotic disease, and larger prospective studies are needed to assess clinical utility. Nevertheless, research indicates promising results for a few of these biomarkers, such as serum angiotensin-converting enzyme (ACE), human chitotriosidase, C-reactive protein (CRP), and Krebs von den Lungen-6 (KL-6).

Serum ACE is a glycoprotein produced by alveolar macrophages that converts angiotensin I to angiotensin II in the renin-angiotensin pathway and degrades bradykinin. Granulomas express alveolar macrophages, and serum ACE levels may reflect granulomatous burden [71]. ACE levels are currently the most frequently used laboratory testing in sarcoidosis as a marker for disease activity, although they are neither sensitive nor specific [12,72–74]. High serum ACE levels may be seen in patients with greater HRCT abnormalities, including ground-glass opacities, interlobular septal thickening, nodularity, and consolidation [75]. They may be used to monitor treatment effects in sarcoidosis patients. An observational cohort study assessing treatment response with methotrexate by measuring serum ACE and soluble IL-2 receptor (sIL-2R), a marker of T-cell activation, found high baseline levels of ACE correlated with lung function improvement after treatment; and decreases in ACE and sIL-2R after treatment correlated with improved lung function, especially with change in DLCO [73]. In addition, T-helper type 1 cells secrete IL-2 and bind to IL-2R, stimulating T-cell proliferation [76]. sIL-2R is a marker of T-cell activation, whereas ACE reflects total body granulomas. In this study, ACE had a greater correlation with lung function change after methotrexate therapy than sIL-2R [73]. CRP is a proinflammatory acute phase reactant elevated in chronic sarcoidosis, and elevated baseline values may correlate with disease severity, physiologic progression of disease, and treatment response [77,78]. CRP may be useful in monitoring disease activity but requires validation. Further research of serum biomarkers is needed on the clinical utility of these in sarcoidosis in general as well as fibrotic pulmonary sarcoidosis.

## 4. Prognosis

The presence of fibrosis on high-resolution computed tomography (HRCT) scans indicates a poorer prognosis, disease progression, and an elevated risk of mortality [13,55,58,79]. One study proposed a clinicoradiological staging system using HRCT patterns and composite physiological indices (CPI, a weighted index of lung function variables) to determine prognosis in pulmonary sarcoidosis [58]. The staging system was composed of CPI, main pulmonary artery diameter to ascending aorta diameter ratio (MPAD/AAD), and fibrosis threshold of $\geq$20% [58]. The staging system was found to be straightforward yet reliable for identifying patients with increased risk of mortality [58]. The results further emphasized that CPI was the strongest predictor of mortality [58].

A prospective study in fibrotic pulmonary sarcoidosis evaluated the feasibility of employing percent fibrosis on HRCT, reduced DLCO, or increased CPI score to predict a clinal worsening event over an 18-month study period [80]. A clinical worsening event was defined as death, lung transplant, or greater than absolute 10% drop in percent predicted FVC [80]. Though the study was underpowered at 16 participants due to poor enrollment, it found that individuals with at least 20% fibrosis on HRCT and DLCO less than 30% predicted were more likely to experience a clinical worsening event [80].

In a recent study, HRCT features of fibrotic pulmonary sarcoidosis and its impact on pulmonary function and survival were assessed [81]. The study found that the presence of over 20% fibrosis and basal subpleural honeycombing were predictive of deteriorating pulmonary function and worse survival in fibrotic pulmonary disease [81]. Moreover, the researchers found that independent predictors of poor survival included basal subpleural honeycombing, DLCO < 40%, and White race [81]. This is the first study to assess patterns of fibrosis with mortality.

Associations between race and survival have been made by prior studies. As mentioned earlier, a United States population-based study found increased rates of pulmonary hypertension and pulmonary fibrosis in African Americans, and a significantly disproportionate increase in mortality amongst young African-American women compared with their Caucasian counterparts [6]. The recent finding of higher mortality in White race as noted above was shown after controlling for extent of fibrosis, fibrotic pattern on HRCT, presence or absence of sarcoidosis-associated pulmonary hypertension, age, and study location. The uncertainty surrounding the relationship between race, sex, and mortality in fibrotic pulmonary sarcoidosis underscores the need for additional research.

In a retrospective study conducted in France, individuals with fibrotic pulmonary sarcoidosis displayed a mortality rate of 11.3% over an average follow-up period of seven years [12]. Respiratory complications accounted for 75% of patient deaths, while 31.2% were attributed to pulmonary hypertension, and 25% were linked to chronic respiratory failure [12]. Other complications as contributory causes of death included extrapulmonary cardiac involvement, immunosuppressive therapy, and aspergilloma infection [12]. On univariate analysis, the authors found New York Heart Association [82] (NYHA) functional class, forced expiratory volume in 1 s (FEV1) below 63% predicted, forced vital capacity (FVC) below 72% predicted, total lung capacity (TLC) below 74% predicted, diffusion capacity of carbon monoxide (DLCO) below 58% predicted, room-air arterial oxygen tension (PaO2) below 81 mmHg, and the presence of pulmonary hypertension exhibited a significant association with increased risk of mortality [12].

## 5. Management

Management of fibrotic pulmonary sarcoidosis is challenging, largely due to the lack of standardized therapy and variability in presentation and evolution of the disease and needs long-term studies into treatment options. Treatment decisions are often guided by clinical experience and expert opinion. In general, a comprehensive approach involves the integration of various diagnostic tools, including serum biomarkers, PFT, 6MWT, imaging studies, and echocardiography. These assessments can be used to monitor disease progression, identify exacerbations and new complications such as pulmonary hypertension, and progressive respiratory failure. A personalized and multidisciplinary treatment strategy is necessary to address the complexities of the disease, manage comorbidities, deliver supportive care, and consider the possibility of lung transplantation (Figure 4). The next few paragraphs cover the basics of management of patients with fibrotic pulmonary sarcoidosis, but details can be found in corresponding sections of this series.

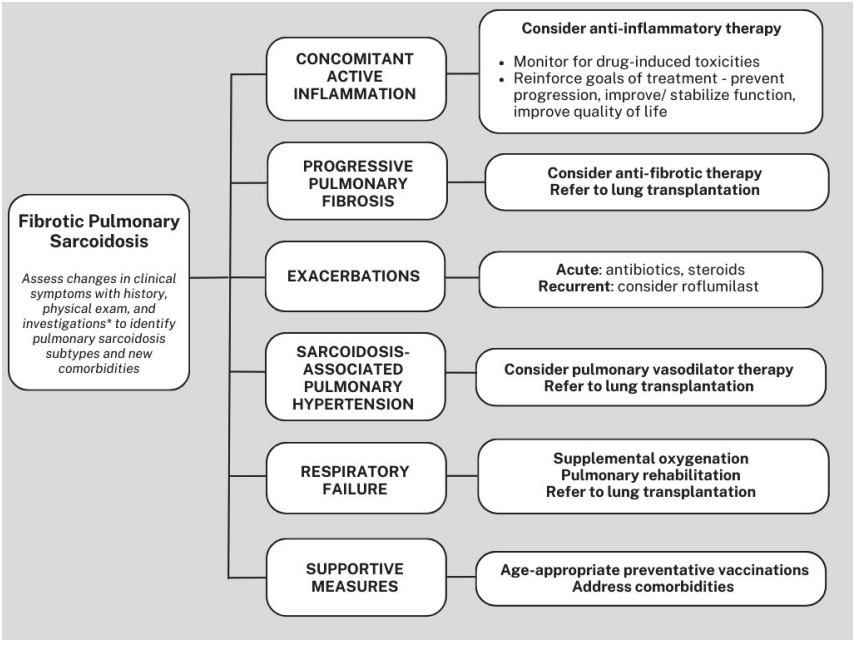


**Figure 4.** Simplified algorithm for the management of fibrotic pulmonary sarcoidosis. *Investigations with pulmonary function test, 6-min walk test, high-resolution computed tomography, echocardiogram, and fluorodeoxyglucose positron emission tomography integrated with computed tomography.

### *5.1. Anti-Inflammatory Therapy*

Anti-inflammatory agents may preserve or improve lung function, aid in symptom management, and prevent progression of disease in certain patients with fibrotic pulmonary sarcoidosis [12,83]. However, identifying which patients would benefit from treatment remains uncertain. Due to a lack of evidence-based therapies in fibrotic pulmonary sarcoidosis, the Delphi consensus and the ERS clinical practice guidelines on treatment of pulmonary sarcoidosis have not focused on this subset [83,84]. Currently, anti-inflammatory therapy in the setting of fibrotic pulmonary sarcoidosis is done in a case-by-case scenario.

In patients with acute or chronic disease, the primary method for managing inflammation involves the use of glucocorticoids (prednisone 20–40 mg daily) as the initial treatment [83,84]. As clinical symptoms resolve, glucocorticoids are rapidly tapered to doses less than 10 mg or to the lowest effective dose. In cases where glucocorticoids are unable to be tapered, the addition of antimetabolites with methotrexate or azathioprine as second-line agents is considered [83–85]. In the context of progressive fibrotic disease, prior use of methotrexate may pose a challenge by raising concerns about pulmonary toxicity, necessitating a thorough evaluation of patients for potential adverse effects. If feasible and without financial barriers, FDG-PET/CT may be useful in identifying areas of inflammation. If unavailable, other disease-modifying agents may have to be chosen. Anti-TNF-alpha agents such as infliximab can also be considered and have been shown to improve or maintain FVC [86,87]. In certain situations with ongoing disease progression, repository corticotrophin injections, rituximab, and JAK inhibitors can be explored, although a consensus is yet to be established [83]. The potential for adverse effects induced by chronic glucocorticoids and chronic immunosuppressive agents requires frequent monitoring and vigilance in identifying drug-induced toxicities. Relapse after discontinuation of therapy can occur, and patients require clinical monitoring. Use of anti-inflammatory agents in the setting of fibrotic pulmonary sarcoidosis needs more evidence. While there are multiple agents being studied in the management of pulmonary sarcoidosis, most

of these studies exclude patients with fibrosis >20%. It would be intriguing to see how these agents potentially impact the course of chronic pulmonary sarcoidosis and fibrotic pulmonary sarcoidosis.

### 5.2. Sarcoidosis-Associated Bronchiectasis

Patients with advanced pulmonary sarcoidosis can develop granulomatous infiltration of the airways, causing fibrotic changes with airway distortion and traction bronchiectasis. Airway abnormalities, along with chronic inflammatory treatments and poor mucociliary clearance, create optimal environments for infections and mycetomas [88–90].

### 5.3. Acute Pulmonary Exacerbations of Sarcoidosis

There is no consensus on the definition of acute exacerbations in sarcoidosis. Exacerbations have been described in the literature as new or worsening pulmonary symptoms with a decline in FVC or FEV1 for greater than one month, and exclusion of alternative causes [91,92]. Exacerbations may be related to bronchiectasis, infection, and impaired immune response, and require treatment with antibiotics and/or glucocorticoids [88]. In patients with fibrotic sarcoidosis, a small trial ($n$ = 38) found that patients with greater than two exacerbations who were treated with roflumilast, a phosphodiesterase-4 inhibitor, had improved FEV1 in subsequent visits and quality of life than those treated with placebo [93]. A larger prospective trial confirming these results would provide valuable insights into the efficacy of roflumilast and could help establish a more standardized approach in identifying and managing acute exacerbations.

### 5.4. Infections

Infections such as aspergillus, mycobacteria, cryptococcus, nocardia, and histoplasma can complicate clinical course and increase morbidity and mortality in patients with sarcoidosis [94,95]. Mycetomas, particularly chronic pulmonary aspergillosis, have been reported in 3–12% of patients with APS [96]. Though frequently asymptomatic, they can cause life-threatening hemoptysis and may require long-term antifungal therapy, bronchial artery embolization, and surgical resection [97].

### 5.5. Sarcoidosis-Associated Pulmonary Hypertension

Sarcoidosis-associated pulmonary hypertension (SAPH) is classified into World Health Organization (WHO) group 5 and has been noted to be in 73.8% of patients with advanced pulmonary sarcoidosis awaiting lung transplantation [98]. It is a major cause of morbidity and mortality in APS and a predictor of lung transplant waitlist mortality [13,79,98,99]. Not all pulmonary vasodilator therapies may be appropriate, and treatment decisions regarding pulmonary vasodilator therapy should be made by experts with clinical experience in SAPH due to the multifactorial nature of SAPH and limited double-blind placebo-control trials in patients with precapillary SAPH.

### 5.6. Antifibrotic Therapy

There are no established guidelines for the use of antifibrotic therapies in the context of fibrotic pulmonary sarcoidosis. Targeted treatments are considered on an individualized basis and continue to be investigated. Insights from the INBUILD trial demonstrated that nintedanib decreased the rate of decline in FVC in progressive pulmonary fibrosis. However, the trial was underpowered for fibrotic sarcoidosis ($n$ = 12), and nintedanib needs to be examined in a larger cohort [100]. Similarly, the RELIEF trial showed that pirfenidone had a slower decline in percent predicted FVC, but the study was terminated prematurely due to challenges related to slow recruitment in non-IPF progressive fibrotic lung disease [101]. Moreover, the study excluded patients with sarcoidosis, and the results limit the applicability to this cohort [101]. The PirFS trial, initially designed as a double-blind placebo controlled trial to assess the antifibrotic effect of pirfenidone on fibrotic pulmonary sarcoidosis, was subsequently converted to a phase-4 feasibility trial due

to poor enrollment during the COVID pandemic [80]. Preliminary results suggested the potential use of DLCO < 40% predicted as an inclusion criterion for evaluating the efficacy of antifibrotic agents as these patients reached the defined time to clinical worsening [80]. Due to the inflammatory basis of fibrosis in pulmonary sarcoidosis and potential improvement in symptomology and physiologic parameters, the exact role of antifibrotic therapy in fibrotic pulmonary sarcoidosis is unclear at this time. Currently, there is no consensus on whether antifibrotic therapy should be used alone, in conjunction with, or after anti-inflammatory therapy has failed to slow the progression of fibrosis in patients with fibrotic pulmonary sarcoidosis. This needs to be decided on an individual basis.

### *5.7. Supportive Management*

Supportive management, including pulmonary rehabilitation, preventative vaccinations, and supplemental oxygen therapy, may improve overall wellbeing for individuals affected by fibrotic pulmonary sarcoidosis. Pulmonary rehabilitation is a comprehensive program tailored to each patient's needs, and involves personalized evaluations, exercise training, educational sessions, and behavioral modifications aimed at enhancing overall wellbeing [102]. Studies primarily conducted among patients diagnosed with chronic obstructive pulmonary disease (COPD) have demonstrated significant improvements in mortality, exercise capacity, overall quality of life, and efficient utilization of healthcare resources [103–106]. Emerging evidence suggests that individuals with interstitial lung disease, pulmonary hypertension, and those undergoing evaluation for lung transplantation derive benefit as well in exercise tolerance and decreased dyspnea [107–109]. According to the latest guidelines from the European Respiratory Society, pulmonary rehabilitation for a duration of 6–12 weeks is conditionally recommended for managing fatigue in patients with chronic sarcoidosis [84]. One observational pilot study evaluated the impact of a 12-week physical training program in 24 patients with IPF and fibrotic pulmonary sarcoidosis. Upon finishing the program, over 50% of patients had improvements in exercise capacity as assessed by 6-min walk distance, while others maintained their initial levels [110]. Another systematic review found that pulmonary rehabilitation may enhance exercise capacity and alleviate dyspnea in individuals with sarcoidosis, irrespective of stage of the disease [111]. These results highlight the potential in enhancing overall functional status among patients with sarcoidosis in general and with fibrotic pulmonary sarcoidosis.

Patients with sarcoidosis have dysregulated immune responses caused by underlying granulomatous inflammation and concurrent use of immunosuppressive agents, which can affect the efficacy of vaccinations [112]. Considering this, the timing of immunosuppressive treatments must be taken into account when administering inactivated and live vaccines. In the case of live vaccinations, the benefits should be carefully weighed against the associated risks, and therapy should be temporarily delayed before and after administration of live vaccinations [112]. Especially with B-cell depleting therapies such as rituximab, vaccination dosing and frequency require careful consideration of scheduling [112,113].

Though the ERS treatment guidelines on sarcoidosis do not make specific recommendations regarding oxygen supplementation, patients with chronic hypoxemic respiratory failure due to pulmonary sarcoidosis should be supported with supplemental oxygen therapy [114]. Non-invasive ventilation may be used as supportive therapy in cases of respiratory failure. Currently, there is limited evidence regarding the potential benefits or risks associated with the use of supplemental oxygenation in pulmonary sarcoidosis, particularly concerning aspects such as nocturnal hypoxemia, exertional hypoxemia, dyspnea, and exercise endurance. Further studies in this area are essential for a comprehensive understanding of the implications and appropriate management strategies for these patients with chronic hypoxemic respiratory failure due to APS.

### *5.8. Lung Transplantation*

Lung transplantation serves as a final option for patients with fibrotic pulmonary sarcoidosis suffering from respiratory failure and pulmonary hypertension. According to

International Society for Heart and Lung Transplantation (ISHLT) registry data, sarcoidosis accounts for 2.4% of all lung transplantations, and has a median survival of 6.1 years following transplantation [115,116]. There are no guidelines specifically tailored to sarcoidosis for lung transplantation; they currently follow those for ILD [117,118]. Following the implementation of the lung allocation score (LAS) in 2005, a greater percentage of sarcoidosis patients received lung allografts, leading to reduced waitlist mortality [119]. However, recent studies have found that, compared with patients with COPD and IPF, individuals with sarcoidosis continue to face disproportionately higher waitlist mortalities [120]. The several factors contributing to waitlist mortality were identified as pulmonary hypertension, poorer functional status, oxygen dependence, lower reduced output, and female sex [121,122]. Moreover, waitlisted patients' percent predicted FVC was found to be significantly lower than the thresholds recommended by ISHLT lung transplant referrals, underscoring potential delays in referral for lung transplant [122]. Following transplantation, patients may experience increased perioperative morbidity and mortality attributed to higher rates of primary graft dysfunction, hemothorax, and prolonged dependence on ventilatory support [116,123–125]. Despite these initial risks, long-term survival rates appear to be comparable to those observed in other chronic lung conditions with a risk for disease recurrence [116,123,126]. Further research and development of more specific guidelines on selection and post-transplant management for patients with fibrotic pulmonary sarcoidosis are needed.

## 6. Conclusions

Patients suffering from fibrotic pulmonary sarcoidosis experience higher morbidity and mortality compared with those without chronic and/or advanced disease. This may be due to the progressive nature of the disease with variable complications. Factors such as age, imaging findings, respiratory failure, and pulmonary hypertension may assist in prognostication, but this needs refinement and validation. The variability in disease presentation and progression makes determining the best approach for management challenging, and the approach should be individualized for each patient. There is a critical need to evaluate management strategies and continue research efforts aimed at improving patient outcomes and quality of life.

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*Review*

# Emerging Therapeutic Options for Refractory Pulmonary Sarcoidosis: The Evidence and Proposed Mechanisms of Action

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**Abstract:** Sarcoidosis is a systemic disease with heterogenous clinical phenotypes characterized by non-necrotizing granuloma formation in affected organs. Most disease either remits spontaneously or responds to corticosteroids and second-line disease-modifying therapies. These medications are associated with numerous toxicities that can significantly impact patient quality-of-life and often limit their long-term use. Additionally, a minority of patients experience chronic, progressive disease that proves refractory to standard treatments. To date, there are limited data to guide the selection of alternative third-line medications for these patients. This review will outline the pathobiological rationale behind current and emerging therapeutic agents for refractory or drug-intolerant sarcoidosis and summarize the existing clinical evidence in support of their use.

**Keywords:** sarcoidosis; refractory; therapy; granuloma; fibrosis

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## 1. Introduction

### *1.1. What Is Sarcoidosis?*

Sarcoidosis is a multisystem disease of unknown etiology characterized by non-caseating granulomatous inflammation in affected organs, most commonly in the lung and intrathoracic lymph nodes [1]. The natural history of pulmonary sarcoidosis varies, ranging from asymptomatic interstitial involvement to advanced fibrotic lung disease. Not surprisingly, treatment indications and responses mirror the disease's clinical heterogeneity [2].

### *1.2. Pathobiology of Granuloma Formation*

The compact, non-necrotizing epithelioid granuloma, which is the pathologic hallmark of sarcoidosis, has been well described [3–6]. In the lung, the granulomas of sarcoidosis are classically found in a lymphatic distribution along bronchovascular bundles. They are primarily comprised of activated macrophages, multinucleated giant cells, mononuclear cells, and lymphocytes. In the acute stages of granuloma development, they exhibit a highly polarized expression of T helper Type 1 (Th1) cytokines, including interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), along with evidence of Th17 cell signaling [7,8]. While most disease either remits spontaneously or proves responsive to treatment with corticosteroids, approximately one third of patients experience persistent or recurrent inflammation [9,10]. The mechanisms underlying the progressive fibrotic phenotype remain an area of research and have been hypothesized to reflect a transition from Th1- to Th2-mediated pathways [11–13].

