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Updated Guidelines for the Treatment of Pulmonary Sarcoidosis

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1. Introduction

Sarcoidosis is a systemic granulomatous disease that affects the lungs in 90% of cases. The stage of the disease is determined by the level of pulmonary damage as assessed by a chest x-ray. This pulmonary damage varies widely between stages I, when lymph node damage has no repercussions on lung functioning, and stage IV, in which interstitial pulmonary damage and the development of fibrosis has clear repercussions on lung functioning.

Systemic corticosteroids are the drugs of choice for the treatment of sarcoidosis, although no clear consensus exists regarding when to start treatment, the correct doses, or how long treatment should be maintained. We must keep in mind that the progression of this disease is often unpredictable, with frequent cases of spontaneous remission, above all in stage I patients. However, systemic steroids have side effects and the decision to start treatment is determined by the intensity of the symptoms, especially exercise-induced dyspnoea, and the level of lung functioning deterioration.

Sarcoidosis can affect both the upper and lower airways. Endobronchial damage occurs in 40% of stage I patients and approximately 70% of stage III and IV patients. Endobronchial granulomas have been described along with stenosis of the airway due to peribronchial damage. Clinically relevant airway stenosis is uncommon but difficult to treat. In the upper airway, granulomas can appear in the submucosa of the larynx, pharynx, and paranasal sinuses. Sleep apnoea has been described as a result of involvement of the epiglottis. This damage to the airway is occasionally manifested as the presence of persistent cough, with no findings in the pulmonary parenchyma. In up to 50% of cases, spirometry reveals obstructive phenomena, especially in patients with endobronchial damage due to sarcoidosis.

The treatment of choice for pulmonary sarcoidosis is oral corticosteroids. Other alternative treatments have been described, such as immunosuppressive agents (methotrexate, azathioprine, cyclophosphamide, leflunomide, cyclosporine, and chlorambucil), cytokine inhibitors (thalidomide and pentoxifylline), and immunomodulatory agents (TNF-alpha antagonists, infliximab, adalimumab, and antimalarial agents such as chloroquine) (Table 1). Currently, no clear evidence exists showing the usefulness of these drugs, and they are only indicated when the sarcoidosis does not respond to conventional treatment with oral
corticosteroids, in patients with intolerance to corticosteroids (poorly controlled diabetes, myopathy, osteoporosis), or in order to reduce the dosage of corticosteroids (King, 2010). However, these drugs require close monitoring as they can cause severe adverse effects. Here, we will review the different treatment options for patients with pulmonary sarcoidosis.

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Table 1. Drugs used for the treatment of sarcoidosis

2. Treatment options in patients with pulmonary sarcoidosis

2.1 Inhaled corticosteroids
The mild ocular and cutaneous manifestations of sarcoidosis can be treated using topical corticosteroids. For the treatment of pulmonary damage, an alternative to the use of systemic corticosteroids is inhaled corticosteroids, which can be useful in selected groups of patients. This treatment has been used in two types of patients: a) those with an affected airway, with chronic coughing as the primary symptom, and b) as a treatment used for suspending or at least reducing the need for systemic corticosteroids. Several randomised studies have compared the efficacy of inhaled corticosteroids with that of a placebo. The characteristics of both patient groups were similar with regard to radiological findings, lung function (FEV1), DLCO (%), and symptoms. Alberts et al (Albert et al., 1995) compared the administration of 1.2mg budesonide with a placebo in a group of stage I-III sarcoidosis patients during 6 months of treatment and another 6 months of follow-
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up. DuBois et al (DuBois et al., 1999) compared the administration of 2mg/day of fluticasone with a placebo in stage II-III sarcoidosis patients for 6 months, with no follow-up. Erkkila et al (Erkkila et al., 1988) compared the treatment of stage I-II sarcoidosis patients with 0.8mg budesonide twice/day with a placebo for 10 weeks. None of these studies demonstrated improvement in lung function or radiological parameters in the treatment group compared to the placebo group. Only the study by Alberts et al (Albert et al., 1995) found that the group treated with budesonide at high doses improved in the global clinical index, including symptoms. In all other studies regarding treatment with inhaled corticosteroids, symptoms were not improved when compared to the placebo group. One study did demonstrate that inhaled fluticasone could help to reduce coughing in cases of acute sarcoidosis (Baughman et al., 2002). It has been reported that treatment with inhaled steroids may reduce the need for systemic steroids, and thus considerably reduce the adverse effects from this type of treatment. Milman et al (Milman et al., 1994) studied the use of budesonide at 1.2-2mg/day and oral steroids in 8 patients with stage I-II sarcoidosis. The study lasted 12 months, with 18 months of follow-up. They found no beneficial effect from the use of inhaled budesonide. Pietinalho et al (Pietinalho et al., 1999) compared a group of patients initially treated with 10-20mg prednisolone during 3 months, followed by inhaled budesonide at 1.6mg/day during 15 months, with a control group that received a placebo. After 3 months of treatment, a radiological improvement was observed in the treatment group compared to the control group. At 6 months of treatment, these differences were still significant, but from that time on, there were no differences between the two groups. In patients that started the study in stage I of the disease, neither FVC nor DLCO changed during the study, since they were at normal levels at the start of the treatment. In patients that started the study in stage II, FVC did not change during the treatment period. In this group, those patients that were treated for 18 months did show significant differences in FVC and DLCO. These difference were greater in patients with initial values of FVC<80% and DLCO<75%. The authors concluded that, in stage II sarcoidosis patients, treatment change from initial oral steroids to inhaled steroids is a good option to avoid the long-term administration of oral corticosteroids. However, based on the information that is currently available (Paramothayan & Lasserson, 2008), we can conclude that insufficient evidence exists based on randomised clinical trials that could establish the efficacy and/or usefulness of inhaled corticosteroids in the treatment of sarcoidosis.

