Discovering and Managing Sarcoidosis: The Mystery Disease

Rena Laliberte BS, CPFT, RRT, FAARC
Clinical Education Specialist
Henry Ford Hospital

Disclosures

- **Research assistant at HFH with a grant from Novartis: anti-IL 18 for sarcoidosis.**
- **Research assistant at HFH with a grant from aTyr pharmaceutical: Efzofitimod for sarcoidosis.**
- **Research assistant at HFH with a grant from Xentria pharmaceutical: 072110 / XTMAB-16-201/20 for sarcoidosis.**
- **Honorarium AARC Blood Gas Laboratory Manager-Microcredential**
- **Member of AARC, CPG, SESG, Clinical Educator Taskforce (committees)**
- **Honorarium – Respiratory Associates**
- **MSRC Conference Committee, District 10 representative, HOSA committee**

Educational Objectives

- Review the history and pathophysiology of Sarcoidosis and various presentations
- Examine pharmacologic interventions and treatments
- Discuss clinical cases

Sarcoid-What is it? History

- First described by Jonathan Hutchinson in 1869.
- In Hutchinson's day, it was considered a dermatological condition, which gradually evolved into a multisystem disorder associated in the majority of cases with respiratory abnormalities.
- Sarcoidosis is a chronic systemic disease of unknown origin
- Presents with bilateral hilar lymphadenopathy, pulmonary infiltrates and ocular and skin lesions
- The diagnosis is established when characteristic clinical-radiological features are supported by compatible histopathology of epithelioid cell granulomas, following exclusion of known causes of granulomatous inflammation.

Sarcoid – What is it? History

- In 1869 Hutchinson (most distinguished medical consultant of all time at the Blackfriars Hospital for diseases of the skin of London) had a visitor- a 58 y/o wharf worker. The patient complained of purple, symmetrical skin plaques on his leg and hands .
- Hutchinson described the lesions, that were neither painful nor tender, as livid papillary psoriasis and considered them related to the patient's gout.
- Hutchinson's next patient, Lady Mortimer, presented with raised red lesions on her face and forearms that increased in size over the following 6 months.
- Hutchinson could not attribute them to Tuberculosis nor Lupus, so he labeled her condition as “Mortimers Malady”.

Sarcoid from dermatological condition to systemic disease

- Ernest Besnier, a French dermatologist coined the term “lupus pernio” to describe a patient with purplish swelling of the nose, ears and fingers in 1889. (image to follow)
- In 1899, Caeser Boeck, a Norwegian dermatologist, presented to the Medical Society of Christiania, a patient with multiple benign “sarkoid” of the skin. He emphasized the similarity to Mortimers Malady.
- Boeck coined the term “sarkoid” because the lesions resembled sarcoma. He was also the first to describe the granulomatous histology of sarcoidosis.
- Before his death he published a series of 24 cases of benign miliary lupoids, some which showed involvement of the lungs, conjunctiva, bone, lymph nodes, spleen and nasal membranes.
- The multi-organ nature of the disease was beginning to emerge.

Subacute Variants of Sarcoid

- Lupus pernio
- Heerfordt syndrome
- Lofgren syndrome

Lupus Pernio

Heerfordt Syndrome

- Subacute variant of Sarcoid characterized by the following:
  - Enlargement of parotid and salivary glands
  - Facial nerve paralysis
  - Anterior uveitis – an inflammation of the iris and ciliary body in the front of the eye

Heerfordt Syndrome

Lofgren Syndrome

- First described in 1946 by Sven Lofgren, a Swedish pulmonologist
- Rare phenotype of Sarcoid
- Lungs most common organ affected with second being skin
- Cutaneous manifestations are now seen in 33% of the cases and often first clinical sign of the disease

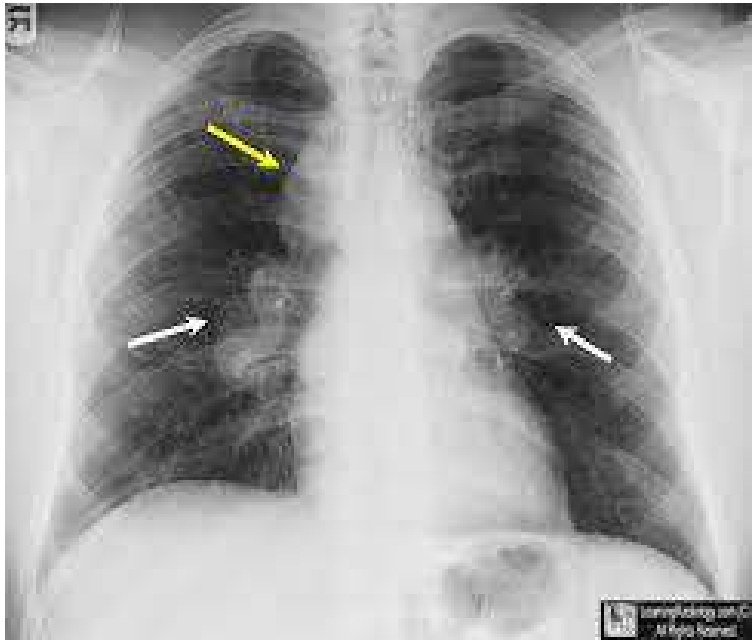
Lofgren syndrome

- Lofgren's syndrome presents acutely
- It typically presents in younger patients
- Acute onset erythema nodosum
- Bilateral hilar lymphadenopathy (pawnbrokers sign)
- Fever
- Migratory polyarthritis
- Without granulomatous skin involvement.