### *1.3. Who Needs Treatment?*

Most patients with pulmonary sarcoidosis either do not require treatment or respond to first-line corticosteroids. Deciding whom to treat, how to adjust therapy, and which therapies to choose for patients with progressive or refractory disease remain crucial questions of significant clinical relevance [14–17]. Ideally, the decision to initiate,

maintain, discontinue, resume, or escalate therapy should be based on evidence of active granulomatous inflammation, with a resulting physiological or functional impairment impacting the patient's quality-of-life [18]. Due to limited randomized controlled clinical trials, expert consensus provides much of the guidance in sarcoidosis management [19]. Key treatment concepts emerged from a 2020 international conference of experts participating in a Delphi process, which resulted in published guidelines advocating for therapy escalation or adjustment based on disease severity, progression from acute to chronic phenotypes, or pharmacologic toxicity. While the expert panel achieved consensus regarding indications for adding a third-line biological agent, specifically TNF-inhibitors, no additional consensus was reached for therapeutic options for refractory disease. To date, corticosteroids and repository corticotropin injection remain the only medications with Food and Drug Administration (FDA) approval for the treatment of sarcoidosis [19].

### *1.4. What Is Considered Refractory Sarcoidosis*

While there is no consensus or data-driven definition of refractory sarcoidosis, several have been proposed. Most suggested definitions include a situation in which second-line treatments (methotrexate, azathioprine, leflunomide, antimalarials, or mycophenolate mofetil) prove to be insufficient to achieve clinical remission with corticosteroid dosing under 10 mg per day (prednisone equivalents) [20]. An obvious challenge in the treatment of refractory pulmonary sarcoidosis is a lack of clear understanding of the pathobiological processes that have resulted in the disease and its resistance to therapy. This review will address the emerging potential therapeutic modalities for refractory pulmonary sarcoidosis, with a focus on their proposed biologic role (Figure 1) in mitigating granulomatous inflammation or pro-fibrotic pathways, available evidence, and salient clinical parameters to monitor for efficacy or harm (Table 1).

## 2. Treatment Options for Refractory Sarcoidosis

### *2.1. TNF-Inhibitors*

#### 2.1.1. Rationale

TNF-α is a pro-inflammatory cytokine with a broad range of biological activities. Initially recognized in the 1970s for its ability to induce hemorrhagic necrosis of transplantable tumors in murine models, it was later identified as a catabolic hormone mediating anorexia and weight loss in chronic disease (and, thus, briefly named "cachectin") [21]. It has since been shown to play a critical role in directly and indirectly promoting the release of many inflammatory mediators in both acute and chronic disease. Interest in its potential as a therapeutic target for sarcoidosis was solidified after trials demonstrated its efficacy in other chronic inflammatory conditions, including rheumatoid arthritis and Crohn's Disease [22].

A series of experiments beginning in the 1990s demonstrated an association between TNF-α and active sarcoidosis. Müller-Quernheim and colleagues measured TNF-α and interleukin-1 (IL-1) spontaneously produced by alveolar macrophages (AM) cultured from the bronchoalveolar lavage (BAL) fluids of 43 patients with sarcoidosis [23]. They observed a significant increase in both cytokines released by AMs from patients with clinically active disease (defined by progressive symptoms, pulmonary function impairment, or radiographic involvement) compared to inactive disease or healthy controls. Interestingly, a corresponding increase in TNF-α and IL-1 measured in peripheral blood monocyte cells (PBMC) was not observed, supporting a model of "compartmentalized" inflammation at the site of the affected organ. Zheng and colleagues reproduced this finding and demonstrated a correlation between TNF-α and percentage CD4+ (cluster of differentiation) lymphocytes, suggesting that this may serve as a surrogate marker for disease activity [24]. Müller-Quernheim's group subsequently demonstrated that patients without a clinical indication for treatment at initial assessment were at higher risk of disease progression if they were found to have elevated AM production of TNF-α at baseline [25].

TNF-α is known to play an integral role in maintenance of granulomas during infection with *Mycobacterium tuberculosis*, which it does via chemokine induction, immune cell recruitment, and facilitating leukocyte aggregation [26,27]. Among patients with sarcoidosis, TNF-α has also been observed to upregulate intracellular adhesion molecule-1 (ICAM-1) expression on AMs, which is believed promote granuloma formation [28]. A meta-analysis found that *TNF* promotor polymorphism is associated with sarcoidosis [29]. It is, therefore, widely hypothesized that TNF-α plays a key role in granuloma formation and persistence in sarcoidosis, and by blocking this cytokine, the disease may be attenuated.

#### 2.1.2. Clinical Evidence

The first trial to evaluate a TNF inhibitor (etanercept) in pulmonary sarcoidosis was terminated early due to treatment failure [30]. This was in contrast to its amelioration of cutaneous and joint manifestations in earlier case series and case reports [31]. Discrepancies in efficacy might be explained by differences in the targeting of the TNF-α molecule. Unlike other TNF-inhibitors, which are monoclonal antibodies that bind to both soluble and membra-bound TNF, etanercept is a soluble receptor construct that can only bind to soluble TNF [32]. Nevertheless, interest in the therapeutic class persisted, and a retrospective case series of patients treated with infliximab subsequently demonstrated improvement in manifestations of corticosteroid refractory sarcoidosis, many with severe cutaneous or other extrapulmonary manifestations of disease [33]. The efficacy of infliximab for pulmonary sarcoidosis was later supported by a pair of randomized placebo-control trials published in 2006. The first of these trials detected a trend towards increased vital capacity in 18 patients with active stage II–IV pulmonary sarcoidosis, all of whom were either on at least three months of steroids, required alternative therapy due to suboptimal steroid response, or exhibited steroid intolerance [34]. The second trial enrolled 134 patients with chronic pulmonary sarcoidosis (also defined as having been treated for more than three months). In this trial, Baughman and colleagues found that infliximab (at 5 mg/kg) resulted in an increase in forced vital capacity (FVC) compared to placebo (mean percentage of predicted increase of 2.5% over 24 weeks) [35]. Improvement in FVC was greater among those with longer disease duration, lower baseline FVC, and higher Saint George Respiratory Questionnaire (SGRQ) scores. The study did not demonstrate any significant difference in secondary respiratory endpoints, including SGRQ, 6-minute walk distance (6MWD), or Borg dyspnea score. A retrospective analysis of data from this trial suggested that this effect may be most significant among patients receiving lower doses of maintenance corticosteroids and demonstrated diminished improvements in FVC among patients receiving maintenance doses $\geq$15 mg/d prednisone [36]. Additional sub-analysis of this cohort evaluated the effect of infliximab on extrapulmonary manifestations and showed an improvement during the 24-week trial period, with relapse during the subsequent washout period [37].

A recently published real-world analysis of infliximab used in 14 patients with previously refractory pulmonary sarcoidosis observed a treatment success of 78.6% (95% confidence interval, CI, 49.2–95.3). Treatment success was defined as either improvement or stability in measurements of FVC or forced expiratory volume in a one-second (FEV1) percentage of the predicted results [38]. The therapy proved even more efficacious for 6 patients with central nervous system (CNS) involvement and 12 patients with cutaneous disease, achieving 100% (95% CI 54.1–100%) and 91.7% (95% CI 61.5–99.8%) treatment success rates, respectively.

In 2011, Kamphuis and colleagues published a case series consisting of five patients with chronically active pulmonary and extrapulmonary sarcoidosis treated with adalimumab [39]. Four of the five patients achieved radiographic improvement in thoracic lymphadenopathy, as well as subjective improvement in fatigue and dyspnea during a 12-week observational period. With increased dosing frequency, radiographical and symptomatic improvement were also achieved in the fifth patient. Sweiss and colleagues

described an additional 11 patients with refractory pulmonary sarcoidosis treated with adalimumab over a 52-week study period [40]. During this time, four patients achieved a >5% increase in absolute FVC, five patients improved in terms of 6MWD, and nine noted improvement in Borg dyspnea scores. In 2016, Crommelin et al. evaluated the efficacy of adalimumab in 18 patients who had discontinued infliximab due to adverse events or lost efficacy in the setting of antibody formation [41]. Of these patients, 13 experienced stabilization or improvement in FVC and all exhibited stabilization or improvement in measurements of soluble IL2 receptor (sIL2R) over a 12-month treatment period. Despite these promising observational reports, a placebo-controlled trial of 16 subjects with pulmonary and cutaneous sarcoidosis demonstrated improvement in the skin lesion area with adalimumab but no significant difference in radiographical manifestations of pulmonary sarcoidosis or pulmonary function at the end of the study period [42]. However, the 12-week study period may have been too short in duration to evaluate for a potential positive or even negative effect of adalimumab on chest radiography or pulmonary physiology.

To date, infliximab remains the only biological therapy promoted as a third-line treatment option for pulmonary sarcoidosis in the Delphi consensus recommendations [19].

#### 2.1.3. Adverse Effects and Clinical Monitoring

Safety data from the early randomized control trials of infliximab in pulmonary sarcoidosis showed similar rates of serious adverse events in patients treated with infliximab compared to placebo during the study period (23.1% vs. 18.2%), with adverse events leading to discontinuation in 4.5% of the placebo group and 5.5% in the treatment group [35]. However, in a real-world assessment of infliximab used in patients with sarcoidosis, adverse events led to permanent discontinuation of the therapy in 20% of patients. The most commonly observed adverse event was pneumonia (18%), followed by leukopenia (15%) and infusion reaction (12%). Anaphylaxis was also observed in four patients (12%) [38].

Some case reports describe paradoxical adverse events (PAE) occurring during TNF-α inhibitor therapy, whereby patients developed the new onset of a disease that is typically improved by this class of medication. The most commonly described PAE is psoriasis [43,44]. The mechanism for these PAEs is uncertain, but hypotheses include an imbalance in cytokine production, the differential immunological properties between the monoclonal antibodies and TNF-α soluble receptor, an unopposed type I interferon production, and/or a shift towards a Th1/Th2 profile [45]. One large retrospective study of patients with spondylarthritis found no significant difference in PAEs among patients taking TNF-α inhibitors and those treated with conventional disease-modifying anti-rheumatic agents [46].

The reactivation of latent tuberculosis is a well-documented risk of treatment with TNF-inhibitors [47–49]. The reactivation of hepatitis is also a concern [50,51]. For this reason, pre-treatment testing for latent infections is generally recommended, particularly in patients with increased baseline risk. Clinical monitoring for all patients includes routine lab testing for leukopenia and transaminitis.

### *2.2. Anti-CD20*

#### 2.2.1. Rationale

Sarcoidosis is generally considered to be a T-cell mediated disease. Nevertheless, it is associated with hypergammaglobulinemia, circulating immune complexes, and perigranuloma infiltration of B-cells, which suggests a supporting role for humoral immunity in its pathogenesis [52,53]. One proposed mechanism for B-cell involvement is via the Th1 cell production of IFN-γ, which stimulates the B-cell activating factor (BAFF), an anti-apoptotic signal involved in B-cell differentiation [54]. Several studies have demonstrated increased BAFF activity in patients with active sarcoidosis compared to those with quiescent disease and healthy controls [55,56]. Patients with active sarcoidosis have also been shown to have distinct patterns of B-cell populations, with higher proportions of transitional B-cells and

lower proportions of memory B-cells, though the clinical significance of this pattern is unclear [53,55].

The putative involvement of B-cells in the pathogenesis of sarcoidosis suggests a potential role for B-cell blocking agents as a therapeutic class in its treatment. Rituximab is a chimeric monoclonal antibody which, when bound to the transmembrane protein CD20, induces B-cell destruction via antibody and complement-mediated cytotoxicity, as well as the induction of apoptotic pathways [57].

#### 2.2.2. Clinical Evidence

There are several case reports of patients with pulmonary sarcoidosis who have experienced clinical improvement with rituximab. In 2008, Belkhou and colleagues published their experience of treating a woman with sarcoidosis with moderate restrictive pulmonary disease and polyarthritis who remained steroid-dependent despite the addition of methotrexate. Three months after the initiation of rituximab, her PFTs had normalized and prednisone was discontinued [58]. In 2015, Cinetto and colleagues published a case series of three patients with pulmonary sarcoidosis with variable responses to rituximab [59]. The first patient was a man with pulmonary and extra-thoracic lymph node involvement who had previously proved responsive to corticosteroids and methotrexate; however, he had experienced progression when taken off therapy. He was intolerant of azathioprine and progressed on cyclophosphamide but experienced radiographical and symptomatic improvement with rituximab administered biweekly over 12 weeks, with sustained remission over an 18-month follow-up period. The second patient had pulmonary, extra-thoracic lymph node, and cutaneous disease, and he remained steroid-dependent despite treatment with azathioprine and methotrexate. He experienced symptomatic improvement and was able to discontinue steroids after three monthly infusions of rituximab (1 g) with concurrent hydroxychloroquine. He experienced relapse four months later, prompting a second course of rituximab with a less robust response. The third patient was a woman with pulmonary, cutaneous, and ocular disease who had exhibited improvement with various lines of therapy including TNF-inhibitors but experienced frequent exacerbations (primarily of her cutaneous and ocular manifestations) during periods of maintenance therapy. While the addition of rituximab to her regimen did not achieve remission in symptoms, subsequent re-treatment with infliximab achieved complete resolution of skin lesions and improvement in ocular disease.

In a 2015 letter to the European Respiratory Journal, Sweiss and colleagues recounted the results of a prospective phase I/II clinical trial of rituximab in ten patients with at least two years of moderate-to-severe pulmonary refractory sarcoidosis with at least three months of $\geq$10 mg prednisone daily or any dose of prednisone with one or more steroid-sparing agent [60]. Participants received 1 g of rituximab at baseline and then again two weeks later. Treatment response was defined as a >5% absolute improvement in FVC and/or a >30 m increase in 6MWD. At 24 weeks, 5 out of 10 patients met the predicted endpoint of >5% absolute improvement in FVC percentage and 5 out of 10 patients had >30 m improvement in their 6MWD. However, disappointingly, at 52 weeks, only 2 out of 10 met the endpoint of FVC improvement and three of 10 exhibited improvement in 6MWD. Although this trial suggests that there may be a role for rituximab in treatment for refractory pulmonary sarcoidosis, more data are needed in order to determine whether it represents an efficacious treatment option. Moreover, the absence of a consistent administration schedule or dosage of rituximab, as well as co-treatment with different immune-suppressants in all of these studies, makes it difficult to compare results or translate them into clinical practice.

#### 2.2.3. Adverse Effects and Clinical Monitoring

In a phase I clinical trial of 15 patients with B-cell lymphoma treated with 10–500 mg/m$^2$ of rituximab, mild and moderate infusion-related side effects were observed, including nausea, headache, fever, chills, bronchospasm, and orthostatic hy-

potension. The most commonly observed side effect was fever during infusion, which was observed in 13 patients [61]. Observational data in cancer patients treated with rituximab corroborate the finding that adverse events are predominately mild or moderate in severity, typically occur during the first infusion, and do not usually recur with subsequent infusions [62]. The side effect profile has been observed to be lower among patients with lower levels of circulating B-cells prior to treatment, which may suggest that patients being treated for autoimmune conditions rather than B-cell lymphomas are at lower risk of reaction [57,61].

Several studies have demonstrated a rapid decrease in B-cells after rituximab infusion that typically persists for several months, placing patients at risk of infection. A 1998 prospective multicenter trial of rituximab in 166 patients with lymphoma reported 68 (41%) infections by the one-year follow-up period, with the majority being bacterial in origin. Most of these (61/68) were characterized as mild [63].

In 2019, Lower and colleagues performed a retrospective review of 2109 patients at a single center treated with the TNF-inhibitors or rituximab [64]. Rituximab had the lowest rate of discontinuation (29%) compared to infliximab (55%) and adalimumab (58%). The most common reason for the discontinuation of rituximab was the lack of treatment response, followed by insurance coverage and allergic reactions. No patients discontinued the drug due to infections during the study period.

The reactivation of indolent infections is also a concern. Several retrospective case studies have not found any association between rituximab therapy and cases of tuberculosis in endemic regions [65,66]. The reactivation of hepatitis B with rituximab therapy has been documented, and this risk is likely higher in patients receiving rituximab with chemotherapy. There may be a role for the concurrent initiation of nucleoside analog in patients with a history of hepatitis B [67,68]. Appropriate immunizations must be provided several weeks prior to initiation [69]. In addition, accumulating evidence has implicated anti-CD20 therapy with a risk of severe outcomes related to COVID-19 infections, which must be considered in the current era [70].

Prior to initiating therapy, serum immunoglobulin levels and hepatitis serologies should be obtained [71]. Routine clinical monitoring generally includes evaluation for cytopenia, hypogammaglobulinemia, and infection.

### *2.3. JAK-Inhibitors*

#### 2.3.1. Rationale

The Janus kinase/signal transduction and activator of transcription (JAK/STAT) signaling pathway plays an integral role in cell function and homeostasis and regulates the expression of key mediators of hematopoiesis, apoptosis, tissue repair, and inflammation [72]. Discovered in the 1990s through work that sought to outline how interferon triggers the expression of genes, the dysregulation of this pathway has been subsequently recognized in various pathologies, ranging from malignancies to autoimmune disease [73]. A number of cytokines believed to be key to macrophage activation and granuloma formation, including IFN-$\gamma$, IL-2, IL-4, and IL-23, are known to signal via this pathway, which is initiated by the binding of the cytokine or growth factor with its specific cellular transmembrane receptors, thus activating JAKs and enabling interaction with intracellular STAT proteins, which then travel to the nucleus to affect gene transcription.

In 2009, a small study by Rosenbaum and colleagues demonstrated that messenger RNA (mRNA) transcripts associated with STAT signaling were upregulated in the peripheral blood, lung parenchyma, and thoracic lymph nodes of patients with sarcoidosis compared to healthy controls, with a marked increase in phosphorylated STAT1 transcripts observed within the granuloma [74]. A subsequent analysis of six patients with pulmonary sarcoidosis and six healthy control subjects demonstrated that genes differentially expressed in the lung tissue of patients with sarcoidosis were most closely related to the JAK/STAT signaling pathway [75]. In a slightly larger study, differentially expressed genes related to JAK/STAT signaling measured in the measured in PBMC of patients were shown

to distinguish between healthy controls and pulmonary sarcoidosis, and, furthermore, they differentiated stable disease from that with a progressive or multiorgan involvement phenotype [76].

#### 2.3.2. Clinical Evidence

In 2018, Damsky and colleagues published their experience of treating a patient with pulmonary and refractory cutaneous sarcoidosis with the small molecule JAK inhibitor tofacitinib [77]. The patient had Scadding Stage II disease with non-caseating granulomas evident on transbronchial lung biopsy but no significant respiratory symptoms. She had extensive indurated papules and plaques covering large portions of her scalp, neck, torso, arms, and legs, which had proven refractory to topical glucocorticoids, minocycline, hydroxychloroquine, methotrexate, adalimumab, tacrolimus, and apremilast (systemic glucocorticoids had been withheld due to comorbid diabetes and hypertension). The initiation of tofacitinib resulted in clinical and histological remission of her skin lesions, which recurred following the cessation of the therapy.

Subsequent reports have described additional JAK inhibitors (ruxolitinib and barcitinib) and improvement in pulmonary sarcoidosis [78–80]. The results of an ongoing open-labeled trial (NCT03910543) evaluating the efficacy of tofacitinib in refractory cutaneous sarcoidosis included eight patients with active pulmonary sarcoidosis and one patient with active myocardial disease [81]. Internal organ disease activity was assessed via whole body positron emission tomography and computed tomography (PET-CT). Of eight interpretable images, five demonstrated total lesion glycolysis that decreased by $\geq$50% (three with complete resolution), and the other patients were able to discontinue their other anti-granulomatous therapies without experiencing a clinically significant worsening of disease. In general, cutaneous manifestations improved to a greater extent than the other organ disease manifestations; however, as the authors note, tofacitinib led to overall disease control that had not been previously achieved via alternative regimens. Their work demonstrated a significant decrease in Th1-mediated markers of inflammation.

It is important to note that there is both specificity and redundancy in JAK-STAT inhibition with varying activity against individual cytokines based on the inhibition of individual or combination JAKs. Particularly relevant to sarcoidosis, IFN-$\gamma$ signals via JAK1 and JAK2, which, in turn, activate STAT1, while IL-6 signals via JAK1, JAK2, and/or TYK2 and activates STAT3 [82]. Ultimately, all of the current FDA-approved JAK inhibitors—tofacitinib (JAK 1/3), ruxolitinib (JAK1/2), barcitinib (JAK 1,2), and upadacitinib (JAK 1)—have variable but clinically relevant targets [83].

#### 2.3.3. Adverse Effects and Clinical Monitoring

In the preliminary report of the ongoing open-label clinical trial evaluating tofacitinib efficacy in refractory cutaneous sarcoidosis, the therapy was well tolerated, and there were no significant or dose-limiting adverse events [81]. Nevertheless, all JAK inhibitors carry risks of infection, cytopenia, and hyperlipidemia [73]. Opportunistic infections are likely the most common adverse effect associated with tofacitinib. The reactivation of tuberculosis was the most common infection observed in one review [84]. Increased rates of herpes zoster have also been observed [85]. The use of tofacitinib has been associated with lower gastrointestinal tract perforation [86]. There is also evidence of an increased risk of venous thromboembolism (VTE) in patients with cardiovascular risk factors or elevated VTE risk at baseline [87]. Additionally, treatment with tofacitinib conveyed an increased risk of major adverse cardiovascular events (MACE), including MI, cardiovascular death and stroke, in a cardiovascular risk-enriched population with rheumatoid arthritis [88].

Clinical monitoring generally involves routine evaluation for cytopenia, hyperlipidemia, hypertension, transaminitis, and infection.