2.2 Oral corticosteroids

2.2.1 Introduction

The US guidelines and the recently updated BTS guidelines substantially updated the treatment options for pulmonary sarcoidosis (American Thoracic Society [ATS], 1999; Bradley et al., 2008). Dempsey OJ et al. later summarised and published a treatment update based on both guidelines (Dempsey et al., 2009). One of the main recommendations that they made was to carefully assess the decision to start treatment with corticosteroids (the most frequently used treatment), comparing the benefits with potential risks. In general, treatment should be considered when organ function is affected. The primary conclusions obtained from conferences and consensus documents developed by experts are summarised in Table 2 (Bradley et al., 2008).
Many patients do not require treatment and the disease can regress spontaneously.

Erythema nodosum can be painful, and treatment should be paracetamol or NSAID on a short-term, on-demand basis.

Treatment is not indicated in:
- Asymptomatic stage I disease
- Stable stage II asymptomatic disease
- Stage III disease with slightly altered lung function

Oral steroids can benefit patients:
- In stage II or III with moderate, severe, or progressive symptoms
- With changes observed in chest x-rays

Absolute indications for oral steroids include:
- Hypercalcaemia
- Neurological involvement
- Cardiac involvement
- Ocular involvement (only when topical treatment fails)

Table 2. Primary conclusions obtained from conferences and consensus documents developed by experts (Baughman et al. 2003)

### 2.2.2 Treatment plan

The UK guidelines indicate that treatment should start with prednisolone at 0.5mg/kg/day for 4 weeks (Bradley et al., 2008). The dosage should then be gradually reduced over the next 6 months, with an ideal dose of ≤10mg/day. In order to avoid bone loss caused by the corticosteroids, patients must also start treatment with oral bisphosphonates along with bone densitometry tests. The duration of treatment can vary, but frequently ranges between 6 months and 2 years. Some patients need more than 10mg/day of prednisolone in order to control the disease. In these circumstances, another drug may be added in order to further decrease the dosage of corticosteroids (steroid-sparing), thus achieving a final dosage of ≤10mg/day of prednisone.

A systematic review of randomised placebo-controlled clinical trials on patients with pulmonary damage that started treatment with oral or inhaled corticosteroids concluded that oral corticosteroids improved chest x-ray results and overall score in symptoms, spirometry, and radiological tests between 3 and 24 months of treatment. However, little evidence pointed towards improved lung function, and data were scarce regarding the impact of oral corticosteroids in the long-term progression of the disease (Paramothayan et al., 2000).

