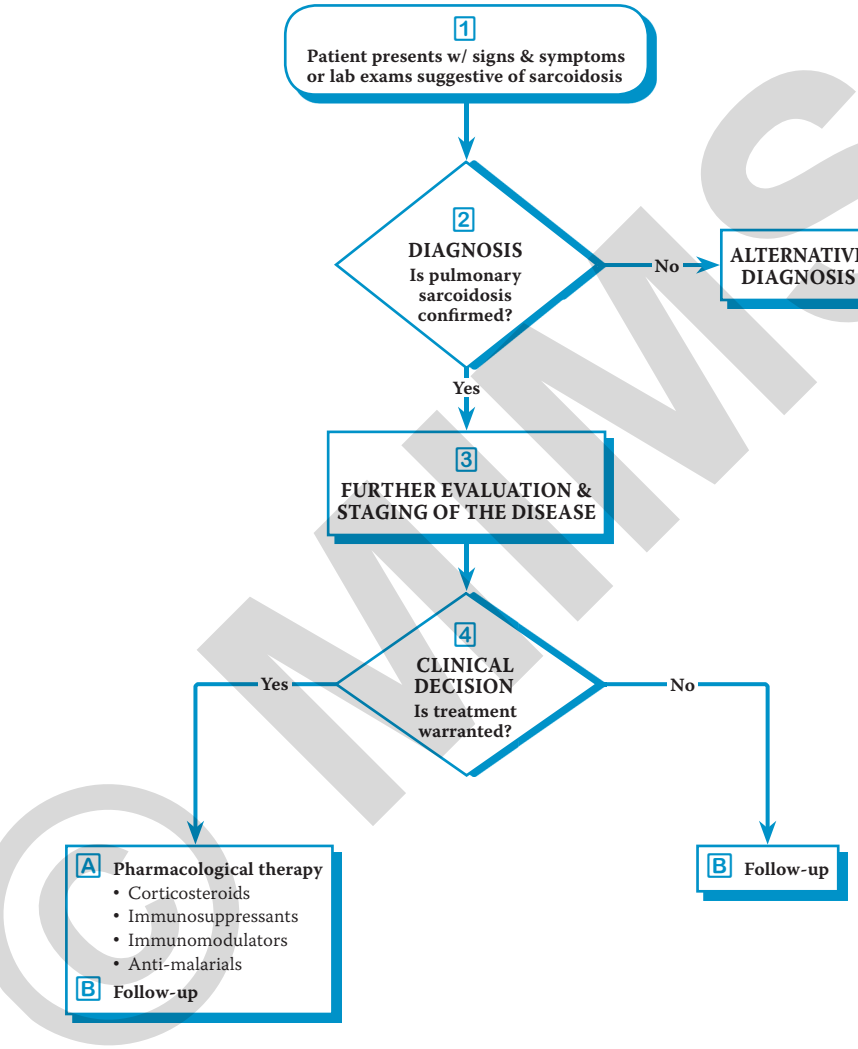
Sarcoidosis - Pulmonary (1 of 6)



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1 SIGNS & SYMPTOMS OF PULMONARY SARCOIDOSIS

- **Sarcoidosis:** A multisystem disease which may present w/ non-specific symptoms or symptoms related to organ-specific involvement

Non-specific Symptoms
- Fever
- Malaise, fatigue
- Wt loss

Pulmonary Involvement
- Pulmonary involvement is seen in >90% of sarcoidosis patients
- Symptoms include:
  - Cough
  - Dyspnea
  - Chest pain or discomfort
- Sarcoidosis commonly presents as an interstitial disease
- One half of cases are detected incidentally by chest x-ray abnormality in asymptomatic patients
- Initial pulmonary defects may either be restrictive or obstructive
- Symptoms of sarcoidosis are usually already present for a mth prior to diagnosis

Findings on Routine Chest X-Ray
- 30-50% of patients are asymptomatic & are diagnosed by chest X-rays obtained for non-pulmonary indications
- X-rays may show hilar adenopathy, infiltrates, or fibrosis

Signs & Symptoms Related to Involvement of Other Organs
- Palpable lymph nodes
- Cardiac arrhythmias
- Erythema nodosum, lupus pernio or other dermatologic manifestations
- Uveitis
- Cranial nerve palsies
- Joint pains
- Hypercalcemia & hypercalciuria

