SARCOIDOSIS

CHI Formulary Development Project

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Council of Health Insurance

November 2023

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

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Abbreviations

AC	Anterior Chamber
ACE	Angiotensin Converting Enzyme
AOE	Airborne Occupational Exposures
ATS	American Thoracic Society
AU	Anterior Uveitis
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CMR	Cardiac Magnetic Resonance Imaging
CT	Computed Tomography
CXR	Chest X-Ray
D_{LCO}	Diffusing Capacity of the Lungs for Carbon Monoxide
DMARD	Disease-Modifying Antirheumatic Drug
EBUS	Endobronchial Ultrasound
ECG	Electrocardiogram
EMA	European Medicines Agency
EOS	Elderly-Onset Sarcoidosis
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in the First Second of Expiration
FVC	Forced Vital Capacity
GC	Glucocorticoid
GP	General Practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
ICD	Implantable Cardioverter Defibrillator
IDF	Insurance Drug Formulary
IPF	Idiopathic Pulmonary Fibrosis

IQWIG	Institute for Quality and Efficiency in Health Care
IU	Intermediate Uveitis
IWOS	International Workshop on Ocular Sarcoidosis
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Ocular Sarcoidosis
PBAC	Pharmaceutical Benefits Advisory Committee
PET	Positron Emission Tomography
PICO	Patients, Intervention, Comparison, Outcomes
PML	Progressive Multifocal Leukoencephalopathy
PU	Posterior Uveitis
QOL	Quality of Life
RCI	Repository Corticotropin Injection
RID	Relative Infant Dose
SAF	Sarcoidosis-Associated Fatigue
SFDA	Saudi Food and Drug Authority
SFN	Small-Fiber Neuropathy
TLC	Total Lung Capacity
TNF	Tumor Necrosis Factor
WASOG	World Association of Sarcoidosis and Other Granulomatous Disorders

Executive Summary

Sarcoidosis is an inflammatory disease characterized by the growth of small collections of inflammatory cells (granulomas) in various parts of the body. Sarcoidosis most commonly affects the lungs and lymph nodes, but it can affect any organ including the eyes, skin, heart, and nervous system. The etiology of sarcoidosis is not known, but it is thought to involve a combination of genetic and environmental factors. Some risk factors include residing near dusty or moldy environments, **female gender**, African or Scandinavian descent, and **ages between 30-50 years old**[1]. Sarcoidosis may also be present in elderly ≥ 65 years old and is termed elderly-onset-sarcoidosis (EOS). It is usually more difficult to detect due to its low prevalence. Compared with younger patients, fatigue, uveitis, and specific skin lesions are more common, while erythema nodosum and chest x-ray abnormalities are less frequent. However, treatment remains the same for all age groups of sarcoidosis.

There is no gold standard diagnostic test, procedure, or algorithm for sarcoidosis. The diagnosis of sarcoidosis is based on three key criteria: (1) a clinical and **radiological presentation** consistent with the condition, (2) the presence of noncaseating granulomas in pathological examinations, and (3) the exclusion of other diseases that share similar characteristics (e.g., tuberculosis, malignancies). Since sarcoidosis has mainly pulmonary manifestations, the Scadding Staging System is used (table 1). It is important to know that the stages (except stage IV) are not progressive as patients may switch back and forth between stages. Stage I includes lymphadenopathy, stage II includes lymphadenopathy & pulmonary infiltrates, and stage III includes pulmonary infiltrates only. Patients in stages I to III may be asymptomatic and require no treatment, as they will eventually achieve spontaneous resolution. However, stage IV is irreversible as radiography will show pulmonary fibrosis. Patients are most likely symptomatic in this stage and will require treatment[2].

Table 1. Scadding Staging System Used for Sarcoidosis and Other Diseases. Adapted from Belperio et al. (2022)

Scadding stage	Radiographic findings	Frequency at presentation	Pulmonary obstruction	Follow-up of 1-15 years	
				Radiographic resolution	Mortality
0	Normal	8-10%	-	-	0
I	Bilateral hilar lymphadenopathy without	40-51%	6% of patients	49-82%	0-9%

	pulmonary infiltrates				
II	Bilateral hilar lymphadenopathy with pulmonary infiltrates	29-40%	13% of patients	31-68%	5-11%
III	Pulmonary infiltrates without bilateral hilar lymphadenopathy	12-20%	16% of patients	10-38%	12-18%
IV	Extensive fibrosis with distortion or bullae	2-5%		0	16-17%

The prevalence of sarcoidosis differs significantly across the globe, ranging from 1-5 cases per 100,000 individuals in South Korea, Taiwan, and Japan, to a higher prevalence of 140-160 cases per 100,000 in Sweden and Canada[3]. Numerous cases of sarcoidosis patients in Saudi Arabia have been documented since 1993. According to a study conducted at the Dhahran Health Centre, the estimated prevalence of sarcoidosis in the Eastern region of Saudi Arabia was 13 cases per 100,000 people[4].

Sarcoidosis may exhibit a gradual onset, with symptoms persisting for years. In other cases, symptoms may appear suddenly and then disappear abruptly. The clinical manifestations of sarcoidosis may vary depending on the organs affected. Pulmonary involvement is the most common, presenting as cough, shortness of breath, and chest discomfort. Extrapulmonary manifestations include a spectrum of symptoms, involving skin (erythema nodosum, lupus pernio), eyes (uveitis), heart (cardiac arrhythmias, heart block), and nervous system (neuropathy). Lofgren syndrome, a specific subset of acute sarcoidosis, is characterized by erythema nodosum, bilateral hilar lymphadenopathy, fever, and arthralgia, often with a favorable prognosis. The diverse range of clinical manifestations seen in sarcoidosis emphasizes the need for a thorough assessment to inform proper treatment strategies and enhance outcomes for individuals affected by the condition[5].

This report compiles all clinical and economic evidence related to Sarcoidosis according to the relevant sources. The ultimate objective of issuing Sarcoidosis guidelines by the Council of Health Insurance (CHI) is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to Sarcoidosis patients in Saudi Arabia**.

The main focus of the review was on North American, European, and other international guidelines issued within the last five years. To clarify, North American guidelines detailed the approach and management of pulmonary sarcoidosis in adult patients. European guidelines provided rigid recommendations on the treatment of various types of sarcoidosis while also reenforcing the management of pulmonary sarcoidosis as the North American Guidelines. The guidelines also briefly mentioned other agents such as Rituximab and Repository Corticotropin Injection (RCI) that require further clinical trials to assess their effectiveness on refractory sarcoidosis. The international guidelines provided a more detailed overview of the management of cardiac sarcoidosis while reemphasizing the treatment of sarcoidosis as previous guidelines.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in Sarcoidosis were reviewed and summarized under each drug therapy table in Section 2.0. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

Prognosis in sarcoidosis is typically more favorable for individuals with limited organ involvement (stages 0, I, and II) compared to those with more extensive disease (stages III and IV). However, it's important to note that the course of sarcoidosis can be unpredictable, and some individuals may experience spontaneous remission, while others may have a chronic and progressive course. Sarcoidosis is often asymptomatic and requires no treatment as most patients undergo remission. However, if symptoms are present and progressively worsening, patients will require pharmacological therapy. Glucocorticoids are the mainstay treatment. Addition of conventional then biological DMARDs were considered for steroid refractory sarcoidosis patients. Drugs outside of the scope of practice such as Rituximab and RCI have shown positive results when indicated for patients that have failed all previous therapies. In advanced sarcoidosis, it is best to implement an interdisciplinary approach that involves a team of healthcare workers such as a cardiologist, pulmonologist, radiologist, and dermatologist to tackle all possible complications of sarcoidosis to limit disease progression and provide relief of symptoms[6].

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of Sarcoidosis.

Major recommendations for suggested drug therapies are summarized in the tables below:

For SFDA Registered Drugs:

Table 2. SFDA-Registered Drugs for the Management of Sarcoidosis

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Prednisone/ Prednisolone	Treatment of patients with sarcoidosis	**1st Line**	1A	Not available
Methotrexate	Treatment of patients with sarcoidosis	**2nd Line**	1B	Not available
Azathioprine	Treatment of patients with sarcoidosis	**2nd Line**	2B	Not available
Leflunomide	Treatment of patients with sarcoidosis	**2nd Line**	2B	Not available
Mycophenolate Mofetil	Treatment of patients with sarcoidosis	**2nd Line**	2C	Not available
Hydroxy-chloroquine	Treatment of patients with sarcoidosis	**2nd Line**	No Level of Evidence	Not available
Infliximab	Treatment of patients with **refractory** sarcoidosis	**3rd Line**	1A	**Conditional Positive Recommendation – January 2017** From NICE[7] Infliximab could be considered as a potential treatment for individuals with severe, treatment-resistant extrapulmonary

				sarcoidosis, especially cases involving the skin or nervous system. This may apply to individuals experiencing significant disability or disfigurement, or whose life expectancy is expected to be shortened.
Adalimumab	Treatment of patients with **refractory** sarcoidosis	**3rd Line**	2B	Not available
Rituximab	Treatment of patients with **refractory pulmonary** sarcoidosis	**4th Line/ Alternative Therapy**	No Level of Evidence	Not available

For Non-SFDA Registered Drugs:

Table 3. Non-SFDA-Registered Drugs for the Management of Sarcoidosis

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation
RCI	Treatment of patients with **refractory pulmonary** sarcoidosis	**4th Line/ Alternative Therapy**	No Level of Evidence

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

To date, there are no clinical guidelines issued by Saudi bodies on the management of sarcoidosis.

1.2 European Guidelines

1.2.1 European Respiratory Society (ERS) Clinical Practice Guidelines on Treatment of Sarcoidosis [2021]

The previous international statement for the diagnosis and management of sarcoidosis was developed in 1999 by the European Respiratory Society (ERS), American Thoracic Society (ATS), and World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG). Over time, there has been a shift of emphasis on who, when and with what to treat sarcoidosis patients.

A Task Force committee was developed by the ERS to develop new guidelines for treating sarcoidosis using a standardized methodology. The committee systematically reviewed treatment for pulmonary, cutaneous, cardiac, and neurologic manifestations as well as sarcoidosis-associated fatigue (SAF) and small-fiber neuropathy (SFN).

The ERS Task Force committee composed of clinicians, methodologists, and patients with experience in sarcoidosis developed recommendations based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology (tables 4 and 5). The committee developed eight PICO (Patients, Intervention, Comparison, Outcomes) questions and these were used to make specific evidence-based recommendations[7].

Table 4. Certainty of Evidence (GRADE Approach)

CERTAINTY OF EVIDENCE	INTERPRETATION
High ⨁⨁⨁⨁	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate ⨁⨁⨁◯	We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low ⨁⨁◯◯	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very Low ⨁◯◯◯	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Table 5. Strengths of Recommendation (GRADE Approach)

Strength of Recommendation	Criteria	Interpretation	Additional Information
Strong recommendation for or against	The panel was certain that the desirable consequences of the intervention outweighed the undesirable consequences and a strong recommendation against an intervention was made when the opposite was true.	A strong recommendation indicates that most patients and healthcare providers would choose to have, or not to have, the intervention.	
Conditional recommendation for or against	The panel was uncertain that the desirable consequences of an intervention outweighed the undesirable consequences in most patients and a conditional recommendation against an intervention was made when uncertainty existed that undesirable consequences of an intervention outweighed the desirable consequences in most patients.	A conditional recommendation indicates that different patients and healthcare providers may make different choices regarding an intervention.	Reasons for uncertainty included low quality of evidence, a close balance between desirable and undesirable effects or patients' values and preferences.

I. Pulmonary sarcoidosis

Glucocorticoid treatment versus no immunosuppressive treatment

- For patients with untreated severe pulmonary sarcoidosis, who are thought to face an elevated risk of future mortality or permanent disability due to sarcoidosis, the initiation of glucocorticoid therapy is recommended. This is intended to improve and/or preserve their FVC and QoL. (Strong recommendation, low quality of evidence.)

Adding immunosuppressive treatment versus remaining on glucocorticoid monotherapy

- For patients with symptomatic pulmonary sarcoidosis, who are thought to be at an elevated risk of future mortality or permanent disability from the condition and have already undergone glucocorticoid treatment but continue to have active disease or encounter undesirable side effects, it is recommended to consider the incorporation of methotrexate. This approach aims to improve and/or preserve their FVC and QoL. (Conditional recommendation, very low quality of evidence).
- For patients with symptomatic pulmonary sarcoidosis, and who are thought to be at an elevated risk of future mortality or permanent disability from the condition, and have already undergone glucocorticoid or immunosuppressive treatment, and have continued disease, the addition of infliximab is suggested to improve and/or preserve FVC and QoL. (Conditional recommendation, low quality of evidence).

Figure 1 represents the pharmacological algorithm for management of pulmonary sarcoidosis:

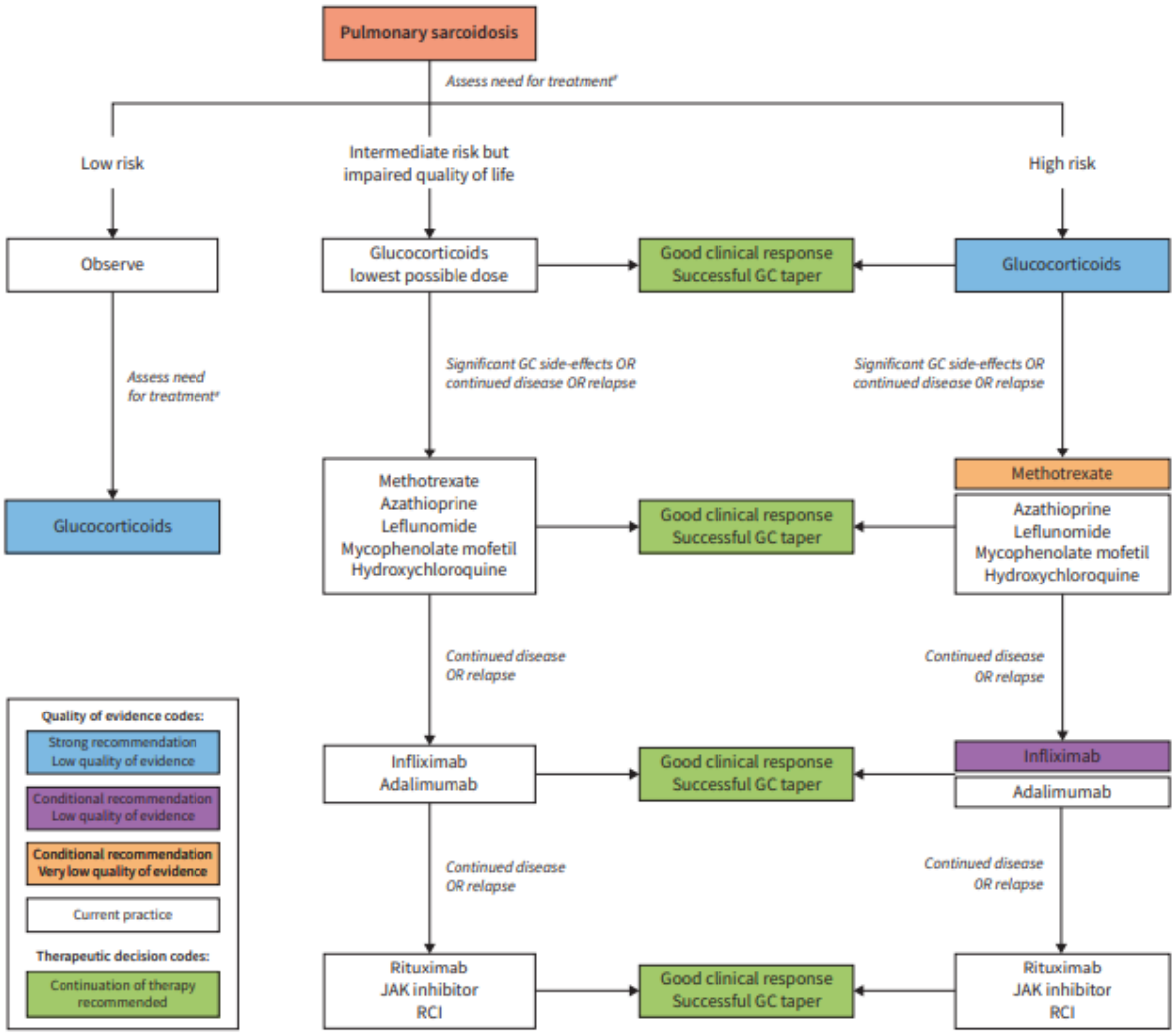


Figure 1. *Treatment Approach for Pulmonary Sarcoidosis. Retrieved from the ERS 2021 Guidelines.*

Use of rituximab, JAK inhibitor and repository corticotropin injection (RCI) should be on a case-by-case basis. This figure is a combination of the recommendations made in this guideline and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. #: assess need for treatment based on low risk, intermediate risk but impaired quality of life or high risk as discussed in text. GC: glucocorticoid.

II. Cutaneous sarcoidosis

Glucocorticoid treatment versus no immunosuppressive treatment

- For patients with cutaneous sarcoidosis who have active skin lesions of cosmetic significance that are not effectively managed with local treatments,

oral glucocorticoids are considered as an option to diminish the skin lesions. (Conditional recommendation, very low quality of evidence).

Adding immunosuppressive treatment for patients who have failed glucocorticoid monotherapy.

- For patients with cutaneous sarcoidosis who have received treatment with glucocorticoids and/or other immunosuppressive medications and still experience cosmetically significant active skin disease, the addition of infliximab is considered, as opposed to no additional intervention, to reduce skin lesions (Conditional recommendation, low quality of evidence).

Figure 2 represents the pharmacological algorithm for management of skin/cutaneous sarcoidosis:

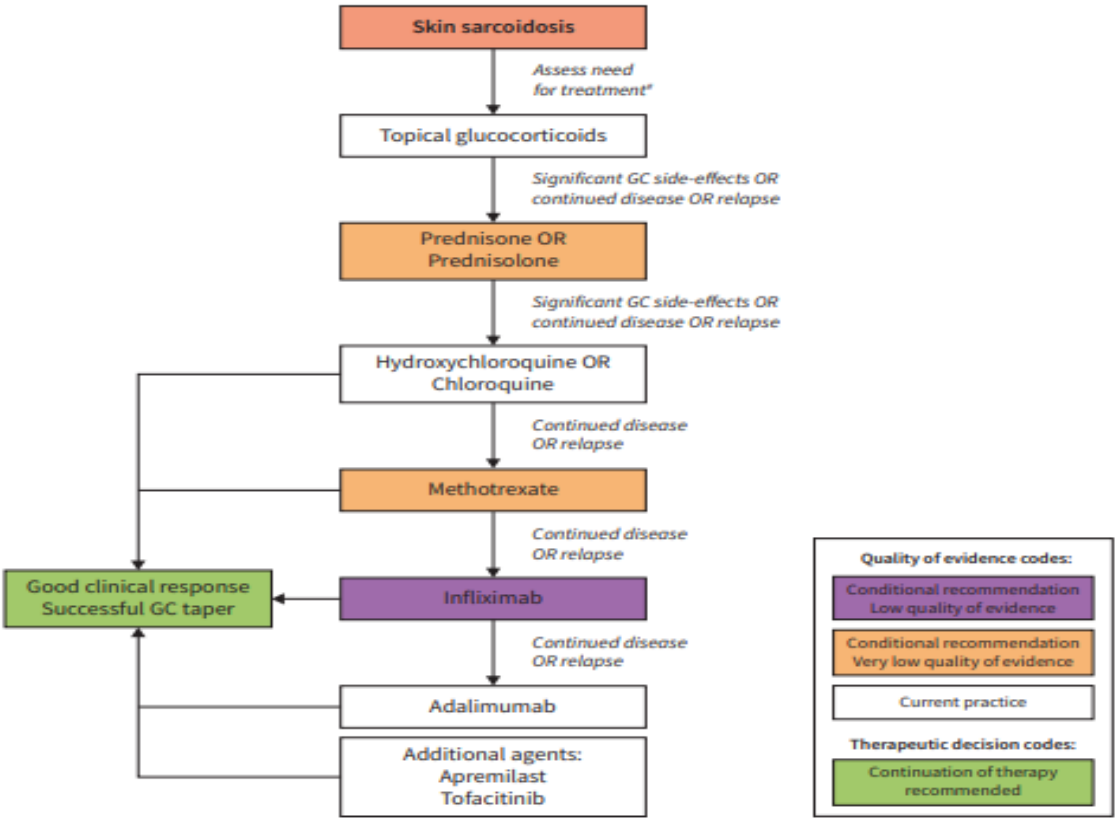


Figure 2. *Treatment Approach for Skin Sarcoidosis. Retrieved from the ERS 2021 Guidelines.*

Use of apremilast and tofacitinib should be on a case-by-case basis. This figure is a combination of the recommendations made in this guideline and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. #: assess need for treatment as discussed in text. GC: glucocorticoid.