### 2.4. Anti-IL6

#### 2.4.1. Rationale

Elevations in the pleiotropic pro-inflammatory cytokine IL-6 have been observed in the serum and BAL fluid of patients with active pulmonary sarcoidosis since the 1990s [89–91]. Produced primarily by innate immune cells (including macrophages and dendritic cells) in response to local infection or tissue injury and signaling primarily via JAK/STAT and MAPK pathways, IL-6 functions as a systemic alert signal and helps to orchestrate the ensuing adaptive immune response [92,93]. Among other functions, it is known to promote (in conjunction with tissue growth factor-beta TGF-β) the differentiation of Th17 and Th17.1 effector T cells, which produce IL-17 and IFN-γ, respectively, which are both recognized as key cytokines involved in granuloma formation [94]. Additionally, it exerts an inhibitory effect on regulatory T cells (Tregs), which are responsible for reigning in the inflammation promulgated by effector T lymphocytes [95]. This exaggerated Th17 immune response (and the imbalanced Th17/Treg cell ratio) has been well described in the sera and BAL fluids of patients with sarcoidosis [96,97].

Additionally, early studies of IL-6 demonstrated its key role in inducing the hepatic production of acute phase reactants, including C-reactive protein (CRP), fibrinogen, haptoglobin, and serum amyloid A (SAA) [98]. Work by Chen, Moller, and colleagues has identified SAA, which is notably abundant in the granulomas of sarcoidosis, as a potential key mediator that perpetuates the production of cytokines promoting chronic granulomatous inflammation through stimulation of Toll-Like Receptor-2 (TLR2) in the absence of acute replicating infection [99,100]. In addition to its role in upregulating Th17 pathways of inflammation, IL-6 blockade is proposed to mitigate granulomatous inflammation via the downregulation of this insoluble acute-phase protein [101].

#### 2.4.2. Clinical Evidence

In 2019, Sharp and colleagues reported their experience in treating four patients with refractory, steroid-dependent pulmonary sarcoidosis with the anti-IL-6 receptor monoclonal antibody tocilizumab [101]. All four patients were noted to have had multiple years (decades in three cases) of persistent respiratory symptoms despite chronic prednisone use and various steroid-sparing therapies, including TNF-inhibitors. Within two months of tocilizumab initiation, all four patients reported significant symptomatic improvement and were able to decrease their daily prednisone dose: three patients achieved steroid reduction of 50% or more, but all four patients remained on steroids at daily doses of 5–10 mg of prednisone. Three of the four patients experienced improvement in measures of lung function. At the time of their report, two of the four patients remained on anti-IL6 therapy. Tocilizumab had been discontinued briefly in one patient due to an episode of bronchitis. It had been held indefinitely in two other patients (one of whom developed breast cancer, while the other developed peripheral neuropathy).

Sarilumab, an IL-6 receptor monoclonal antibody, was recently evaluated in a phase II clinical trial for patients with refractory pulmonary sarcoidosis (NCT04008069). Of the fifteen patients enrolled, four discontinued due to the worsening of their sarcoidosis, and five experienced the worsening of CT chest imaging. Compared to placebo, patients treated with sarilumab had no meaningful improvement in endpoints, including flare-free survival, changes in pulmonary function tests, chest imaging, patient-reported outcomes, and laboratory values [102].

#### 2.4.3. Adverse Effects and Clinical Monitoring

The IL-6 receptor antibodies tocilizumab and sarilumab have gained FDA approval for use in the treatment of refractory rheumatoid arthritis [103]. They are generally well tolerated and have a safety profile that is comparable to those of other immunosuppressive therapies. They carry a risk of infection, including the reactivation of latent infection. The most common adverse reactions observed with intravenous monotherapy include upper respiratory tract infection, nasopharyngitis, headache, hypertension, and an increase in

serum alanine aminotransferase. Additionally, studies have shown an elevated risk of lower intestinal perforation in patients with rheumatoid arthritis treated with tocilizumab, particularly those with a history of prior diverticulitis [104].

### *2.5. Anti-IL-1*

#### 2.5.1. Rationale

IL-1 is often considered the prototypical pro-inflammatory cytokine, and efforts to curtail its activity in acute and chronic inflammatory conditions have been undertaken [105]. Along with TNF-α, IL-1 is released by activated macrophages in response to pathogen and damage-associated molecular patterns, and it is known to signal via the nuclear transcription factor NF-*k*B, a target of glucocorticoid therapy, thus drawing attention as a possible integral component in the inflammatory cascade that culminates in granuloma formation [4]. Early in vitro studies demonstrated that this Th1-cytokine (previously known as lymphocyte-activating factor) was produced in high quantities by the activated AM of patients with pulmonary sarcoidosis, and evidence of high-intensity alveolitis is shown in [106]. As previously described, an experiment by Müller-Quernheim and colleagues demonstrated higher spontaneous release of IL-1 and TNF-α by AM from patients with active sarcoidosis compared to inactive disease [23]. In 2000, Mikuniya and colleagues showed that the ratio of IL-1 receptor antagonist and IL-1β in the BAL fluids of patients with pulmonary sarcoidosis was positively correlated with improvements in chest radiograph and vital capacity, as well as negatively correlated with markers of disease activity, such as serum ACE levels [107]. In 2009, Wiken and colleagues demonstrated increased expression of pattern recognition receptors (specifically toll-like receptors 2 and 4) on the PBMCs of patients with sarcoidosis compared to healthy controls and a corresponding higher secretion of TNF-α and IL-1β when these TLRs were stimulated [108]. TNF-α and IL-1β have also been shown to increase the alveolar macrophage production of the chemokine ligand-20 (CCL20), which recruits dendritic cells, B cells, and T cells to the lungs [109,110].

#### 2.5.2. Clinical Evidence

Canakinumab, a monoclonal antibody directed against IL-1β, was recently studied in a phase II placebo-controlled trial to evaluate its safety and efficacy for treating patients with pulmonary sarcoidosis (NCT02888080). Unfortunately, this trial explicitly excluded patients identified as having refractory disease. The posted results show no statistically significant difference in the primary outcome, which was FVC at 24 weeks. Anakinra, a recombinant human IL-1 receptor antagonist that is approved for use in rheumatoid arthritis, is currently being evaluated for use in cardiac sarcoidosis (NCT04017936) [111].

#### 2.5.3. Adverse Effects and Clinical Monitoring

In the aforementioned phase II placebo-controlled trial of canakinumab in patients with pulmonary sarcoidosis (NCT02888080), three serious adverse events were reported among 20 patients receiving treatment (fewer than were observed in the corresponding placebo group), and 15 non-serious events were reported (14 in the placebo group). When used to treat non-sarcoidosis illnesses, the most commonly described adverse events associated with canakinumab include injection site reaction, gastrointestinal symptoms, rash, headache, and infection [112,113]. Patients should be evaluated for latent tuberculosis prior to the initiation of therapy.

A large clinical trial of anakinra in a rheumatoid arthritis population revealed the most frequent adverse events to be injection site reactions and URIs. Serious infections were higher in the treatment group than the placebo group but were relatively low (5.37 events/100 patient years) [114]. Monitoring usually includes routine testing for neutropenia and changes in kidney function.

### 2.6. Neuropilin-2 Immunomodulator

#### 2.6.1. Rationale

An emerging novel therapy for sarcoidosis sits at the intersection of two independent avenues of therapeutic investigation for immune-mediated disease: the proposed immune-mitigating effects of extracellular aminoacyl-transfer RNA (tRNA) synthetases and a class of receptors known as neuropilins.

Aminoacyl-tRNA (tRNA) synthetases are enzymes essential for intracellular protein synthesis [115]. Autoantibodies to these enzymes, including anti-histidyl-tRNA synthetase (commonly known as anti-Jo-1), represent a key feature of anti-synthetase syndrome, characterized by the co-occurrence of immune cell-mediated interstitial lung disease and myositis [116,117]. There is evidence that extracellular fragments of these enzymes play a role in regulating innate and adaptive immunity [118–120]. Adams and colleagues recently confirmed that extracellular histidyl-tRNA synthetase is present in the sera of healthy humans but absent in patients with anti-Jo-1 positive anti-synthetase syndrome [121]. Their murine models suggest that the enzyme exerts an inhibitory effect on effector T cell activation, while the depletion of the enzyme through antibody neutralization augments immune-mediated inflammation [121].

Neuropilins (NRPs) are non-tyrosine kinase transmembrane glycoproteins expressed on the surface of many cells, including macrophages, dendritic cells, and T lymphocytes [122]. Originally identified as a coreceptor for vascular endothelial growth factor (VEGF) and class III semaphorins, early studies of NRPs elaborated their role in neural development and angiogenesis. Additionally, an important function in innate and cellular immunity has emerged. NRP1 expressed on the surface of myeloid dendritic cells (DCs) have been shown to facilitate their migration to lymphatics following antigen exposure and appear to be integral to the primary immune synapse of DCs with T-cells, thus initiating the process of antigen presentation [123,124]. Certain tumor-associated macrophages, which have been found to enable tumor progression by promoting angiogenesis and immune tolerance, are recruited to the hypoxic core of the tumor via the expression of NRP1 [125]. Both NRP1 and NRP2 are expressed on alveolar and bronchial macrophages, and there are some data to suggest that there is increased NRP2 expression on macrophages found within granulomas [126,127]. Efzofitimod (ATYR1923) is a first-in-class immunomodulator composed of a splice-variant of histidyl-tRNA synthetase, the sole binding partner of which is NRP-2 [127].

#### 2.6.2. Clinical Evidence

A phase I/II randomized, double-blinded, and placebo-controlled trial evaluating the safety and efficacy of efzofitimod was recently published [128]. In this trial, 37 patients with pulmonary sarcoidosis (median disease duration, 4.2 years; range, 0.5–28 years) were randomized in a 2:1 fashion such that 25 patients received the study drug at various doses (1, 3, and 5 mg/kg per day). All patients were receiving corticosteroids at baseline (mean prednisone equivalent dose 13.2 $\pm$ 4.4 mg/day). The study population did not necessarily represent a refractory patient cohort, as more than 60% had received no additional therapies. While the primary outcome of the study was concerned with safety and tolerability, the authors reported a dose-dependent trend towards decreased steroid dependence over the 24-week trial period, specifically observing a 58% reduction in corticosteroid dose from baseline in the 5 mg/kg/day arm compared to a 48% reduction in the placebo group. Notably, three patients in the 5 mg/kg/day treatment group were able to be completely weaned from steroids with sustained remission, whereas no patients in any other treatment group exhibited sustained steroid-free remission. The two highest dose groups also exhibited improvement in lung function (percentage of predicted FVC and diffusing capacity of the lungs for carbon monoxide, DLCO) that did not reach statistical significance but was maintained throughout all time intervals of the study [128]. These findings support further investigation of this therapy with a larger study population and perhaps in a treatment refractory cohort.

#### 2.6.3. Adverse Effects and Clinical Monitoring

In this phase I/II clinical trial, efzofitimod was tolerated at all tested doses and deemed safe. Among the patients treated with the study drug, three Grade 3 (nonserious) adverse events were observed (depression, toothache, and myalgias), none of which were deemed to be likely related to the study drug. The only serious treatment-emergent adverse event (acute cholecystitis) observed among patients in the treatment arm was similarly deemed to be unlikely related to the study drug. One patient discontinued efzofitimod (at 1 mg/kg) due to alopecia, which was deemed to be likely related to the study drug [128].

### *2.7. mTOR Inhibitor*

#### 2.7.1. Rationale

Abnormal macrophage aggregation represents a key step in all granulomatous disease, including sarcoidosis. The mammalian target of the rapamycin (mTOR)-signaling pathway regulates macrophages, as well as monocytes and dendritic cells, via a metabolic checkpoint kinase, i.e., the mTOR complex 1 (mTORC1) [129]. A study by Linke and colleagues demonstrated that the activation of mTORC1 in macrophages induced the hypertrophy and proliferation of macrophages in mice, leading to granuloma formation [130].

#### 2.7.2. Clinical Evidence

In 2020, Gupta and colleagues reported their experience in treating a patient with pulmonary sarcoidosis who was unable to taper below 15 mg of prednisone per day [131]. Following 10 months of treatment with the mTOR inhibitor sirolimus at 2 mg per day, the patient experienced symptomatic and radiographic improvement. A study of a large solid organ transplant population evaluated incident sarcoidosis among patients receiving mTOR inhibitors compared to calcineurin inhibitors [132]. There was no incident sarcoidosis among patients treated with mTOR inhibitors (compared to 0.2% incidence in the calcineurin-treated patients).

#### 2.7.3. Adverse Effects and Clinical Monitoring

Experience with sirolimus for the treatment of other indications (solid organ transplant, lymphangioleiomyomatosis, vascular anomalies) suggests that the most adverse effects may vary based on indication, but they commonly include peripheral edema, diarrhea, nausea, hypercholesterolemia, and bone marrow toxicity, as shown in [133,134]. Routine monitoring usually uses metabolic panels to assess for renal dysfunction and dyslipidemia and complete blood counts for cytopenias.

### *2.8. GM-CSF Inhibitor*

#### 2.8.1. Rationale

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine involved in the recruitment of innate immune cells with an implicated role in a variety of autoimmune and inflammatory diseases [135]. It has been observed in the BAL fluid and serum of patients with pulmonary sarcoidosis and is generally associated with a chronic or progressive phenotype [136–138]. In vitro studies have demonstrated an exaggerated amount of TNF-α and IL-1β secreted by AMs and peripheral monocytes following GM-CSF stimulation in peripheral blood obtained from patients with sarcoidosis compared to healthy controls [139].

#### 2.8.2. Clinical Evidence

A phase II randomized placebo-controlled study is currently evaluating the efficacy and safety of namilumab, a monoclonal antibody directed against GM-CSF, in patients with chronic pulmonary sarcoidosis (NCT05314517). Preliminary results from this trial have not yet been published.

#### 2.8.3. Adverse Effects and Clinical Monitoring

Namilumab has been studied in refractory rheumatoid arthritis [140]. The most commonly listed adverse events were nasopharyngitis, dyspnea, bronchitis, and headache.

### *2.9. Anti-Fibrotic Therapy*

#### 2.9.1. Rationale

Advanced and end-stage pulmonary sarcoidosis is characterized by progressive pulmonary fibrosis and loss of lung function. Importantly, fibrotic changes occur at the sites of long-standing active granulomatous inflammation and typically exhibit histopathological features that are distinct from those of usual interstitial pneumonia (UIP) [141–143].

#### 2.9.2. Clinical Evidence

The results of the Inbuild Trial support the use of antifibrotics to preserve lung function among patients with a progressive fibrosing phenotype of interstitial lung disease other than idiopathic pulmonary fibrosis [144]. Fewer than 10% of patients included in this trial carried a diagnosis of sarcoidosis, but there are no rigorous trials evaluating the use of anti-fibrotics to prevent progressive fibrosis in this population. A cogent case can be made that many patients with fibrosing pulmonary sarcoidosis can be controlled via anti-granulomatous therapy [145]. There is an ongoing placebo-controlled trial assessing the effectiveness of pirfenidone use in progressive fibrotic sarcoidosis (NCT03260556).

#### 2.9.3. Adverse Events and Clinical Monitoring

Safety data from clinical trials of pirferidone in patients with idiopathic pulmonary fibrosis (IPF) reveal that the drug is generally well tolerated, with the most commonly encountered adverse events being gastrointestinal symptoms and photosensitivity [146]. The drug can also be associated with transaminitis, and the routine monitoring of liver function tests is recommended.

## 3. Conclusions

To date, clinical data remain limited for guiding therapeutic decisions for the management of refractory pulmonary sarcoidosis. This is further confounded by the lack of FDA approval of therapies beyond steroids for a sarcoidosis indication. Nevertheless, there are multiple promising classes of medications currently being used or under investigation for patients with chronic, progressive disease. The use of these therapies is informed by our expanding understanding of the pathobiology of the granuloma and phenotypes of disease, and emerging data from small trials and case series are promising.

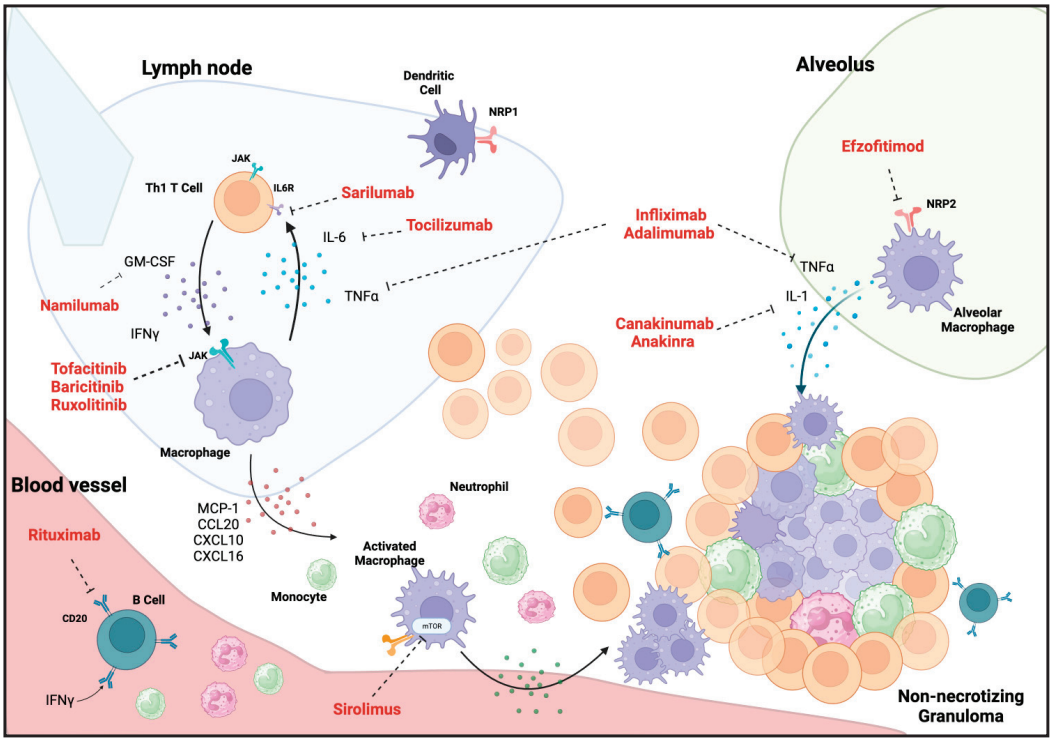


**Figure 1.** Schematic for non-necrotizing granuloma formation in pulmonary sarcoidosis highlighting emerging therapeutic targets and medications. Abbreviations: CCL20—chemokine ligand 20; CXCL10—C-X-C ligand 10; CACL16—C-X-C ligand 16, GM-CSF—granulocyte-macrophage colony-stimulating factor, IFN-γ—interferon-gamma, IL—interleukin; IL6R—interleukin-6 receptor, JAK—janus kinase; mTOR—mammalian target of rapamycin; MCP-1—monocyte chemoattractant protein-1; NRP—neuropilin; TNFα—tumor necrosis factor-alpha. Created with BioRender.com.

**Table 1.** Current and Emerging Third Line Therapies for Sarcoidosis.

| Therapy | Clinical Evidence | Route | Side Effects | Clinical Monitoring |
|---|---|---|---|---|
| TNF Inhibitors | | | | |
| Infliximab | RTCs [34,35] | IV | Hypersensitivity reaction, infection, paradoxical adverse events, hepatotoxicity | Initial: hepatitis serologies, TB screen<br>Ongoing LFT, CBC |
| Adalimumab | Case series [39]<br>Clinical trial [40] | SQ | Hypersensitivity reaction, infection, paradoxical adverse events, hepatotoxicity | Initial: hepatitis serologies, TB screen<br>Ongoing: LFT, CBC |
| Anti-CD20 | | | | |
| Rituximab | Case series [59]<br>Clinical trial [60] | IV | Infusion reaction, infection, severe COVID-19 infections, PML | Initial: hepatitis serologies, TB screen<br>Ongoing: CBC, IgG levels |
| JAK Inhibitor | | | | |

**Table 1.** *Cont.*

| Therapy | Clinical Evidence | Route | Side Effects | Clinical Monitoring |
|---|---|---|---|---|
| Tofacitinib | Case report [77]<br>Ongoing clinical trial (NCT03910543) | PO | Infection, Cytopenia, Hyperlipidemia, GI perforation, VTE, Diarrhea, hypertension, major adverse cardiovascular events, infection | Initial: TB screen, hepatitis serologies<br>Ongoing: CBC, BMP, LFT, lipid panel |
| Baricitinib | Case report [79] | PO | Infection, Cytopenia, Hyperlipidemia, GI perforation, VTE, Infection | Initial: TB screen, hepatitis serologies<br>Ongoing: CBC, BMP, LFT, lipid panel |
| Ruxolitinib | Case report [78] | PO | Hypertension, hyperlipidemia, cytopenias, GI distress, dizziness, elevated aminotransferases, cough, dyspnea, muscle pain, fever | Initial: TB screen,<br>Ongoing: CBC, LFT, lipid panel, BMP, blood pressure |
| Anti-IL6 | | | | |
| Tocilizumab | Case series [101] | IV/SQ | Hypersensitivity reaction, infection, headache, hypertension, constipation, hyperlipidemia, GI tract perforation | Initial: TB screen, lipid panel at baseline and 4–8 weeks after initiation<br>Ongoing LFT, CBC |
| Anti-IL6 Receptor | | | | |
| Sarilumab | Ongoing clinical trial (NCT04008069) | SQ | Hypersensitivity reaction, infection, headache, hypertension, constipation, hyperlipidemia, GI perforation | Initial: TB screen, lipid panel at baseline and 4-8 weeks after initiation<br>Ongoing: LFT, CBC |
| Neuropilin 2 Immunomodulator | | | | |
| Efzofitimod | Ongoing clinical trial (NCT05415137) | IV | Under investigation | Under investigation |
| Anti-IL1β | | | | |
| Canakinumab | Ongoing clinical trial (NCT02888080) | SQ | Gout flares, diarrhea, nausea, abdominal pain, cytopenias, injection site reaction, headache, muscle cramps | Initial: TB screen<br>Ongoing: CBC |
| Anti-IL1 | | | | |
| Anakinra | Ongoing clinical trial (NCT04017936) | SQ | Infection, injection site reaction, headache, arthralgias | Initial: TB screen<br>Ongoing: CBC |
| mTOR inhibitor | | | | |
| Sirolimus | Case report [131] | PO | Edema, hyperlipidemia, diarrhea, cytopenias, arthralgias, increased serum creatinine | Lipid panel, urine protein creatinine ratio, BMP, CBC, serum drug level, blood pressure |
| Anti-GM-CSF | | | | |
| Namilumab | Ongoing clinical trial (NCT05314517) | SQ | Under investigation | Under investigation |
| Anti-fibrotic | | | | |
| Pirfenidone | Ongoing clinical trial (NCT03260556) | PO | Rash, abdominal pain, diarrhea, anorexia, nausea, vomiting, fatigue, dizziness, URI, increased aminotransferases | LFT |

Abbreviations: BMP basic metabolic panel; CBC complete blood count; CD cluster of differentiation; GI gastrointestinal; GM-CSF granulocyte-macrophage colony-stimulating factor; JAK janus kinase; IL interleukin; IV intravenous; LFT liver function test; mTOR mammalian target of rapamycin; PML progressive multifocal leukoenceophalopathy; PO per os (by mouth); Ref reference cited in the text; RTC randomized control trial; SQ subcutaneous; TB tuberculosis; TNF tumor necrosis factor; URI upper respiratory tract infection; VTE venous thromboembolism.