However, there are no clear guidelines for the initiation of corticosteroid treatment, when to decide that treatment has failed or consider a therapeutic alternative for pulmonary sarcoidosis. As such, the use of corticosteroids in pulmonary sarcoidosis continues to be discussed, and a final conclusion has yet to be made regarding the optimal duration of treatment. With the medical literature currently available, we do not know if oral corticosteroids can alter the final result of this disease. However, the benefits of this type of treatment do now outweigh the side effects. Some retrospective studies have suggested that patients with sarcoidosis and do not take corticosteroids (Gottlieb et al., 1997) or only at low doses (Rizzato et al., 1998) have a lower rate of relapse. These data suggest that, when making a decision to treat acute pulmonary sarcoidosis with oral corticosteroids, the lowest dosage possible must be used.
In this respect, McKinzie et al. (McKinzie et al., 2010) performed a retrospective study of patients with pulmonary sarcoidosis that were treated with $\leq 20\text{mg}$ of oral prednisone during exacerbations, and clinical evolution and changes in spirometry values were assessed after two weeks. This study demonstrated that these patients improved in clinical symptoms and spirometry values, although it did have some limitations: 1) the study was retrospective, implying a patient selection bias; 2) it did not follow up on long-term patient progression, and therefore, we cannot comment on the evolution of the disease; 3) the study was not designed specifically to measure the adverse effects of corticosteroid treatment; 4) it lacked a control group; 5) the two-week follow-up period was not maintained in all patients (median: 21 days). Even so, it did show that the treatment of acute exacerbations of pulmonary sarcoidosis using 20mg of prednisone for a median 21 days significantly improves symptoms and lung function test results. This low dosage with a short duration of treatment has the potential to minimise the side effects of corticosteroids. This study opened the possibility of performing prospective studies that compare long- and short-term treatment plans, low and high doses, and the side effects and recurrence of the disease for each method of treatment.

Even so, it is clear that there is no standardisation in the treatment of pulmonary sarcoidosis, and this is due to the lack of clinical trials. The majority of published studies are not blinded, randomised, or controlled, and involve a very small number of patients, using different doses or lengths of treatment and different endpoints (McKinzie et al., 2010). For these reasons, Schutt et al. (Schutt et al., 2010) used the Delphi research technique. The Delphi method uses an expert panel with a voting system in order to reach a consensus in special situations in which insufficient data exists in order to come to an objective conclusion. The aim of this study was to gather a panel of experts in the treatment of pulmonary sarcoidosis to formulate a consensus whenever possible, using rigorous Delphi methods including interactive questions and feedback for previous responses. The conclusions from this study of expert opinions were the following: 1) oral corticosteroids are the initial treatment recommended for pulmonary sarcoidosis; 2) it is not recommended to start concomitant treatment using inhaled corticosteroids as a general practice; 3) treating pulmonary sarcoidosis with dosages $>40\text{mg}$ of prednisolone or equivalent does not provide any additional benefit; 4) regarding the treatment of chronic pulmonary sarcoidosis, the dosage should be decreased to a minimum maintenance dose of 10mg of prednisone or equivalent. The final conclusion was that methotrexate was the preferred agent for replacing or reducing the dosage of corticosteroids. Several different controversies arose in various subjects that could aid in developing future studies, as no consensus was reached 1) regarding the dosage of corticosteroids to be administered in de novo pulmonary sarcoidosis; 2) regarding the decision to treat or observe patients with mild sarcoidosis based on symptoms, lung function, and chest x-ray results.

This study also had several limitations. First, the use of multiple-choice questions can limit or potentially affect the responses. Second, there were experts that did not answer all questions. Third, it was not established whether all participants in the study were in fact pulmonary sarcoidosis experts. Fourth, the majority of experts worked in the USA.

### 2.3 Immunosuppressive agents

#### 2.3.1 Methotrexate

**Mechanism of action:** Methotrexate is an immunosuppressive and anti-inflammatory agent. After corticosteroids, this is the most commonly used drug for the treatment of sarcoidosis. It is also used in other pathologies such as rheumatoid arthritis, Crohn’s disease, and psoriasis.

Several studies have evaluated the efficacy of this treatment in systemic sarcoidosis (cutaneous, ocular, pulmonary, and neurological sarcoidosis) (Baughman & Lower, 1999;
Lacher, 1968; Lower & Baughman, 1990, 1995). In 2000, Baughman focused on the efficacy of methotrexate as a corticosteroid saver, performing a prospective randomised study in which one group of patients took prednisone with methotrexate and the control group took a placebo. This study demonstrated that patients treated with methotrexate required smaller amounts of prednisone after 6 months than those that took the placebo (Baughman et al., 2000).