III. Cardiac sarcoidosis

Glucocorticoid therapy with or without immunosuppressives versus no immunosuppressive therapy for patients with clinically relevant cardiac sarcoidosis

- For patients with evidence of functional cardiac abnormalities, including heart block, dysrhythmias or cardiomyopathy, the use of glucocorticoids is recommended (with or without other immunosuppressives). (Strong recommendation, very low quality of evidence.)

Figure 3 represents the pharmacological algorithm for management of clinically relevant cardiac sarcoidosis:

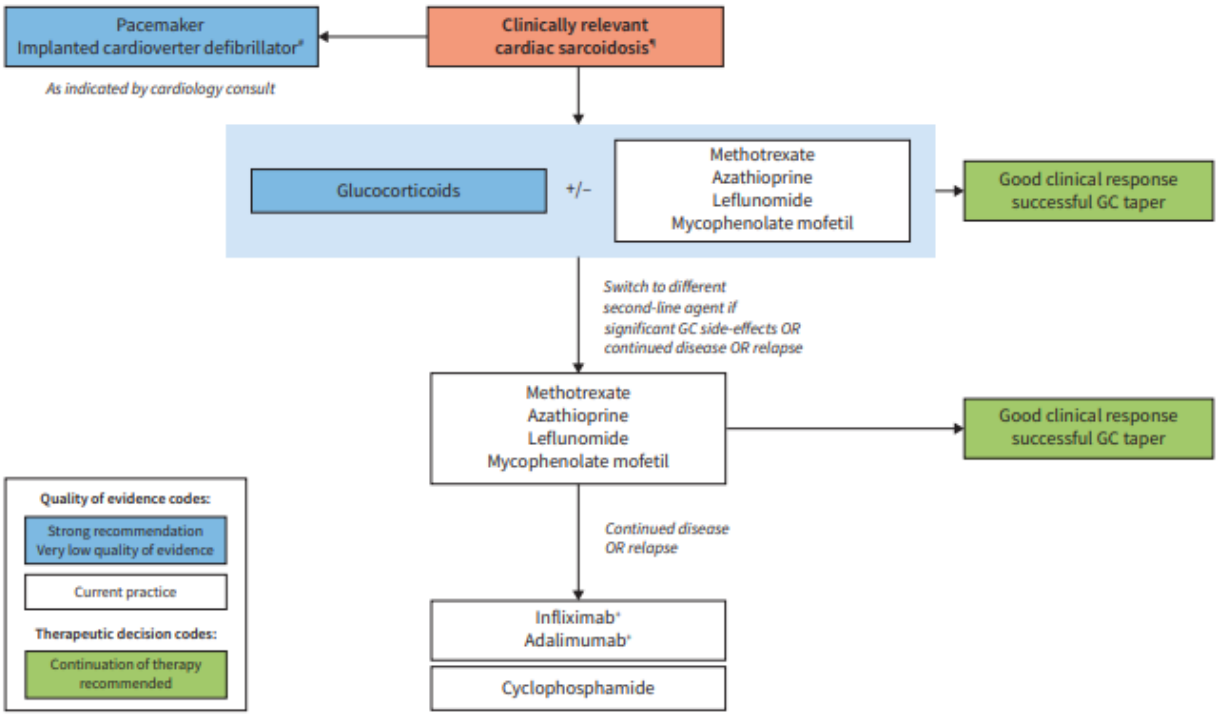


Figure 3. *Treatment Approach for Cardiac Sarcoidosis. Retrieved from the ERS 2021 Guidelines.*

This figure is a combination of the recommendations made in this guideline and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. #: use of implanted cardioverter defibrillator recommendation adapted from the Heart Rhythm Society: clinically relevant cardiac sarcoidosis is defined as rhythm disturbances, heart failure or high risk for sudden cardiac death; +: infliximab and adalimumab are usually used in combination with second-line agents. GC: glucocorticoids.

IV. Neuro-sarcoidosis

Immunosuppressive treatment versus no immunosuppressive treatment

- For patients with clinically significant neuro-sarcoidosis, glucocorticoid treatment is recommended. (Strong recommendation, very low quality of evidence.)
- For patients with neuro-sarcoidosis that have been treated with glucocorticoids and still have continued disease, the addition of methotrexate is considered. (Conditional recommendation, very low quality of evidence.)
- For patients with neuro-sarcoidosis that have been treated with glucocorticoids and a second-line agent (methotrexate, azathioprine, mycophenolate mofetil) and still have continued disease, the addition of infliximab is considered. (Conditional recommendation, very low quality of evidence.)

Figure 4 represents the pharmacological algorithm for management of symptomatic neuro-sarcoidosis:

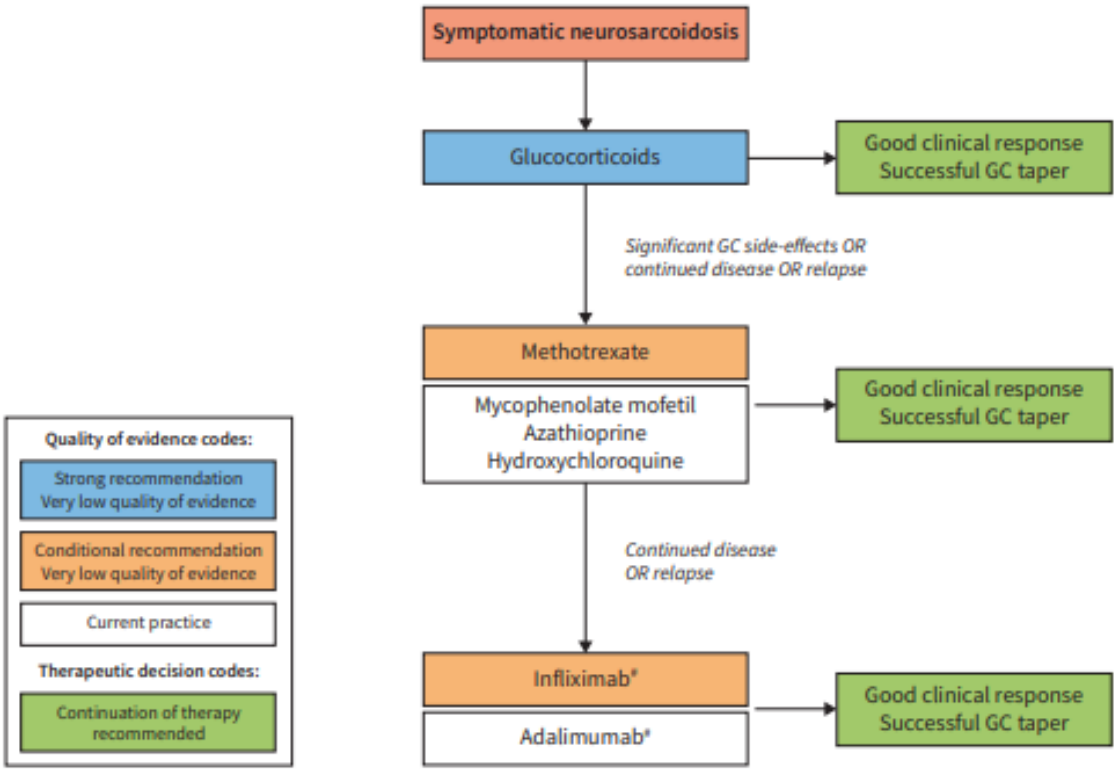


Figure 4. *Treatment Approach for Symptomatic Neuro-sarcoidosis. Retrieved from the ERS 2021 Guidelines.*

This figure is a combination of the recommendations made in this guideline, and a description of Task Force members' current practice in situations where there was not

enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. #: infliximab and adalimumab are usually used in combination with second-line agents. GC: glucocorticoids.

V. Sarcoidosis-associated fatigue (SAF)

Immunosuppressants, neuro-stimulants, exercise, or other treatments versus no treatment

- In patients with sarcoidosis who have troublesome fatigue, pulmonary rehabilitation program and/or inspiratory muscle strength training is considered for 6–12 weeks to improve fatigue. (Conditional recommendation, low quality of evidence.)
- In patients with sarcoidosis who have troublesome fatigue that is not related to disease activity, and after consideration of a pulmonary exercise or rehabilitation program, the use of D-methylphenidate or armodafinil is considered for 8 weeks to test its effect on fatigue and tolerability. (Conditional recommendation, low quality of evidence.)

Figure 5 represents the pharmacological and non-pharmacological algorithm for management of SAF:

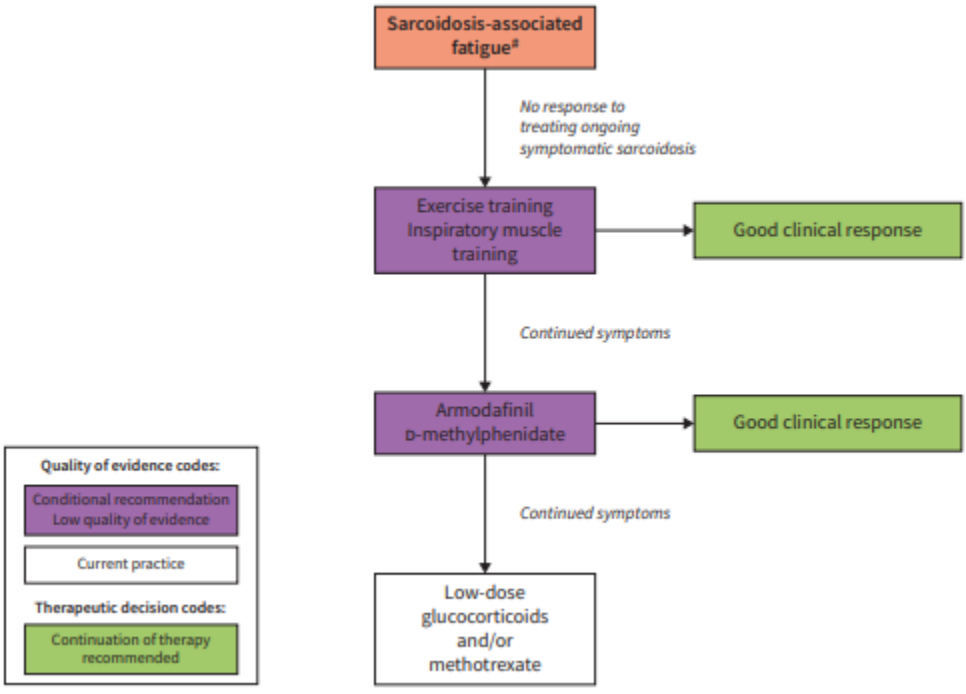


Figure 5. *Treatment Approach of Sarcoidosis-Associated Fatigue. Retrieved from the ERS 2021 Guidelines.*

The use of low-dose corticosteroids with or without methotrexate should be considered on a case-by-case basis. This figure is a combination of the recommendations made in this guideline, and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. #: other causes of fatigue include diabetes mellitus, thyroid dysfunction, neuroendocrine disorders, sleep apnea, small-fiber neuropathy, vitamin D deficiency with low 1,25-dihydroxycholecalciferol, congestive heart failure and neurologic disease.

VI. Small-fiber neuropathy (SFN)

Immunosuppressants or intravenous immunoglobin treatment versus no treatment

- No recommendations were made regarding this question due to a lack of sufficient evidence.

Figure 6 represents the treatment algorithm for management of SFN:

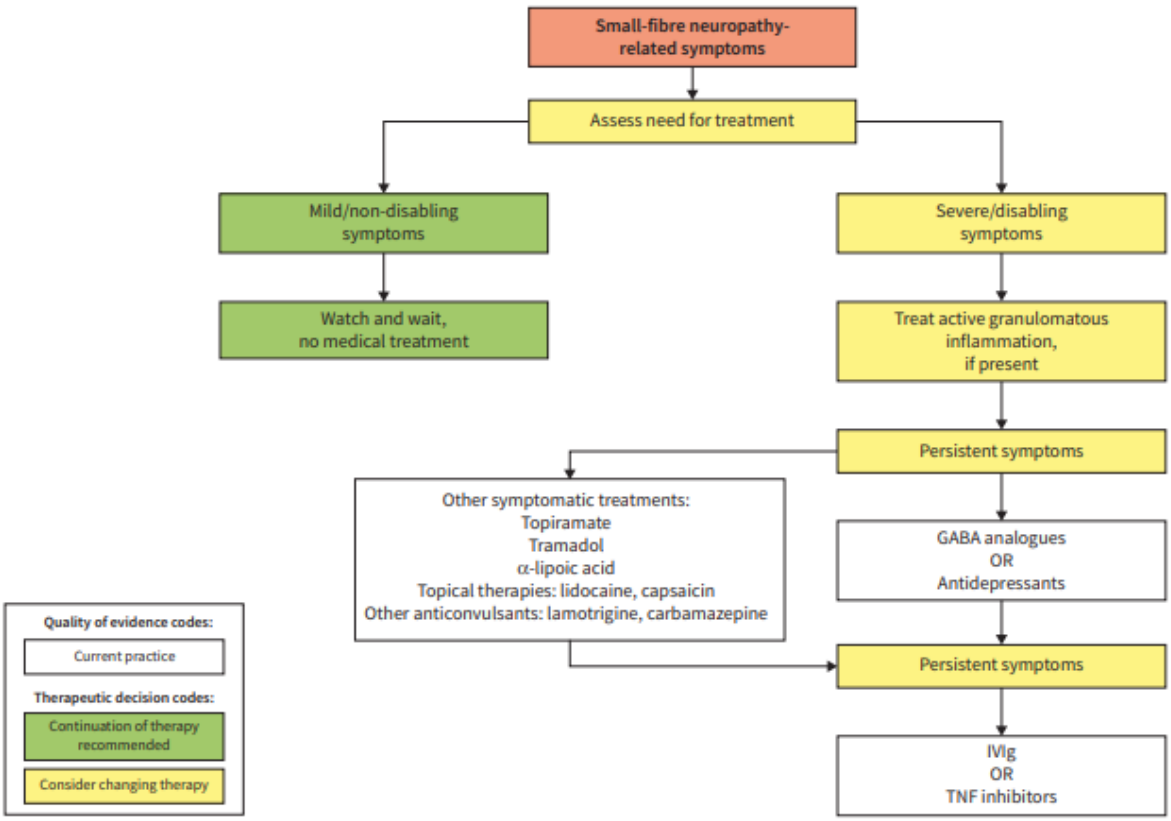


Figure 6. *Treatment Approach for Small-Fiber Neuropathy-Related Symptoms. Retrieved from the ERS 2021 Guidelines.*

The use of intravenous immunoglobulin (IVIg) or anti-tumor necrosis factor (TNF) antagonists should be considered on a case-by-case basis. This figure is a combination of the recommendations made in this guideline and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. GABA: γ-aminobutyric acid.

1.2.2 International Workshop on Ocular Sarcoidosis (IWOS) Recommendations for the Management of Ocular Sarcoidosis [2020]

The following consensus does not provide a specified grade of evidence or level of recommendation.

A question-based survey on the management of ocular sarcoidosis (OS) was circulated to international uveitis experts (members of the International Uveitis Study Group and the International Ocular Inflammation Society) electronically. Following this, a **consensus** workshop was held during the 7th International Workshop on Ocular Sarcoidosis (IWOS) in June 2019 in Sapporo, Japan, as part of the broader Global Ocular Inflammation Workshops. During this workshop, statements regarding the management of OS were considered to have achieved a consensus agreement if they received the support of a **two-thirds majority** among the 10 international panel members. These agreements were reached through thorough discussion and voting.

The below statements are the summarized consensus recommendations that were agreed upon in the International Workshop[8]:

Drugs for the management of ocular sarcoidosis (OS)

- Mean initial dose of systemic prednisone/prednisolone is 0.5–1.0 mg/kg/day, to a maximum dose of 80 mg/day.
- The mean duration of the initial dose of systemic prednisone/ prednisolone is 2–4 weeks.
- The mean duration of total treatment with systemic prednisone/ prednisolone is 3–6 months.
- The initial corticosteroid-sparing immunosuppressive drugs include methotrexate, azathioprine, mycophenolate mofetil and ciclosporin.
- In selected settings of severe disease, some specialists may consider intravenous pulse corticosteroid.
- Biologic drugs (adalimumab) are used if necessary.

Management of anterior uveitis (AU) in ocular sarcoidosis (OS)

- Ocular manifestations that are indicators for treatment in AU include anterior chamber (AC) cells, new-onset keratic precipitates, iris nodules, angle nodules, new-onset posterior synechia and raised IOP (not corticosteroid-induced). The mean duration of the initial dose of systemic prednisone/ prednisolone is 2–4 weeks.
- First-line therapy for severe AU (AC cell ≥3+, new-onset KPs, iris nodules) is instillation of corticosteroid eye drops (prednisolone acetate 1% or similar) at least 10 times per day.
- First-line therapy for moderate AU (AC cell <3+) is instillation of corticosteroid eye drops at least 6 times per day.
- Second-line therapy in severe AU includes subconjunctival dexamethasone injection, periocular triamcinolone acetonide injection and systemic corticosteroid.
- Second-line therapy for moderate AU includes more frequent corticosteroid eye drops, subconjunctival dexamethasone injection, periocular triamcinolone acetonide injection and systemic corticosteroid.
- Inactive AU does not require treatment.
- Mydriatic eye drops are used when AU is active.

Management of intermediate uveitis (IU) in ocular sarcoidosis (OS)

- Ocular manifestations that are indicators for treatment in IU include diffuse vitreous opacities, snowball-like vitreous opacities, snowbanks, and macular oedema.
- First-line therapy for active bilateral IU includes local corticosteroid (periocular, intravitreal, implant) and systemic corticosteroid.
- First-line therapy for active unilateral IU includes local corticosteroid (periocular, intravitreal, implant) and systemic corticosteroid.
- Second-line therapy for active bilateral IU includes local corticosteroid (periocular, intravitreal, implant), systemic corticosteroid, and non-biologic corticosteroid-sparing systemic immunosuppressive drugs.
- Second-line therapy for active unilateral IU includes local corticosteroid (periocular, intravitreal, implant), systemic corticosteroid, and non-biologic corticosteroid-sparing systemic immunosuppressive drugs.