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# Sarcoidosis-Associated Pulmonary Hypertension

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**Abstract:** Sarcoidosis-associated pulmonary hypertension (SAPH) is a very severe complication of the disease, largely impacting its morbidity and being one of its strongest predictors of mortality. With the recent modifications of the hemodynamic definition of pulmonary hypertension (mean arterial pulmonary pressure >20 instead of <25 mmHg,) its prevalence is presently not precisely known, but it affects from 3 to 20% of sarcoid patients; mostly, although not exclusively, those with an advanced, fibrotic pulmonary disease. Its gold-standard diagnostic tool remains right heart catheterization (RHC). The decision to perform it relies on an expert decision after a non-invasive work-up, in which echocardiography remains the screening tool of choice. The mechanisms underlying SAPH, very often entangled, are crucial to define, as appropriate and personalized therapeutic strategies will aim at targeting the most significant ones. There are no recommendations so far as to the indications and modalities of the medical treatment of SAPH, which is based upon the opinion of a multidisciplinary team of sarcoidosis, pulmonary hypertension and sometimes lung transplant experts.

**Keywords:** sarcoidosis; pulmonary hypertension; advanced pulmonary sarcoidosis complications

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## 1. Introduction

Sarcoidosis-associated pulmonary hypertension (SAPH) is a very severe complication of sarcoidosis, strongly impacting its morbidity and being one of its strongest predictors of mortality [1–6]. Its prevalence is highly variable according to the populations studied and the diagnostic tool used. In addition, the definition of pulmonary hypertension has been recently modified [7] to a mean pulmonary artery pressure of 20 mmHg. Even when right heart catheterization (RHC) was used in previous studies to establish the diagnosis, this threshold was 25 mmHg and no prospective study has been published since then, precluding the possibility of present and reliable data about this prevalence. However, it is well known to be most frequent, although not exclusively, in advanced pulmonary sarcoidosis, and particularly in patients with end-stage disease on lung transplant waiting lists. Its physiopathology is complex, generally multifactorial and evolving during the course of the disease, and thus it is assigned to WHO Group 5 pulmonary hypertension (PH). Due to the very aspecific nature of its main clinical symptoms, mainly a persistent dyspnea frequently out of proportion with the parenchymal sarcoid involvement, systematic screening strategies should be established, particularly in cases with a recent decrease in DLCO $\leq$ 40% and/or a 6 mn walk distance $\leq$300 m. The definitive diagnosis requires right heart catheterization, the gold-standard diagnostic procedure. The decision to perform it in cases of clinical suspicion, possibly reinforced by imaging data, (CT scan, transthoracic echocardiography) has to be discussed within a multidisciplinary team comprising a sarcoidosis and a pulmonary hypertension expert. Considering its dark prognostic impact, the most appropriate treatment of SAPH if confirmed will be based upon the main pathogenic

mechanisms underlying pulmonary hypertension, most often involving pulmonary vasculopathy or fibrotic processes. The optimal medical treatment of SAPH is not presently consensual, but in any case aims to specifically address the predominant mechanisms underlying SAPH in each individual patient. Establishing the most accurate SAPH phenotype is therefore crucial for appropriate and personalized management.

## 2. Epidemiology

The prevalence of SAPH remains difficult to evaluate due to the extreme heterogeneity of studies focusing on the topic. Averaging 3 to 8% in unselected populations of sarcoid patients, it has been reported (Table 1) with a range as wide as 2 to 74% [8]. This large heterogeneity is driven by three main explanations. Firstly, the large variety of methodologies reported partly accounts for this largely varying prevalence across the studies. Indeed, they include mostly retrospective studies but also some prospective ones, including registries, cross-sectional studies or studies based on the extraction of healthcare data. Secondly, the reported prevalence also varies with the type of sarcoidosis populations included in these studies. Indeed, the lowest prevalence is reported in studies focusing on general sarcoid populations, whereas that reported in patients with suggestive symptoms or signs of PH or with a more advanced disease is by far much higher. Thirdly, the prevalence also varies with the diagnostic tool used, with some studies using mostly transthoracic echocardiography (TTE), while others used right heart catheterization (RHC), the latter being the gold standard for diagnosis. Studies based on TTE usually report a higher prevalence of SAPH with a probable overestimation.

**Table 1.** Studies reporting the prevalence of sarcoidosis-associated pulmonary hypertension and their characteristics.

| Study | Year | N | Country | Ethnicity | Study Design | Diagnostic Method | Pre-Capillary PH by RHC | Prevalence | Comment |
|---|---|---|---|---|---|---|---|---|---|
| Sulica et al. [9] | 2005 | 106 | USA | NA | Retrospective | TTE | NA | 51 | 48% of patients with stage 4 |
| Shorr et al. [10] | 2005 | 363 | USA | A-A (71.6%) | Retrospective | RHC | NA | 73.8 | Population of sarcoidosis listed for lung transplant |
| Handa et al. [11] | 2006 | 212 | Japan | Japanese | Prospective | TTE | NA | 5.7 | |
| Bourdonnais et al. [12] | 2008 | 162 | USA | A-A (88%) | Prospective | TTE ± RHC | 22/25 (88%) | 14 | |
| Baughman et al. [13] | 2010 | 130 | USA | 50.8% Caucasian | Retrospective | RHC | 50/70 (71%) | 38.5 | Patients with persistent dyspnea |
| Alhamad et al. [14] | 2010 | 96 | Saudi Arabia | NA | Retrospective | TTE | NA | 20.8 | |
| Nardi et al. [15] | 2011 | 58 | France | 65% Caucasian, 31% black | Retrospective | TTE | NA | 26 | Stage 4 sarcoidosis |
| Rapti et al. [16] | 2013 | 313 | Greece | NA | Cross-sectional | TTE ± RHC | NA | 2.9 | |
| Patel et al. [17] | 2018 | 609051 | USA | NA | Cohort database | NA | NA | 8.7 | Healthcare database |
| Kirkil et al. [2] | 2018 | 452 | USA | 69% Caucasian, 30 A-A | Retrospective | RHC | 29 | 6.4 | |
| Tiosano et al. [18] | 2019 | 3993 | Israël | NA | Cohort database | NA | NA | 6.74 | Healthcare database |
| Frank et al. [19] | 2019 | 9106 | Germany | NA | Cohort database | NA | NA | 2.8 | Healthcare database |
| Huitema et al. [20] | 2019 | 399 | Netherlands | Dutch | Prospective | TTE ± RHC | NA | 2.9 | |
| Pabst et al. [12] | 2020 | 111 | Germany | NA | Prospective | TTE ± RHC | 4/5 (80%) | 3.6 | |

Abbreviations: TTE: transthoracic echocardiography; RHC: right heart catheterization NA: not available; USA: United States of America; A-A: African American.

One of the first studies to report SAPH prevalence is a prospective TTE-based Japanese one published in 2006 [11] which reported a prevalence of 5.7% in 212 patients. In this study, the diagnosis was based upon a right ventricle systolic pressure (RVSP) $\geq$ 40 mmHg. More recently, the PULSAR study (PULmonary hypertension in pulmonary SARcoidosis) [20], a large Dutch study investigating the PH prevalence in a predominantly Caucasian cohort of almost 400 consecutive sarcoid patients referred to a tertiary sarcoidosis center, used echocardiography and, if indicated, RHC. It reported a SAPH prevalence of 3%. These data are supported by the results of another study, which reported a prevalence of 2.9% in a smaller cohort from a German tertiary center [12]. Schimmelpennink et al. [21]. showed that the prevalence of SAPH in patients with a PF-ILD phenotype of advanced sarcoidosis, solely evaluated by the mean pulmonary artery diameter/ascending aorta diameter ratio, was more prevalent in progressive (24%) than in non-progressive (10%) fibrotic pulmonary sarcoidosis, but the difference was not significant. This diagnostic tool is in any case clearly not the recommended one. A recent meta-analysis by Zhang et al. that included 25 studies across the world demonstrated, despite the substantial heterogeneity of the studies, that SAPH prevalence widely varied with (1) the diagnostic method used, with RHC providing lower values than TTE; (2) the geographic origin of the patients; and (3) the type of sarcoid population studied. Indeed, SAPH was found in 16.4% of sarcoid patients when evaluated by TTE vs. 6.4% when RHC was used [22], supporting the requirement of using the gold standard, RHC, to establish a reliable diagnosis. The meta-analysis also showed that SAPH diagnosed with RHC reached a prevalence of 62.3% in patients with an advanced disease.

Other retrospective studies based upon data extracted from National Healthcare diagnostic code databases are also available from the USA [17], Israël [18] and Germany [19], reporting a SAPH prevalence of 8.6%, 6.7% and 2.8%, respectively. Despite the very large numbers of patients included, these studies present a major limitation due to data (such as diagnosis) not being manually extracted and checked.

Various parameters have been associated with a higher SAPH prevalence, such as age, female gender and mostly more advanced parenchymal lung disease. Indeed, stage 3 or 4 sarcoidosis patients have the highest prevalence of SAPH, which is as high as 73.8% in sarcoid patients referred for lung transplantation [10]. These epidemiological data should prompt clinicians to specifically look for SAPH in the most severe patients. Potential predisposing rare genetic variants have been recently reported in SAPH patients, indicating a possible implication of genetics in its development [23]. Finally, among the factors predisposing the development of SAPH, ethnic differences should be taken into account. Though most studies focused on Caucasian populations, Bourbonnais reported a prevalence of 14% in a prospective study of a large majority of African Americans [24], while Alhamad reported that of 20.8% in a cohort of 96 Arabic sarcoid patients [14].

Most importantly, the hemodynamic definition of PH was modified in 2022 [7], lowering the threshold of the mean PAP from 25 mmHg to 20 mmHg. No prospective study has been published since then on SAPH, and therefore data to identify the real prevalence of this very severe sarcoidosis complication are lacking and all the studies referred to were based upon the old definition of pulmonary hypertension. All the prevalence data published so far are bound, therefore, to be underestimated. Only prospective studies using the new hemodynamic definition of PH will be able to produce more accurate reports of the real prevalence of SAPH.

However, in 2021, S. Nathan reported a study aiming at analyzing the impact of the prevalence and outcome of PH in patients with COPD or IPF [25]. Not unexpectedly, the prevalence of precapillary PH was higher in both groups compared to that reported with the old definition. In the IPF group, the new definition might have performed slightly better than the old one in predicting outcome. Sarcoidosis was not included in the study and no data about SAPH prevalence can be derived from it.

Finally, three recent papers clearly summarize the important steps associated with the new PH definition [26–28]. They all highlight several crucial points: (1) the concept of mild PAH (mPAP between 20 and 25 mmHg, PVR between 2 and 3 WU), pointing to its

value as an early indicator of increased risks of severe outcomes; (2) the negative impact of comorbidities on either cardio-vascular or respiratory outcome, with the individualization of a particular phenotype of patients with a decreased DLCO (<45% pred), usually affecting males and smokers with mild CT parenchymal lung abnormalities; and (3) the crucial step for the most appropriate individualized SAPH management, i.e., that of its most precise phenotyping, particularly its vasculopathic one.

Again, none of them specifically addressed SAPH, but rather iPAH and ILD-associated PH. All of these key observations might pave the way for very informative specific studies to come regarding sarcoidosis.

### 3. Classification and Pathogeny

One of the main difficulties of SAPH management is that it may be related to multiple and potentially entangled mechanisms. Considering this most often mixed pathogeny, the ESC/ERS Task Force and 6th World Symposium on Pulmonary Hypertension have placed SAPH in WHO group 5 [29] (Figure 1). Indeed, if SAPH is usually predominantly related to the underlying parenchymal lung disease, it may also involve mechanisms belonging to groups 1, 2, 3 and/or 4 (Figure 2). In any case, establishing the most precise cartography of the mechanisms underlying SAPH in each individual patient is absolutely key to the delineation of the subsequent therapeutic strategy. Therefore, despite the difficulty, the clinician should always, for the sake of the most appropriate individualized therapeutic management, aim at defining the predominant mechanism underlying SAPH.

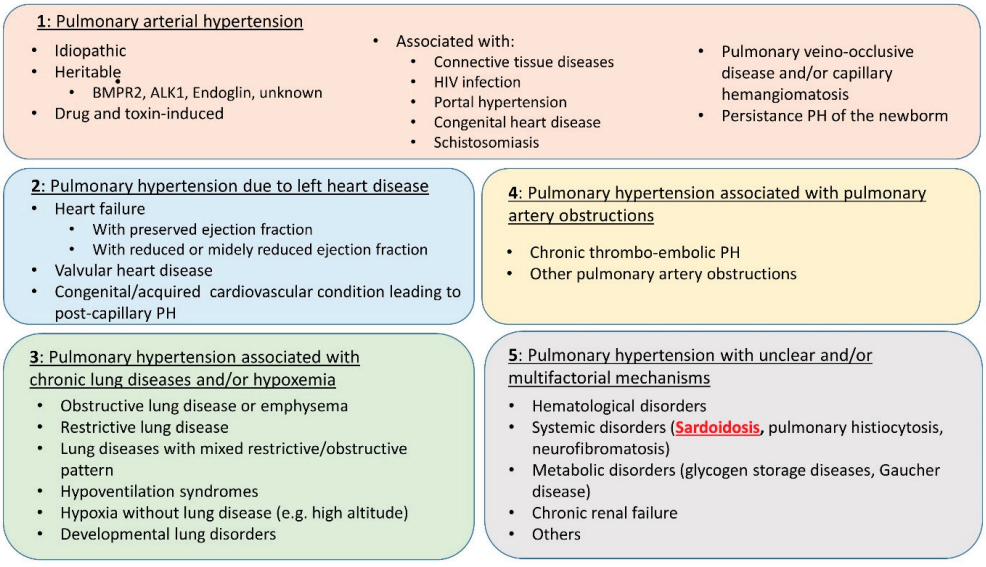


**Figure 1.** Clinical classification of pulmonary hypertension from [29].

Two studies [23,30] showed that the expression of several genes clearly separates sarcoid patients with and without SAPH. The potential role of these particular genetic backgrounds in the development of SAPH is under investigation.

As stated above, patients with more advanced parenchymal lung disease are more likely to develop PH, especially in cases of pulmonary fibrosis (stage 4). The pathophysiological mechanisms involved here are those observed in group 3 PH, such as capillary destruction due to parenchymal involvement and hypoxic pulmonary arterial vasoconstriction from ventilation/perfusion mismatches. This mechanism is the most frequent one in SAPH, with nearly 75% affected patients in a recent cohort of 40 subjects [31]. However,

the degree of parenchymal alteration and functional restriction does not correlate with the severity of PH, and up to 20% of patients with SAPH do not have any radiographic evidence of parenchymal lung disease [9].

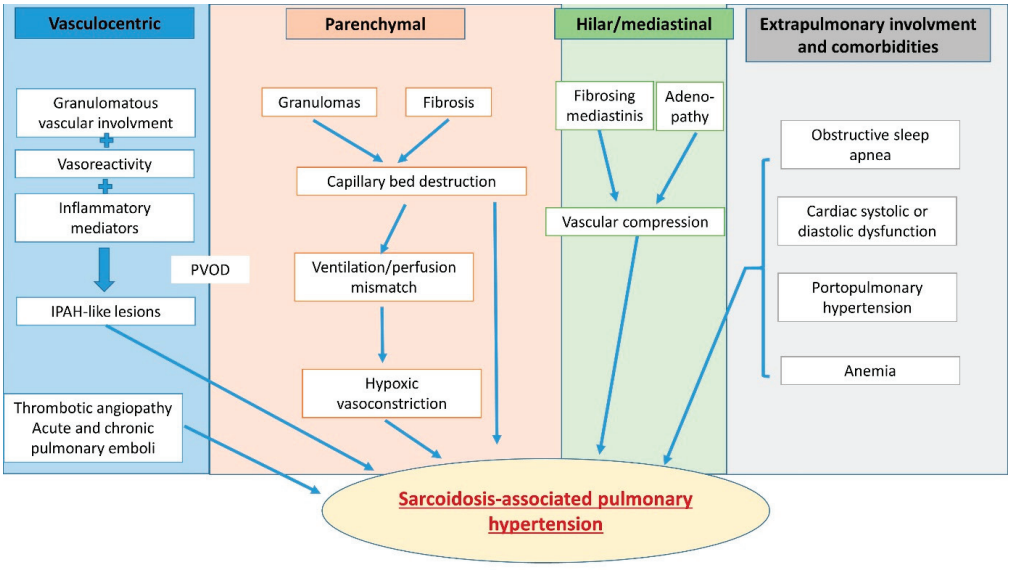


**Figure 2.** Multifactorial mechanisms lead to pulmonary hypertension in sarcoidosis and may include hypoxic vasoconstriction, pulmonary vascular rarefaction, parenchymal destruction, left heart disease with postcapillary PH, portal hypertension from liver disease, pulmonary vascular remodeling, changes resembling pulmonary veno-occlusive disease and extrinsic vascular compression due to fibrosing mediastinitis or enlarged lymph nodes.

Among the other mechanisms potentially involved in sarcoidosis, vasculopathy may develop, mostly but not exclusively due to the granulomatous infiltration of pulmonary arterial and/or veinous walls. In this case, pathological changes as well as high levels of inflammatory mediators mimic alterations described in idiopathic pulmonary arterial hypertension (PAH, group 1) [32]. As in PAH, granulomatous vessel involvement may affect all the layers of the vasculature from the intima and media to the adventitia and smooth muscle. It may also affect the entirety of the pulmonary vascular tree [33] from the elastic arteries to the collecting venules, mimicking in this case a pulmonary veno-occlusive disease. In PAH, cigarette smoking contributes to the vasculopathy associated with endothelial dysfunction, apoptosis and remodeling, causing the "capillary drop-out" [26]. As sarcoid patients are mostly nonsmokers, this observation might not be relevant in SAPH. In contrast, a recent observation [34] details the mechanisms underlying sarcoid vasculopathy, particularly its venous component. It shows the presence of vascular granulomas adjacent to the perilymphatic ones and/or their vascular transmural spread. Even more interestingly, it shows the presence of numerous independent, unorganized intimal granulomas bulging into the vessels' lumina, overlaid by endothelial cells with no thrombosis, whether or not a transmural granulomatous infiltration is observed. This might explain, at least in part, the development of pulmonary hypertension despite limited pulmonary involvement, for instance. Postcapillary PH, either alone or associated with precapillary PH, can also be observed in SAPH. Approximately 5–20% of patients, according to [35], develop cardiac sarcoidosis which might in turn lead to group 2 PH [36]. If conduction troubles and arrhythmias are the most frequent signs of cardiac sarcoidosis, systolic and even diastolic dysfunction can also occur during the course of the disease and lead to postcapillary PH.

When both pre- and postcapillary PH are associated, RHC measurements will show a pulmonary artery wedge pressure (PAWP) > 15 mmHg in addition to a pulmonary vascular resistance >3 Wood's units (WU). Chronic thromboembolism is also a potential mechanism of SAPH. Indeed, sarcoidosis is associated with a 2–3-fold risk of pulmonary embolism (PE) [37,38], and this association increases disease severity [39]. Sarcoid patients are therefore at increased risk of developing chronic thromboembolic pulmonary hypertension (CTEPH, group 4 PH) [40]. This should be systematically screened for because of the specific therapeutic management that ensues.