2 DIAGNOSIS

- Diagnosis is often delayed because of the usual non-specific presentation

Diagnosis is based on the following:
- Compatible clinical or radiologic picture or both
- Histologic proof of non-caseating granuloma
- Exclusion of similar diseases

Clinical History & Physical Exam
- A thorough clinical history & physical exam should be obtained
- Though the cause of sarcoidosis is unknown, the patient should be questioned carefully about exposure to both inorganic & organic antigens
- Investigate possible environmental & occupational exposures that may reveal an alternative diagnosis
  - Exposure to metal dusts, fumes & organic antigens may cause granulomatous diseases that are difficult to differentiate from sarcoidosis

Extrapulmonary Disease
- Physical exam should include a search for evidence of extrapulmonary disease
  - Evidence of multi-organ involvement is supportive of a diagnosis of sarcoidosis

Radiologic Studies

Chest X-ray (CXR)
- Presence of bilateral hilar enlargement may speed up the diagnostic process
- Interstitial disease alone may be seen

Computed Tomography (CT) scan
- May be used to identify patients w/ parenchymal disease not seen on CXR
- Demonstrates hilar & mediastinal lymphadenopathy
- May also be done when patients present w/ atypical clinical or radiologic findings
- Allows detection of complications of the disease (eg bronchiectasis, aspergilloma, pulmonary fibrosis)
- Consider CT when there is clinical suspicion of the disease but the CXR is normal

Biopsy & Histology
- Transbronchial lung biopsy to demonstrate granulomas is recommended in most cases
  - Has a higher yield for patients w/ parenchymal lung disease seen on CXR or CT scan
- Accessible skin lesions &/or lymph nodes may also be biopsied
- Surgical biopsy is indicated when transbronchial or bronchial biopsies are not diagnostic & no other accessible biopsy sites are identified

2 DIAGNOSIS (CONT'D)

Other Diagnostic Procedures/Lab Exams

Bronchoalveolar Lavage (BAL)
- Increased lymphocytes are seen or an increased CD4:CD8 ratio
- Findings are supportive, but not definitive of a diagnosis

Total Body Gallium Scan
- Appearance of a Panda pattern combined w/ a Lambda pattern may support diagnosis
- Findings are present only in a small number of patients

Angiotensin Converting Enzyme (ACE) Levels
- Elevations are not diagnostic since other diseases & granulomatous conditions may present w/ high levels of ACE

3 FURTHER EVALUATION

- Additional evaluation is recommended in all patients diagnosed w/ sarcoidosis

Lab Exams
- Pulmonary function tests
  - Spirometry
  - Diffusing capacity for carbon monoxide (DLco)
- Peripheral blood counts
- Serum chemistries
  - Blood urea nitrogen (BUN), creatinine, calcium
  - Liver enzymes: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP)
- Urinalysis
  - Patients may present w/ hypercalciuria
- Electrocardiogram (ECG)
  - Patients may manifest w/ cardiac arrhythmias
- Routine ophthalmologic evaluation
  - To determine if eye involvement is present
- Tuberculin test

Staging of Pulmonary Sarcoidosis based on Chest X-ray

Stage 0
- Normal CXR

Stage 1
- Lymphadenopathy
  - Hilar & paratracheal nodes are usually involved
  - Parenchymal granulomas may be found on biopsy even in the absence of infiltrates on CXR

Stage 2
- Lymphadenopathy w/ parenchymal infiltrates

Stage 3
- Parenchymal infiltration w/o lymphadenopathy
- Progressive loss of lung function may occur

Stage 4
- Advanced fibrosis
- Other findings include emphysema, bullae, cysts, hilar retraction & honey-combing
- Progressive loss of lung function may occur

4 CLINICAL DECISION

- Decision to treat sarcoidosis depends on the presence of symptoms & stage of the disease

Pulmonary Disease
- Pulmonary disease is a relative indication for treatment

Stage 1
- Studies show that no treatment is necessary for patients w/ stage 1 disease

Stage 2-3
- Asymptomatic patients w/ stage 2 or 3 disease may not benefit from systemic therapy
  - Treatment may be required in asymptomatic patients w/ progressive loss of lung function & persistent infiltrates