Management of posterior uveitis (PU) in ocular sarcoidosis (OS)

- Ocular manifestations that are indicators for treatment in PU include macular oedema, optic disc nodules/granulomas, nodular and/or segmental peri-phlebitis, active chorioretinal peripheral lesions and choroidal nodules.
- First-line therapy for active bilateral PU includes systemic corticosteroid alone or with corticosteroid-sparing non-biologic systemic immunosuppressive drugs and local corticosteroid (periocular, intravitreal, implant).
- First-line therapy for active unilateral PU includes systemic corticosteroid alone or with corticosteroid-sparing non-biologic systemic immunosuppressive drugs and local corticosteroid (periocular, intravitreal, implant).
- Second-line therapy for active bilateral PU is same as first-line, with exception that biologic drugs are included.
- Second-line therapy for active unilateral PU is same as first-line, with exception that biologic drugs are included.

1.2.3 British Thoracic Society (BTS) Clinical Statement on Pulmonary Sarcoidosis [2020]

The British Thoracic Society issued a clinical statement for pulmonary sarcoidosis which summarizes the key points for the clinical practice and management of pulmonary sarcoidosis as summarized below[9]:

Clinical Presentation

- In pulmonary sarcoidosis, the respiratory examination is frequently unremarkable and cannot be relied upon to gauge the extent or severity of the disease.
- Non-fibrotic sarcoidosis often yields normal results in pulmonary function tests, which may not accurately reflect the activity or burden of the disease.
- It is crucial to screen for extra-thoracic manifestations of the disease. Initially, patients should undergo a complete blood count, biochemical tests (including urea and electrolytes, liver function tests, and calcium levels), serum angiotensin converting enzyme (ACE) levels (although consensus on this is not unanimous), and a 12-lead electrocardiogram (ECG).
- For patients experiencing eye-related symptoms, it is advisable to conduct an initial ophthalmic assessment by either an optician or an ophthalmologist, depending on the severity of the symptoms.

- It is important to routinely inquire about fatigue and any disturbances in the mood of patients.
- A thorough assessment of exposure history and occupational background is essential to rule out conditions like berylliosis and silicosis, which can present with symptoms like those of sarcoidosis.

Cardiac sarcoidosis and pulmonary hypertension

- For individuals with pulmonary sarcoidosis experiencing breathlessness that exceeds their level of lung function impairment, it is important to consider the possibility of cardiac sarcoidosis and/or pulmonary hypertension.
- When assessing patients suspected of having cardiac sarcoidosis (those with abnormal ECG results, cardiac symptoms, or breathlessness inconsistent with their pulmonary function), it is recommended to conduct baseline testing including an ECG and an echocardiogram. Any abnormalities indicating cardiac sarcoidosis on the ECG or echocardiogram should be confirmed through cardiac magnetic resonance imaging (CMR) or positron emission tomography (PET).
- Individuals experiencing palpitations should be offered a 24-hour Holter monitor.
- In cases of pulmonary sarcoidosis, if cardiac involvement is suspected based on advanced imaging results (CMR or PET), it is advised to have a multidisciplinary team with expertise in both sarcoidosis and other cardiac conditions confirm the findings. There is an ongoing effort to identify specialized centers for interstitial lung disease that have immediate access to expertise in cardiac sarcoidosis.

Diagnosis

- Every patient suspected of having sarcoidosis should undergo a chest X-ray (CXR). If the radiograph shows typical findings along with a matching clinical presentation (such as in the case of Lofgren's disease), a computed tomography (CT) scan may not be immediately required. Instead, patients should be regularly monitored in the clinic with a follow-up CXR within three months, and a CT scan should be considered if there are any changes in circumstances.
- It is advised to have a multidisciplinary team review chest imaging for patients whose clinical presentation or CT appearance is atypical. This review helps determine whether a confirmatory bronchoscopy or biopsy is necessary.

- During a bronchoscopy, patients primarily affected by lymph node disease should undergo an endobronchial ultrasound (EBUS), while those with predominantly parenchymal disease should have transbronchial biopsies. In cases where both nodal and parenchymal disease are present, EBUS is the preferred initial diagnostic procedure.
- It is important to involve all patients in the decision-making process regarding the necessity of a biopsy or the feasibility of monitoring them in the clinic alone. This approach allows for a collaborative approach, with the option to revisit the need for a biopsy if circumstances change.

Management

- Deciding when to initiate pharmacological treatment can be a delicate balance, and it's important that all patients are well-informed and actively involved in this decision-making process.

Steroids

Although there is limited evidence supporting specific drug regimens for sarcoidosis, most patients requiring treatment are typically started on steroids. The dosage may range from 10mg of prednisolone daily for cases of long-standing, slowly progressing disease, to 20 to 40mg per day for more acute situations. Following these initial doses, a maintenance dose of 5 to 10mg for a period of 6 to 12 months is commonly prescribed.

Second Line Immunosuppressants

Indication for the addition of second-line agents include:

- Advancement of pulmonary disease or an unsatisfactory symptom load despite appropriate steroid treatment.
- Unbearable side effects from steroids.
- Difficulty in reducing steroid dosage below 10 to 15mg per day.
- The existence of significant comorbidities expected to be negatively impacted by steroid therapy (such as severe obesity, diabetes mellitus, osteoporosis, hypertension).
- Strong patient reluctance to use steroids, in which situation, a second-line agent may be used at times as initial therapy.

Methotrexate is usually the initial choice for a second-line agent. In retrospective studies (requiring careful interpretation), methotrexate has demonstrated an effectiveness of 50% and a response rate ranging from 40% to 60% when employing FVC and DLco as indicators of outcomes. Methotrexate is given either orally or subcutaneously in situations where there is persistent nausea or an inadequate

response after six months. The usual starting dose is 5 to 10mg per week, with increments every two weeks until reaching a target of 15 to 20mg per week, as tolerated. To minimize the risk of myelosuppression, it is advisable to routinely prescribe folic acid at a weekly dosage of 5mg.

Azathioprine: The typical initiation dose for azathioprine is 50mg per day, with increments of 25mg every 2 to 3 weeks until reaching the maintenance dose, usually set at 2mg/kg. Common adverse effects encompass nausea, vomiting, diarrhea, rash, fever, and malaise. There were no substantial variations in effectiveness observed in a direct comparison between methotrexate and azathioprine, except for a greater incidence of infections with azathioprine (35% compared to 18%). This discrepancy might be attributed to the selective application of prophylactic antibiotics in methotrexate treatment.

Mycophenolate Mofetil: Information on the utilization of mycophenolate mofetil (MMF) in sarcoidosis is restricted, and it should not be prioritized over methotrexate or azathioprine unless there is a particular rationale.
Neutropenia is a less prevalent issue with mycophenolate mofetil (MMF) compared to other immunosuppressive agents, although it can still occur. Dose limitations may be imposed due to nausea and diarrhea, and like other second-line agents, MMF poses potential teratogenic risks in women of childbearing age.

Leflunomide: An antimetabolite like methotrexate but causing less gastrointestinal distress, can be employed either independently or in conjunction with methotrexate. Although most of the knowledge comes from its application in rheumatoid arthritis, limited case series indicate potential advantages for forced vital capacity (FVC) improvement and reduced steroid usage with leflunomide. Common adverse effects associated with leflunomide encompass nausea, diarrhea, abdominal pain, hypertension, hepatotoxicity, rash, and peripheral neuropathy.

Cyclophosphamide: Is an alkylating agent that undergoes metabolism through the cytochrome P-450 system to produce active metabolites, which reduces both the number and function of lymphocytes and may exhibit anti-inflammatory effects. While it is among the more frequently employed immunosuppressive agents, **it is seldom utilized as a steroid-sparing option in sarcoidosis treatment because of its associated toxicity.**

Hydroxychloroquine: Hydroxychloroquine is primarily recommended for addressing fatigue, joint issues, and cutaneous manifestations in sarcoidosis. However, it can also be employed as a supplementary treatment to assist patients in tapering off higher doses of prednisolone. The typical dosage is 200mg once or twice daily. Although retinal and cardiac toxicities are infrequent, they can be potentially severe. It is advised to conduct an ophthalmic examination at the initiation of treatment Additionally, a baseline electrocardiogram (ECG) is recommended to rule out a prolonged QT interval.

Biological agents and antifibrotics

Biological agents are considered third-line therapeutic agents, to be initiated in pulmonary disease only after a failure of second line treatment. Tumor necrosis factor (TNF) is a cytokine with pro-inflammatory properties believed to expedite the inflammatory processes in sarcoidosis by contributing to the maintenance of granuloma formation. Consequently, the use of agents that inhibit the effects of TNF may prove advantageous in the treatment of sarcoidosis.

Infliximab: a TNF agent given in combination with methotrexate or azathioprine appears to improve disease control. The primary side effects involve heightened vulnerability to infections, particularly from mycobacteria and invasive fungi, infusion-related reactions, hair loss, oral candidiasis, visual field impairment, and an elevated risk of fatal pulmonary embolism.
Interestingly, the formation of non-caseating granulomas, indicative of sarcoidosis, has been documented as a paradoxical occurrence during anti-TNF therapy for different medical conditions. Infliximab is given initially every 2 weeks and then every 4 to 8 weeks as part of maintenance therapy.

Pirfenidone & Nintedanib: Only available in the UK for idiopathic pulmonary fibrosis. Nonetheless, the recent INBUILD study investigated individuals with non-IPF fibrotic lung conditions, encompassing NSIP (non-specific interstitial pneumonitis), hypersensitivity pneumonitis, and sarcoidosis. Despite the relatively small number of participants with sarcoidosis in the study, there was a general decrease in the annual rate of forced vital capacity (FVC) decline among patients treated with nintedanib compared to the control group[10]. This suggests a potential role for antifibrotic agents in the management of progressive fibrotic lung diseases, including sarcoidosis, once alternative immunosuppressive therapies have been exhausted.

Lung Transplantation

The indications for lung transplantation in sarcoidosis fall beyond the scope of this statement; however, one potential approach is to align with criteria like those applied for idiopathic pulmonary fibrosis (IPF). These criteria typically involve a substantial acute decline (e.g., 10% over 6 months) in forced vital capacity (FVC) or diffusing capacity of the lungs for carbon monoxide (DLco) coupled with respiratory failure. It's worth noting that bilateral lung transplantation appears to be associated with slightly superior survival rates compared to single lung transplantation. While asymptomatic non-caseating granulomas indicative of recurrent disease have been detected in the allografts of sarcoidosis patient's post-lung transplantation, instances of clinically significant organ dysfunction due to recurrent sarcoidosis are infrequent.

Monitoring, discharge, and withdrawal of treatment

- Patients taking medication should not be exclusively managed by primary care providers. Even patients who are stable and doing well should receive monitoring in a hospital setting while on treatment. Those who are under the ongoing care of their general practitioner (GP) should be referred to a hospital respiratory physician if they experience new or worsening symptoms.
- All patients receiving active monitoring or treatment should undergo regular lung function tests as a standard part of their care.
- In most cases, patients with well-managed disease who have been on medication for 6 to 12 months should undergo a trial of reducing or discontinuing steroid therapy.
- As is the case with other chronic lung conditions, patients should be offered guidance on smoking cessation, and support for anxiety or depression should be provided if necessary.

Communication

- Healthcare providers should take into consideration the potential necessity for benefits guidance, home assessments by occupational therapists, referrals for pulmonary rehabilitation, and collaboration with the general practitioner for palliative care support if warranted, such as in cases of progressive fibrotic pulmonary sarcoidosis leading to respiratory failure.
- It is recommended that all patients are encouraged to complete an assessment of their quality of life. Within this process, clinicians should stress the importance of "self-care," which involves conscious efforts by sarcoidosis patients to maintain their physical, mental, or emotional well-being.
- Effective communication between different service providers (including both tertiary and secondary care, as well as specialists in various organ systems) is essential. Additionally, all patients should be offered a collaborative care approach whenever it is feasible.

1.3 North American Guidelines

1.3.1 Review Article Diagnosis and Treatment of Pulmonary Sarcoidosis [*JAMA*, 2022]

This review article published by Belperio et al. in the Journal of the American Medical Association (JAMA) in March 2022 summarizes recommendations regarding the diagnosis and treatment of pulmonary sarcoidosis[11]:

Common Clinical Manifestations for Patients with Pulmonary Sarcoidosis

- Common signs of pulmonary sarcoidosis include cough (69%), dyspnea (29%), and chest pain (23%).
- Nevertheless, a significant portion, ranging from 30% to 60% of sarcoidosis patients do not experience any pulmonary symptoms.
- In these cases, the presence of sarcoidosis is frequently discovered through a chest X-ray or a chest CT scan.

Lofgren Syndrome

- Lofgren syndrome is a sudden-onset variant of sarcoidosis that presents with symptoms like erythema nodosum, bilateral hilar lymphadenopathy, fever, and arthritis in the ankles.
- Without treatment, the erythema nodosum, fever, and ankle arthritis typically subside in about 6 weeks, while the lymphadenopathy in the chest area usually resolves within 1 to 2 years.
- If treatment is pursued, the initial approach for patients with Lofgren syndrome typically involves using nonsteroidal anti-inflammatory drugs.

Pulmonary Sarcoidosis Diagnosis

- Over 90% of sarcoidosis patients experience pulmonary involvement. If chest imaging reveals pulmonary infiltrates or lymphadenopathy in the hilar or mediastinal regions, it is advisable to conduct a flexible fiberoptic bronchoscopy.
- The flexible fiberoptic bronchoscopy procedure should include transbronchial lung biopsies or endobronchial ultrasound-guided transbronchial needle aspiration, both of which demonstrate a sensitivity of 80% or higher in detecting pulmonary sarcoidosis.
- Additionally, if any abnormalities are observed during the bronchoscopy, endobronchial biopsies should also be taken.
- Sarcoidosis is characterized by the presence of non-necrotizing granulomas in the pathology. Prior to confirming a diagnosis of sarcoidosis, it is imperative to rule out other potential causes of granulomas, such as mycobacterial and fungal diseases, as well as other interstitial lung conditions like hypersensitivity pneumonitis or chronic beryllium disease.

Management of Pulmonary Sarcoidosis

- Patients with sarcoidosis who exhibit abnormalities in the pulmonary tissue and experience significant respiratory symptoms like cough and shortness of breath or show signs of disease progression (indicated by worsening symptoms, pulmonary function test results, or chest imaging), should undergo treatment.
- The preferred approach involves administering oral glucocorticoids, either alone or in combination with a glucocorticoid-sparing agent like azathioprine, methotrexate, or a biological medication such as an anti-tumor necrosis factor agent.
- Typically, for pulmonary sarcoidosis, oral glucocorticoids are prescribed at a dose of 20 mg/d to 40 mg/d of prednisone, which is then gradually tapered to 0 mg/d to 10 mg/d over a period of 6 to 18 months.
- However, patients with persistent symptoms, abnormal pulmonary function tests, and unresolved radiographic abnormalities may require an extended course of oral glucocorticoids beyond one year.

Pharmacological therapies for the management of pulmonary sarcoidosis and their respective level of evidence/grade of recommendation are summarized in the tables below:

Table 6. Level of Evidence/Grade of Recommendation adapted from guideline Diagnosis and Treatment of Pulmonary Sarcoidosis (2022)

Level/Grade	Definition
1	Strong recommendation
2	Weak recommendation
Grade A	Evidence from ≥ 1 randomized clinical trial with positive results, and ≥ 1 case series supporting the results
Grade B	Evidence from most case series showing positive results
Grade C	Evidence from case series with mixed reports of effectiveness or a small number of case reports.

Table 7. Therapies for Pulmonary Sarcoidosis

Therapy	Mechanism	Indications	Dose	Adverse Effects	Efficacy Grade
Oral glucocorticoids	Anti-inflammatory	Patients with stage II to III disease with symptoms (cough, dyspnea) or stage IV disease with significant ground glass on radiography and ruled out for infection.	20-40 mg/d for 2-6 week and then tapered over 6 to 18 months	Alterations in weight and mood, risk for cataracts, glaucoma, osteopenia, osteoporosis, and infections (eg, herpes zoster)	1A
Azathioprine	An inhibitor of purine metabolism that predominately effects lymphocytes and mononuclear phagocytes.	Recommended for patients not responsive to prednisone, for those who have an adverse reaction to prednisone, or to facilitate use of lower prednisone doses. Azathioprine may be associated with higher rates of infection than methotrexate.	50-200 mg/day	Hepatotoxicity, bone marrow suppression, hypersensitivity reaction, gastrointestinal upset, and infections. When combined with prednisone, the patient is at risk for Pneumocystis jiroveci and herpes zoster.	2B
Methotrexate	A folic acid antagonist that inhibits purine	Recommended for patients not responsive to prednisone, for those who	5-25mg/week	Hepatotoxicity, bone marrow suppression,	1B

	and pyrimidine metabolism as well as polyamine and amino acid synthesis that effects multiple leukocyte subpopulations.	have an adverse reaction to prednisone, or to facilitate use of lower prednisone doses.		gastrointestinal upset, pneumonitis, and infections. When combined with prednisone, the patient is at risk for P jiroveci and herpes zoster. The patient will need to take folic acid.	
Mycophenolate mofetil	Inhibits purine nucleotide synthesis predominately in lymphocytes.	Recommended for patients not responsive to prednisone, for those who have an adverse reaction to prednisone, or to facilitate use of lower prednisone doses.	500-3000 mg/day	Hepatotoxicity, bone marrow suppression, gastrointestinal upset, and infections. When combined with prednisone, the patient is at risk for P jiroveci and herpes zoster.	2C
Leflunomide	Dihydroorotate dehydrogenase inhibitor that predominately inhibits dividing lymphocytes.	Recommended for patients not responsive to prednisone, for those who have an adverse reaction to prednisone, or to facilitate use of lower prednisone doses.	10-20 mg/day	Hepatotoxicity, bone marrow suppression, gastrointestinal upset, neuropathy,	2B

				pneumonitis, and infections.	
Anti–tumor necrosis factor agents	Neutralization of tumor necrosis factor α.	Recommended for patients not responsive to prednisone, for those who have an adverse reaction to prednisone, or to facilitate use of lower prednisone doses.	**Infliximab:** 3-5 mg/kg intravenously at time 0, 2 weeks, and then every 4-8 week **Adalimumab:** 40 mg subcutaneously every 1-2 week	Injection site reaction, activation of tuberculosis, demyelination syndrome, malignancy, and sarcoidosis-like reactions.	1A 2B

1.4 International Guidelines

1.4.1 Japanese Circulation Society (JCS) Guideline on Diagnosis and Treatment of Cardiac Sarcoidosis [2016]

The recommendations of the Japanese Circulation Society Guidelines on Diagnosis and Treatment of Cardiac Sarcoidosis were based on the Grade of Recommendations, Level of Evidence, and Classification of Recommendations that are included in the following tables:[12]

Table 8. Levels of Evidence

Level of Evidence	
Level 1	Data derived from systematic reviews or meta-analyses of multiple randomized clinical studies
Level 2	Data derived from one or more randomized clinical studies
Level 3	Data derived from non-randomized studies
Level 4a	Data derived from analytical epidemiological studies (cohort studies)
Level 4b	Data derived from analytical epidemiological studies (case-control studies or cross-sectional studies)
Level 5	Data derived from descriptive studies (case reports or case series)
Level 6	Reports of expert committees and opinions of experts

- The level of evidence is classified according to the type of study design.
- When more than one literature with different levels of evidence is available, the highest level of evidence is indicated.

Table 9. Grades of Recommendation

Grade of Recommendation	
Grade A	Strongly recommended and supported by strong evidence
Grade B	Recommended with moderately strong supporting evidence
Grade C1	Recommended despite no strong supporting evidence
Grade C2	Not recommended because of the absence of strong supporting evidence
Grade D	Not recommended as evidence indicates that the treatment is ineffective or even harmful.
The grade of recommendation is determined through:	

- Level of evidence
- Number of evidence sources and the distribution of numbers of evidence sources by evidence level
- Magnitude of clinical efficacy
- Clinical applicability (e.g., physicians' capabilities, local characteristics, medical resources, and health insurance systems)
- Evidence on harmful effects and costs.