Less frequently involved, several other mechanisms may underlie the development of SAPH, such as vascular compression by large mediastinal adenopathy [41] or fibrosis [42]. Liver sarcoidosis involvement might also be associated with porto-pulmonar hypertension [43]. Chronic anemia due to inflammation or to granulomatous bone marrow involvement can lead to high output heart failure and PH. Finally, obstructive sleep apnea syndrome (OSAS) with nocturnal hypoxemia, frequently observed in sarcoid patients, should be cited as a potentially worsening factor of a pre-existing PH [44].

Altogether, considering that SAPH may be due to various and frequently combined and evolving mechanisms, clinicians will frequently be very challenged about the exact phenotype in which to classify their patients. This step is, however, required for optimal management, and they should always try to dissect and weight the main drivers involved in each individual patient.

## 4. Diagnosis

SAPH strongly impacts morbidity, transplant-free survival and mortality of sarcoidosis [1–3]. Considering its dark prognosis; the requirement for a prompt referral to lung transplantation (LTx) centers for appropriate patients; the extreme difficulty in properly diagnosing the type of PH developed in sarcoid patients, usually very complex and multifactorial; and the therapeutical uncertainties associated with SAPH, these patients should benefit from a stepwise and comprehensive approach, non-invasive in the first step and then based upon RHC when appropriate. This diagnostic approach is the only valid one able to document the multidisciplinary discussions (expert centers with pulmonologists, cardiologists and PH experts) which will have to phenotype these patients [1,8] and to lead them to the most appropriate management.

The delay between the diagnosis of sarcoidosis and that of SAPH can be over a decade long, according to a French study [41] and a multi-national one [45]. If only less than 10% of patients can be asymptomatic, the diagnosis of SAPH can be largely delayed due to very aspecific symptoms such as chest pain, palpitations and/or cough. Only 8% of patients can be symptomatic.

While some studies have long described several features (decreased pulmonary function and/or walk distance, DLCO < 60% pred, oxygen saturation <90% on 6MWT) as clinical predictors of PH in sarcoidosis [24], a recent one [46] used a multidisciplinary Delphi study to establish recommendations for screening strategies for PH in patients with interstitial lung diseases. The consensual triggers for PH suspicion were clinical signs and symptoms, chest CT and other imaging modalities, an abnormal pulse oxymetry, increase in serum BNP/NT-proBNP and worsening in pulmonary function tests or 6 min walk distance. Echocardiography and BNP/NT-proBNP were identified as relevant screening tools, while RHC was confirmed as the sole diagnostic proof.

### *4.1. Symptoms and Signs*

The most frequent symptom is an increasing and/or persistent dyspnea, sometimes out of proportion with the underlying parenchymal extent of the disease, with most patients presenting with a WHO functional class of III-IV and/or increase in supplemental oxygen needs [47–49]. Other clinical signs can include chest pain, light-headedness or even syncopes, and sometimes cough, none of these bearing any specificity. An increased P2 or

S4 sound can also be noticed, while other signs of right ventricular dysfunction usually occur much later or in a rapidly evolutive disease.

*4.2. ECG*

Its utility as a screening tool for PH is uncertain and a normal result cannot rule out its presence [50]. A right axis deviation, a right ventricular hypertrophy or strain, and a right bundle block are usually signs of a late phase of the disease.

*4.3. Pulmonary Function Tests (PFT)*

No correlation exists between any of the spirometric nor plethysmographic values and the severity of PH, but a significant one does exist between the latter and a low DLCO < 60% pred [24,47,51,52]. SAPH is frequently associated with a decreased FVC and DLCO compared to sarcoid patients without PH [47,53]. However, as many as 28% of patients have a near-normal lung function [54]. Jose et al. showed in a cohort of 156 patients that a cutoff of % FVC < 60 pred and % DLCO < 50 pred reached a sensitivity of 62% and a negative predictive value of 85% for PH [55], confirming previous reports in the literature [9,24,56–58]. However, in the multidisciplinary Delphi study [46] cited above, the only PFT-related trigger for SAPH suspicion that reached a consensus were a % DLCO < 40% pred or rapidly declining (>15%), disproportionate to lung volumes (FVC/DLCO > 1.6). No consensus was reached on the use of FVC or TLC or any threshold for these parameters to be used as predictive factors.

Decreased DLCO is a strong predictive marker of PH, as a % DLCO <60% pred indicates a 7-fold increase risk of PH [59,60] and as a reduced DLCO is among these parameters that with a consistent correlation with PH [10,57]. Finally, a significant correlation between BNP levels, 6-minute walk distance (6MWD), % DLCO and TTE-evaluated PASP was found in a small cohort of sarcoid patients [61].

In addition to being predictive for PH, both DLCO < 35% pred and a preserved FEV1/FVC were shown to be independent markers of outcome [45].

*4.4. WMT*

A decreased 6MWD < 350 m and a large desaturation (<90%) have long been reported to have a predictive value for SAPH in the literature [24]. A recent decrease in 6MWD should undoubtedly prompt a thorough evaluation for SAPH [46]. Of note is the fact that, in contrast, the absence of desaturation on exertion is strongly indicative of the absence of SAPH [59]. In Gupta's study [62], a 6MWD < 300 m was the strongest predictor of mortality or LTx in SAPH, whereas no association with outcome was found with either a desaturation > 5%, an $O_2$ saturation < 88% at the end of the test or a composite product of 6MWD and oxygen saturation. The 6MWD was significantly inversely correlated with sPAP. This held true for pre- as well as postcapillary PH. Although this is by no means specific to SAPH due to several potential confounding factors such as airway disease, fatigue and muscle involvement [62,63], the fact that in this study 6MWD correlated with Borg score as well as with FAS indicates that it is not only a strong predictor of PH severity in sarcoid patients but that it moreover seems to be able to capture the multifactorial effects of sarcoidosis on the 6MWT.

Again, in addition to being predictive for PH, a reduced 6MWD < 300m was associated with a reduced transplant-free survival [45].

*4.5. Imaging*

Multimodal imaging techniques in SAPH include chest X-ray, CT scan, ventilation/perfusion (V/Q) scanning, CMR and other innovative techniques [64].

4.5.1. Chest X-ray

Although most patients with SAPH have an advanced pulmonary fibrosis [9,41], it can develop whatever the Scadding stage. A retrospective study of 22 patients with SAPH showed that 32% of them had no fibrosis at the time of PH diagnosis (6). In a recent study,

only half of the patients in a large cohort of SAPH were at stage 4, with no correlation between stages and mPAP, in line with the 66% stage 4 value in a more recent one [45]. In contrast, stage 1 was very rare (2%), supporting the idea that a quite normal parenchyma in sarcoid patients might indicate the absence of SAPH.

#### 4.5.2. Thoracic CT Scan

Patients with SAPH are more likely to have a certain extent of pulmonary fibrosis compared to sarcoid patients without, leading to the recommendation of looking for SAPH in all sarcoid patients with fibrosis [53]. However, some patients with no consistent parenchymal abnormalities develop seemingly out-of-proportion PH [65]. A prospective evaluation of a large cohort of patients ($n$ = 246) showed no difference on CT scan between patients with or without PH in terms of lymph node enlargement, parenchymal involvement and thickening of bronchovascular bundles [11]. In contrast to parenchymal abnormalities, some vascular images are good indicators of PH, such as a pulmonary artery diameter > 29 mm, a right ventricle (RV)-to-left ventricle (LV) ratio > 1, or a pulmonary artery (PA)/ascending aorta (AA) > 1 [53,64,65], with a 65% sensitivity and a 83% specificity for the latter [66]. The ratio of PA diameter to BSA is even more predictive [67].

A recent study [68] combining PET scanning and CMR showed a clear 18F-FDG uptake in the PA wall in 33 subjects with suspected cardiac sarcoidosis. Very interestingly, it also showed that in those undergoing an RHC, the mean PAP pressure was higher in those with a 18F-FDG uptake compared to those without ($p$ = 0.003). SUV max in the PA wall correlated with PA pressure derived from RHC and/or TTE. In summary, 18F-FDG uptake in PA wall is associated with PH with an intensity correlating with the mean PAP.

Given the well-known risk of VTE episodes and of CTEPH in sarcoidosis [40,69,70], a systematic search for the latter should be performed in sarcoid patients with a suspected PH. Pulmonary angiography will help to reach this diagnosis, but dual-energy CT (DECT) [64,71,72] provides more information, including morphological information on the vasculature and functional information on perfusion. Primarily used to replace V/Q scanning, which does not allow any evaluation of the lung parenchyma nor mediastinal lymph nodes, it has also been investigated as a screening tool for pulmonary hypertension whatever its cause [73]. Its value in the clinical work-up in this context, and particularly in SAPH, is still undetermined.

Finally, a loss of small pulmonary vessels on quantitative CT might indicate severe PH [74], but this has not been evaluated in the context of sarcoidosis.

#### 4.5.3. Cardiac MRI

Non-compulsory in the diagnostic approach of SAPH, it has proved to be of some help in other ILD-associated severe PH [75].

#### 4.5.4. TTE

The most important non-invasive tool to diagnose PH [50,76] it is highly recommended in patients with the above cited clinical symptoms and signs, reduced 6MWD, desaturation on exercise, reduced DLCO and PA/AA > 1 on CT scan.

A multi-national study based on ReSAPH, PULSAR and the Cincinnati Sarcoid Clinic database evaluated 124 patients with an RHC-confirmed SAPH [77]. It showed a strong correlation between right ventricular systolic pressure (RVSP) and pulmonary artery systolic pressure (PASP) in patients with a FVC > 60% pred, less significant in those with a FVC < 50% pred. TTE estimation was inaccurate in as many as 51% of the patients, with an underestimation in those with a severe PH and an overestimation mostly in those without PH.

Tricuspid regurgitant velocity (TRV) value, when measurable, is crucial to the evaluation of PH likeliness [78]: it rules out PH when < 2.9 m/s and confirms it when > 3.4 m/s. Other TTE indicators of probable PH are the analysis of both ventricles, pulmonary arteries, inferior vena cava and right atrium. An echocardiographic score including right atrial area,

left ventricular eccentricity index and right-to-left ventricle ratio has been shown to be an accurate indicator of PH whatever the presence of a measurable TRV [76].

The ESC/ERS PH guidelines [7] have proposed an algorithm taking into account TVR and other indirect measures to classify patients with a high, intermediate and low probability of PH. In any case, and particularly for those with an intermediate TRV value and/or a low probability of PH, an expert team is required to define on a case-by-case basis which patients should undergo an RHC. For the expert authors of the WASOG statement on diagnosis and management of SAPH [1], factors influencing the decision to perform an RHC included evidence of RV dysfunction on TTE, a FVC < 50% pred, a decreased 6MWD and increased levels of BNP-NT-proBNP. They found no consensus for an RHC indication in patients with an intermediate probability of PH and severe parenchymal disease. However, TTE and RHC are compulsory in the pre-LTx evaluation.

TTE can be difficult to perform and interpret due to the extent of parenchymal lung disease. Three-dimensional TTE has been shown to better evaluate RV function and regional abnormalities in other conditions, with a good predictive value of the outcome and mortality and a good correlation with cardiac magnetic resonance-derived RV ejection fraction [79–82]. These data have not been evaluated yet in SAPH.

#### 4.5.5. RHC

The gold standard for the diagnosis of PH (1), it should be performed in an expert PH center and its results discussed within a multidisciplinary team comprising PH, sarcoidosis and imaging experts. Compulsory in patients listed for LTx, it is otherwise discussed on a case-by-case basis, particularly taking into account the likelihood of PH established on the above parameters and the effects on therapeutical and management decisions.

A cut-off mPAP value of >20 mmHg has been established in the recent guidelines for the diagnosis and treatment of PH [7], replacing that of >25 mmHg which had prevailed for decades.

RHC provides a very consistent diagnosis of PH-ILD in cases of precapillary PH (mPAP $\geq$ 20 mmHg, PVR > 2 WU, PCWP $\leq$ 15 mmHg) with evidence of ILD on imaging [83].

Precapillary PH due to vascular disease is robustly defined by a PVR $\geq$ 3 WU, but remains likely if between 2 and 3 [1].

As far as the definition of severe SAPH goes, with the foreseeable impact of therapeutic measures and timing on LTx evaluation, one study showed that both mPAP $\geq$ 40 mmHg and PVR $\geq$ 5 WU were strongly associated with a shorter transplant-free survival and increased risk of death or LTx [84]. Interestingly, and in contrast to common definitions of severe PH in chronic lung diseases, neither a mPAP > 35 mmHg nor mPAP > 25 mmHg with cardiac index $\leq$ 2 L/min/m$^2$ were associated with these outcomes.

As pre- and postcapillary PH can coexist in SAPH, provocative maneuvers such as fluid challenge or exercise [1] might be necessary to definitely characterize them.

#### 4.5.6. Biomarkers

BNP or NT-proBNP, good predictors of RV overload and worse outcome, are often increased in SAPH but with low sensitivity and specificity.

## 5. Phenotypes

After an extensive but again case-by-case diagnostic approach, the most precise characterization of the mechanisms underlying SAPH in individual patients is desirable for the sake of the most appropriate and specific therapeutic management in the era of personalized medicine. It should, however, be highlighted that SAPH phenotyping is not a straightforward process but rather a dynamic one with multiple and evolving phenotypes during the course of the disease.

Several recent studies have addressed SAPH phenotyping [31,85] aiming at establishing the predominant pathomechanisms in their cohorts: parenchymal lung disease, extrinsic

compression of pulmonary vessels, pulmonary angiitis and microangiopathy (defined by Mathijssen as a precapillary PH with PVR > 3 WU with no or mild parenchymal disease and after exclusion of all other causes of PH), LV dysfunction and portal hypertension.

In the precapillary PH groups, Mathijssen [31] showed that 6 of 37 patients were classified as having compression of pulmonary vasculature (4 due to fibrotic disease and 2 due to active sarcoidosis), 29 as parenchymal, 1 as suspected vasculopathy and 1 as CTEPH.

In a number of cases, the development of SAPH is unpredictable from patients' presentation at diagnosis. Even though it is known to mainly affect those with advanced pulmonary sarcoidosis, with 65 to 80% of sarcoid patients with precapillary PH having stage 4 disease [31,41,47,48,57], fibrosis is not necessary for PH development. Surprisingly, no correlation has been found between mPAP or PVR and any spirometric or plethysmographic features. Patients with comparable radiological and functional presentations displayed very different PH severity [3,10,13]. Whether this might be partly related to genetic predispositions is under study [23].

## 6. Treatment

The optimal treatment of SAPH is not clearly established because of the limited number of well-designed studies [1,8]. Decisions should be made on a case-by-case basis and patients should be managed by an experienced multidisciplinary team with at least a sarcoidosis and PH expert [1,8]. The therapeutic approach depends primarily on the dominant pathophysiologic phenotype of SAPH, as illustrated in Figure 3. Supportive therapy remains the cornerstone of treatment, including supplemental oxygen in patients with resting and exertional hypoxemia, diuretics as needed and pulmonary rehabilitation to address possible deconditioning [1,8]. In addition, identification and appropriate treatment of comorbidities is critical, including OSAS, left heart dysfunction, acute or chronic thromboembolic disease, anemia and iron deficiency [1,8].

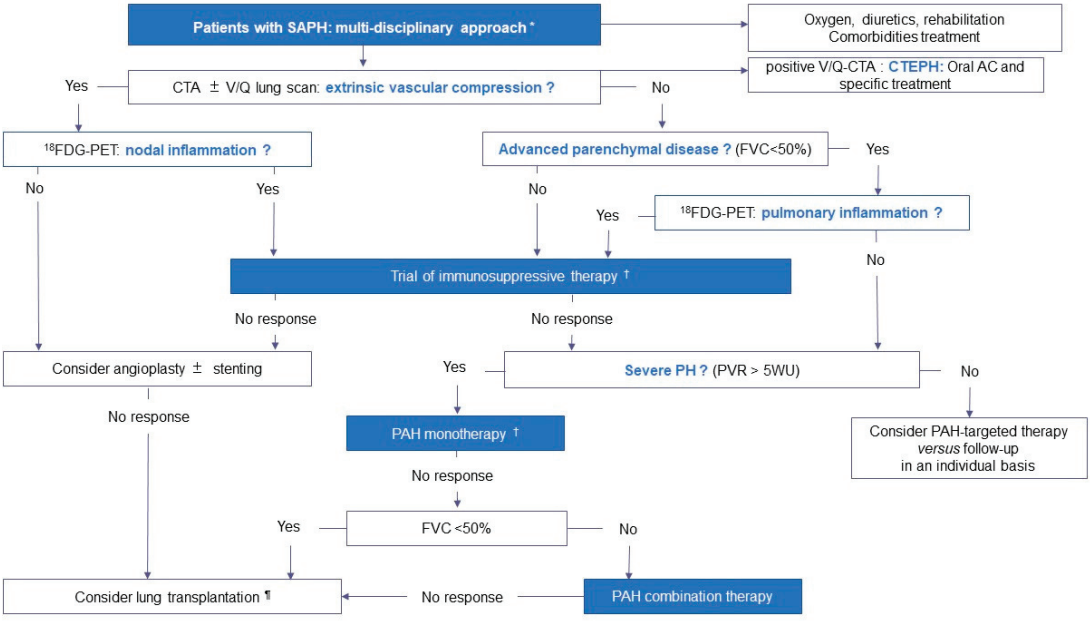


**Figure 3.** Proposed therapeutic approach of SAPH based on the mechanisms and phenotypes involved. * The therapeutic approach should be multidisciplinary, involving a sarcoidosis and a PH expert, and take into account the mechanisms involved in the development of PH, the severity of PH and the severity of the underlying parenchymal lung disease. † Anti-inflammatory treatment can be

initiated before PAH-targeted therapy or in parallel. ¶ Referral for lung transplantation should not be delayed. Abbreviations: SAPH: sarcoidosis-associated pulmonary hypertension, CTA: computed tomography angiography, V/Q: ventilation/perfusion, AC: anticoagulant, CTEPH: chronic thromboembolic pulmonary hypertension, FVC: forced vital capacity, 18FDG-PET: 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography, PVR: pulmonary vascular resistance, PAH: pulmonary arterial hypertension.

### 6.1. Obstructive Pulmonary Vasculopathy

The first step of management is the identification and treatment of extrinsic vascular compression [1,8]. In fact, anti-inflammatory therapy can lead to a reduction in lymph node size and relief of vascular compression, which may be predicted by $^{18}$FDG-PET scans [41]. In the French registry, of the five patients with obstructive PH treated with anti-inflammatory therapy, two with metabolically active lymph nodes had a response at 6 months, but none of the three with mediastinal fibrosis did [41].

In highly selective cases with mediastinal fibrosis and proximal PA stenosis, angioplasty with or without stent placement may be beneficial, even though endovascular procedures are associated with high morbidity [86,87]. In a prospective Chinese series, eight patients with SAPH and PA stenosis failing to respond to 2 months of prednisone underwent interventional therapy (balloon angioplasty in all cases plus stenting in five) and exhibited a dramatic improvement in hemodynamics (decrease in mPAP from 42.5 $\pm$ 4.6 to 20.5 $\pm$ 3.2 mmHg, $p$ = 0.035, and PVR from 12.3 $\pm$ 1.2 to 3.8 $\pm$ 0.3 WU, $p$ = 0.004) and in 6MWD (increase from 236.8 $\pm$ 36.7 to 456.4 $\pm$ 48.2 m, $p$ = 0.028) at 3 months [86]. One patient developed tachycardia, one thromboembolism, one hemoptysis and one PA dissection [86].

### 6.2. Treatment of Parenchymal Lung Disease

Despite little available data, it makes intuitive sense to control inflammation either before or in parallel to PH treatment in patients with SAPH and active parenchymal granulomas [1,8]. In an early series including 24 patients with pulmonary sarcoidosis, of whom 3 showed PH at rest and 18 showed PH on exercising, treated with 12 months of corticosteroids, 92% showed improvements on chest radiography and PFTs, but only half demonstrated improved hemodynamics [88]. In another study on 10 patients with SAPH, 3–6 months of corticosteroids resulted in a sustained amelioration of hemodynamics in 3/5 cases without pulmonary fibrosis, but no change in those 5 with stage IV [57]. Among the six patients with severe SAPH and parenchymal lung disease who had immunosuppressive therapy alone in the French registry, two with stage IV improved in terms of hemodynamics at 6 months, but not in terms of NYHA functional class or 6MWD [41]. $^{18}$FDG-PET scan may be particularly useful for gauging residual activity in patients with SAPH and fibrotic pulmonary disease and guide decisions regarding the initiation or escalation of immunosuppressive therapy [1,8].

### 6.3. Treatment of Vascular Disease and Use of PAH Agents

There are four main classes of drugs accepted for PAH therapy [7]: (1) calcium channel blockers, which are reserved for patients with a positive acute vasodilator response but are not indicated in group 5 PH, (2) endothelin-1 receptor antagonists (ERA) (including Bosentan and Ambrisentan), (3) phosphodiesterase-5 inhibitors (PDE5-i) (including Sildenafil and Tadalafil) and guanylate cyclase stimulators (including Riociguat), and (4) prostacyclin analogues (including inhaled Iloprost, inhaled Treprostinil and intravenous epoprostenol) and prostacyclin receptor agonists (including Selexipag).