Symptomatic Disease
- Treatment w/ corticosteroids provides acute relief & reversal of organ dysfunction

Absolute Indications for Treatment of Sarcoidosis Include the following:
- Cardiac involvement
- Neurosarcoidosis
- Hypercalcemia
- Ocular disease that is refractory to topical therapy

Other Extra Pulmonary Diseases
- Treatment is usually administered in progressive, symptomatic, extrapulmonary disease

A PHARMACOLOGICAL THERAPY

Corticosteroids

Systemic Corticosteroids

- The mainstay in the treatment of pulmonary sarcoidosis
- Recommended for patients w/ hypercalcemia, stage II/III pulmonary sarcoidosis w/ moderate-severe or progressive disease, & those w/ radiographic evidence of pulmonary changes
- Usually results in improvement of resp symptoms, lung function studies & CXR findings
  - Reappearance of symptoms & CXR abnormalities are frequent after discontinuation of treatment
- A meta-analysis concluded that corticosteroid use in pulmonary sarcoidosis results in improvement of CXR & spirometry over 6-24 mth, but there is minimal proof of improvement in lung function
  - It is not clear whether these improvements are maintained beyond 2 yr
  - It is not known whether corticosteroids improve long-term pulmonary function or favorably alter disease progression
- Corticosteroid use should be reserved for those w/ clear clinical indication because of its known potential toxicity & lack of evidence of sustained benefit

Follow-Up & Duration of Therapy

- Patient should be evaluated after 1-3 mth of corticosteroid therapy
  - Patients who fail to respond after 3 mth are unlikely to respond to a longer course of therapy
- Patients who respond should have their corticosteroid dosages tapered & treatment continued for a minimum of 12 mth
- After a treatment period of 6-24 mth, withdrawal of corticosteroids should be considered, w/ continued monitoring for relapse
  - Certain patients may still require long-term low-dose therapy to prevent recurrent disease

Complications of Therapy

- Patients receiving chronic corticosteroid therapy are at risk for osteoporosis
  - Bisphosphonates & Calcitonin may be used for prevention of osteoporosis complications

Inhaled Corticosteroids

- An alternative to oral corticosteroids
- May be used for patients w/ pulmonary symptoms esp chronic coughing, & for those whose systemic steroid medications are due for reduction/tapering
- Studies show that patients experienced symptom improvement while on inhaled Budesonide treatment

Immunosuppressants

- Eg Azathioprine, Methotrexate, Cyclophosphamide, Chlorambucil, Cyclosporine, Leflunomide
- May benefit patients who fail to respond to corticosteroids
- Usually given in combination w/ corticosteroids but may also be used as monotherapy

Azathioprine

- Second-line treatment for sarcoidosis; as a corticosteroid-sparing agent
- Preferred agent, along w/ Methotrexate, because of a more favorable safety profile
- Usual dose: 50-100 mg daily initially, then up to 3 mg/kg daily as maintenance

Chlorambucil

- Rarely used because of its increased risk of malignancy

Cyclophosphamide

- Decreases lymphocyte proliferation & function thereby decreasing the immune response
- Seldom used as 3rd-line treatment because of increased appearance of pancytopenia
- Has been effective in some patients who have failed therapy w/ corticosteroids & Methotrexate
- Significant toxicity limits its use in patients w/ severe, refractory disease

Leflunomide

- Recommended for patients w/ chronic sarcoidosis intolerant to Methotrexate therapy
- May also be used in combination w/ Methotrexate in patients w/ chronic pulmonary sarcoidosis refractory to other therapies

Methotrexate

- Recommended as 1st-line treatment when in combination w/ steroids
- Recommended 2nd-line treatment for steroid-refractory patients as a steroid-sparing agent
  - Used especially w/ the presence of adverse effects of corticosteroid therapy
- Usual dose: 10 mg once a wk initially, then 2.5-15 mg once a wk as maintenance

A PHARMACOLOGICAL THERAPY (CONT'D)

Immunomodulators

- 3rd-line treatment option for patients unresponsive to corticosteroids &/or immunosuppressants
- Lacks evidence for the treatment of sarcoidosis
- Adequate tests for presence of ongoing infection (ie latent tuberculosis) should be done prior to initiation of treatment