Table 10. Classification of Recommendations

Classification of Recommendations	
Class I	There is evidence and/or general agreement that a given procedure or treatment is useful and effective
Class II	There is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a given procedure or treatment
Class IIa	Weight of evidence and data and opinion is in favor of usefulness and/or effectiveness.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	There is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful.

Clinical Findings Defining Cardiac Involvement

- Cardiac findings must be assessed based on the major and minor criteria. Clinical findings that satisfy statement #1 or #2 strongly suggest the presence of cardiac involvement.
    1. Two or more of the five major criteria (a) to (e) are satisfied.
    2. One of the five major criteria (a) to (e) and two or more of the three minor criteria (f) to (h) are satisfied.

Table 11 details the major and minor criteria that aid in defining cardiac involvement:

Table 11. Criteria for Cardiac Involvement

Major criteria
High-grade atrioventricular block (including complete atrioventricular block) or fatal ventricular arrhythmia (e.g., sustained ventricular tachycardia, and ventricular fibrillation)

Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional ventricular wall thickening)
Left ventricular contractile dysfunction (left ventricular ejection fraction less than 50% or focal ventricular wall asynergy
^{67}Ga citrate scintigraphy or ^{18}F-FDG PET reveals abnormally high tracer accumulation in the heart
Gadolinium-enhanced MRI reveals delayed contrast enhancement of the myocardium
Minor criteria
Abnormal ECG findings: ventricular arrhythmias (nonsustained ventricular tachycardia, multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal Q waves
Perfusion defects on myocardial perfusion scintigraphy (SPECT)
Endomyocardial biopsy: monocyte infiltration and moderate or severe myocardial interstitial fibrosis

Diagnostic Guidelines for Cardiac Sarcoidosis

- Histological diagnosis group (Patients with positive myocardial biopsy findings). Cardiac sarcoidosis is diagnosed histologically when endomyocardial biopsy or surgical specimens demonstrate non-caseating epithelioid granulomas.
- Clinical diagnosis group (Patients with negative myocardial biopsy findings/ those not undergoing myocardial biopsy), diagnosis is confirmed when:
    1. Epithelioid granulomas are detected in organs other than the heart, and there are clinical signs strongly indicating of the above-mentioned cardiac involvement are present.

       or

    2. The patient shows clinical findings strongly suggestive of pulmonary or ophthalmic sarcoidosis.

Treatment of Cardiac Sarcoidosis

Pharmacotherapy – Immunosuppressive Therapy

- The “Views on the treatment of sarcoidosis - 2003” published in 2003 describe that corticosteroid therapy should be considered for individuals with cardiac sarcoidosis experiencing high-grade atrioventricular block, ventricular

arrhythmias, or cardiac dysfunction. (Evidence level 6, Recommendation grade C1).

- Reports have described that prognosis was better when corticosteroid therapy for cardiac sarcoidosis was initiated before rather than after the occurrence of cardiac dysfunction. (Evidence level 4b, Recommendation grade C1).
- According to the "Views on the Treatment of Sarcoidosis - 2003," oral corticosteroid therapy for sarcoidosis should be started with the initial dose of 30mg daily (0.5mg/kg daily) as or 60mg every other day (1.0mg/kg every other day) prednisolone equivalent for the first 4 weeks. Then the dose should be reduced by 5mg daily or 10 mg every other day at intervals of 2 to 4 weeks to maintain at 5 to 10mg daily or 10 to 20mg every other day (Evidence level 6, Recommendation grade C1).
- Some patients may discontinue corticosteroid therapy, but many patients continue corticosteroid therapy for a long period of time (Evidence level 6, Recommendation grade C1).
- Second-line immunosuppressive therapy for patients with extracardiac involvement of sarcoidosis such as those with intractable pulmonary sarcoidosis has been tried using cyclophosphamide, cyclosporine, azathioprine, methotrexate, thalidomide, hydroxychloroquine, pentoxifylline, and mycophenolic acid, among others. (Evidence level 5)
- These medications can be employed either as monotherapy or alongside corticosteroids for patients who do not show significant improvement with corticosteroid treatment, are unable to use them, or experience adverse reactions preventing an increase in dosage. However, the use of these secondary medications for cardiac sarcoidosis has only been documented in isolated case reports. In Japan, low-dose methotrexate (Evidence level 5, Recommendation grade C1) is the most prevalent choice for this purpose. It is anticipated to reduce the reliance on steroids or alleviate the intensity of adverse reactions to corticosteroids.
- Third-line agents include as of recently, infliximab, an anti-TNFα antibody which relieves inflammation by preventing TNF-α from binding to receptors and eliminating cells that produce TNF-α. This drug has mostly been used for pulmonary sarcoidosis in Western countries. (Evidence level 5).

Pharmacotherapy – Treatment of Heart Failure

- There has been no specific clinical research dedicated to addressing heart failure management in individuals with cardiac sarcoidosis. Therefore, the recommended approach is to administer immunosuppressive therapy for

treating cardiac sarcoidosis, along with standard heart failure management, regardless of the heart failure stage. (Evidence level 6, Recommendation grade C1)

Pharmacotherapy – Treatment of Arrhythmias

- Indications for corticosteroid therapy for the treatment of tachyarrhythmia and bradyarrhythmia associated with cardiac sarcoidosis:
    - Class I: Patients with cardiac involvement demonstrated by positive Ga scintigraphy or F-FDG PET findings (Evidence level 4a, Recommendation grade A)
    - Class IIa: Patients without cardiac involvement demonstrated by positive Ga scintigraphy or F-FDG PET findings (Evidence level 4b, Recommendation grade C1)
- Indications for antiarrhythmic drugs for the treatment of tachyarrhythmia associated with cardiac sarcoidosis: (* Indicates Vaughan Williams Classification)
    - Class I: None
    - Class IIa:
        - Beta blockers (Evidence level 6, Recommendation grade C1)
        - Amiodarone, sotalol, and class 1b* antiarrhythmic drugs for the treatment of uncontrollable ventricular tachycardia (Evidence level 6, Recommendation grade C1)
    - Class IIb:
        - Amiodarone, sotalol, and verapamil for the treatment of controllable ventricular tachycardia (Evidence level 6, Recommendation grade C2)
        - Class 1a* and 1c* antiarrhythmic drugs for the treatment of uncontrollable ventricular tachycardia (Evidence level 6, Recommendation grade C2)
    - Class III:
        - Class 1a* and 1c* antiarrhythmic drugs for the treatment of controllable ventricular tachycardia (Evidence level 6, Recommendation grade D)

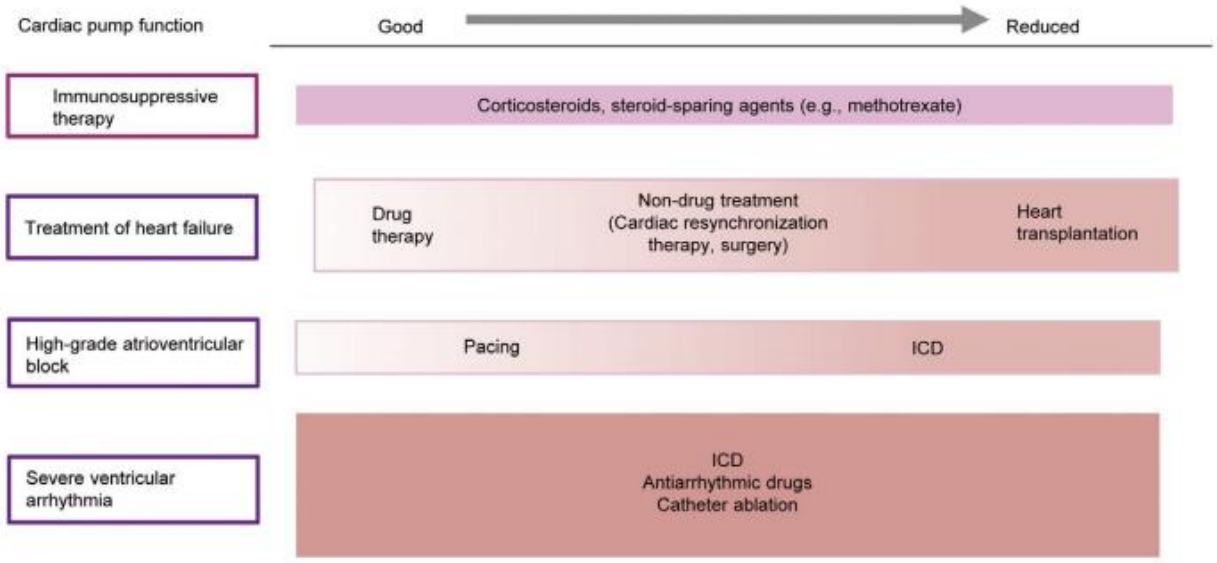
Non-Pharmacological Therapy

- Non-pharmacological therapies in the management of cardiac sarcoidosis include permanent pacing, implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy, and catheter ablation. These therapies are used in specific patient populations.

Surgical Therapy

- Left Ventricular Restoration and Mitral Valvuloplasty: Individuals with localized injuries may undergo a procedure involving resection and reconstruction to enhance the shape and functionality of the left ventricle.
- Heart Transplantation: Heart transplantation is a potential treatment choice for individuals with cardiac sarcoidosis, both in Japan and in other nations (Evidence Level 5, Recommendation grade C1).

Figure 7 represents the cardiac sarcoidosis treatment algorithm:



ICD, implantable cardioverter defibrillator.

Figure 7. *Treatment Algorithm for Cardiac Sarcoidosis. Retrieved from the JSC 2016 Guideline.*

1.4.2 Review Article Sarcoidosis: Causes, Diagnosis, Clinical Features, and Treatments [*J Clin Med*, 2020]

The following review article does not provide a specified grade of evidence or level of recommendation.

Recommendations of this guidelines are summarized below:[13]

- Not all patients require treatment. The choice to initiate treatment for a sarcoidosis patient is determined by the emergence of specific symptoms and the progression of the disease, as indicated by a decline in functional status and abnormalities seen in imaging.

Corticosteroids

- Typically, treatment begins with a daily dose of prednisolone ranging from 0.5 to 0.75 mg per kg of body weight for a duration of 4 weeks. This dosage is then gradually reduced by 10 mg every 4 weeks, based on the response to the treatment.
    - Dose can be replaced by 20mg of prednisone.
- When pulmonary function has improved, therapy can be terminated, which is usually within 6-12 months.
- Patients with minor clinical symptoms like skin lesions, anterior uveitis, or cough should be considered for corticosteroid treatment.
- Most patients recover in a reasonably short time frame, but a small group of patients develop chronic disorders that necessitate long-term treatment, and this warrants the use of corticosteroids or additional therapies for more than 5 years.

Cytotoxic or Immunomodulatory drugs

- Patients who experience intolerable adverse reactions to steroids may be prescribed alternative treatments that reduce the reliance on corticosteroids. These are considered second-line treatment options, which include medications such as azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, cyclophosphamide, leflunomide, and hydroxychloroquine. They aim to provide relief from symptoms.
    - However, all these drugs have shown to be less effective than steroids.

Anti Cytokine monoclonal antibodies

- Third line therapies include cytokine-directed treatments. Monoclonal antibodies targeting cytokines offer a specialized approach to regulating cytokine networks, thereby impacting the progression of the disease.
- TNF-α is recognized for its substantial involvement in the development of sarcoidosis-associated granulomas.
- The therapeutic benefits of utilizing anti-TNF antibodies like infliximab or adalimumab have been observed, although the improvements have been modest in nature.

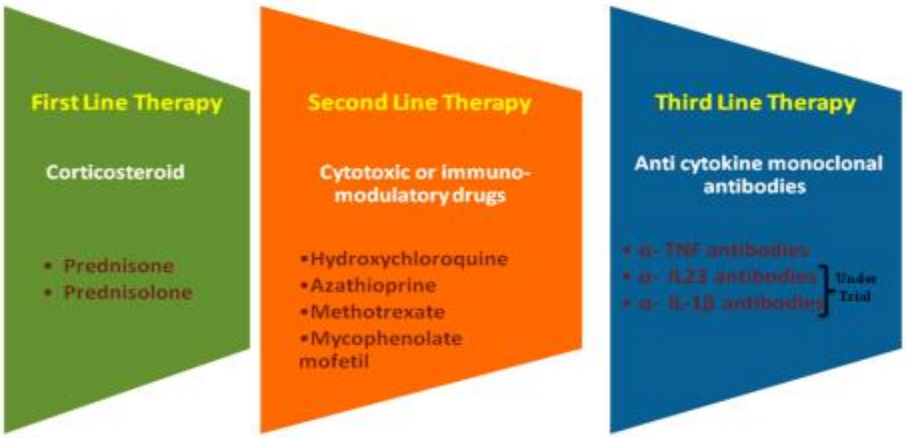


Figure 8. *Therapeutic Options for First, Second, and Third-Line Treatment of Sarcoidosis. Retrieved from Jain et al. (2020)*

1.5 Systematic Reviews & Meta Analyses

The table below tackles a systematic review and meta-analyses issued in 2022 for Sarcoidosis.

Table 12. Systematic Review and Meta-Analysis for Sarcoidosis

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Razaee et al. (2022)[14]	**"Role of anti-tumor necrosis factor-alpha agents in treatment of sarcoidosis: A meta-analysis"**	A systemic meta-analysis was performed that included all studies reporting the therapeutic effects of anti-TNF drugs on patients with pulmonary and extra-pulmonary sarcoidosis, published up to April 10, 2022. This aimed to determine the effectiveness and obtain a deeper understanding of the role of anti-TNF-α in the treatment of sarcoidosis.	Overall treatment success was defined as either no disease progression or improvement in symptoms.	Efficacy of anti-TNF-α agents varied depending on the choice of the agent and the location of the disease. Infliximab is the most common and effective anti-TNF-α agent in various types of sarcoidosis. Adalimumab and etanercept show promising results in extrapulmonary sarcoidosis. While considered a final resort for certain patients, these agents seem to present a viable and beneficial treatment choice. Nevertheless, more comprehensive randomized controlled trials (RCTs) are needed to establish the effectiveness of the anti-TNF-α agent across different forms of sarcoidosis. Additionally, future RCTs should adhere to a standardized definition for determining treatment success, to limit heterogeneity in results.

2	Huntley et al. (2022)[15]	**"Airborne occupational exposures associated with pulmonary sarcoidosis"**	Systemic review and meta-analysis were performed on odds ratios (OR) for specified airborne occupational exposures (aOE) with pulmonary sarcoidosis. This aided in the description and definition of the specific aOE that is associated with and preceding diagnosis of pulmonary sarcoidosis.	Outcomes include the occupational exposures identified preceding diagnosis.	Exposure to occupational factors such as silica, mold, mildew, and pesticides is linked to higher chances of developing pulmonary sarcoidosis. However, uncertainty remains regarding the impact of occupational exposure to metals and common organic dust. The multiple identified exposures suggest that it's highly unlikely for a single antigen to be solely responsible for the onset of sarcoidosis. Instead, it is more likely to result from a complex genetic-environment-immunological interaction. Future research should investigate the intricate connection between genetic elements, airborne occupational exposures, and the mineral composition of sarcoidosis granulomas.

Section 2.0 Drug Therapy

2.1 Corticosteroids

2.1.1 Prednisone

Information on Prednisone is detailed in the table below[16,17]:

Table 13. Prednisone Drug Information

SCIENTIFIC NAME Prednisone	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D86
Drug Class	Corticosteroids
Drug Sub-class	Glucocorticoids
ATC Code	H02AB07
Pharmacological Class (ASHP)	Corticosteroids
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	Initial 20-40 mg once a day; follow-up 5–10 mg once a day to once every other day
Maximum Daily Dose Adults*	60-80mg/day
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	ST, PE
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	

G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): First line treatment for sarcoidosis	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): Initial 20-40 mg once a day for 2-6 weeks, then tapered over 6-18 months.	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** weight gain, mood swings, headache **Most serious:** osteoporosis, hypertension, hyperglycemia, cataracts
Drug Interactions*	**Category X:** • Aldesleukin • BCG (Intravesical) • BCG Vaccine (Immunization) • Brivudine • Cladribine • Dengue Tetravalent Vaccine (Live) • Desmopressin • Disulfiram • Indium 111 Capromab Pendetide • Macimorelin • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Methotrimeprazine • Mifamurtide • MiFEPRIStone • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Ornidazole • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral)

	• Ritlecitinib • Ruxolitinib (Topical) • Secnidazole • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Typhoid Vaccine • Varicella Virus Vaccine • Yellow Fever Vaccine
Special Population	**Older adults:** Use with caution in older adults with the smallest possible effective dose for the shortest duration. **Pediatrics:** May affect growth velocity; growth and development should be routinely monitored in pediatric patients.
Pregnancy	Prednisone ≤10 mg/day is acceptable for use in pregnant patients with rheumatic and musculoskeletal diseases. Higher doses should be tapered to <20 mg/day with the addition of pregnancy compatible immunosuppressants. Stress dosing is not recommended during vaginal delivery.
Lactation	Prednisone and its metabolite, prednisolone, are present in breast milk. Corticosteroids are generally considered acceptable in breastfeeding women when used in usual doses; however, monitoring of the breastfeeding infant is recommended. Prednisone is one of the oral corticosteroids preferred for use in breastfeeding women. Breastfeeding is acceptable for patients with rheumatic and musculoskeletal diseases taking prednisone <20 mg/day.
Contraindications	Hypersensitivity to prednisone or any component of the formulation; administration of live or live attenuated

	vaccines with immunosuppressive doses of prednisone; systemic fungal infections.
Monitoring Requirements	Blood pressure; weight; serum glucose; electrolytes; creatine kinase; growth in pediatric patients; presence of infection, bone mineral density; assess HPA axis suppression (eg, ACTH stimulation test, morning plasma cortisol test, urinary free cortisol test); Hgb, occult blood loss; chest x-ray (at regular intervals during prolonged therapy); IOP with therapy >6 weeks, eye examination.
Precautions	Adrenal suppression: May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children. ***Disease-related concerns:*** Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis [nonspecific]) due to perforation risk. Head injury: Increased mortality was observed in patients receiving high-dose IV methylprednisolone; high-dose corticosteroids should not be used for the management of head injury. Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; effects may be enhanced. Myasthenia gravis: Use may cause transient worsening of myasthenia gravis (MG) (eg, within first 2 weeks of treatment); monitor for worsening MG. Ocular disease: Use with caution in patients with a history of ocular herpes simplex; corneal perforation has

	occurred; do not use in active ocular herpes simplex. Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur. Seizure disorders: Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. Systemic sclerosis: Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis incidence has been observed with corticosteroid use. Monitor BP and renal function in patients with systemic sclerosis treated with corticosteroids. Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients. **Discontinuation of therapy:** Withdraw therapy with gradual tapering of dose.
Black Box Warning	N/A
REMS*	N/A

Prednisone and prednisolone can be used interchangeably for the treatment of sarcoidosis.

Table 14. Prednisone/Prednisolone Conversion Table

Steroid	Equivalent dose (mg)	Glucocorticoid Potency	Mineralocorticoid Potency	Half-Life (hours)
Prednisone	5	4	0.8	12-36
Prednisolone	5	4	0.8	12-36

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of sarcoidosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies

in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for prednisone.**

Table 15. Prednisone HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Prednisone	NICE	No recommendation for this indication
	CADTH	No recommendation for this indication
	HAS	No recommendation for this indication
	IQWIG	No recommendation for this indication
	PBAC	-

CONCLUSION STATEMENT- Prednisone

The use of oral corticosteroids; prednisone most commonly, is recommended as a first line agent for the treatment of sarcoidosis. Initial therapy will be prednisone 20-40mg/day for 2-6 weeks, then gradually tapered over a period of 6-18 months. It is important to know that dosing should be highly individualized, considering disease severity, the specific disorder, and disease manifestations.