In SAPH, the use of therapy directed against vascular disease is still a matter of debate [1,8]. On the one hand, the possible role of dominant vasculopathy makes this therapeutic option appealing [1,8]. On the other, there is some concern over systemic pulmonary vasodilators in SAPH. First, they may lead to hypoxemia worsening in patients with parenchymal lung disease, because of the inhibition of hypoxic pulmonary

vasoconstriction with subsequent increased ventilation/perfusion mismatch and shunting [1,8]. Second, the venous component that exists in a subset of patients may be at risk of drug-induced pulmonary edema [1,8].

In the French registry, 97/126 (77%) patients with severe SAPH received PAH-targeted therapy, including 86% with monotherapy (ERA: n = 60, PDE5-i: n = 20, intravenous Epoprostenol: n = 2, inhaled Iloprost: n = 1) and 14% with combination therapy (ERA + PDE5-i: n = 12, ERA + prostanoid: n = 2) [41]. In the international registry including unselected patients with SAPH, 115/159 (72.3%) received PAH-targeted therapy, which consisted of monotherapy in 88.2% (PDE5-i: n = 86, ERA: n = 56), bitherapy in 17.6% (PDE5-i + ERA: n = 28), and tritherapy in 6.3% (PDE5-I + ERA + prostanoid: n = 10) [45]. In both registries, PAH-targeted therapy was not associated with decreased mortality, provided that treated patients had a significantly worse condition at baseline than the untreated ones [41,45,84].

The available data on the long-term efficacy and safety of PAH-targeted therapy in SAPH are scarce and results are conflicting [1,8]. The main studies are summarized in Table 2. Most studies are retrospective small series that report diverse PAH regimens and do not take into account the variability of SAPH phenotypes [1,8]. To date, there are only three prospective uncontrolled open-label trials on inhaled iloprost [89], Ambrisentan [90] and Tadalafil [91], and two double-blind randomized placebo-controlled trials (RPCTs) on Bosentan [92] and Riociguat [93].

**Table 2.** Main studies on PAH-targeted therapy for SAPH.

| Number of Patients | Drug | Results | Study |
|---|---|---|---|
| Retrospective case series including more than 10 patients | | | |
| n = 12 | Sildenafil | After 4–6 months: improvement in hemodynamics and no change in 6MWTD | [94] |
| n = 22 | Initial monotherapy<br>- Bosentan (n = 12)<br>- Sildenafil (n = 9)<br>- Epoprostenol (n = 1)<br>Combination therapy if inadequate response (n = 8) | After 11–15.2 months: improvement in hemodynamics and in 6MWTD; improvement of NYHA functional class in nine patients | [95] |
| n = 33 | - Sildenafil (n = 29)<br>- Sildenafil + Bosentan (n = 4) | After 6 months: Increase in 6MWTD, BNP levels and TAPSE; improvement of WHO functional class in 14 patients | [96] |
| n = 13 | Prostanoids as monotherapy or in combination therapy<br>- Epoprostenol (n = 7)<br>- Treprostinil (n = 6) | After a mean of 12.7 months: improvement in PVR but not in mPAP<br>At 3 years, improvement in NT-pro BNP levels and WHO functional class | [97] |
| n = 12 | Epropostenol (n = 12)<br>+ Tadalafil (n = 4)<br>+ Sildenafil (n = 1)<br>+ Ambrisentan (n = 1) | After a mean of 4.1 years: improvement in hemodynamics | [98] |
| n = 97 with severe PH | Monotherapy (n = 83)<br>- ERA (n = 60)<br>- PDE-5i (n = 20)<br>- Epoprostenol (n = 2)<br>- Inhaled Iloprost (n = 1)<br>Combination therapy (n = 14)<br>- ERA + PDE-5i (n = 12)<br>- ERA + Prostanoid (n = 2) | After a median of 4.5 months: improvement in hemodynamics, and NYHA functional class; no change in 6MWTD | [41] |

**Table 2.** *Cont.*

| Number of Patients | Drug | Results | Study |
|---|---|---|---|
| Prospective open-label trial | | | |
| n = 15/22 completed trial | - Inhaled Iloprost | After 16 weeks: 8/15 responders (either increased 6MWTD $\geq$ 30 m or decreased PVR $\geq$ 20%); overall significant improvement in SGRQ score | [89] |
| n = 10/21 completed trial | - Ambrisentan | After 24 weeks: improvement in WHO functional class and SGRQ; no change in 6MWTD, BNP levels, Borg scale or SF-36 score | [90] |
| n = 7/12 completed trial | - Tadalafil | After 24 weeks: no change in 6MWTD, dyspnea, BNP levels or QOL scores | [91] |
| Randomized placebo-controlled trial | | | |
| 23/25 completed trial | - Bosentan vs. placebo | After 16 weeks: improvement in hemodynamics compared to placebo; no change in 6MWTD, dyspnea or QOL scores | [92] |
| 8/8 completed trial | - Riociguat vs. placebo | At 1 year: delayed time to clinical worsening compared to placebo (defined as time to all-cause mortality, need for hospitalization because of worsening cardiopulmonary status, >50 m decrease in 6MWTD, or worsening of WHO functional class); improvement in 6MWTD compared to placebo; no change in QOL scores | [93] |

Abbreviations: PAH: pulmonary arterial hypertension, SAPH: sarcoidosis-associated pulmonary hypertension, 6MWTD: six-minute walk test distance, mPAP: mean pulmonary arterial pressure, PVR: pulmonary vascular resistance, NYHA: New York Heart Association, WHO: World Health Organization, TAPSE: tricuspid annular plane systolic excursion, BNP: bone natriuretic peptide, ERA: endothelin-1 receptor antagonist, PDE-5i: phosphodiesterase-5 inhibitors, SGRQ: St Georges respiratory questionnaire; QOL: quality of life, SF-36: short-form 36 questionnaire, FAS: fatigue assessment scale.

PAH therapy is generally beneficial in SAPH in terms of hemodynamics, but this effect is inconsistently accompanied by improvements in exercise capacity, quality of life (QOL) or BNP [1,8]. The Bosentan RPCT included 39 patients with no restrictions upon the severity of PH or functional alteration (Bosentan: n = 25, placebo: n = 14) [92]. Twenty-three patients completed 16 weeks of Bosentan and showed improvement in mPAP (decrease of 4 $\pm$ 6.6 mm Hg, $p = 0.0105$) and PVR (decrease of 1.7 $\pm$ 2.75 WU, $p = 0.0104$), whereas there was no change in hemodynamics with placebo. No significant change was observed in 6MWD or QOL [92]. Changes in hemodynamics and 6MWD on Bosentan did not differ according to FVC > or $\leq$50% [92]. The proportion of patients with worsening desaturation was similar between Bosentan and placebo [92].

The Riociguat RPCT included 16 patients with SAPH and FVC > 50% (Riociguat: n = 8, placebo: n= 8) [93]. After 1 year, treated patients demonstrated a significantly delayed time to clinical worsening compared to placebo [93]. The Riociguat group had an improvement in 6MWTD of +42.7 m ($p < 0.025$), whereas the placebo group had a decline of 55.9 m. No significant change was observed in QOL [93]. In addition, no worsening in oxygenation was noted under Riociguat [93].

In the French registry repeat assessments were performed after a median period of 4.5 months in 81/97 patients initiated on PAH-targeted therapy [41]. There were significant improvements in all hemodynamic variables (mPAP fell from 48 $\pm$ 9 to 42 $\pm$ 11 mmHg, $p < 0.00001$ and PVR from 9.7 $\pm$ 4.4 to 6.9 $\pm$ 3.0 WU, $p < 0.00001$). There was also an improvement in NYHA functional class but no significant change in 6MWD (324 $\pm$ 138 versus 311 $\pm$ 127, $p = 0.33$) [41]. Interestingly, in contrast to a previous study suggesting a better effect of PAH therapy in patients with more preserved FVC [95], no difference was found in both 6MWTD and hemodynamics on treatment according to the presence of stage IV disease or severity of restrictive physiology (FVC > or $\leq$50%) [41].

To summarize, off-label use of PAH drugs should be considered on an individualized basis in a expert PH center after taking into account the mechanisms involved in the development of PH, the severity of PH and the severity of the underlying parenchymal lung disease (Figure 3) [1,8]. There is no definite advantage of one drug over the others in SAPH [1,8]. In patients with a predominant parenchymal lung disease phenotype, PDE5-i is usually preferred [7]. Experts should facilitate the entry of patients into RPCT. After the positive results of INCREASE trial [99], inhaled treprostinil has been approved in the United States for treating ILD-PH and it is currently being studied in SAPH in the SAPPHIRE RPCT (NCT03814317). The SPHINX RPCT on Selexipag has been stopped after the enrollment of 10 patients (NCT03942211). Even though the hazard of PAH therapy seems marginal, it is prudent to monitor gas exchanges in patients with parenchymal lung disease [1,8].

### *6.4. Transplantation*

Given the high mortality rate of SAPH, lung or heart–lung transplantation should be considered in otherwise eligible candidates [1,8]. However, the difficulty of prognosticating survival is a major factor confounding the issue of timing of referral in SAPH. Patients with SAPH have a greater likelihood of succumbing while on the waiting list [100], suggesting that referral tends to occur too late. In patients with advanced pulmonary sarcoidosis, the presence of PH should prompt referral for lung transplantation [1,8]. In case of predominant vascular phenotypes, it seems reasonable to refer patients who have failed to respond to PAH-targeted therapy [1,8]. Post-transplant survival in sarcoidosis patients is similar to that of other indications, and SAPH does not seem to be associated with higher mortality after lung transplantation [101].

## 7. Outcomes

As an independent risk factor for mortality [1,3,41,45,50,102], SAPH carries a 10-fold increased risk of death [24,56,103]. The predictors of adverse outcomes in SAPH are WHO functional class IV, RV dysfunction, severe lung fibrosis, 6MWD < 300m, DLCO <35% pred, and persistent increase in NT-proBNP after 3–9 months of vasodilators [45,49,62].

In a recent study of predictors of mortality on the LTx waitlist for sarcoidosis, severe PH was the most significant one [103], whereas a previous study [100], carried out in a single center, identified other markers (including DLCO and composite physiological index), but not PH, as predictors of death on the waiting list [100].

In addition to its strong impact on mortality, SAPH also increases morbidity with increased supplemental oxygen requirements [41,47], healthcare resource utilization [104], burden of functional capacity [48,49,100] and need for caregiver assistance. It also negatively impacts quality of life and the employment status.

Finally, a recent study has addressed the question of risk factors for hospitalization in patients with SAPH undergoing LTx evaluation [105], as it has been addressed in group 1 PH [106,107]. It showed that 60% of sarcoid patients with PH were hospitalized at least once for respiratory failure before LTx or death. Treatment with vasodilators was significantly associated with a 80% decrease in risk of hospitalization [105]. This important finding might be taken into account in therapeutic decision making for SAPH patients, in whom guidelines are presently poorly validated.

## 8. Conclusions

SAPH is a very severe complication of sarcoidosis, resulting from complex and often entangled mechanisms. Its diagnosis is often very challenging due to the poor specificity of its warning signs. These should lead to a thorough non-invasive work-up and, to confirm the diagnosis after a multidisciplinary discussion, to right heart catheterization. Only the most precise evaluation of the underlying mechanisms involved will allow proper therapeutic management. A part of the medical treatment will specifically address the vascular component of the disease, but the proper vasodilators to be used are not presently

consensual. Ongoing properly designed clinical trials will largely help to define strong recommendations of the subject. In any case, this strategy will have to be discussed, repeatedly if necessary, with an expert team of sarcoidosis, pulmonary hypertension and at times lung transplant experts.

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## Abbreviations

| | |
|---|---|
| 6MWD | 6 min walk test distance |
| 6MWT | 6 min walk test |
| AA | ascending aorta |
| CMR | cardiac MRI |
| CT | computed tomography |
| CTEPH | chronic thromboembolic pulmonary hypertension |
| DECT | dual-energy CT |
| DLCO | lung diffusing capacity for carbon monoxide |
| ERA | endothelin receptor antagonist |
| ESC/ERS | European Society of Cardiology/European Respiratory Society |
| FEV1 | forced expiratory volume in 1 s |
| FVC | forced vital capacity |
| ILD | interstitial lung disease |
| LTx | lung transplantation |
| LV | left ventricle |
| MRI | magnetic resonance imaging |
| NYHA | New York Health Organization |
| OSAS | obstructive sleep apnea syndrome |
| PA | pulmonary arteries |
| PAH | pulmonary arterial hypertension |
| PAWP | pulmonary artery wedge pressure |
| PDE-5i | phosphodiesterase-5 inhibitors |
| PFT | pulmonary function testing |
| PH | pulmonary hypertension |
| PVR | pulmonary vascular resistance |
| QOL | quality of life |
| RHC | right heart catheterization |
| RPCT | randomized placebo-controlled trial |
| RVSP | right ventricular systolic pressure |
| SAPH | sarcoidosis-associated pulmonary hypertension |
| TRV | tricuspid regurgitant velocity |
| TTE | transthoracic echocardiography |
| V/Q | ventilation/perfusion |
| WASOG | World Association of Sarcoidosis and other Granulomatosis |
| WHO | World Health Organization |
| WU | Wood's units |

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# Infectious Complications of Pulmonary Sarcoidosis

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**Abstract:** In this review, the infectious complications observed in sarcoidosis are considered from a practical point of view to help the clinician not to overlook them in a difficult context, as pulmonary sarcoidosis makes the recognition of superinfections more difficult. An increased incidence of community-acquired pneumonia and of opportunistic pneumonia has been reported, especially in immunosuppressed patients. Pulmonary destructive lesions of advanced sarcoidosis increase the incidence of chronic pulmonary aspergillosis and infection by other agents. Screening and treatment of latent tuberculosis infection are crucial to prevent severe tuberculosis. Severity in COVID-19 appears to be increased by comorbidities rather than by sarcoidosis per se. The diagnosis of infectious complications can be challenging and should be considered as a potential differential diagnosis when the exacerbation of sarcoidosis is suspected. These complications not only increase the need for hospitalizations, but also increase the risk of death. This aspect must be carefully considered when assessing the overall health burden associated with sarcoidosis. The impact of immune dysregulation on infectious risk is unclear except in exceptional cases. In the absence of evidence-based studies on immunosuppressants in the specific context of pulmonary sarcoidosis, it is recommended to apply guidelines used in areas outside sarcoidosis. Preventive measures are essential, beginning with an appropriate use of immunosuppressants and the avoidance of unjustified treatments and doses. This approach should take into account the risk of tuberculosis, especially in highly endemic countries. Additionally, parallel emphasis should be placed on vaccinations, especially against COVID-19.

**Keywords:** infection; sarcoidosis; opportunistic infections; mycoses; tuberculosis; COVID-19

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## 1. Introduction

Pulmonary sarcoidosis is a systemic granulomatous disease primarily affecting the lungs and lymphatic system, with a range of clinical presentations and outcomes spanning from spontaneous remission to progressive, severe respiratory dysfunction [1,2]. The etiology remains unknown [1,2]. While some patients may require no intervention, more than half of patients with sarcoidosis require immunosuppressive therapy, such as glucocorticosteroids, cytotoxic drugs, or biologics, for periods ranging from one to several years [3].

The relationship between infectious agents and sarcoidosis is complex. Although there is a hypothesis that infectious agents may play a role in the pathogenesis of sarcoidosis, this remains speculative. Conversely, infectious diseases can also complicate sarcoidosis, leading to repeated hospitalizations, respiratory exacerbations, and/or death [4]. Infectious complications consist primarily of community-acquired pneumonia (CAP) and immunocompromised host pneumonia (ICHP) associated with immunosuppressive treatment. Parenchymal fibrocystic lung disease may increase susceptibility to superinfections [5–7].

Some infectious diseases may be associated with epidemiologic conditions, such as exposure to tuberculosis, histoplasmosis, or the risk of COVID-19. Another important issue is to determine whether sarcoidosis itself may increase the likelihood of infection, independent of immunosuppressants and fibrocystic lung lesions.

It can be challenging to distinguish an extraneous infection from a true exacerbation of sarcoidosis or another complication, such as left ventricular failure or pulmonary thromboembolism [8,9]. Detecting manifestations of infection on lung imaging can be particularly challenging. In specific cases, the severity of an infection may be more dependent on the underlying advanced pulmonary, cardiac, or neurologic sarcoidosis than on the infection itself. Infections can pose an additional health burden, affecting hospitalizations, care, work disability, quality of life, and mortality [10,11].

This review aims to provide practical insights into the management of infectious complications in sarcoidosis. Dedicated sections will address data obtained from well-conducted epidemiologic studies, reports on immunocompromised host infections, fungal infections, the suprainfections of pulmonary fibrocystic lesions, tuberculosis, COVID-19, and curative and preventive treatments. Additionally, the review will explore the key impaired anti-infectious mechanisms in sarcoidosis, facilitate discussion on these critical topics, and provide future research directions in this field.

## 2. Methods

We searched through PubMed for original articles and reviews, and, in some cases, reports published in the English language after 2020; older publications have also been included according to the importance of the information. Therefore, we used the term "sarcoidosis" in combination with the following terms: "infectious risk", "hospitalized infections", "death certificate", "tuberculosis", "COVID-19", "Aspergillosis", "Pneumocystosis", "community-acquired pneumonia", "opportunistic infection", "vaccination", "prevention", and "treatment". Eventually, articles about B-cell immunity, T Regs and autophagy, and defenses against infectious agents in sarcoidosis were considered. In general, the main goal of this review was to focus on the infectious complications by themselves.

## 3. Well-Conducted Epidemiologic Studies on the Association between Infectious Diseases and Sarcoidosis

Several studies providing insights into the association between infectious diseases and sarcoidosis are based on registry-based studies conducted in Sweden, the US, Taiwan, and France [12–18]. These studies have focused on (i) infections that occurred prior to the diagnosis of sarcoidosis, (ii) infections that occurred after the diagnosis of sarcoidosis, (iii) the exploration of the relationship between tuberculosis and sarcoidosis, and (iv) the investigation of the impact of infectious diseases as a cause of death in patients with sarcoidosis.

Studies investigating the causal role of infectious diseases in sarcoidosis are warranted, because the "nature" heritability of sarcoidosis is reported to account only for 31% of the causes of sarcoidosis, whereas the "nurture" exposure to occupational, environmental, or infectious airborne contaminants accounts for up to 69% [19]. An association has been identified with a history of infectious disease, including upper respiratory and ocular infections, at least three years prior to the sarcoidosis diagnosis. This association is linked to a 25% increased likelihood of being diagnosed with sarcoidosis [12]. A causal role for infections must be considered with caution. Assuming that 1 in 10 infections occurs in preclinical sarcoidosis, with a possible underlying immune disorder, the increased risk is substantially mitigated. In addition, this study showed that, if there is indeed a true causal role of infection in the development of sarcoidosis, its quantitative impact appears to be relatively weak. Taking into account the risk of infection postdiagnosis of sarcoidosis, a study conducted between 2006 and 2013, before the COVID-19 outbreak, found that sarcoidosis was associated with a 1.8-fold increased risk of first serious infection, i.e., hospitalization with an ICD code for an infectious disease, compared to the general

population. Notably, this increased risk was most significant in the first two years after the diagnosis of sarcoidosis [13]. The hazard ratio for serious infection was three times higher in individuals who received immunosuppressants after diagnosis. Even untreated sarcoidosis patients had a 50% increased risk of serious infection compared to controls. Interestingly, the risk was much lower in sarcoidosis than in lupus or COPD. The rate of recurrent serious infections was also doubled in sarcoidosis patients.

Hospitalization for multiple serious infections occurred with unusual frequency in sarcoidosis patients. In another US study, using the Rochester Epidemiology Project, similar results were obtained by comparing the risk of hospitalized infections between sarcoidosis patients and controls [14]. The HR was 1.73 in untreated sarcoidosis patients; the risk was higher (HR = 3.3) in patients on low doses of glucocorticosteroids, and there was a higher risk (HR = 4.48) when glucocorticosteroids were administered at doses above 10 mg/d. Notably, a study by Larsson et al., using the Swedish National Patient Register, showed a higher incidence of influenza or pneumonia in sarcoidosis patients compared to controls (HR 2.98) [17].

Methotrexate and azathioprine are immunosuppressants used as a second-line treatment for sarcoidosis [15]. Within 6 months of treatment, methotrexate was associated with a 43% reduced risk of infectious disease compared to azathioprine, with a respective risk of 6.8% versus 12% [15].

A nationwide study of the Taiwan National Health Insurance Database from 2000 to 2015 examined the risk of sarcoidosis after a tuberculosis diagnosis compared to a control population without tuberculosis. Conversely, the risk of tuberculosis based on a prior diagnosis of sarcoidosis was also examined compared to a control population without sarcoidosis [16]. In Taiwan, where the incidence of tuberculosis was still high during the study (57 p 100,000 in 2012), the risk of sarcoidosis was 8.09 times higher in patients with tuberculosis than in controls without tuberculosis, suggesting that a history of tuberculosis is a risk factor for the development of sarcoidosis. A latent onset of sarcoidosis, emerging long after the tuberculosis had been treated, was suggested. Interestingly, the risk of sarcoidosis was higher in extrapulmonary tuberculosis than in pulmonary tuberculosis [16]. Conversely, the risk of tuberculosis after a diagnosis of sarcoidosis was higher than in controls without sarcoidosis (HR 1.85). Given the common presentation of tuberculosis and sarcoidosis, and the possible confusion between the two diagnoses, the interpretation of these results must be discussed (see the Section 12).