**Administration route and dosage:** This medication can be administered orally or intramuscularly, using the second option as an alternative in the case of oral intolerance or a lack of response after 3-6 months of treatment. The initial dosage is 7.5mg once per week, with progressive increases until reaching 10-15mg per week. In order to decrease the level of myelosuppression associated with methotrexate, folic acid must also be administered, and liver function must be periodically checked. This drug is contraindicated in patients with chronic liver disease or chronic infection by HBV or HCV, creatinine clearance <30ml/h, or alcoholism (Saag et al., 2008)

**Side effects:** The most frequent side effects are leukopaenia, hepatic fibrosis, and interstitial pneumonitis (Baughman et al., 2008). In a study of 100 liver biopsies from 68 patients with sarcoidosis, 14 had changes from the use of methotrexate (Baughman et al., 2003). Other, less frequent side effects have also been described, such as baldness, cutaneous rashes, and lymphoproliferative syndrome that occasionally regresses after treatment suspension (Hoshida et al., 2007; Niitsu et al., 2010).

### 2.3.2 Azathioprine

**Mechanism of action:** Azathioprine acts on RNA synthesis from DNA and inhibits the proliferation of lymphocytes, but its mechanism of action in sarcoidosis is unclear.

Second-line drug. In 1985, Pacheco assessed the efficacy of azathioprine in 10 patients with sarcoidosis refractory to corticosteroids. Patients were treated for 6 months with 150mg azathioprine per day, and 70% of cases had clinical and radiological improvements (Pacheco et al., 1985). Currently, this drug is primarily indicated in association with corticosteroids (Baughman, 2004; Bradley et al., 2008). In a study involving 11 patients with chronic sarcoidosis, the efficacy of treatment using azathioprine as a corticosteroid saver was evaluated. Patients underwent a combined treatment for 20 months with 0.1mg/kg prednisolone along with 2mg/kg azathioprine per day, producing clinical and radiological improvements with no evidence of relevant adverse effects (abdominal pain + transitory increase in lipase levels in 1 case) (Mueller-Quernheim et al., 1999).

**Administration route and dosage:** Orally administered, 25mg/day, with progressive increase until reaching 2mg/kg (maximum: 200mg/day). The toxicity of azathioprine is linked to the existence of thiopurine-S-methyltransferase polymorphisms (Bakker et al., 2007).

**Adverse effects:** The most frequent adverse effects are: gastrointestinal discomfort, cutaneous rash, and fever. Another less frequent but more serious side effect is pancytopaenia (difficult to distinguish from suppressed bone marrow, which can occur in sarcoidosis). The patient’s blood cell levels must be checked weekly while the dosage is being increased, and every 8-12 weeks during the first few months of treatment. The frequency can be decreased for long-term treatment in patients with normal levels from previous measurements.

### 2.3.3 Cyclophosphamide

**Mechanism of action:** Cyclophosphamide acts by reducing the number and function of lymphocytes, with an added anti-inflammatory effect.
This third-line drug is not frequently used as a corticosteroid saver in the treatment of sarcoidosis due to its adverse effects (Salomon et al., 1975).  

**Administration route and dosage:** Treatment with this drug starts at 25mg-50mg/day orally, with a progressive increase until reaching white blood cell counts of 4000mm$^3$-7000mm$^3$, with twice-weekly monitoring during the first 3 months, and once per month afterwards. It has been rarely administered intravenously.  

**Adverse effects:** The most important adverse effect is the appearance of pancytopenia, which requires an immediate adjustment of the dosage. Other side effects are: gastrointestinal discomfort, infertility, haemorrhagic cystitis, and it has even been related to the appearance of bladder carcinomas.

### 2.3.4 Chlorambucil

The use of chlorambucil is very limited in the treatment of pulmonary sarcoidosis. Its mechanism of action is similar to that of cyclophosphamide, as inhibits the immune response by reducing the number of lymphocytes and other bone marrow cells. Given the relative efficacy of this drug as a corticosteroid saver (Kataria, 1980) and the important side effects (Sahgal & Sharma, 1984), it is not commonly recommended in the treatment of this disease.