2.2 Conventional DMARDs

2.2.1 Methotrexate

Information on Methotrexate is detailed in the table below[16,17]:

Table 16. Methotrexate Drug Information

SCIENTIFIC NAME Methotrexate	
SFDA Classification	Prescription
SFDA Approval	Yes (Off-Label use)
US FDA	Yes (Off-Label use)
EMA	Yes (Off-Label use)
MHRA	Yes (Off-Label use)
PMDA	Yes (Off-Label use)
Indication (ICD-10)	D86
Drug Class	Conventional Disease modifying antirheumatic drugs

Drug Sub-class	Anti-metabolite, immunosuppressive agent
ATC Code	L01BA01
Pharmacological Class (ASHP)	Anti-metabolite
DRUG INFORMATION	
Dosage Form	Tablet, solution for injection
Route of Administration	Oral, intramuscular
Dose (Adult) [DDD]*	**Initial:** 5 to 7.5 mg once weekly (in combination with folic acid). Increase dose gradually (eg, by 2.5 mg/week every 2 weeks) if needed up to 20 mg/week. **Maintenance dose:** 10 to 15 mg/week
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal**: • CrCl >50 mL/minute: No dose adjustment necessary. • CrCl 10 to 50 mL/minute: Administer 50% of dose. • CrCl <10 mL/minute: Avoid use. Anaphylaxis or other severe hypersensitivity reactions: Discontinue methotrexate (immediately) and manage as appropriate. Dermatologic toxicity: Withhold or discontinue methotrexate as appropriate. For severe toxicity (toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme), discontinue methotrexate. GI toxicity (severe): Withhold or discontinue methotrexate as appropriate. For diarrhea, stomatitis, or vomiting, which may lead to dehydration, withhold methotrexate until recovery.

	Infection (serious): Withhold or discontinue methotrexate and manage infection as appropriate. Neurotoxicity & Pulmonary: Withhold or discontinue methotrexate as appropriate.
Prescribing edits*	CU, MD, ST, QL
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Recommended as second-line treatment for sarcoidosis as an adjunct with glucocorticoids. Methotrexate is also used concurrently with folic acid.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in rheumatology and immunosuppressive therapy should prescribe methotrexate.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): Maximum quantity attained is 20mg/week.	
ST (Step Therapy): Second line therapy after glucocorticoid failure.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Nausea/vomiting, fatigue, diarrhea, dizziness, headache **Most severe:** Steven-Johnson's syndrome, pulmonary toxicity (pneumonitis), hepatotoxicity (cirrhosis, fibrosis)
Drug Interactions*	**Category X**: • Abrocitinib • Acitretin • Aminolevulinic Acid (Systemic) • BCG (Intravesical) • BCG Vaccine (Immunization) • Brivudine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dichlorphenamide

	• Dipyrone • Etrasimod • Fexinidazole • Filgotinib • Foscarnet • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Nitrous Oxide • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral) • Ritlecitinib • Ruxolitinib (Topical) • Tacrolimus (Topical) • Talimogene Laherparepvec • Taurursodiol • Tertomotide • Typhoid Vaccine • Varicella Virus Vaccine • Yellow Fever Vaccine
Special Population	N/A
Pregnancy	Methotrexate crosses the placenta. Following exposure during the first trimester, methotrexate may increase the risk of spontaneous abortion, skull anomalies, facial dysmorphism, CNS, limb, and cardiac abnormalities; intellectual impairment may also occur. Intrauterine growth restriction and functional abnormalities may occur following second or third trimester exposure. The use of methotrexate for the treatment of non-neoplastic indications

	including rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis, and psoriasis, is contraindicated in pregnancy.
Lactation	Methotrexate and 7-hydroxymethotrexate are present in breast milk. Methotrexate has the potential to cause serious adverse reactions in the breast-fed infant. Recommendations for use in patients who wish to breastfeed vary. According to the manufacturer, breastfeeding should be discontinued during treatment and for 1 week after the final methotrexate dose.
Contraindications	• History of severe hypersensitivity (anaphylaxis) • Breastfeeding • Pregnancy • Alcohol use disorder • Alcoholic liver disease or other chronic liver disease • Immunodeficiency syndromes (overt or laboratory evidence) • Preexisting blood dyscrasias (eg, bone marrow hypoplasia, leukopenia, thrombocytopenia, significant anemia).
Monitoring Requirements	CBC with differential and platelets, serum creatinine, and LFTs: Baseline and every 2 to 4 weeks for 3 months after initiation or following dose increases, then every 8 to 12 weeks during 3 to 6 months of treatment, followed by every 12 weeks beyond 6 months of treatment; monitor more frequently if clinically indicated. Dermatologic toxicity, complications of hematologic toxicity, signs, and symptoms of infection (during and after

	treatment); signs and symptoms of pneumonitis (particularly dry, nonproductive cough; fever, dyspnea, hypoxemia, or pulmonary infiltrate); evaluate pregnancy status prior to use in patients who could become pregnant.
Precautions	Infections: Use methotrexate with extreme caution in patients with an active infection. Renal impairment: Dosing adjustment may be required. ***Concurrent drug therapy issues:*** Nonsteroidal anti-inflammatory drugs: Do not administer nonsteroidal anti-inflammatory drugs (NSAIDs) prior to or during high dose methotrexate therapy. Proton pump inhibitors: Concomitant use of proton pump inhibitors with methotrexate (primarily high-dose methotrexate) may elevate and prolong serum methotrexate levels and metabolite (hydroxy methotrexate) levels (based on case reports and pharmacokinetic studies). May lead to toxicities; use with caution. Vaccines: Immunization may be ineffective during methotrexate treatment. Immunization with live vaccines is not recommended.
Black Box Warning	**Methotrexate oral:** • Severe hypersensitivity • Pregnancy **Methotrexate injection:** • Experienced physician (injection): Only experienced physicians should inject methotrexate. • Hypersensitivity • Pregnancy • Bone marrow suppression

	• Renal impairment • Hepatotoxicity • Pneumonitis • GI toxicity • Secondary malignancy • Dermatologic toxicity • Opportunistic infections
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of sarcoidosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for methotrexate.**

Table 17. Methotrexate HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Methotrexate	NICE	No recommendation for this indication
	CADTH	No recommendation for this indication
	HAS	No recommendation for this indication
	IQWIG	No recommendation for this indication
	PBAC	-

CONCLUSION STATEMENT- Methotrexate

The use of methotrexate is recommended as a second line agent therapy for glucocorticoid-refractory sarcoidosis or in patients who require glucocorticoid-sparing therapy. It is initiated at a dose of 5 to 7.5 mg once weekly (in combination with folic acid). Dose is increased gradually (e.g., by 2.5 mg/week every 2 weeks) if needed up to 20 mg/week. Maintenance dose is 10-15mg/week. The duration of methotrexate therapy for sarcoidosis patients can vary widely depending on individual factors, the severity of the disease, and how well the medication is controlling symptoms and inflammation.

2.2.2 Azathioprine

Information on Azathioprine is detailed in the table below[16,17]:

Table 18. Azathioprine Drug Information

SCIENTIFIC NAME Azathioprine	
SFDA Classification	Prescription
SFDA Approval	Yes (Off-Label use)
US FDA	Yes (Off-Label use)
EMA	Yes (Off-Label use)
MHRA	Yes (Off-Label use)
PMDA	Yes (Off-Label use)
Indication (ICD-10)	D86
Drug Class	Conventional Disease modifying antirheumatic drugs
Drug Sub-class	Immunosuppressive agent
ATC Code	L04AX01
Pharmacological Class (ASHP)	Conventional Disease modifying antirheumatic drugs
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	**Initial:** 25 to 50 mg once daily; increase daily dose by 50 mg every 2 to 4 weeks as tolerated to goal **Maintenance:** 2 mg/kg once daily
Maximum Daily Dose Adults*	250mg
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal**: • CrCl ≥30 mL/minute: Initial: No dosage adjustment necessary. • CrCl 10 to <30 mL/minute: Initial: Administer 75% to 100% of the usual indication-specific dose.

	• CrCl <10 mL/minute: Initial: Administer 50% to 100% of the usual indication-specific dose. **Hepatic**: None Rapid WBC count decrease, persistently low WBC count, or serious infection: Reduce dose or temporarily withhold treatment. Severe toxicity (hematologic or other) in kidney transplantation: May require discontinuation. Hepatic sinusoidal obstruction syndrome (SOS; veno-occlusive disease): Permanently discontinue azathioprine.
Prescribing edits*	CU, MD, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Recommended as second-line treatment for sarcoidosis as an adjunct with glucocorticoids.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in rheumatology and immunosuppressive therapy should prescribe azathioprine.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Second line therapy after glucocorticoid failure.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Nausea/vomiting, fatigue, leukopenia **Most severe:** Hepatotoxicity, bone marrow suppression (thrombocytopenia, anemia, leukopenia), infection
Drug Interactions*	**Category X**: • Abrocitinib • Adenovirus (Types 4, 7) Vaccine • Baricitinib • BCG (Intravesical)

	• BCG Vaccine (Immunization) • Brivudine • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Ebola Zaire Vaccine (Live) • Etrasimod • Febuxostat • Fexinidazole • Filgotinib • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mercaptopurine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Ritlecitinib • Rotavirus Vaccine • Ruxolitinib (Topical) • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine

	• Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine • Zoster Vaccine (Live/Attenuated)
Special Population	**Patients with systemic lupus erythematosus (SLE) undergoing hip or knee replacement surgery:** Patients with ***severe*** SLE (referring to patients with severe organ manifestations such as nephritis) should not interrupt therapy when undergoing hip or knee replacement surgery. For patients with SLE ***without*** severe disease**,** hold azathioprine for at least 1 week prior to surgery to reduce infection risk; therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk).
Pregnancy	Azathioprine crosses the placenta. Adverse events, including congenital anomalies, immunosuppression, hematologic toxicities (lymphopenia, pancytopenia), and intrauterine growth retardation have been observed in case reports following maternal use in kidney allograft recipients. Some of these adverse outcomes may be dose-related or a result of maternal disease. Although use for rheumatoid arthritis in pregnant patients is contraindicated by the manufacturer, available guidelines suggest that use of azathioprine may be acceptable for the management of rheumatic and musculoskeletal diseases during pregnancy.

Lactation	The azathioprine metabolite 6-mercaptopurine (6-MP) is present in breast milk. Recommendations for breastfeeding during azathioprine therapy vary. Due to the potential for serious adverse reactions in the infant, breastfeeding is not recommended by the manufacturer. The World Health Organization also recommends breastfeeding be avoided during maternal treatment.
Contraindications	• Hypersensitivity to azathioprine or any component of the formulation.
Monitoring Requirements	CBC with differential and platelets (weekly during first month, twice monthly for months 2 and 3, then monthly thereafter; monitor more frequently with dosage modifications or as clinically indicated), total bilirubin, LFTs (every 3 months), CrCl, monitor for signs/symptoms of infection and malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss). Azathioprine has been associated with skin cancer with long-term use after kidney transplantation. Patients taking azathioprine for a prolonged time should avoid sun exposure and be monitored for skin cancer regularly.
Precautions	***Disease-related concerns:*** Hepatic impairment: Use with caution in patients with hepatic impairment. Renal impairment: Use with caution in patients with renal impairment. ***Concurrent drug therapy issues:*** Vaccines: Immune response to vaccines may be diminished. Toxicity or adverse reactions to live vaccines may be

	enhanced (depending on the azathioprine dose). ***Other warnings/precautions:*** Discontinuation of therapy: Myasthenia gravis: Abrupt cessation of this or any immunosuppressant, especially in clinically unstable individuals, may result in rapid deterioration of myasthenic symptoms and possibly myasthenic crisis.
Black Box Warning	**Malignancy:** Prolonged chronic use of azathioprine.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of sarcoidosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for azathioprine.**

Table 19. Azathioprine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Azathioprine	NICE	No recommendation for this indication
	CADTH	No recommendation for this indication
	HAS	No recommendation for this indication
	IQWIG	No recommendation for this indication
	PBAC	-

CONCLUSION STATEMENT- Azathioprine

The use of azathioprine is recommended as a second line agent therapy for glucocorticoid-refractory sarcoidosis or in patients who require glucocorticoid-sparing therapy. It is initiated at a dose of 25 to 50mg once daily. The dose is increased gradually by 50mg every 2-4 weeks as tolerated to goal. Maintenance dose is 2mg/kg once daily. The duration of azathioprine therapy for sarcoidosis patients can vary widely depending on individual factors, the severity of the disease, and how well the medication is controlling symptoms and inflammation.

2.2.3 Leflunomide

Information on Leflunomide is detailed in the table below[16,17]:

Table 20. Leflunomide Drug Information

SCIENTIFIC NAME Leflunomide	
SFDA Classification	Prescription
SFDA Approval	Yes (Off-Label use)
US FDA	Yes (Off-Label use)
EMA	Yes (Off-Label use)
MHRA	Yes (Off-Label use)
PMDA	Yes (Off-Label use)
Indication (ICD-10)	D86
Drug Class	Conventional Disease modifying antirheumatic drugs
Drug Sub-class	Immunosuppressive agent
ATC Code	L04AA13
Pharmacological Class (ASHP)	Conventional Disease modifying antirheumatic drugs
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	10-20mg once a day
Maximum Daily Dose Adults*	Not established
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal**: No adjustment necessary. **Hepatic**: Not recommended for use in patients with preexisting liver disease or those with baseline ALT >2 times ULN; monitor liver function closely. Use is contraindicated in severe hepatic impairment. **Hepatotoxicity:** ALT elevations >3 times ULN: Discontinue drug therapy and investigate probable cause; if leflunomide-induced, initiate

	accelerated drug elimination process and monitor liver tests weekly until normalized.
Prescribing edits*	CU, MD, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Recommended as second-line treatment for sarcoidosis as an adjunct with glucocorticoids.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in rheumatology and immunosuppressive therapy should prescribe leflunomide	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Second line therapy after glucocorticoid failure.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Nausea, diarrhea, alopecia, headache **Most severe:** Steven-Johnson's syndrome, hepatotoxicity, peripheral neuropathy, sensorimotor neuropathy
Drug Interactions*	**Category X**: • Abrocitinib • Adenovirus (Types 4, 7) Vaccine • Amodiaquine • Asunaprevir • BCG (Intravesical) • BCG Vaccine (Immunization) • Brivudine • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Ebola Zaire Vaccine (Live) • Elagolix • Elagolix, Estradiol, and Norethindrone

	• Elbasvir and Grazoprevir • Etrasimod • Filgotinib • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • PAZOPanib • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Revefenacin • Ritlecitinib • Rotavirus Vaccine • Ruxolitinib (Topical) • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Taurursodiol • Teriflunomide • Tertomotide • Topotecan Depends on Route • Typhoid Vaccine • Varicella Virus Vaccine • Voxilaprevir • Yellow Fever Vaccine • Zavegepant • Zoster Vaccine (Live/Attenuated)
Special Population	N/A

Pregnancy	Leflunomide is contraindicated for use in pregnant women because of the potential for fetal harm.
Lactation	It is not known whether leflunomide is present in breast milk. Due to the potential for serious adverse reactions in the breast-fed infant, the manufacturer recommends discontinuing breastfeeding during leflunomide treatment. Leflunomide is not recommended for use in patients with rheumatic and musculoskeletal diseases who are breastfeeding.
Contraindications	• Known hypersensitivity (including anaphylaxis) to leflunomide or any component of the formulation. • Severe hepatic impairment • Concomitant treatment with teriflunomide • Pregnant females.
Monitoring Requirements	Pregnancy test to rule out pregnancy prior to initiating therapy (in females of reproductive potential); baseline evaluation for tuberculosis (TB) disease (active TB) and screen patients for TB infection (latent TB); blood pressure (baseline and periodically thereafter); signs/symptoms of severe infection or pulmonary symptoms (eg, cough, dyspnea); CBC (WBC, platelet count, hemoglobin, or hematocrit) at baseline and monthly during the initial 6 months of treatment; if stable, monitoring frequency may be decreased to every 6 to 8 weeks thereafter; hepatic function (transaminases) at least monthly for the first 6 months of treatment, then every 6 to 8 weeks thereafter (discontinue if ALT >3 times ULN, treat with accelerated elimination procedure, and

	monitor liver function at least weekly until normal).
Precautions	***Concerns related to adverse effects:*** Malignancy: Chronic use may increase the risk of malignancies (lymphoproliferative disorders); development and course are not fully defined. ***Disease-related concerns:*** Immunodeficiency or infection: Use caution in patients with a history of new/recurrent infections, with conditions that predispose them to infections, or with chronic, latent, or localized infections. Renal impairment: Use with caution in patients with renal impairment. ***Concurrent drug therapy issues:*** Immunizations: Vaccination with live vaccines is not recommended; consider the long elimination half-life of the leflunomide active metabolite (eg, teriflunomide) when considering live vaccine administration after leflunomide discontinuation. ***Other warnings/precautions:*** Drug elimination procedure: Due to slow elimination and variations in clearance, it may take up to 2 years to reach low levels of leflunomide metabolite (eg, teriflunomide) serum concentrations. An accelerated drug elimination procedure using cholestyramine or activated charcoal is recommended when a more rapid elimination is needed. Initiate accelerated elimination procedures in patients when a severe adverse reaction occurs (eg, severe dermatologic reaction, suspected liver injury, bone marrow suppression, serious infection,

	interstitial lung disease, peripheral neuropathy, suspected hypersensitivity) or if pregnancy occurs during treatment.
Black Box Warning	• Embryofetal toxicity • Hepatotoxicity
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of sarcoidosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Leflunomide.**

Table 21. Leflunomide HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Leflunomide	NICE	No recommendation for this indication
	CADTH	No recommendation for this indication
	HAS	No recommendation for this indication
	IQWIG	No recommendation for this indication
	PBAC	-

CONCLUSION STATEMENT- Leflunomide

The use of leflunomide is recommended as a second line agent therapy for glucocorticoid-refractory sarcoidosis or in patients who require glucocorticoid-sparing therapy. It is maintained at a dose of 10-20mg once a day. The duration of leflunomide therapy for sarcoidosis patients can vary widely depending on individual factors, the severity of the disease, and how well the medication is controlling symptoms and inflammation.