Thanks to an analysis by the French Epidemiological Center for Medical Causes of Death from 2002 to 2011, it was possible to calculate age- and sex-adjusted observed/expected ratios in sarcoidosis patients compared to the general population for the underlying cause of death when sarcoidosis was listed as a nonunderlying cause of death. The analysis showed an increased ratio for infection in sarcoidosis [18]. Infection was the underlying cause of death in 11.7% of women and 8.6% of men with sarcoidosis.

## 4. Immunocompromised Host Infections

In this section, we will focus on the so-called immunocompromised host pneumonia (ICHP) and briefly address extrapulmonary sites of infection. ICHP was recently defined by the American Thoracic Society workshop as an infectious pneumonia affecting an individual with a quantitative or functional host immune defense disorder [20]. Chronic immunosuppression is a major risk for sarcoidosis patients. This is most frequently attributed to the use of immunosuppressants, which are administered to approximately half of all patients. These treatments include corticosteroids, cytotoxic agents, and biologics. In addition, solid organ transplantation, including lung, heart, liver, and kidney transplantation, may also contribute to immunosuppression.

Most of sarcoidosis treatments impair the function of various immune cell types, including macrophages and T-lymphocytes. This may increase the risk of developing *Pneumocystis* pneumonia, invasive aspergillosis, as well as typical CAP.

It is important to emphasize the need to systematically exclude granulomatosis-associated common variable immunodeficiency disorder as a differential diagnosis, which often results in frequent suprainfections. This can be done by measuring and looking for hypogammaglobulinemia with decreased serum levels of immunoglobulin G (IgG) and immunoglobulin A (IgA) or immunoglobulin M (IgM) [2].

### 4.1. Risk of Immunosuppressants

Corticosteroids are recommended as first-line treatment option and may compromise immunity when administered at a dose of at least 20 mg/day of a prednisone equivalent for at least two weeks or 10 mg/day for a longer period. Methotrexate is the preferred second-line treatment, while TNFα blockers, such as infliximab or adalimumab, are preferred as the third-line treatment. TNFα blockers significantly increase susceptibility to *Mycobacterium tuberculosis* and endemic fungal infections [21]. Therefore, individuals from regions with a high incidence of tuberculosis, or those with latent tuberculosis, are at increased risk of developing tuberculosis disease in the absence of preventive measures. The same is true, to a lesser extent, for histoplasmosis. Rarely used, JAK inhibitors and IL6—possibly used in the treatment of multiresistant sarcoidosis—are associated with an increased risk of tuberculosis.

Corticosteroids have been studied in randomized controlled trials for rheumatoid arthritis, but these trials were not well-powered to assess the risk of infection. These studies did not show an increased risk of infection associated with corticosteroids [22]. Nevertheless, observational studies have demonstrated a dose- and duration-dependent increased risk of infections, especially tuberculosis, pneumocystosis, and herpes [22]. In a retrospective study, Vorselaars et al. compared the incidence of infections based on antibiotic use or hospital admissions and found a higher incidence of infections with azathioprine (36.8%) compared to methotrexate (18.1%). This finding is consistent with Rossides' epidemiologic study in Sweden [15,23]. Several studies have evaluated sarcoidosis patients treated with TNFα blockers, either alone or in combination with other immunosuppressants [24,25]. In Jamilloux's cohort of 132 patients, one-third of patients experienced infections, such as pneumonia, recurrent urinary tract infections, and bacterial sepsis, often requiring hospitalization and the withdrawal of sarcoidosis treatment [24].

This was often followed by a relapse of sarcoidosis. Patients experienced legionellosis, invasive aspergillosis, pneumocystosis, primary cytomegalovirus infection, cryptococcosis, hepatitis B reactivation, and nontuberculous mycobacterial infection, which occurred in one case each. No case of tuberculosis was reported, probably due to recommended preventive measures [24]. Of note, the Heidelberg study, with a median follow-up of 45 months and 46 patients with skin lesions, categorized patients into those receiving treatment for the skin ($n = 21$) or those receiving treatment for an extradermatologic reason ($n = 25$), resulting in a notable finding [25]. There was a significant contrast in infection rates between the two groups, with rates of 9.5% and 48%, respectively. This suggests that the use of TNFα blockers, together with more corticosteroids and cytotoxic drugs in the second group, increased the risk of infection compared to the use of TNFα blockers alone, which were more frequently used in the first group [25].

### 4.2. Pulmonary and Extrapulmonary Opportunistic Infections in Sarcoidosis

A study conducted in Rennes, France, showed evidence of a variable risk of *Pneumocystis* pneumonia in non-HIV patients depending on the underlying disease. Among these diseases, sarcoidosis had one of the lowest risks, with fewer than 5 cases per 100,000 patient-years, in contrast to diseases with a high risk, exceeding 70 cases per 100,000 patient-years, such as vasculitis [26].

Interestingly, the incidence of invasive aspergillosis has been reported in rare cases of sarcoidosis [7,24].

In a study of 234 patients with neurosarcoidosis receiving immunosuppressive therapies, 7.2% developed treatment-related secondary infections, resulting in three deaths from

sepsis [27]. The reporting of infections in this article is critical, as it could potentially lead to significant diagnostic errors, particularly when dealing with sarcoidosis extrapulmonary localizations, and may lead to harmful drug-prescribing. It also raises questions about a defective immunity in some patients with sarcoidosis. According to a Mayo Clinic study, sarcoidosis was the cause of up to 9% of non-HIV-related cases of progressive multifocal leukoencephalopathy (PML), a disease caused by the JC virus (JCV) [28]. The JCV, along with immunosuppression, plays a critical role in the development of PML [28,29]. While corticosteroid therapy, a well-established cause of immunosuppression leading to PML, was present in most sarcoidosis patients, PML has also been observed in several sarcoidosis patients without any immunosuppressive therapy or comorbidity prior to therapy, with PML sometimes being the primary presenting manifestation of sarcoidosis [29]. In PML, brain MRI findings typically differ from those of central nervous system sarcoidosis, with asymmetric subcortical white-matter lesions that are hypointense on T1, hyperintense on T2, and nonenhancing, with the rare exception of contrast enhancement versus contrast-enhancing lesions in the meninges and/or parenchyma. While the cerebrospinal fluid (CSF) cell counts and biochemistry are typically normal in PML, they are more often abnormal in central nervous system sarcoidosis. Therefore, it is important to consider the possibility of PML when the diagnosis of neurosarcoidosis is uncertain, especially in the presence of atypical findings, such as MRI and CSF results. PCR testing is essential for the diagnosis of JCV, with a sensitivity rate of 72–92%. If uncertainty remains, a brain biopsy may be recommended. The prognosis is typically poor, and treatment requires the reversal of immunosuppression.

In addition, Cryptococcosis is a potential opportunistic infection seen in cases of sarcoidosis. Patients, representing 2.9% of HIV-negative cryptococcosis cases recorded in France [30], manifested the infection during the treatment of sarcoidosis with corticosteroids. However, similar to PML, one-third of the patients experienced cryptococcosis as a revealing manifestation of sarcoidosis, leading to its diagnosis. Organs affected by cryptococcosis included the central nervous system (72%), skin or soft tissue (22%), bones or joints (17%), and liver (11%). Although it is possible, lung infection is very rare. The CSF investigation is highly sensitive, using an India ink preparation, CSF culture, and/or CSF antigen. Patients had a positive prognosis after an antifungal treatment. Interestingly, routine evaluations of immune defenses in both PML and cryptococcosis patients without corticosteroid therapy showed no impairment [30].

Herpes zoster may also be responsible for suprainfections, mainly at the ocular level, in patients treated with systemic or topical corticosteroids [31].

**5. Community-Acquired Pneumonias**

Using the National Board of Health of Care and Welfare in Sweden, Larsson demonstrated the higher rate of influenza and pneumonia in sarcoidosis patients compared to controls [17]. *Pneumococcus pneumoniae* is the most common bacterium isolated from adult patients with community-acquired pneumonia. Immunocompromised status increases the prevalence of pneumococcal disease in patients receiving corticosteroids and other immunosuppressive therapies [32,33]. However, there are no available studies in the literature comparing bacterial strains causing pneumonia among sarcoidosis patients and controls.

**6. Fungal Infections**

Several fungal infections have been reported in patients with sarcoidosis. In a US study by Baughman et al. [34] of 753 patients, 0.9% were found to have fungal infections. These included *Histoplasma capsulatum* and *Blastomyces dermatitidis*, both affecting the lungs, and one case of *Cryptococcus neoformans*, leading to meningitis. Diagnosis was most often confirmed by bronchoscopy or lung biopsy, with bone marrow and CSF used in two cases. Histoplasmosis is a fungal infection that is endemic in the United States and some other regions, but not in Europe, except Italy [35]. All documented cases to date have involved patients receiving immunosuppressive treatments, such as corticosteroids with or without

methotrexate, and have been successfully treated with antifungal agents after the taper of immunosuppressive medications [34].

On the other hand, pulmonary aspergillosis, which is a widespread infection, has a prevalence of approximately three million cases [36]. Invasive aspergillosis occurs in severely immunocompromised individuals, while chronic pulmonary aspergillosis is commonly associated with tuberculosis, COPD, and sarcoidosis [36]. According to the classification of the European Society of Clinical Microbiology and Infectious Diseases and the European Respiratory Society, chronic cavitary pulmonary aspergillosis is the predominant manifestation of sarcoidosis preceding simple aspergilloma, while chronic fibrosing aspergillosis is extremely rare [7,37]. Allergic bronchopulmonary aspergillosis is occasionally observed [7]. In the largest study of chronic pulmonary aspergillosis complicating sarcoidosis, patients presented with the following symptoms: cough (86%), hemoptysis (36%), fever (29%), and weight loss (40%) [7]. All but 1 patient (64 out of 65) had at least one cavitation, with multiple cavitations observed on lung CT scans [7]. Positive *Aspergillus* serology was observed in 92% of patients, while *Aspergillus* was found in 77.9% of bronchial endoscopic or sputum specimens. Coinfection with bacteria was observed in 46.4% of patients, mainly with *Pseudomonas aeruginosa*. Nontuberculous mycobacteria were also detected. Serum C-reactive protein levels were elevated in 87% of cases. The severity of pulmonary sarcoidosis was demonstrated by a Composite Physiologic Index score above 40 in 62% of cases, with pulmonary fibrosis present in almost 90% of cases, with an average extent of 22%. Pulmonary hypertension was detected in 30.7% of the cases. Sixty-seven % of patients met the high-risk prognostic criteria according to Walsh [38]. The survival rate was comparable to a control group of sarcoidosis patients, who were matched with patients without Aspergillus infection based on their fibrocystic pattern and the date of fibrocystic lung detection on the imaging. Specifically, the survival was 73% at 5 years and 61% at 10 years. Although 3 patients died due to massive hemoptysis, interventional radiology effectively managed 14 cases of massive hemoptysis. The use of antifungal medications was shown to be effective based on symptom resolution and improvement in the chest CT. In particular, a decrease in the maximum thickness of the cavity wall and pleura has proven to be the most discriminating factor in evaluating the therapeutic response [39]. Nevertheless, the complete response and long-term recovery were rare occurrences, probably due to the persistent cavitary lesions in fibrocystic lung. To date, there are no studies comparing antifungal drugs and their duration of treatment, and thus no protocol can be recommended. However, a recent interesting prospective study on the duration of itraconazole treatment in chronic pulmonary aspergillosis in underlying lung diseases other than sarcoidosis suggested a better outcome at 2 years, with fewer relapses when the treatment duration was extended to 12 months compared to 6 months [40]. High occupational exposure is a risk factor for chronic pulmonary aspergillosis. This condition is associated with jobs that have a high risk of exposure to molds (37.5%) compared to sarcoidosis patients without aspergillosis infection (17.5%) [7].

**7. Suprainfections in Fibrotic Lung Lesions**

Baughman et al. observed the frequent occurrence of bacterial suprainfections responsible for acute exacerbation in fibrotic lung sarcoidosis, with a favorable response to short courses of antibiotics [5]. Bronchiectasis and the use of immunosuppressants, especially TNFα blockers, have been associated with an increased risk of infection [5]. In a monocentric study of 142 patients with fibrosing pulmonary sarcoidosis, Nardi et al. found that chronic pulmonary aspergillosis occurred in 11.3% of cases, while tuberculosis occurred in 7% of cases, both during the 7.1-year follow-up of the study. Nontuberculous mycobacterial infections accounted for 2% of cases, while pneumonia due to various agents accounted for 7%. In this series, 1 out of 16 deaths was attributed to *Nocardia* infection [6]. Although dedicated studies on the subject are lacking, patients with advanced pulmonary sarcoidosis often experienced suprainfections, including those caused by *Pseudomonas aeruginosa*, a common pathogen associated with bronchiectasis.

## 8. Tuberculosis

One-third of the world's population carries latent tuberculosis infection [16]. The majority of these people live in countries where tuberculosis is endemic. Therefore, clinicians can use the TB profile reference [41] to assess the incidence of tuberculosis in different regions and determine the potential threat of tuberculosis. Some individuals in countries with low incidence of tuberculosis may contract the disease through travel to high-incidence countries or contact with an infectious person.

Sarcoidosis patients undergoing immunosuppressive therapy, especially with corticosteroids or TNFα blockers, are at increased risk of developing tuberculosis. It is widely recognized that differentiating between pulmonary sarcoidosis and tuberculosis can be challenging due to confusing imaging and even pathology. Granulomas are not always necrotic in tuberculosis, whereas fibrinoid necrosis is possible in sarcoidosis. Microbiologic studies for *M. tuberculosis* may produce false-negative results, even when tuberculosis is present [42]. Diagnosing tuberculosis suprainfection in a patient with confirmed sarcoidosis is a difficult task, with a high risk of overdiagnosing a sarcoidosis exacerbation. Such a misdiagnosis may lead to the initiation or escalation of immunosuppressive treatment, with potentially disastrous consequences. The rule should be to consider an alternative cause—such as an infectious, cardiac, or thromboembolic cause—when there is an unexpected progression of symptoms in a patient who previously had a well-controlled disease and no recent changes in their treatment regimen. In this context, it is important to have a thorough understanding of the patient's risk factors. If a patient has a history of travel in a highly endemic country, and presents with general symptoms, such as fever or weight loss, productive cough with purulent sputum, hemoptysis, and new chest CT imaging findings, such as cavities or necrotic lymphadenopathy, may suggest mycobacterial infection. Microbiological stains and techniques can be used to look for mycobacteria in sputum, bronchoalveolar lavage, or tissue samples. It is important to note that interferon-γ release assays and tuberculin tests can produce false-negative results, especially in elderly patients with low blood lymphocyte counts. Wang's research showed a significant increase in the risk ($\times$1.85) for tuberculosis in sarcoidosis patients [16]. However, the study did not compare the risk between patients based on their sarcoidosis treatment. Moreover, the close temporal association between tuberculosis and sarcoidosis diagnosis, coupled with the challenge of distinguishing the two diseases, raises the possibility of the misdiagnosis of sarcoidosis as tuberculosis in some patients [16].

## 9. Coronavirus Disease 2019 (COVID-19) and Sarcoidosis

### *9.1. COVID-19 Severity in Patients with Sarcoidosis?*

The 2019 coronavirus pandemic was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Several risk factors for admission in the intensive care unit (ICU) and/or mortality have been identified, including advanced age, male sex, and comorbidities, such as obesity, cardiovascular disease, diabetes mellitus, and chronic respiratory disease [43]. Since 2020, several cohort studies have attempted to determine whether patients with sarcoidosis are at an increased risk of developing severe COVID-19 or experiencing poor outcomes (Table 1). It is important to note that all the studies discussed here regard the severity of enrolled patients at the onset of the pandemic, before the introduction of vaccines and the emergence of new, less severe variants.

**Table 1.** Summary of the studies evaluating the risk of severe COVID-19 associated with sarcoidosis.

| Population Study with COVID-19 (*n*) | Patients with COVID-19 and Sarcoidosis (*n*) | Hospitalizations *n* (%) | ICU Admision *n* (%) | Deaths *n* (%) | Mode of Recruitment/Location | Risk of Severe COVID-19 Associated with Sarcoidosis | Ref. |
|---|---|---|---|---|---|---|---|
| 36 | 36 | 28 (78%) | 13 (36%) | 5 (14%) | Tertiary centers/France | NA | [44] |
| 45 | 45 | 14 (31%) | 2 (5%) | 4 (9%) | Nationwide, multicenter registry from tertiary centers/Spain | NA | [45] |
| 7337 | 37 | 22 (59.5%) | NA | 6 (16.2%) | Tertiary centers/US | Not associated with intubation and mechanical ventilation or in-hospital mortality | [46] |
| 119 | 77 | 19 (24.7%) | 6 (7.9%) | 1 (1.3%) | One tertiary center/US | NA | [47] |
| 8 | 8 | 3 | 2 | 1 | One tertiary center/France | NA | [48] |
| 1213 | 64 | NA | 24 (37%) | 11 (17%) | Paris University Hospital Database and a national cohort from tertiary centers/France | Independent factor of severe COVID-19 (i.e., hospitalization in the ICU and/or death) (aOR = 5.19, 2.15–12.3) | [49] |
| 8,256,161 | 17 624 | 84 (0.5%) | 10 (0.1%) | 32 (0.2%) | Database from English general practices linked to Public Health England's database of SARS-CoV-2 testing, along with records of English hospital admissions, ICU admissions, and COVID-19-related deaths | Independent factor (after adjusting for comorbidities) of hospitalization (but not in ICU, HR 1.36 (1.10–1.68)), and of increased death HR 1.41 (0.99–1.99) | [50] |
| 278,271 | 954 | 185 (19.4%) | 66 (6.9%) | 41 (4.31%) | Multicenter research network TriNETX in United States. Participating organizations: large academic centers that operate both tertiary care and satellite secondary or primary office locations | No significant association between sarcoidosis and the risk of hospitalization, nor a higher morality, when adjusted for demographics and comorbidities | [51] |
| 117,694 | 892 (systemic autoimmune diseases) 149 (sarcoidosis) | All hospitalized | 98 (11%) | 174 (20%) | Nationwide retrospective study Spain using ICD10 codes in the National Registry of Hospital Discharges | SADs not associated with a higher risk of COVID-19 mortality (OR = 0.93; 95% CI, 0.78–1.11) | [52] |

Several series studies with small numbers of patients with sarcoidosis and COVID-19 have reported significantly high rates of ICU admission and mortality, reaching 37.5% and 17.2%, respectively [44–49]. These series had selection biases, as the research was primarily conducted in hospital-based and tertiary centers, potentially leading to the inclusion of a greater proportion of hospitalized COVID-19 patients and individuals with more severe sarcoidosis who had additional comorbidities and were undergoing immunosuppressive treatments. For example, the study conducted by Chevalier et al. analyzed 1213 patients with autoimmune/inflammatory rheumatic diseases with COVID-19 from two French national databases: the EDS (Entrepôt des Données de Santé, including all patients followed in Paris university hospitals) and the French multicenter COVID-19 cohort French Rheumatic and Musculoskeletal diseases (RMDs). Among the 64 patients with both sarcoidosis and COVID-19, the study found that sarcoidosis was an independent factor for severe COVID-19 (i.e., ICU admission and/or death) in the multivariate analysis (aOR = 5.19, 2.15–12.3), along with other factors, such as older age, interstitial lung disease, arterial hypertension, and obesity [49].

In contrast, a representative with a large unselected cohort in England was designed to provide a risk estimate for severe COVID-19 among individuals with chronic respiratory disease, while adjusting for demographic and socioeconomic status and comorbidities associated with severe COVID-19 [50]. This study used a database from English general practices, which was linked to Public Health England's database of SARS-CoV-2 testing, and records of English hospital admissions, intensive care unit (ICU) admissions, and COVID-19-related deaths [50]. The cohort for this study consisted of 8,256,161 individuals, of whom 14,479 (0.2%) were hospitalized with COVID-19 and 5956 (0.1%) died. Among the 17,624 patients with sarcoidosis, 84 (0.5%) required hospitalization and 32 (0.2%) succumbed to the disease. The study found that individuals with sarcoidosis, along with other respiratory diseases, like COPD and ILD, had an increased risk of hospitalization, but not ICU admission, with a hazard ratio of 1.36 (1.10–1.68), compared to those without these respiratory diseases after adjusting for comorbidities. Patients with sarcoidosis were also at increased risk of death, but with imprecise estimates (HR 1.41 (0.99–1.99)). According to the authors, sarcoidosis patients appeared to have a modestly increased risk of severe disease, but their risk of death from COVID-19 at the height of the epidemic was mostly much lower than the usual risk of death from any cause [50].

Another large retrospective cohort study in the United States examined the risks of COVID-19 in patients with pulmonary sarcoidosis compared to a propensity-matched cohort on comorbidities and the demographics of patients without sarcoidosis using a multicenter research network called TriNEXT. The study identified a total of 278,271 COVID-19 patients within the research network, of which 954 patients (0.34%) had a diagnosis of pulmonary sarcoidosis. Common comorbidities, including hypertension, chronic lower respiratory disease, diabetes mellitus, ischemic heart disease, nicotine dependence, and chronic kidney disease, were found to be more prevalent in patients with pulmonary sarcoidosis. In the initial unmatched analysis, the pulmonary sarcoidosis group had a higher mortality rate (4.3% versus 2.06%) and an increased risk of ICU admission (6.92% versus 3.05%). However, after applying propensity score matching, no significant differences were observed between the groups [51]. These analyses suggest that the higher mortality observed in sarcoidosis patients may be due to the increased burden of comorbidities rather than the disease itself.