### 2.3.5 Cyclosporine

Cyclosporine is an immunosuppressive drug that is widely used in organ transplants in order to reduce the risk of rejection. It is also used in diseases that involve T-cells, such as uveitis and rheumatoid arthritis. Its use is very limited in pulmonary sarcoidosis due to the lack of experience and its severe side effects (Wyser et al., 1997).

### 2.3.6 Leflunomide

**Mechanism of action:** Leflunomide is a cytotoxic agent used alone or in combination with methotrexate for the treatment of rheumatoid arthritis, but little experience has been gained in its use for treating pulmonary sarcoidosis. In a study published in 2004 (Baughman & Lower, 2004) that treated 32 patients using leflunomide (15 of them also were administered methotrexate), good tolerance was observed to leflunomide with a response at least as efficient as methotrexate and with lower toxicity. Its use was then recommended in patients with chronic sarcoidosis and intolerance to methotrexate, or in combination with methotrexate in patients with chronic pulmonary sarcoidosis refractory to other second-line drugs (Baughman et al., 2001).  

**Administration route and dosage:** 20mg/day orally, starting with 10mg and increasing dosage in the presence of good tolerance.  

**Adverse effects:** Gastrointestinal symptoms, rash, peripheral neuropathy, and hepatotoxicity (Emery et al., 2000; Savage et al., 2006; Utz et al., 2003), which increases in the case of previous hepatopathy or concomitant treatment with hepatotoxic treatments.

### 2.4 Immunomodulatory agents

#### 2.4.1 Tumour necrosis factor (TNF) antagonists

- **Etanercept**  

  Utz et al started a clinical trial in which etanercept was used for the treatment of stage II-II sarcoidosis. This study was suspended due to a lack of results from the treatment, defined as progression of the disease, need for other immunosuppressive agents, or intolerance to treatment (Utz et al., 2003). Its use is not currently indicated in the treatment of sarcoidosis.
2.4.2 Monoclonal antibodies

- Infliximab
Infliximab is a monoclonal antibody with important anti-inflammatory activity. Several different studies have proven its efficacy in the treatment of pulmonary and extrapulmonary sarcoidosis refractory to corticosteroids (Baughman et al., 2006; Pritchard & Nadarajah, 2004). In a double-blind study which divided 138 patients with chronic pulmonary sarcoidosis into three groups: one treated with low doses of infliximab, other treated with placebo, and the third treated with high doses of infliximab at the start of treatment and at weeks 2, 6, 12, and 24, forced vital capacity improved during weeks 24-54, compared to initial values. There were no significant differences regarding the adverse effects produced in the three groups (Baughman et al., 2006). According to a study published in 2010 (Crouser et al., 2010), patients with decreased CD4+ T-cell count and resistance to conventional immunosuppressive treatment have a better response to this drug. Although its long-term toxicity is still unclear, some severe complications have been associated with its use, such as the appearance of tuberculosis (Kean et al., 2001).

- Adalimumab
The experience with this drug has been limited to extrapulmonary chronic sarcoidosis (Heffernan & Smith, 2006; Patel, 2009).

2.4.3 Thalidomide
Just as in the case of the previous drug, the use of thalidomide has only been described in the treatment of extrapulmonary sarcoidosis, mainly the cutaneous form (Baughman et al., 2002). Its use in pulmonary sarcoidosis appears to provide no benefit, as was observed in a study by Judson et al. published in 2006, in which no clinical improvements were documented, and dosage had to be reduced in 9 out of the 10 patients due to adverse effects produced, including excessive somnolence and peripheral neuropathy (Judson et al., 2006).

2.4.4 Pentoxifylline
In a clinical trial by Zabel et al., they observed a positive response to treatment with pentoxifylline in patients with acute pulmonary sarcoidosis (Zabel et al., 1997) although no studies currently exist testing its use in chronic sarcoidosis.

2.5 Antimalarial agents

2.5.1 Chloroquine and hydroxychloroquine
These drugs have been used for the treatment of chronic sarcoidosis for many years (British Tuberculosis Association, 1967). They have a low level of toxicity, and have proven effective in treating cutaneous sarcoidosis (Siltzbach & Teirstein, 1964). Some studies also exist in which these drugs have been used to treat pulmonary sarcoidosis (Chloroquine in pulmonary sarcoidosis, 1968). Bazan et al. (Baltzan et al., 1999) studied the use of chloroquine to treat chronic sarcoidosis. After treating 18 patients for 6 months, treatment was continued with a group of patients with a slower decrease in FEV1 and diffusion capacity, but no changes in forced vital capacity were registered, although important adverse effects were produced in 13% of cases.