2.2.4 Mycophenolate Mofetil

Information on Mycophenolate Mofetil is detailed in the table below[16,17]:

Table 22. Mycophenolate Mofetil Drug Information

SCIENTIFIC NAME Mycophenolate Mofetil	
SFDA Classification	Prescription
SFDA Approval	Yes (Off-Label use)
US FDA	Yes (Off-Label use)
EMA	Yes (Off-Label use)
MHRA	Yes (Off-Label use)
PMDA	Yes (Off-Label use)
Indication (ICD-10)	D86
Drug Class	Conventional Disease modifying antirheumatic drugs
Drug Sub-class	Immunosuppressive agent
ATC Code	L04AA06
Pharmacological Class (ASHP)	Conventional Disease modifying antirheumatic drugs
DRUG INFORMATION	
Dosage Form	Tablet or Capsule
Route of Administration	Oral
Dose (Adult) [DDD]*	500-1500mg Twice a day **Note: Mycophenolate mofetil and mycophenolate sodium doses aren't equivalent. Conversion to equimolar doses is necessary. Mycophenolate mofetil 500 mg is considered equivalent to mycophenolate sodium 360 mg**
Maximum Daily Dose Adults*	3g/day
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal**: eGFR <25 mL/minute/1.73 m^2: No initial dosage adjustment necessary; use with caution. For nontransplant indications,

	consider limiting dose to mycophenolate mofetil 1 g twice daily or mycophenolate sodium delayed release 720 mg twice daily, or monitor closely for adverse effects such as leukopenia from increased MPA exposure. **Hepatic**: No adjustment needed **Neutropenia** (ANC <1.3 x 10^3/mcL): Dosing should be interrupted, or the dose reduced, appropriate diagnostic tests performed, and patients managed appropriately
Prescribing edits*	CU, MD, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): Recommended as second-line treatment for sarcoidosis as an adjunct with glucocorticoids.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in rheumatology and immunosuppressive therapy should prescribe mycophenolate mofetil	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Second line therapy after glucocorticoid failure.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Edema, tachycardia, rash, GI upset **Most severe:** Acute inflammatory syndrome, bone marrow suppression (anemia, leukopenia), increased infections
Drug Interactions*	**Category X**: • Abrocitinib • Adenovirus (Types 4, 7) Vaccine • Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Brivudine

	• Cholera Vaccine • Cholestyramine Resin • Cladribine • Colesevelam • Colestipol • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Ebola Zaire Vaccine (Live) • Etrasimod • Filgotinib • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Ritlecitinib • Rotavirus Vaccine • Ruxolitinib (Topical) • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine

	• Zoster Vaccine (Live/Attenuated)
Special Population	Patients with systemic lupus erythematosus (SLE) undergoing hip or knee replacement surgery: Patients with ***severe*** SLE (referring to patients with severe organ manifestations such as nephritis) should not interrupt therapy when undergoing hip or knee replacement surgery. For patients with SLE ***without*** severe disease**,** hold mycophenolate for at least 1 week prior to surgery to reduce infection risk; therapy can be restarted once surgical wound shows evidence of healing (eg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk)
Pregnancy	**Black box warning:** Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Avoid if safer treatment options are available.
Lactation	It is not known if mycophenolate is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. Adverse events were not observed in 7 infants born between 34- and 40-weeks' gestation and exposed to mycophenolate via breast milk for up to 14 months. However, due to the long half-life and lack of information related to mycophenolate and breastfeeding, breastfeeding is not recommended by some guidelines.

Contraindications	• Hypersensitivity to mycophenolate mofetil, mycophenolic acid, mycophenolate sodium, or any component of the formulation. • Pregnancy
Monitoring Requirements	Complete blood count (weekly for first month, twice monthly during months 2 and 3, then monthly thereafter through the first year); renal and liver function; signs and symptoms of organ rejection; signs and symptoms of infection or reactivated viral (including reactivation of HBV or HCV), or opportunistic infections; neurological symptoms (eg, hemiparesis, confusion, cognitive deficiencies, ataxia) suggestive of progressive multifocal leukoencephalopathy; in patients with hepatitis B or hepatitis C, monitor for signs of viral reactivation; monitor for signs/symptoms (eg, fever, arthralgias, arthritis, muscle pain, proinflammatory markers) suggestive of acute inflammatory syndrome; pregnancy test (sensitivity of ≥25 milliunits/mL; immediately prior to initiation and 8 to 10 days later in patients who may become pregnant, followed by repeat tests during therapy); monitor skin (for lesions suspicious of skin cancer); monitor for signs of lymphoma; monitor for signs of pure red cell aplasia or autoimmune hemolytic anemia.
Precautions	***Concerns related to adverse effects:*** CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness (eg, operating machinery, driving).

	Disease-related concerns: Gastrointestinal disorders: Use caution in patients with active serious digestive system disease; patients with active peptic ulcers were not included in clinical studies. Hypoxanthine-guanine phosphoribosyltransferase deficiency: Theoretically, use should be avoided in patients with the rare hereditary deficiency of hypoxanthine-guanine phosphoribosyltransferase (such as Lesch-Nyhan or Kelley-Seegmiller syndrome). Renal impairment: Use with caution in patients with renal impairment as toxicity may be increased; may require dosage adjustment in severe impairment. **Non-interchangeability of dosage forms:** Mycophenolate sodium and mycophenolate mofetil should not be used interchangeably without health care provider supervision because the rate of absorption following the administration of these two products is not equivalent.
Black Box Warning	• Experienced physician (immunotherapy and organ transplant) • Malignancies • Serious Infections • Embryo-fetal Toxicity
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of sarcoidosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency

in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Mycophenolate Mofetil.**

Table 23. Mycophenolate Mofetil HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Mycophenolate Mofetil	NICE	No recommendation for this indication
	CADTH	No recommendation for this indication
	HAS	No recommendation for this indication
	IQWIG	No recommendation for this indication
	PBAC	-

CONCLUSION STATEMENT- Mycophenolate Mofetil

The use of Mycophenolate mofetil is recommended as a second line agent therapy for glucocorticoid-refractory sarcoidosis or in patients who require glucocorticoid-sparing therapy. It is maintained at a dose of 500-1500mg twice a day The duration of mycophenolate therapy for sarcoidosis patients can vary widely depending on individual factors, the severity of the disease, and how well the medication is controlling symptoms and inflammation.

2.2.5 Hydroxychloroquine

Information on Hydroxychloroquine is detailed in the table below[16,17]:

Table 24. Hydroxychloroquine Drug Information

SCIENTIFIC NAME Hydroxychloroquine	
SFDA Classification	Prescription
SFDA Approval	Yes (Off-Label use)
US FDA	Yes (Off-Label use)
EMA	Yes (Off-Label use)
MHRA	Yes (Off-Label use)
PMDA	Yes (Off-Label use)
Indication (ICD-10)	D86
Drug Class	Conventional Disease modifying antirheumatic drugs
Drug Sub-class	Anti-malarial, aminoquinoline
ATC Code	P01BA02

Pharmacological Class (ASHP)	Conventional Disease modifying antirheumatic drugs
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral
Dose (Adult) [DDD]*	200 to 400 mg daily as a single daily dose or in 2 divided doses for ≥3 months to evaluate for efficacy; if there is satisfactory improvement, may consider gradual tapering and discontinuation if response is maintained
Maximum Daily Dose Adults*	Due to the risk of retinal toxicity, most patients should **not** receive a daily dose >5 mg/kg/day using actual body weight **or** 400 mg, whichever is lower.
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal**: None **Hepatic**: None
Prescribing edits*	AGE, CU, ST
AGE (Age Edit): Cannot be used in children <6 years of age.	
CU (Concurrent Use Edit): Recommended as second-line treatment for sarcoidosis as an adjunct with glucocorticoids.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Second line therapy after glucocorticoid failure.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** Nausea, GI upset, rash, headache **Most severe:** Retinopathy (loss of vision), cardiomyopathy, hypoglycemia
Drug Interactions*	**Category X**: • Cimetidine • Mefloquine

	• Remdesivir
Special Population	Glucose-6-phosphate dehydrogenase deficiency: Although the manufacturer's labeling recommends hydroxychloroquine be used with caution in patients with G6PD deficiency due to a potential for hemolytic anemia, there are limited data to support this risk. Many experts consider hydroxychloroquine, when given in usual therapeutic doses to the World Health Organization Class II and III G6PD deficient patients, to probably be safe. In a retrospective chart review, no incidence of hemolytic anemia was found among the 11 patients identified with G6PD deficiency receiving hydroxychloroquine therapy, despite >700 months of exposure (all patients were African American and located in the United States).
Pregnancy	Can be taken safely in pregnancy
Lactation	Hydroxychloroquine and the desethylchloroquine metabolite are present in breast milk. In general, breastfeeding is considered acceptable when the Relevant infant dose (RID) is <10%
Contraindications	• Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivatives, or any component of the formulation. • Preexisting retinopathy • Use in children <6 years or weighing <35 kg
Monitoring Requirements	Ocular exams periodically depending on age. CBC (with differential), liver function, and renal function at baseline and

	periodically during therapy; blood glucose (if symptoms of hypoglycemia occur); muscle strength (especially proximal, as a symptom of neuromyopathy) during long-term therapy; in patients at elevated risk of QTc prolongation, monitor ECG and serum electrolytes at baseline and as clinically indicated and correct any electrolyte imbalances to mitigate the risk of developing torsades de pointes; certain findings may require not initiating or discontinuing therapy. Serum concentration monitoring is recommended in the treatment of fever.
Precautions	***Disease-related concerns:*** Hepatic impairment: Use with caution in patients with hepatic impairment; dosage reduction may be needed. Myasthenia gravis: Use with caution in patients with myasthenia gravis; may exacerbate condition. Porphyria: Avoid use in patients with porphyria unless benefits outweigh risks; may exacerbate or precipitate disease. Use in patients with porphyria cutanea tarda (off-label use) has resulted in hepatotoxicity and presented with marked elevations in transaminases within days to one month after initiation of treatment. In some patients, porphyria cutanea tarda was diagnosed after hepatotoxicity occurred when hydroxychloroquine was used for an approved indication. Psoriasis: Avoid use in patients with psoriasis unless benefits outweigh risks; may exacerbate or precipitate disease.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of sarcoidosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Hydroxychloroquine.**

Table 25. Hydroxychloroquine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Hydroxychloroquine	NICE	No recommendation for this indication
	CADTH	No recommendation for this indication
	HAS	No recommendation for this indication
	IQWIG	No recommendation for this indication
	PBAC	-

CONCLUSION STATEMENT- Hydroxychloroquine

The use of Hydroxychloroquine is recommended as a second line agent therapy for glucocorticoid-refractory sarcoidosis or in patients who require glucocorticoid-sparing therapy. It is indicated at a dose of 200 to 400 mg daily as a single daily dose or in 2 divided doses for ≥3 months to evaluate for efficacy; if there is satisfactory improvement, may consider gradual tapering and discontinuation if response is maintained.

2.3 Biologic DMARDs

2.3.1 Infliximab

Information on Infliximab is detailed in the table below[16,17]:

Table 26. Infliximab Drug Information

SCIENTIFIC NAME Infliximab	
SFDA Classification	Prescription
SFDA Approval	Yes (Off-Label use)
US FDA	Yes (Off-Label use)
EMA	Yes (Off-Label use)
MHRA	Yes (Off-Label use)

PMDA	Yes (Off-Label use)
Indication (ICD-10)	D86
Drug Class	Biological Disease modifying antirheumatic drugs
Drug Sub-class	Tumor necrosis factor blocking agent
ATC Code	L04AB02
Pharmacological Class (ASHP)	Tumor necrosis factor blocking agent
DRUG INFORMATION	
Dosage Form	Powder for concentrate for solution for infusion
Route of Administration	Intravenous
Dose (Adult) [DDD]*	**Initial: IV:** 3 to 5 mg/kg at weeks 0, 2, and. **Maintenance: IV:** 3 to 5 mg/kg every 4 to 8 weeks thereafter. The optimal frequency and duration of therapy are not known and must be individualized based on response; after a stable response is achieved (eg, after ≥6 to 12 months of therapy), may consider gradually prolonging the dosing interval (eg, up to every 12 weeks) or reducing the dose and discontinue if response remains adequate after although approaches vary. Premedication with antihistamines (H_1-antagonist +/- H_2-antagonist), acetaminophen, and/or corticosteroids may be considered to prevent and/or manage infusion-related reactions.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal**: None **Hepatic**: **AST/ALT ≥ 5 times Upper normal limit:** Discontinue infliximab therapy and consult hepatologist ([Ref]). May be indicative of infliximab-induced

	autoimmune hepatitis, which may cause severe liver injury and can be fatal or lead to liver transplantation.
Prescribing edits*	AGE, CU, MD, PA, ST
AGE (Age Edit): Not recommended in children < 3 years of age.	
CU (Concurrent Use Edit): Recommended as third-line agent for the treatment refractory sarcoidosis as an adjunct with glucocorticoids and/or methotrexate (or other conventional DMARDs).	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in rheumatology, immunology, dermatology should prescribe and administer infliximab	
PA (Prior Authorization): Infliximab should be used as adjunctive therapy in patients in whom treatment goals have not been met despite glucocorticoids and other immunosuppressant therapy (eg, methotrexate); Use in combination with glucocorticoids and/or methotrexate may prevent infliximab autoantibody formation. It is initiated at a dose of **3 to 5 mg/kg in weeks 0, 2, and** 6. It is maintained at **3 to 5 mg/kg IV every 4 to 8 weeks thereafter. The optimal frequency and duration of therapy are not known and must be individualized based on response;**	
QL (Quantity Limit): N/A	
ST (Step Therapy): Third line therapy after glucocorticoid and methotrexate failure.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** GI upset, infusion related reactions, infection, headache **Most severe:** Hepatotoxicity, reactivation of hepatitis B, demyelinating disease (multiple sclerosis, Guilliane-barre syndrome)
Drug Interactions*	**Category X**: • Abatacept • Abrocitinib • Adalimumab • Adenovirus (Types 4, 7) Vaccine • Anakinra • Anifrolumab • Baricitinib

	• BCG (Intravesical) • BCG Vaccine (Immunization) • Bimekizumab • Brivudine • Brodalumab • Canakinumab • Certolizumab Pegol • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Ebola Zaire Vaccine (Live) • Etanercept • Etrasimod • Filgotinib • Golimumab • Guselkumab • Influenza Virus Vaccine (Live/Attenuated) • Ixekizumab • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Rilonacept • Risankizumab • Ritlecitinib • RiTUXimab

	• Rotavirus Vaccine • Ruxolitinib (Topical) • Sarilumab • Secukinumab • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide
Special Population	Patients with rheumatic musculoskeletal disease undergoing hip or knee replacement surgery: Hold biologic disease-modifying antirheumatic drugs prior to surgery and plan surgery after the next dose is due.
Pregnancy	Infliximab may be continued during the first and second trimesters of pregnancy in patients with rheumatic and musculoskeletal diseases. Use should be discontinued during the third trimester in patients with well-controlled disease. Newborn exposure should be considered if treatment cannot be discontinued due to active disease.
Lactation	According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. However, tumor necrosis factor alpha (TNFα)-blocking agents, including infliximab, are considered compatible with breastfeeding.
Contraindications	• Previous severe hypersensitivity (eg, anaphylaxis, hypotension, serum sickness) to infliximab, murine proteins, or any component of the formulation

	• Doses >5 mg/kg in patients with moderate or severe heart failure (NYHA class III/IV). • Severe infections (eg, sepsis, abscesses, tuberculosis, and opportunistic infections).
Monitoring Requirements	CBC with differential (baseline); complete metabolic panel (baseline); tuberculosis (TB) screening prior to initiating and during therapy (chest Xray if TB positive); hepatitis b virus (HBV)/hepatitis C virus screening prior to initiating (all patients), HBV carriers (during and for several months following therapy); HIV screening (baseline); LFTs (baseline and periodically during therapy; more frequently in patients with elevated LFTs; discontinue if >5 times ULN); signs/symptoms of infection, heart failure, hypersensitivity reaction, lupus-like syndrome, malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss); signs and symptoms suggestive of blood dyscrasias (eg, persistent fevers). During infusion, if reaction is noted, monitor vital signs every 2 to 10 minutes, depending on reaction severity, until normal. If a serious reaction occurs (eg, cardiovascular or cerebrovascular reaction), discontinue the infusion. Monitor improvement of symptoms and physical function assessments.
Precautions	***Concerns related to adverse effects:*** Antibody formation: Formation of neutralizing anti-drug antibodies may occur with biologic tumor necrosis factor (TNF) inhibitors and may be associated with loss of efficacy.

	Cardiovascular/cerebrovascular reactions during and following infusion: Cerebrovascular accidents, MI (some fatal), hypotension, hypertension, and arrhythmias have been reported within 24 hours of infusion. Transient vision loss has also been reported during or within 2 hours of infusion. Discontinue therapy if a serious reaction occurs. Hematologic disorders: Hematologic toxicities (eg, leukopenia, neutropenia, thrombocytopenia, pancytopenia) have been reported (could be fatal). ***Disease-related concerns:*** Active infection: Do not initiate infliximab therapy in patients with an active infection, including clinically important localized infection. HIV: Use with caution in HIV-positive patients; TNF-α inhibitors may be appropriate in patients receiving highly active antiretroviral therapy, provided they have normal CD4 counts, no viral load, and no recent opportunistic infections. Seizure disorders: Use with caution in patients with a history of seizures; discontinue if significant CNS adverse reactions develop. Solid organ transplant: Consider holding infliximab prior to living donor solid organ transplant (eg, hold IV infliximab for at least 4 weeks; hold SUBQ infliximab for 1 week). Immunizations: Live vaccines should not be given concurrently.
Black Box Warning	• Serious infections • Malignancy
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of sarcoidosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Infliximab.**

Table 27. Infliximab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Infliximab	NICE[18]	**Conditional Positive Recommendation – January 2017** The studies included 155 cases of refractory extrapulmonary sarcoidosis, primarily in the nervous system (34%) or skin (25%), who were treated with infliximab. Of these cases, extrapulmonary sarcoidosis resolved in a third and improved in around half. However, observational studies are subject to bias and confounding and have many limitations affecting their application to clinical practice. According to experts who contributed to this review of evidence, infliximab could be considered as a potential treatment for individuals with severe, treatment-resistant extrapulmonary sarcoidosis, especially cases involving the skin or nervous system. This may apply to individuals experiencing significant disability or disfigurement, or whose life expectancy is expected to be shortened.
	CADTH	No recommendation for this indication
	HAS	No recommendation for this indication
	IQWIG	No recommendation for this indication
	PBAC	-

CONCLUSION STATEMENT- Infliximab

The use of infliximab is recommended as a third-line agent for the treatment refractory sarcoidosis as an adjunct with glucocorticoids and/or methotrexate (or other conventional DMARDs). It is initiated at a dose of 3 to 5 mg/kg in weeks 0, 2, and 6. It is maintained at 3 to 5 mg/kg IV every 4 to 8 weeks thereafter. The optimal

frequency and duration of therapy should be individualized based on response. It is also conditionally recommended by NICE. Its use is limited by the increased infection risk and hepatotoxicity.