Tumor Necrosis Factor-Alpha (TNF-alpha) Inhibitors

- Eg Infliximab, Adalimumab
- Evidence to support Adalimumab's efficacy for pulmonary chronic sarcoidosis are limited
- Infliximab is used as an alternative pulmonary & extrapulmonary sarcoidosis therapy for patients refractory to corticosteroids
- Studies show that Infliximab is an effective TNF-alpha inhibitor not only against pulmonary, but also for other types of sarcoidosis (ie skin, kidney, muscle, bone), & for patients w/ hypercalcemia, neuropathy & disabling fatigue

Etanercept

- Further studies are needed to prove the efficacy of Etanercept therapy against sarcoidosis

Pentoxifylline

- Studies show that patients w/ acute pulmonary sarcoidosis respond well to Pentoxifylline

Thalidomide

- Studies proving the efficacy of Thalidomide for pulmonary sarcoidosis is lacking

Anti-malarial Agents

Chloroquine & Hydroxychloroquine

- **Action:** May inhibit macrophage production of TNF-α
- Efficacy for the treatment of chronic sarcoidosis has been established
- Effect on disease activity is more likely suppressive than curative
- Chloroquine has been shown to be particularly helpful in hypercalcemia & lupus pernio
- Hydroxychloroquine is usually preferred because of lower risk of ocular toxicity
- Usual dose:
  - Chloroquine: 500 mg daily initially then 250 mg daily as maintenance
  - Hydroxychloroquine: 200-400 mg daily

B FOLLOW-UP

General Surveillance Principles

- Sarcoidosis patients should be monitored regularly
- Monitoring should include a review of symptoms, physical exam, CXR & lung function tests
  - Perform other tests as necessary based on organ involvement
- Monitor & treat patients for complications of sarcoidosis & related conditions (eg aspergilloma, osteoporosis, hypercalcemia, hypercalciuria)
- Patients who have undergone therapy should be monitored for 3 yr after cessation of treatment
- Intermittent monitoring (every 3-6 mth) is recommended for patients on TNF-alpha inhibitor therapy

Monitoring Intervals Based on Disease Stage

Stage 1

- Initially every 6 mth then once a yr if stable

Stage 2, 3, 4

- Initially every 3-6 mth; monitor indefinitely

Serious extrapulmonary involvement, regardless of radiographic stage

- Monitor indefinitely

Dosage Guidelines

CORTICOSTEROIDS (SYSTEMIC)		
Drug	**Dosage**	**Remarks**
Methylprednisolone	*Individualize dose* **Initial dose:** 4-48 mg/day PO or 0.139-0.835 mg/kg IM 12-24 hrly	**Adverse Reactions** • Endocrine effects (growth suppression, Cushing's syndrome, adrenal insufficiency, menstrual irregularities); Misc effects (fluid & electrolyte disturbance, muscle weakness, hypertension, cataract, delayed wound healing) **Special Instructions** • Not to be given intrathecally/intravenously • Should not be given to patients w/ systemic fungal infections • Use w/ caution in patients w/ ocular herpes simplex, psychological instability, ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal impairment, hypertension, osteoporosis, & myasthenia gravis
Prednisolone, Prednisone	30-40 mg/day PO Reduce dose to 5-10 mg PO daily if w/ positive patient response & continue minimum effective dose for 12-18 mth before attempting to withdraw **Alternative dose:** **Initial dose:** 40 mg every other day, followed by **Maintenance dose:** 5-10 mg every other day	**Adverse Reactions** • GI effects (peptic ulcer, acute pancreatitis); Musculoskeletal effects (muscle wasting, osteoporosis, spontaneous fractures, avascular necrosis of bone); Endocrine effects (amenorrhea, menstrual irregularities); Misc effects (increase susceptibility to infections, impaired growth, hyperhydrosis, benign intracranial hypertension) **Special Instructions** • Use w/ caution in patients w/ heart failure, recent myocardial infarction, hypertension, diabetes mellitus, epilepsy, glaucoma, hypothyroidism, hepatic/renal failure, osteoporosis, peptic ulcer, or psychological instability • Contraindicated in patients w/ ongoing disease unresponsive to appropriate antimicrobial treatment • Live vaccine administration is contraindicated

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.
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Specific prescribing information may be found in the latest MIMS.

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