A smaller nationwide retrospective study conducted in Spain showed similar results in assessing the clinical status of patients with systemic autoimmune diseases (SADs) hospitalized with COVID-19. The study included 149 sarcoidosis patients. It was found that the in-hospital mortality was higher in patients with SADs compared to the control group (20% vs. 16%, $p < 0.001$). However, after adjustment for baseline conditions, SADs were not associated with a higher risk of mortality (odds ratio = 0.93; 95% confidence interval, 0.78–1.11). The mortality observed in patients with SADs was mainly influenced by factors such as age, heart failure, chronic kidney disease, and liver disease [52].

The risk of severe COVID-19 in sarcoidosis patients seems to be mainly influenced by comorbidities. However, it is conceivable that the severity may be partly due to the impaired lung function associated with sarcoidosis or the use of immunosuppressive drugs [45,46].

Morgenthau et al. found that sarcoidosis was associated with severe COVID-19 outcomes only in patients with moderately and/or severely impaired pulmonary function (aOR 7.8; 95% CI, 2.4–25.8), independent of demographics and comorbidities [46].

Immunosuppressive medications may be associated with the risk of severe sarcoidosis. In the study by Chevalier et al., treatment with corticosteroids (aOR 2.47 (1.58–3.87)) or rituximab (aOR 3.32 (1.45–7.49)) was an independent factor of severe COVID-19 [49]. It seems that the risk only affects patients with a corticosteroid dose $\geq$10 mg/day [53]. Interestingly, treatment with leflunomide and methotrexate was significantly associated with a better outcome [49]. The TNF-alpha antagonists do not seem to be associated with severe COVID-19 in this and other studies [44,49,53]. The effect of corticosteroids on severe COVID-19 in sarcoidosis and other immune system diseases may be driven by a defective ability to respond to the vaccine and/or to control SARS-CoV-2 infection. In a small series of sarcoidosis patients, corticosteroids were associated with a defective T-cell response against the spike protein [54].

In conclusion, the risk of severe COVID-19 (i.e., ICU admission and/or death) associated with sarcoidosis appears to be moderate, especially in large unselected studies. However, the increased severity observed in these patients may be driven by known comorbidities associated with COVID-19 (e.g., age, cardiovascular disease, etc.), severe ILD, and the use of glucocorticoids. As the studies were conducted before the advent of vaccines, it is possible that the risk of severe COVID-19 associated with sarcoidosis is even lower now.

*9.2. Risk of Sarcoidosis and Sarcoidosis Flare-Ups after COVID-19 and LINKS to Pathogeny*

Several case reports and series have reported the detection of sarcoidosis following COVID-19 [55,56]. Rare cases of sarcoidosis flares have also been reported in a few isolated case reports [57,58]. These flare-ups can be severe, as evidenced by the description of three patients who presented with cardiac sarcoidosis and ventricular tachycardia following SARS-CoV-2 infection [58]. Certainly, further research is warranted to understand how inflammatory processes during COVID-19 might trigger or intensify sarcoidosis activity. While the overall risk of infection-triggered sarcoidosis appears to be remarkably low among the large population of patients with a history of COVID-19, this suggests that various risk factors may contribute to the development of this disease in the relatively few cases reported to date [4]. A recent retrospective population-based study using nationwide data in Korea found that individuals with COVID-19 had a significantly increased risk of developing sarcoidosis (aHR, 1.59; 95% CI, 1–2.52). However, it is important to note that the confidence interval in this study was imprecise and the number of incident sarcoidosis cases per year in the COVID-19 group was low ($n$ = 3) [59].

Sarcoidosis and COVID-19 may share some common mechanistic immune responses, including the renin–angiotensin system in the lungs and some cell death pathways related to the regulation of autophagy [60], apoptosis, and programmed cell death (PD-1/PD-L1 axis) [61].

Pacheco et al. conducted a study aimed at identifying the genetic factors that could potentially increase the susceptibility of sarcoidosis patients to severe forms of SARS-CoV-2 infection. Their research involved a comprehensive whole-exome screening of 13 predisposed to sarcoidosis families and a healthy control group. The team then compared the genes sharing mutations with the list of genes involved in the SARS-CoV-2 host–pathogen protein–protein interactome.

Their results showed that approximately 10% of the genes listed in the SARS-CoV-2 interactome were affected by pathogenic mutations shared between sarcoidosis patients and controls. These mutations were found to disrupt interactions between host and viral proteins during infection. In particular, the RIG-I (retinoic acid-inducible gene 1)/MDA-5

pathway was identified as the primary affected pathway, leading to the attenuation of antiviral immunity and the facilitation of viral replication.

In addition, sarcoidosis patients were found to accumulate a significant number of mutations in genes associated with intracellular trafficking and the regulation of autophagy and mitophagy, with a particular focus on the mTOR functional hub. The researchers postulated that sarcoid granulomas may potentially represent the pathogenic manifestation of a common response to various environmental triggers and viral infections [62].

## 10. Treatments

### *10.1. Curative Treatments*

Two points need to be considered: first, to provide appropriate anti-infective treatment; second, the reconsideration of immunosuppressive treatment depending on the stakes involved. To achieve this goal, the best means to isolate the responsible infectious agent should be used. There are no specific guidelines for the treatment of respective infections in the specific situation of sarcoidosis patients. Thus, in most situations, anti-infective treatments will be administered according to the guidelines developed for other diseases, when available.

There are insufficient data concerning how to modify immunosuppressive treatments in case of suprainfection. In addition, the situation may vary greatly depending on the infectious agent, the efficacy of available anti-infectious drugs, and the severity and control of sarcoidosis. In the case of severe infection, most authors tend to stop or reduce immunosuppressive drugs with not-unfrequent ulterior relapses of sarcoidosis [24,34]. This is particularly indicated when the efficacy of the anti-infective treatment is uncertain, as in PML.

### *10.2. Preventive Measures*

Preventive measures for tuberculosis include hygienic practices, prophylactic medications, and vaccines.

#### 10.2.1. Hygiene Measures

Hygiene measures should be explained to patients receiving immunosuppressive treatment, especially for those traveling to areas with a high incidence of tuberculosis (with the recommendation to wear a protective face mask). Although research on this topic is still limited, it is advisable to inform patients with advanced pulmonary sarcoidosis about the dangers associated with heavy exposure to molds in the workplace and at home.

#### 10.2.2. Preventive Medications

Preventive treatments may be used to reduce the risk of pneumocystosis, herpes zoster, and tuberculosis. Although sarcoidosis is considered a low risk for *Pneumocystis* infection, authors recommend the use of prophylactic antimicrobials [4,26]. Specific guidelines for immunosuppressed patients should be implemented in treated sarcoidosis patients [63,64]. The identification of possible sources of transmission is essential. The use of tuberculin skin test and/or an interferon-gamma release assay is recommended, as well as a systematic treatment involving isoniazid or rifampicin for confirmed latent tuberculosis [63,64]. Interestingly, antimycobacterial therapy does not benefit sarcoidosis patients without a tuberculosis association, as confirmed by the CLEAR study [65].

#### 10.2.3. Vaccination and Sarcoidosis

Is It Safe? What Is the Efficacy?

In sarcoidosis, inflammation is thought to result from maladaptive immune responses triggered by chronic immune stimulation, leading to an increased risk of lymphocyte anergy, exhaustion, and depletion [66,67]. This impaired immune response could potentially result in a reduced vaccine efficacy compared to the general population. Current data on the efficacy of vaccination in sarcoidosis patients are limited and conflicting. For example, in a study focusing on tetanus vaccination in 48 sarcoidosis patients, it was found that 50% of

the participants had an inadequate increase in antibody titers, regardless of their sarcoidosis disease status, stage, duration, or ongoing treatment [68]. Another study, evaluating a three-dose series of the hepatitis B vaccine, showed that none of the 16 subjects with sarcoidosis had detectable antibody levels during the 1-month follow-up period [69]. In contrast, a study focusing on the trivalent influenza vaccine showed that both subjects with sarcoidosis ($n$ = 23) and controls had a similar serologic response [70]. Recently, a study testing the efficacy and response on the COVID-19 vaccine showed that 14 subjects with sarcoidosis had a decreased quantitative antibody (antitrimer) response to the BNT162b2 mRNA COVID-19 vaccine, but their functional neutralizing antibody response was comparable to controls, indicating conferred immunity. Their results suggest that sarcoidosis subjects mount a robust initial trimer IgG antibody response to vaccination, with a subsequent quantitative decline by 6 months, perhaps driven by those on immunosuppression [71].

Certainly, the use of immunosuppressive drugs has been associated with decreased antibody responses to various types of vaccinations, including mRNA COVID vaccines. However, data on the effect of immunosuppressive drugs on the vaccine efficacy on sarcoidosis are limited, and recommendations are often inferred from studies of other immune-related diseases [72–74]. For example, if the disease activity permits, methotrexate is recommended for 2 weeks after the influenza vaccination, pneumococcal vaccination [72], and COVID-19 booster vaccine [75]. A meta-analysis of 13 studies involving 886 rheumatoid arthritis patients evaluated the rates of seroprotection, which were similar between rheumatoid arthritis patients on glucocorticoids and healthy controls [76].

Vaccination is widely considered to be a safe, effective, and cost-effective measure that can potentially reduce the morbidity and mortality associated with sarcoidosis patients [77]. The current literature on sarcoidosis is too limited to clearly state whether or not vaccination exacerbates or induces sarcoidosis. However, some authors have hypothesized a role for the adjuvant in inducing inflammatory, autoimmune diseases, and sarcoidosis [78–80]. In a small study of influenza vaccination in sarcoidosis patients, no evidence of disease flares or serious adverse events were observed in the sarcoidosis group after 6 months of follow-up [70]. More recently, a nationwide population-based study was conducted in South Korea to investigate the incidence and risk of autoimmune connective tissue diseases after the mRNA-based COVID-19 vaccination. Among 3,838,120 vaccinated individuals, the study found no increased risk of developing sarcoidosis or other autoimmune disorders compared to unvaccinated controls. However, caution should be exercised in interpreting the results for rare outcomes due to the limited statistical power of the study [81]. Interestingly, in a Danish-registry-based incidence study, the period of high BCG vaccination uptake was associated with a lower incidence rate of sarcoidosis, mostly in men. This supports the hypothesis of a potential protective effect of BCG vaccination against the development of sarcoidosis, which could be due to a trained immunity against *Mycobacterium* spp. [82].

When Is It Indicated?

Given the limited data available on the efficacy of vaccination for sarcoidosis, Syed et al. used evidence from the vaccination of immunosuppressed populations to propose general vaccination recommendations for sarcoidosis patients. These recommendations have been endorsed by the World Association of Sarcoidosis and Other Granulomatous Disorders [83]. Essentially, their recommendation was to administer inactivated vaccines, including pneumococcal, influenza, and hepatitis B vaccines, regardless of the patient's current immunosuppressive regimen. Live attenuated vaccines should be administered prior to the initiation of any biologic therapy and should be avoided if the patient is already on a biologic therapy. Of note, these recommendations have been endorsed by the World Association of Sarcoidosis and other Granulomatous Disorders [77].

Of note, a population-based study in Sweden found that the pneumococcal conjugate vaccine administered during the childhood immunization program was associated with an increased burden of nonvaccine serotypes of invasive pneumococcal disease in individuals with comorbidities, including those with sarcoidosis. This finding suggests the potential

need for the administration of the 23-valent pneumococcal polysaccharide vaccine (PPV23) in this population [84].

Given the severity of the COVID-19 pandemic, and the increased risk of severe pulmonary outcomes in sarcoidosis, experts in sarcoidosis strongly recommend that patients with sarcoidosis receive the COVID-19 vaccination [83], especially those with comorbidities, impaired pulmonary function, and those taking immunosuppressive drugs.

**11. Are Anti-Infectious Mechanisms Associated with Sarcoidosis Impaired?**

As developed above, and already mentioned [4], the relationship between sarcoidosis and infection is complex and difficult to decipher. The first question would be to consider sarcoidosis per se as a fertile ground for bacterial, fungal, or viral infections, but infections are relatively rare. The second question would be to consider infections as a consequence of tissue damage related to sarcoidosis, such as pulmonary fibrotic and destructive lesions, or immunodepression related to the treatments patients receive (steroids, immunosuppressants, etc.). Furthermore, this topic is particularly complex because infectious agents are suspected to be causative agents in sarcoidosis.

Sarcoidosis is characterized by a paradoxical immune status, i.e., an exaggerated immune response within the granulomas, in contrast to various immune defects, as indicated by the anergy to the tuberculin test and the occurrence of some opportunistic infections [85]. However, to the best of our knowledge, studies of immunity in sarcoidosis have focused primarily on the pathogenesis of the disease, and studies on the possible impairment of the anti-infectious response are rare, with the exception of vaccination. When considering humoral immunity, the different steps of its knowledge can be summarized as follows. Fifty years ago, a lymphopenia observed mainly in T-lymphocytes, but not in B-lymphocytes, was demonstrated in sarcoidosis patients [86]. Subsequently, suppressor cells, at that time monocytes, were experimentally suspected to be responsible for the immunological abnormalities [87]. Later, T-activated lymphocytes were shown to be active in controlling antibody production, and thus modulating the polyclonal hyperglobulinemia observed in sarcoidosis [88]. Later, a disturbance in B-cell differentiation was observed, with an in vitro decrease in the production of IgG1, IgG3, and IG subclasses [89]. However, in contrast to patients with common variable immunodeficiency, normal levels of total serum IgG, IgA, and IgM, as well as IgG and IgA subclasses, were observed in a series of 32 patients [90]. In addition, patients in this series had normal vaccination responses to the influenza virus (seasonal influenza and Mexican influenza) and encapsulated bacteria (Streptococcus pneumoniae), with normal antigen-specific immunoglobulin responses, whereas the B-memory cells were reduced. More recently, emphasis has been placed on the disruption of Th1, Th17, and Treg lymphocytes. In a comparative series of sarcoidosis and autoimmune diseases, a high level of regulatory T-helper cells > 5.70% was observed in the blood of 91% of sarcoidosis patients [91]. Tregs interacting with innate and adaptive immunity have been shown to limit acute lung inflammation, due to respiratory pathogens, and to provide lung protection [92]. A decrease in the absolute number of circulating Tregs and several alterations in Treg cell subsets have been reported in sarcoidosis [93], and more recently, the cross-talk of B-cells with regulatory T-follicular helper cells (Tfh) has been shown in sarcoidosis [94], suggesting that Tfh2- and Tfh17-like cells—the most effective cell type in supporting B-cell activity, particularly in antibody production—may play a role in the anti-infectious humoral response in sarcoidosis. In conclusion, although the references are not extensive on this topic, the humoral arm does not seem to be defective in sarcoidosis, except against still-unknown very-selective targets, explaining the stochastic occurrence of infections in sarcoidosis.

Two fungi, *Cryptococcus* and *Aspergillus*, are associated with opportunistic infections in sarcoidosis. Macrophages are essential to control mycoses due to *Cryptococcus*, while neutrophils are critical against *Aspergillus* [95].

Cryptococcosis, while rare, is significantly associated with sarcoidosis [30]. The impairment of cell-mediated immunity and long-term corticosteroid therapy is being

evoked to explain this association. But, as reported in the CryptOsarc study, cryptococcosis occurred in one-third of the cases in patients without any treatment [30]. In this study, as well as that reported by Prevel et al., peripheral blood CD4 lymphocytopenia was not an independent risk factor [30,85]. The alteration of qualitative CD4 T-cell function could be involved in the pathophysiology, but T-cell dysfunction in sarcoidosis is poorly understood [85,96]. An altered CD4 T-cell–macrophage crosstalk has experimentally been demonstrated to be involved via the decreased macrophage ability to contain *Cryptococcus* spp. [97]. For instance, macrophage-like cells, called B-1-derived mononuclear phagocytes (BDMPs), have demonstrated to phagocyte *Cryptococcus neoformans* via a complement receptor 3-mediated pathway. This BDMP cell could be one key in the defense against *Cryptococcus*, but it is largely speculative [85].

Anti-GM-CSF antibodies were found in a subset of patients with sarcoidosis, which may impair macrophage phagocytic function and may be another additional mechanism [85].

Aspergillus, suspected to be a driver of sarcoidosis [98], causes chronic pulmonary aspergillosis, which complicates sarcoidosis, with fibrocystic lung remodeling [7]. The pathogenesis of aspergilloma usually involves the colonization and proliferation of the fungus in a pre-existing lung cavity [95]. Neutrophils play a key role in the defense against Aspergillus through phagocytosis, oxidative bursts, and the formation of neutrophil extracellular traps (NETs). This process has received considerable attention and has made rapid progress since NETs [99]. However, to the best of our knowledge, no alterations in neutrophil function have been described in sarcoidosis patients. PML is caused by the human polyomavirus 2/JCV, and is usually associated with immunodeficiency. It can be observed without the overt immunosuppression [100] reported in neurosarcoidosis in immunocompetent adults [101]. Peripheral CD4 lymphocytopenia, evoked by lymphocytic sequestration in granulomas and peripheral anergy, have been discussed, but no clear mechanism of virus escape from immune vigilance is yet proposed.

Finally, it can be hypothesized that one mechanism favoring infections could be the impairment of the autophagy machinery reported in sarcoidosis [62,102]. Autophagy has been implicated in intercepting microbes using various receptors, such as TLR- and NOD-dependent detection for bacteria [103]; however, no association between NOD mutations and an increase in bacterial infections has been reported. NOD2 has an important role in mycobacterial recognition, but the mechanisms by which NOD2 mutations are involved in mycobacterial infection are still unclear [104]. Upon viral infection, autophagy could fight invading viruses by degrading viral particles, initiating the innate immune response, and facilitating viral antigen presentation, all of which contribute to the prevention of viral infection and pathogenesis [105]. However, autophagy and its mechanisms are so complex that it is very difficult to decipher its role in the very rare infectious events associated with sarcoidosis.

## 12. Discussion

First, we would like to provide some take-home messages derived from the relevant sections of this article: (i) to the best of our knowledge, no active infectious disease can be considered as a cause of sarcoidosis, not even tuberculosis; (ii) immunosuppressive drugs given to treat sarcoidosis and fibrocystic lung lesions in advanced pulmonary sarcoidosis may increase the risk of various infections; (iii) latent tuberculosis must be investigated and treated; (iv) infectious diseases must not be overlooked and must be systematically considered in cases of unclear worsening or new localization; (v) immunosuppressants must be optimally adjusted without excess in dose or duration; (vi) patients should receive inactivated vaccines, including pneumococcal, influenza, hepatitis B, and COVID-19 vaccines, regardless of the patient's current immunosuppressive regimen. Regarding the high risk of sarcoidosis following tuberculosis in Wang's study, it is important to emphasize the potential bias arising from the similarities between the presentations of sarcoidosis and tuberculosis [16]. Despite an interesting study on the noninfectious adverse events of

corticosteroids in sarcoidosis [106], the risk of infectious diseases associated with immunosuppressants has not been thoroughly investigated in well-designed studies, especially with regard to the duration of surveillance. This gap exists despite well-conducted studies in sarcoidosis trials [107], and even in rheumatoid arthritis trials [22]. However, thanks to observational studies, the risks have been well-identified.

It is important not to overlook infectious events during follow-up. The main differential diagnosis is sarcoidosis progression, and for the lungs, heart failure or pulmonary thromboembolism. The diagnosis of sarcoidosis progression is mainly based on the serial assessment of symptoms, pulmonary function tests, and imaging [108,109]. For new extrapulmonary manifestations, the use of the WASOG sarcoidosis organ instrument allows for the reduction in the overdiagnosis of sarcoidosis sites [110]. Any atypical finding, especially an unexpected worsening, for example, in a recently well-controlled disease with stable treatment, needs to be investigated. Epidemiologic information, such as travel to a country with a high tuberculosis endemicity, is also essential. In these cases, a multidisciplinary discussion may be helpful.

Some points are still under discussion. There is a need to determine which antifungal drug to prioritize and whether prophylaxis against pneumocystosis should be systematically given to treated patients.

## 13. Future Research Direction

Key information is lacking, particularly regarding the infectious risks of using corticosteroid-sparing agents. Infectious risks need to be carefully assessed in trials. They can be included as secondary outcomes and studied over several years. For certain drugs, registries may also be helpful. The rarity of events, which is unusual even for rare diseases, poses a challenge to the conduct of trials. Designated trials may provide more insight. The pathogenesis of opportunistic infections, such as PML and cryptococcosis, in untreated sarcoidosis requires dedicated research.

## 14. Conclusions

Infectious diseases can occur in the course of sarcoidosis, mainly due to the use of immunosuppressants, advanced pulmonary lesions, and various epidemiologic risks associated with tuberculosis, certain fungal infections, or COVID-19. Early recognition and understanding of these infections are critical, even though their diagnosis may be obscured by sarcoidosis-related findings. Preventive measures are also important. There is a particular need for studies comparing the risk of infection between different corticosteroid-sparing treatment protocols.

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