2.3.2 Adalimumab

Information on Adalimumab is detailed in the table below[16,17]:

Table 28. Adalimumab Drug Information

SCIENTIFIC NAME Adalimumab	
SFDA Classification	Prescription
SFDA Approval	Yes (Off-Label use)
US FDA	Yes (Off-Label use)
EMA	Yes (Off-Label use)
MHRA	Yes (Off-Label use)
PMDA	Yes (Off-Label use)
Indication (ICD-10)	D86
Drug Class	Biological Disease modifying antirheumatic drugs
Drug Sub-class	Tumor necrosis factor blocking agent
ATC Code	L04AB04
Pharmacological Class (ASHP)	Tumor necrosis factor blocking agent
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Subcutaneous
Dose (Adult) [DDD]*	**Initial:** No optimal dosing strategy; 40 to 120 mg subcutaneously on week 0, 40 to 80 mg on week 1, and 40 mg on week 2 **Maintenance: IV:** 40 mg SQ every 1 to 2 weeks. The optimal frequency and duration of therapy are not known and must be individualized based on response; after a stable response is achieved (eg, after 6 months), one option is to gradually prolong the dosing interval (eg, to every 2 weeks)

	and discontinue after 3 months if response remains adequate.
Maximum Daily Dose Adults*	Not established
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal**: None **Hepatic:** None
Prescribing edits*	AGE, CU, MD, PA, ST
AGE (Age Edit): Should not be used in children < 2 years of age.	
CU (Concurrent Use Edit): Recommended as third-line agent for the treatment refractory sarcoidosis as an adjunct with glucocorticoids and/or methotrexate (or other conventional DMARDs).	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in rheumatology, immunology, dermatology should prescribe and administer adalimumab	
PA (Prior Authorization): Adalimumab should be used as adjunctive therapy in patients in whom treatment goals have not been met despite glucocorticoids and other immunosuppressant therapy (e.g., methotrexate). Adalimumab is maintained at a dose of 40 mg SQ every 1 to 2 weeks**. The optimal frequency and duration of therapy are not known and must be individualized based on response;**	
QL (Quantity Limit): N/A	
ST (Step Therapy): Third line therapy after glucocorticoid and methotrexate failure.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**(Less toxic than infliximab)** **Most common:** Injection site reactions, skin rash, headache **Most severe:** Hepatotoxicity, reactivation of hepatitis B, demyelinating disease (multiple sclerosis, Guilliane-barre syndrome)
Drug Interactions*	**Category X**: • Abatacept • Abrocitinib • Adenovirus (Types 4, 7) Vaccine

	• Anakinra • Anifrolumab • Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Brivudine • Canakinumab • Certolizumab Pegol • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Ebola Zaire Vaccine (Live) • Etanercept • Etrasimod • Filgotinib • Golimumab • InFLIXimab • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Rilonacept • Ritlecitinib • RiTUXimab • Rotavirus Vaccine • Ruxolitinib (Topical) • Sarilumab

	• Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tocilizumab • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Vedolizumab • Yellow Fever Vaccine • Zoster Vaccine (Live/Attenuated)
Special Population	Patients with rheumatic musculoskeletal disease undergoing hip or knee replacement surgery: Hold biologic disease-modifying antirheumatic drugs prior to surgery and plan surgery after the next dose is due.
Pregnancy	Based on available data, an increased risk of adverse maternal or fetal effects has not been observed following adalimumab exposure during pregnancy.
Lactation	According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. However, tumor necrosis factor alpha (TNFα)-blocking agents, including infliximab, are considered compatible with breastfeeding.
Contraindications	• Previous severe hypersensitivity (eg, anaphylaxis, hypotension, serum sickness) to adalimumab or any component of the formulation • Moderate-to-severe heart failure (NYHA class III/IV)

	• Severe infections (eg, sepsis, abscesses, tuberculosis, and opportunistic infections).
Monitoring Requirements	CBC with differential (baseline); complete metabolic panel (baseline); tuberculosis (TB) screening prior to initiating and during therapy including risk factors (chest X-ray if TB positive); Hepatitis C virus/hepatitis B virus (HBV) screening prior to initiating (all patients), HBV carriers (during and for several months following therapy); HIV screening in high risk patients (baseline); signs/symptoms of infection, hypersensitivity reaction, new autoimmune disorder (including lupus-like syndrome), or malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss). Monitor improvement of symptoms and physical function assessments.
Precautions	***Concerns related to adverse effects:*** Antibody formation: Formation of neutralizing anti-drug antibodies may occur with biologic tumor necrosis factor (TNF) inhibitors and may be associated with loss of efficacy. Hematologic disorders: Hematologic toxicities (eg, leukopenia, neutropenia, thrombocytopenia, pancytopenia) have been reported (could be fatal). ***Disease-related concerns:*** Active infection: Do not initiate therapy in patients with an active infection, including clinically important localized infection. HIV: Use with caution in HIV-positive patients; TNF-α inhibitors may be appropriate in patients receiving highly active antiretroviral therapy, provided

	they have normal CD4 counts, no viral load, and no recent opportunistic infections. Immunizations: Live vaccines should not be given concurrently.
Black Box Warning	• Serious infections • Malignancy
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of sarcoidosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Adalimumab.**

Table 29. Adalimumab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Adalimumab	NICE	No recommendation for this indication
	CADTH	No recommendation for this indication
	HAS	No recommendation for this indication
	IQWIG	No recommendation for this indication
	PBAC	-

CONCLUSION STATEMENT- Adalimumab

The use of Adalimumab is recommended as a third-line agent for the treatment refractory sarcoidosis as an adjunct with glucocorticoids and/or methotrexate (or other conventional DMARDs). Adalimumab is maintained at a dose of 40 mg subcutaneously every 1 to 2 weeks. The optimal frequency and duration of therapy should be individualized based on response. Its use is limited by the increased infection risk and hepatotoxicity.

2.3.3 Rituximab

Information on Rituximab is detailed in the table below[16,17]:

Table 30. Rituximab Drug Information

SCIENTIFIC NAME Rituximab	
SFDA Classification	Prescription
SFDA Approval	Yes (Off-Label use)
US FDA	Yes (Off-Label use)
EMA	Yes (Off-Label use)
MHRA	Yes (Off-Label use)
PMDA	Yes (Off-Label use)
Indication (ICD-10)	D86
Drug Class	Biological Disease modifying antirheumatic drugs
Drug Sub-class	Anti-CD20, immunosuppressant
ATC Code	L01XC02
Pharmacological Class (ASHP)	Anti-CD20, immunosuppressant
DRUG INFORMATION	
Dosage Form	Concentrate for solution for infusion
Route of Administration	Intravenous
Dose (Adult) [DDD]*	500–1000 IV mg every 1–6 months Premedication: Manufacturer's labeling recommends premedicating ~30 minutes prior to administration with acetaminophen, an antihistamine, and methylprednisolone 100 mg IV (or equivalent) for adults.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Renal**: None **Hepatic**: None
Prescribing edits*	CU, MD, PA, ST
AGE (Age Edit): No age data for sarcoidosis	

CU (Concurrent Use Edit): Used as an adjunct with glucocorticoids and/or methotrexate (or other conventional DMARDs).	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in rheumatology, immunology, oncology should prescribe and administer rituximab	
PA (Prior Authorization): Rituximab should be used as adjunctive therapy in patients in whom treatment goals have not been met despite glucocorticoids and other immunosuppressant therapy (eg, methotrexate) including Infliximab or adalimumab. It is given at a dose of 500–1000 mg IV infusion every 1–6 months	
QL (Quantity Limit): N/A	
ST (Step Therapy): Fourth line therapy after failure of glucocorticoid, conventional (e.g., methotrexate, azathioprine), and biological DMARDS (infliximab, adalimumab)	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** GI upset, chills, night sweats, headache, infection **Most severe:** Cardiac toxicity (MI, arrythmia, hypertension), progressive multifocal leukoencephalopathy, serious infusion related reactions (acute respiratory distress syndrome, hypotension, hypoxia).
Drug Interactions*	**Category X**: • Abatacept • Abrocitinib • Adalimumab • Adenovirus (Types 4, 7) Vaccine • Anakinra • Anifrolumab • Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Belimumab • Brivudine • Certolizumab Pegol

	• Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Ebola Zaire Vaccine (Live) • Etanercept • Etrasimod • Fexinidazole • Filgotinib • XGolimumab • InFLIXimab • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Ritlecitinib • Rotavirus Vaccine • Ruxolitinib (Topical) • Sarilumab • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tocilizumab • Tofacitinib

	• Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine • Zoster Vaccine (Live/Attenuated)
Special Population	Older adult: There is a higher risk of cardiac (supraventricular arrhythmia) and pulmonary adverse events (pneumonia, pneumonitis), and the incidence of grade 3 or 4 adverse reactions are higher in patients ≥65 years of age. Patients with rheumatic musculoskeletal disease undergoing hip or knee replacement surgery: Hold biologic disease-modifying antirheumatic drugs prior to surgery and plan surgery after the next dose is due.
Pregnancy	Although approved for the treatment of rheumatoid arthritis, based on available data, rituximab should be discontinued once pregnancy is detected in patients treated for rheumatic and musculoskeletal diseases; treatment during pregnancy should only be considered for pregnant patients with life- or organ-threatening disease.
Lactation	In general, breastfeeding is considered acceptable when the relative infant dose (RID) of a medication is <10% According to the manufacturer, breastfeeding is not recommended during treatment and for 6 months after the last dose of rituximab. However, based on available data, rituximab is considered compatible with breastfeeding in patients treated for rheumatic and musculoskeletal diseases. In addition, rituximab is

	unlikely to be absorbed by the infant gastrointestinal tract following exposure via breast milk.
Contraindications	• Known type 1 hypersensitivity or anaphylactic reaction to murine proteins, Chinese Hamster Ovary (CHO) cell proteins, or any component of the formulation. • Patients who have or have had progressive multifocal leukoencephalopathy (PML) • Severe infections (eg, sepsis, abscesses, tuberculosis, and opportunistic infections).
Monitoring Requirements	CBC with differential and platelets (obtain prior to treatment and prior to each treatment course, and at weekly to monthly intervals; continue to monitor for cytopenia after the final rituximab dose and until resolution. Monitor electrolytes (in patients at risk for tumor lysis syndrome [TLS]), renal function (in patients at risk for TLS or nephrotoxicity), fluid/hydration status balance. Monitor BP and vital signs. Evaluate pregnancy status (prior to treatment initiation in patients who may become pregnant). Hepatitis B virus reactivation screening: Screen all patients for hepatitis B virus (HBV) infection prior to therapy initiation. Monitor closely for infusion-related reactions, especially in patients with a history of prior cardiopulmonary reactions or with preexisting cardiac or pulmonary conditions or patients with high numbers of circulating malignant cells (≥25,000/mm^3).
Precautions	***Concerns related to adverse effects:***

	Bowel obstruction/perforation: Abdominal pain, bowel obstruction, and perforation have been reported (rarely fatal), with an average onset of symptoms of ~6 days (range: 1 to 77 days); evaluate abdominal pain or repeated vomiting. Cytopenias: Rituximab is associated with lymphopenia, leukopenia, neutropenia, thrombocytopenia, and anemia; the duration of cytopenias may be prolonged and may extend months beyond treatment. Renal toxicity: May cause fatal renal toxicity in patients with non-Hodgkin lymphomas (NHL). Patients who received combination therapy with cisplatin and rituximab for NHL experienced renal toxicity during clinical trials; this combination is not an approved treatment regimen. Renal toxicity also occurred due to tumor lysis syndrome. ***Dosage forms specific issues:*** Administration: Rituximab is for IV administration only. Do not substitute rituximab and hyaluronidase (SUBQ) for rituximab (IV). Use caution during product selection, preparation, and administration. **Other:** Immunizations: Live vaccines should not be given concurrently.
Black Box Warning	• Infusion-related reactions • Mucocutaneous reactions • Hepatitis B virus reactivation • Progressive multifocal leukoencephalopathy
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of sarcoidosis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Rituximab.**

Table 31. Rituximab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Rituximab	NICE	No recommendation for this indication
	CADTH	No recommendation for this indication
	HAS	No recommendation for this indication
	IQWIG	No recommendation for this indication
	PBAC	-

CONCLUSION STATEMENT- Rituximab

The use of rituximab is considered as a fourth-line agent on a case-to-case basis for the treatment of refractory sarcoidosis after failure of glucocorticoids, conventional DMARDS (e.g., methotrexate, azathioprine), and infliximab or adalimumab. It is indicated as an adjunct with glucocorticoids and/or methotrexate (or other conventional DMARDs). Dosing regimen is 500–1000mg IV infusion every 1–6 months. The optimal frequency and duration of therapy should be individualized based on response. Its use is limited by the increased infection risk, PML, and cardiotoxicity. Additional studies are needed to evaluate the efficacy, safety, and cost efficiency of rituximab.

2.4 Other Drugs

This section details drugs that have been approved by the FDA and/or EMA for the treatment of sarcoidosis but are not currently registered by the SFDA.

2.4.1 Repository Corticotropin Injection (RCI); Acthar Gel®

Repository Corticotropin Injection (Acthar® Gel) stimulates the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and several weakly androgenic substances. Corticotropin was FDA approved in 1952 for advanced respiratory sarcoidosis.

Dose: Intramuscular/Subcutaneous 40-80 units twice a week. Generally used as an adjunctive agent in patients whose disease is refractory to conventional treatments. Since full adrenal activation may not take place during the initial days of treatment, alternative treatments should be considered when an immediate response is required.

Adverse effects: Hypertension, diabetes, anxiety, seizures, GI upset.

Monitoring: Blood pressure, cardiac function, weight; serum glucose, electrolytes; signs of adrenal insufficiency; signs of Cushing syndrome; secondary ocular infections. Following prolonged use (Bone mass density, growth in children, signs and symptoms of infection, cataract formation).

Although FDA approved, available data to support use in this condition are limited and use has been replaced by other agents.

Study: "Repository corticotropin injection in patients with advanced symptomatic sarcoidosis: retrospective analysis of medical records"[19].

Methods: Patients ≥ 18 years with symptomatic sarcoidosis, treated with RCI in the previous 36 months, who had completed a course of RCI or received RCI for ⩾6 months at the time of data collection were included.

Results: The research involved 302 patients (average age of 51 years; 52% female) who had been diagnosed with sarcoidosis for an average of 4.8 years. Most patients (76%) experienced involvement of organs outside the lungs, primarily affecting the skin (28%), joints (25%), heart (22%), and eyes (22%). 34% had multiple (⩾2) organ involvement. The average duration of treatment with RCI was 32.5 weeks, and 61.6% of patients continued RCI therapy for at least six months. The utilization pattern of RCI treatment showed a personalized approach, with a higher initial dose associated with a shorter duration of therapy compared to a lower initial dose. The percentage of patients using corticosteroids decreased from 61.3% in the three months prior to starting RCI to 12.9% three months after beginning RCI therapy. The average daily dose of corticosteroid went down from 18.2 mg to 9.9 mg. The proportion of patients receiving less than 10 mg/day of prednisone increased from 21% before RCI use to 47% three months after starting RCI. According to physicians' assessments of the change in patients' health status after RCI therapy, 95% of patients saw an improvement in overall status, 73% experienced an improvement in overall symptoms, 38% saw an improvement in lung function, and 33% experienced a reduction in inflammation.

Conclusion: The results indicate that RCI represents a viable treatment choice for individuals with advanced, symptomatic sarcoidosis and provides insights on patient characteristics and practice patterns to help clinicians determine appropriate use.

Section 3.0 Key Recommendations Synthesis

Diagnosis

- The diagnosis of sarcoidosis typically involves a combination of clinical evaluation, medical history review, imaging studies, laboratory tests, and sometimes, a biopsy.
- Pulmonary involvement is observed in more than 90% of individuals with sarcoidosis. However, it is important to assess symptoms that may show involvement of other organs such as eyes, skin, and the heart.
- Every patient suspected of having sarcoidosis should undergo a chest X-ray, to detect the characteristic granulomas in the lungs, which are a hallmark of sarcoidosis. MRIs can also help detect neuro-sarcoidosis.
- Before establishing a diagnosis of sarcoidosis, it is crucial to rule out other potential causes of granulomas, including mycobacterial and fungal infections, as well as other interstitial lung conditions like hypersensitivity pneumonitis or chronic beryllium disease.

Pharmacological Management

- Treatment is not necessary for every patient. The decision to commence treatment for a sarcoidosis patient relies on the onset of symptoms (cough, breathlessness) and the disease progression, which is evidenced by a deterioration in functional condition and observable anomalies in imaging. (Not graded).
- First line therapies include oral corticosteroids, followed by conventional immunosuppressants (e.g., methotrexate, azathioprine, leflunomide) as second line therapy). The third line therapy includes the utilization of anti-TNF antibodies like infliximab or adalimumab (No grade).
- For patients with severe pulmonary sarcoidosis who have not received prior treatment and are at an increased risk of mortality or disability, the initiation of oral glucocorticoid therapy is recommended. This is aimed at enhancing and/or preserving the FVC and QoL (Strong recommendation, low quality of evidence.)
- Typically, oral glucocorticoids are prescribed at a dose of 20 mg/d to 40 mg/d of prednisone, which is then gradually tapered to 0 mg/d to 10 mg/d over a period of 6 to 18 months which could be extended depending on symptoms and disease progression. (Not graded)

- Some patients may discontinue corticosteroid therapy, but many patients continue corticosteroid therapy for a long period of time (Evidence level 6, Recommendation grade C1).
- Patients with severe pulmonary sarcoidosis who have already undergone glucocorticoid therapy but continue to have an active disease or undesirable side effects, are considered to add methotrexate to improve/preserve FVC and QoL. (Conditional recommendation, very low quality of evidence).
- Patients with severe pulmonary, cutaneous sarcoidosis who continue to active disease or undesirable side effects despite glucocorticoid or immunosuppressive therapy, are suggested the addition of infliximab to improve/preserve FVC and QoL (Conditional recommendation, low quality of evidence).
- In cases of cutaneous sarcoidosis where there are noticeable skin lesions of cosmetic concern that do not respond well to local treatments, it is considered the addition of oral glucocorticoids as a potential approach to reduce the skin lesions. (Conditional recommendation, very low quality of evidence).
- For patients with evidence of functional cardiac abnormalities, including heart block, dysrhythmias or cardiomyopathy, the use of glucocorticoids is recommended (with or without other immunosuppressives). (Strong recommendation, very low quality of evidence.)
- For patients with neuro-sarcoidosis who have been treated with glucocorticoids and a second-line agent (methotrexate, azathioprine, mycophenolate mofetil) and still have active disease, the addition of infliximab is considered. (Conditional recommendation, very low quality of evidence.)
- Patients experiencing troublesome fatigue with sarcoidosis are considered for the implementation of a pulmonary rehabilitation program and/or the engagement in inspiratory muscle strength training for a period of 6 to 12 weeks to address fatigue. (Conditional recommendation, low quality of evidence.)
- Sarcoidosis patients that remain with troublesome fatigue after consideration of a pulmonary exercise or rehabilitation program, are considered to receive D-methylphenidate or armodafinil for 8 weeks to test its effect on fatigue and tolerability. (Conditional recommendation, low quality of evidence.)

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of Sarcoidosis.