Administration route and dosage: The commonly used dosage is 250mg-750mg/day, taken orally for 6 months or 9 months.

Side effects: The most severe side effect is irreversible retinopathy and blindness, therefore, ophthalmologic follow-up is necessary at the start of treatment and after 6 months.
2.6 Conclusions

In patients with chronic pulmonary sarcoidosis in which treatment with corticosteroids has not been sufficient, or when the patient has intolerance to the drug or it is causing severe adverse effects, intensification of the therapy is indicated using methotrexate, azathioprine, or leflunomide (stage IIB). The first choice drug is methotrexate due to the greater experience gained in the treatment of pulmonary sarcoidosis using this drug. If the patient has intolerance or it does not produce a positive response, the use of leflunomide or azathioprine is recommended, and can occasionally lead to a reduced need or even cessation of treatment with corticosteroids.

Given that all of the previously mentioned drugs imply severe side effects such as myelosuppression with predisposition to opportunistic infections and hepatotoxicity, their use must be evaluated on an individual basis. Before starting treatment with methotrexate, azathioprine, and leflunomide, the patient must undergo liver function, haemogram, and creatinine tests. Also, hepatitis B and C tests must be performed before starting treatment with methotrexate and leflunomide.

In patients in which treatment with immunosuppressive agents with or without corticosteroids is insufficient, two different second-line drugs may be combined, or administered along with a TNF antagonist, which should be decided upon according to patient characteristics. Before starting treatment with a TNF antagonist, the patient must also be screened for tuberculosis, hepatitis B, and hepatitis C.

Because of their mechanisms of action, many of the drugs proposed for the treatment of chronic sarcoidosis are not commonly used due to their secondary side effects (colchicine, chlorambucil, cyclophosphamide, cyclosporine, and pentoxifylline).

3. Follow-up

Patients with sarcoidosis must have a periodical follow-up regimen with a specialist. The lung is the primary organ affected by the disease, and so a pneumologist must be involved in the follow-up process. The BTS recommends a multi-disciplinary follow-up by clinics that specialise in interstitial lung diseases (Bradley et al., 2008). Check-ups must be performed initially every 3-6 months, or more frequently if drug treatment is started. Patients with clinically stable disease can be seen less frequently. Patients with stage II-IV must continue with an indefinite follow-up period, whereas patients with mild levels of the disease (stage 0 or I) can be discharged from the follow-up after 2 years. In these check-ups, the patient should undergo clinical (signs and symptoms), radiological (chest x-ray as the primary tool), and functional (respiratory function) tests. The follow-up protocol may also require laboratory analyses (especially if the patient had a previous case of hypercalcaemia, renal or liver involvement, or if tests show some type of alteration in serum angiotensin-converting enzyme). Patients rarely develop progressive pulmonary sarcoidosis with failed pharmacological treatment. In this case, the next step would be a lung transplant.

4. References


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King TE. (2010). Treatment of pulmonary sarcoidosis with alternatives to glucocorticoids. *Up To Date.*


Sarcoidosis is a type of inflammation that occurs in various locations of the body for no known reason. Normally, when foreign substances or organisms enter the body, the immune system will fight back by activating an immune response. Inflammation is a normal part of this immune response, but it should subside once the foreign antigen is gone. In sarcoidosis, the inflammation persists, and some of the immune cells form abnormal clumps of tissue called granulomas. The disease can affect any organ in the body, but it is most likely to occur in the lungs. It can also affect the skin, eyes, liver, or lymph nodes. Although the cause of sarcoidosis is not known, research suggests that it may be due to an extreme immune response or extreme sensitivity to certain substances. It also seems to have a genetic component as well, and tends to run in families. Sarcoidosis most commonly develops in people between 20 and 50 years of age. African Americans are somewhat more likely to develop sarcoidosis than Caucasians, and females are somewhat more likely to develop sarcoidosis than males. The symptoms of sarcoidosis depend on the organ involved. This book deals with the diagnosis and treatment of this mysterious disease of unknown etiology.

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