These recommendations should be used to support and not supplant decisions in individual patient management.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

II. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose. If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

III. What information is available in the notes?

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

IV. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

V. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

VI. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. MeSH Terms PubMed

The following is the result of the PubMed search conducted for guideline search:

Query	Filters	Search Details	Results
((((((((((((((((((((sarcoidosis[MeSH Terms]) OR (Sarcoidoses[Title/Abstract])) OR (Boeck's Sarcoid[Title/Abstract])) OR (Boeck Sarcoid[Title/Abstract])) OR (Boecks Sarcoid[Title/Abstract])) OR (Sarcoid, Boeck's[Title/Abstract])) OR (Schaumann Disease[Title/Abstract])) OR (Disease, Schaumann[Title/Abstract])) OR (Schaumann Syndrome[Title/Abstract])) OR (Syndrome, Schaumann[Title/Abstract])) OR (Besnier-Boeck-Schaumann Syndrome[Title/Abstract])) OR (Besnier Boeck Schaumann Syndrome[Title/Abstract])) OR (Syndrome, Besnier-Boeck-Schaumann[Title/Abstract])) OR (Boeck Disease[Title/Abstract])) OR (Boeck's Disease[Title/Abstract])) OR (Boecks Disease[Title/Abstract])) OR (Besnier-Boeck	Guideline, in the last 5 years	("sarcoidosis"[MeSH Terms] OR "Sarcoidoses"[Title/Abstract] OR "boeck s sarcoid"[Title/Abstract] OR "boeck sarcoid"[Title/Abstract] OR "boecks sarcoid"[Title/Abstract] OR (("sarcoidal"[All Fields] OR "sarcoidosis"[MeSH Terms] OR "sarcoidosis"[All Fields] OR "Sarcoid"[All Fields] OR "sarcoids"[All Fields]) AND "Boeck's"[Title/Abstract]) OR "schaumann disease"[Title/Abstract] OR "disease schaumann"[Title/Abstract] OR "schaumann syndrome"[Title/Abstract] OR (("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "Syndrome"[MeSH Terms] OR "Syndrome"[All Fields] OR "Syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields]) AND "Schaumann"[Title/Abstract]) OR "besnier boeck schaumann syndrome"[Title/Abstract] OR "besnier boeck schaumann syndrome"[Title/Abstract] OR	3

Disease[Title/Abstract])) OR (Besnier Boeck Disease[Title/Abstract])) OR (Schaumann's Syndrome[Title/Abstract])) OR (Schaumann's Syndromes[Title/Abstract])) OR (Syndrome, Schaumann's[Title/Abstract])		(("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "Syndrome"[MeSH Terms] OR "Syndrome"[All Fields] OR "Syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields]) AND "Besnier-Boeck-Schaumann"[Title/Abstract]) OR "boeck disease"[Title/Abstract] OR "boeck s disease"[Title/Abstract] OR ("Boecks"[All Fields] AND "Disease"[Title/Abstract]) OR "besnier boeck disease"[Title/Abstract] OR "besnier boeck disease"[Title/Abstract] OR (("Schaumann"[All Fields] OR "Schaumann's"[All Fields]) AND "Syndrome"[Title/Abstract]) OR (("Schaumann"[All Fields] OR "Schaumann's"[All Fields]) AND "Syndromes"[Title/Abstract]) OR (("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "Syndrome"[MeSH Terms] OR "Syndrome"[All Fields] OR "Syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields]) AND "Schaumann's"[Title/Abstract])) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix C. Treatment Algorithms

The below algorithms are retrieved from the Sarcoidosis Treatment Guidelines by the Foundation of Sarcoidosis Research, Physicians' Protocol [2014][20]

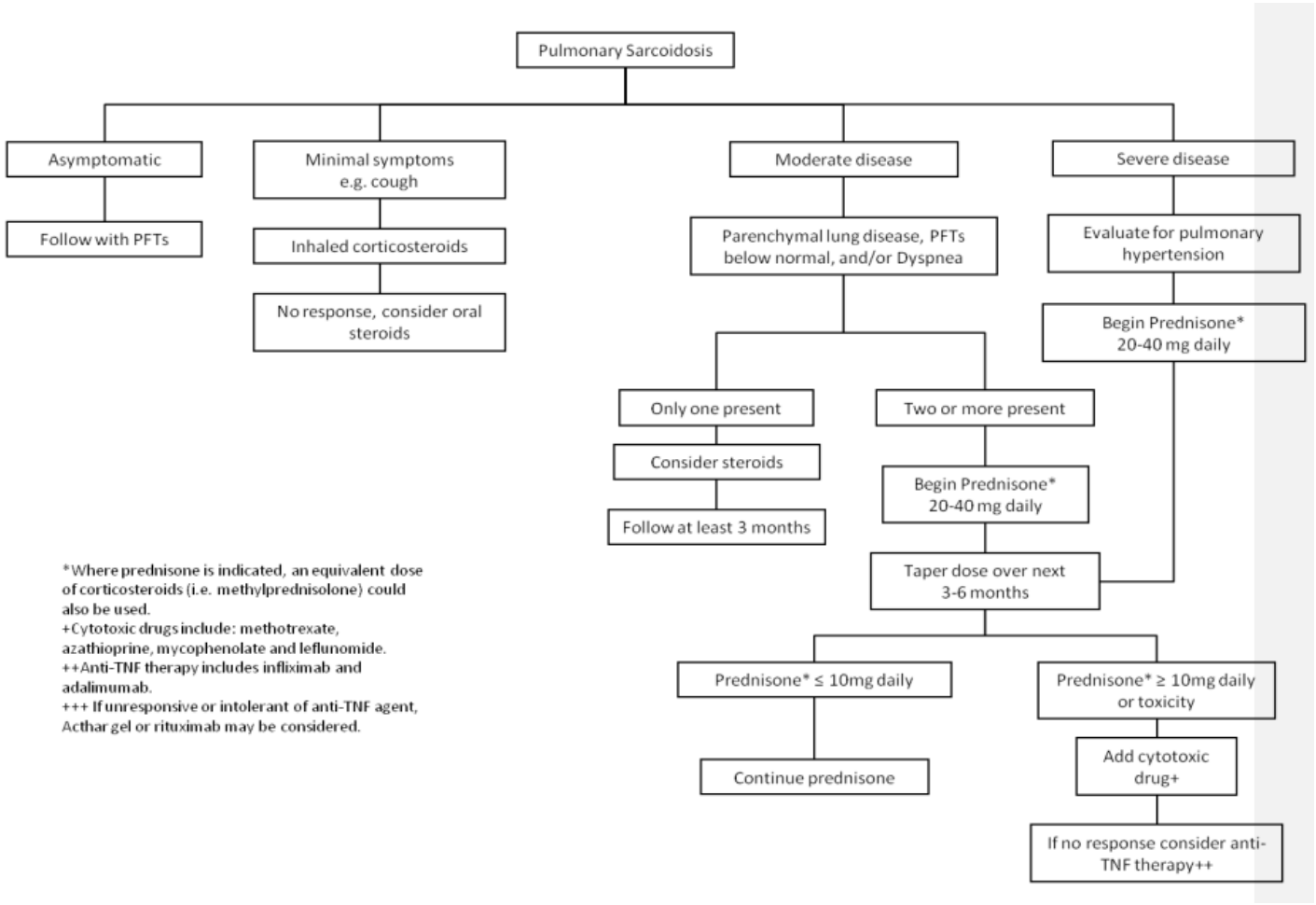


Figure 9. *Treatment Algorithm for Pulmonary Sarcoidosis*

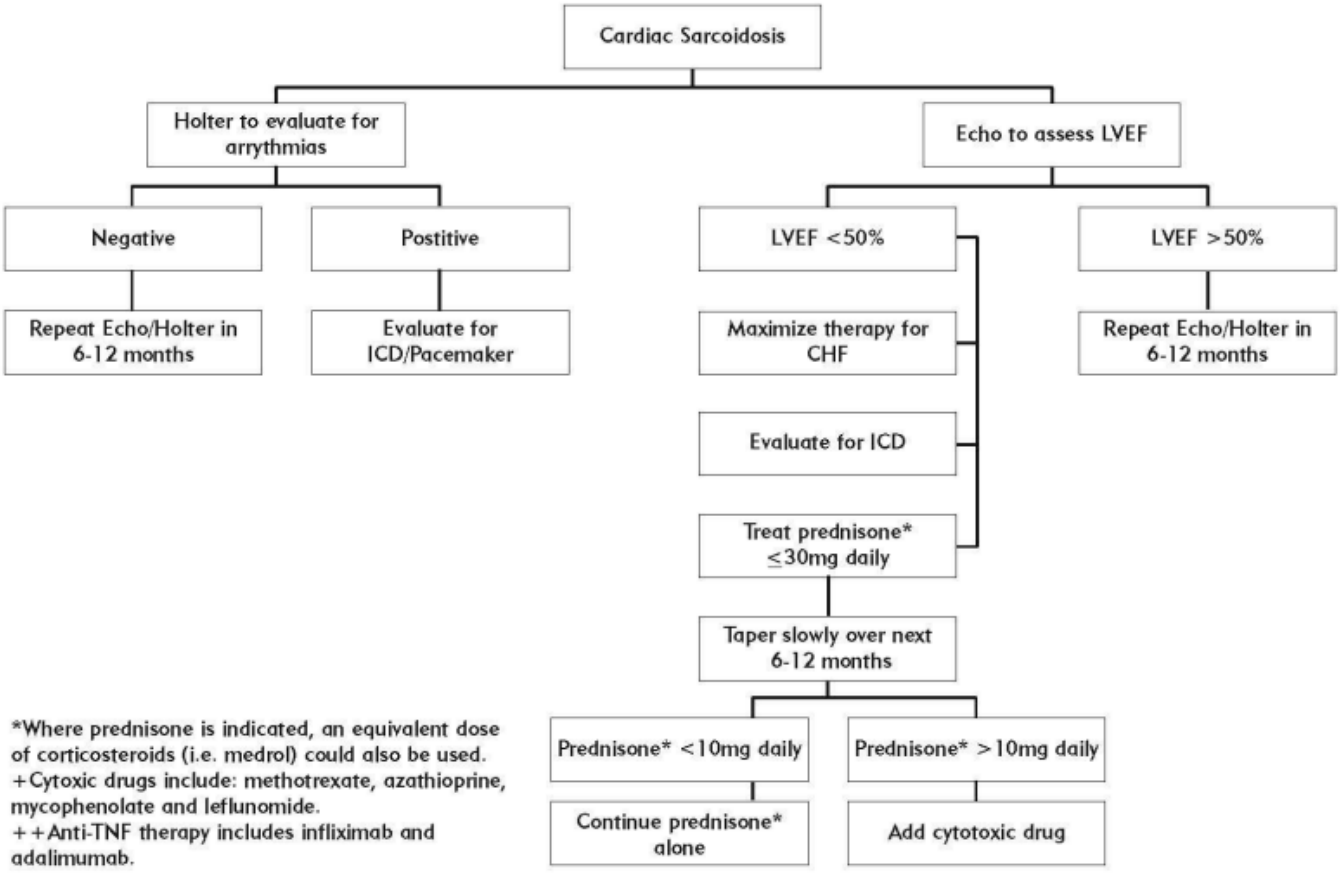
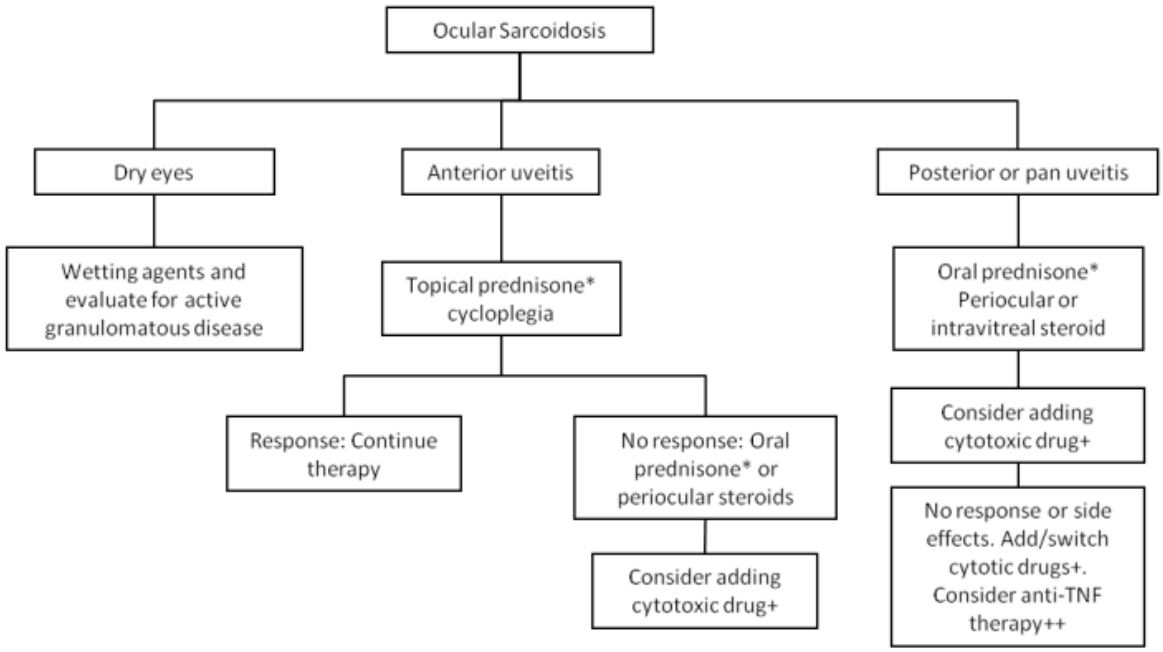


Figure 10. *Treatment Algorithm for Cardiac Sarcoidosis*



*Where prednisone is indicated, an equivalent dose of corticosteroids (i.e. methylprednisolone) could also be used.
+Cytotoxic drugs include: methotrexate, azathioprine, mycophenolate and leflunomide.
++Anti-TNF therapy includes infliximab and adalimumab.
+++ If unresponsive or intolerant of anti-TNF agent, Acthar gel or rituximab may be considered.

Figure 11. *Treatment Algorithm for Ocular Sarcoidosis*

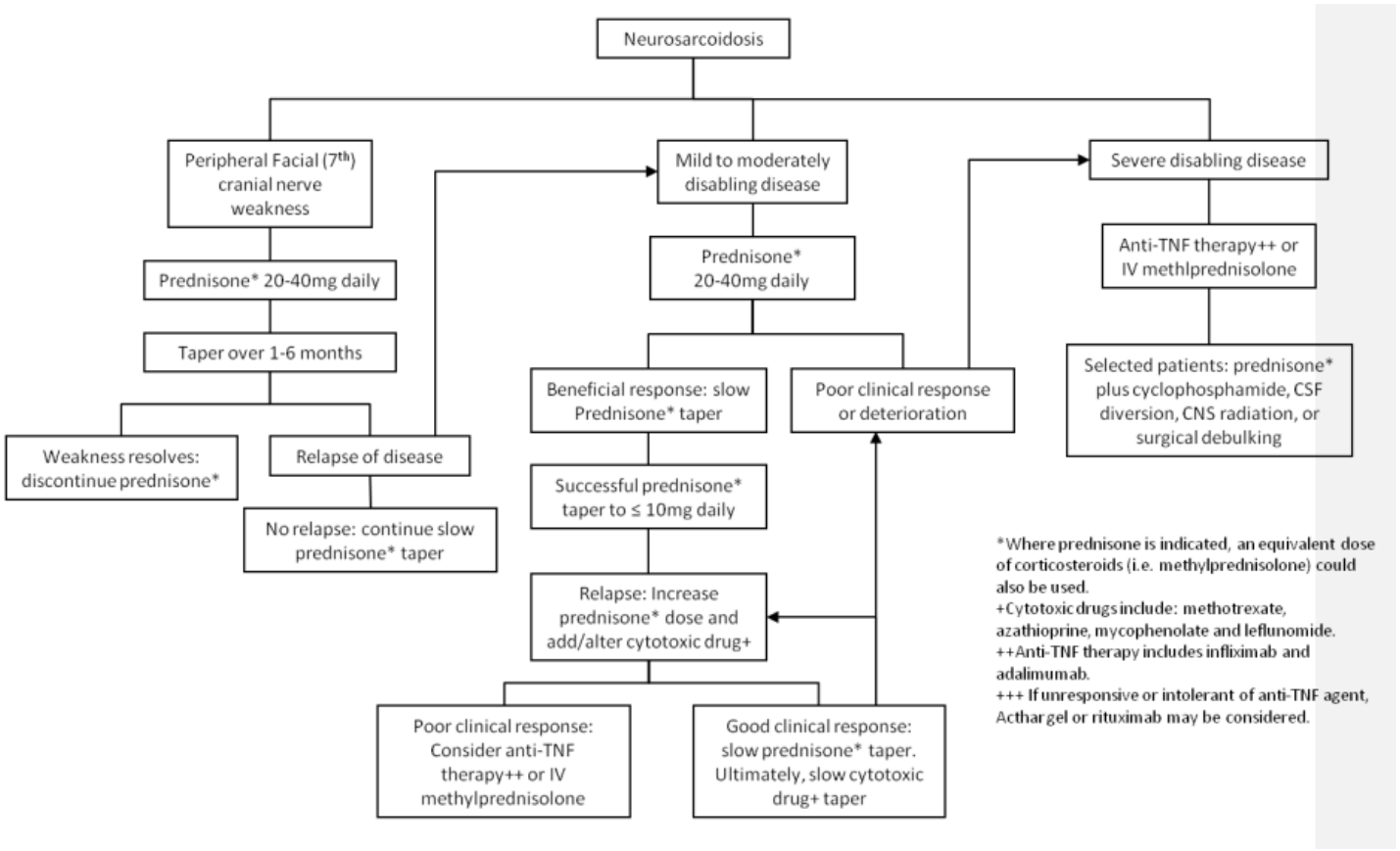


Figure 12. *Treatment Algorithm for Neuro-Sarcoidosis*

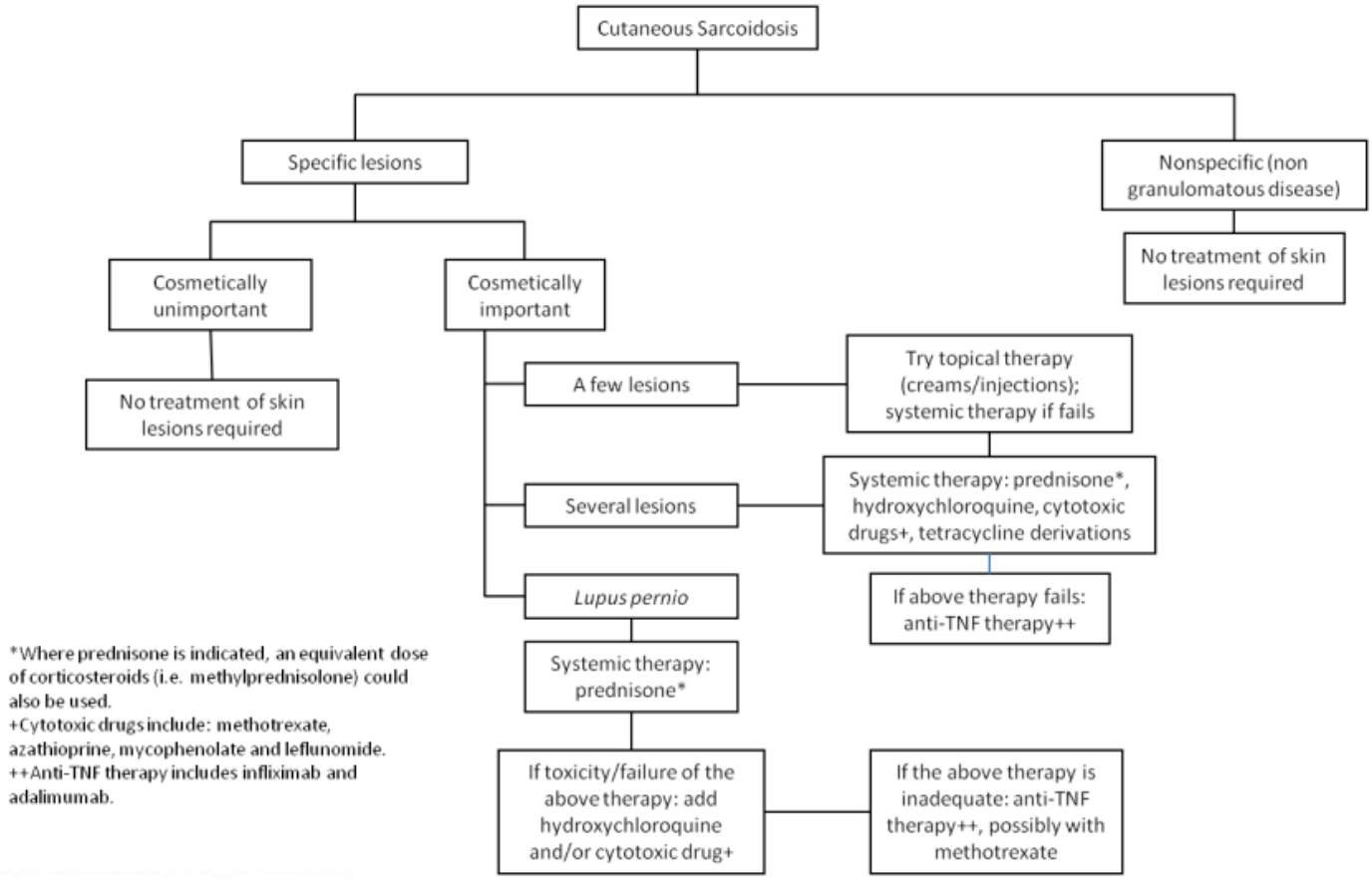


Figure 13.*Treatment Algorithm for Cutaneous Sarcoidosis*