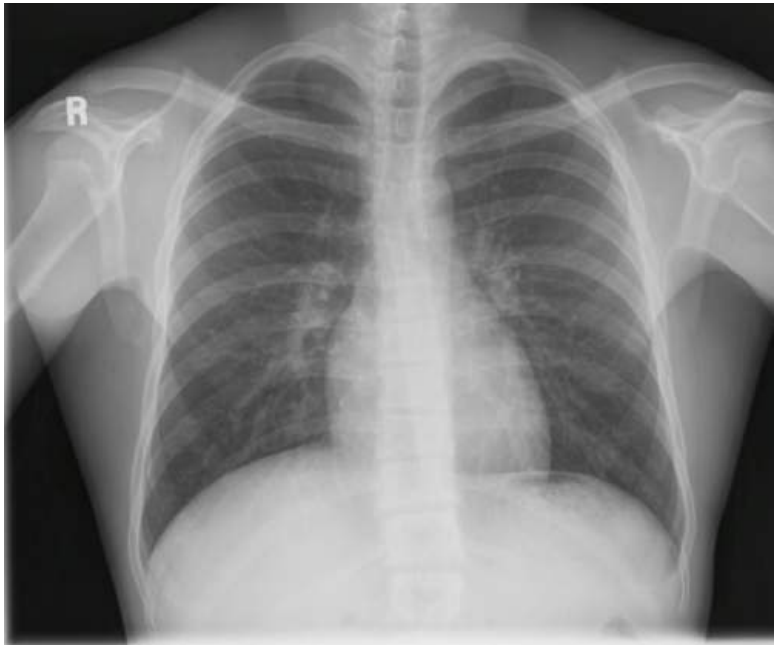
Lofgren syndrome

Erythema nodosum

Pawnbroker Sign



Hilar Lymphadenopathy



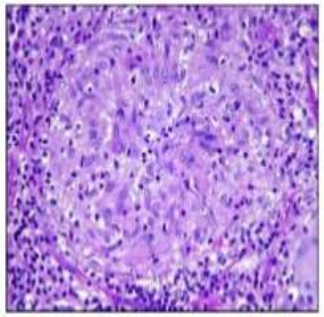
Diagnosing Sarcoid

- Difficult with no definitive tests existing
- Diagnose what it isn't - exclusion of other disease that cause the formation of granulomas, such as tuberculosis
- Presumptive diagnosis is usually made based upon radiographic findings alone
- If the disease deviates from its classic course or fails to resolve
- Histologic diagnosis may be necessary
- Lesions are not good choices for biopsy as granulomas are typically not present
- Lymph nodes are usually chosen and if are not readily accessible superficially, more invasive measures may be necessary
- Flexible bronchoscopy with BAL or EBUS

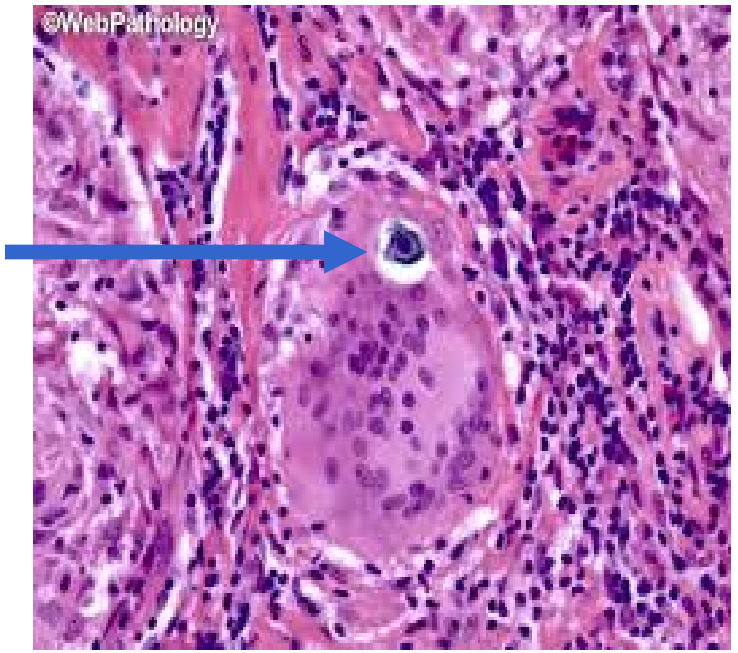
Histology of Sarcoidosis

Sarcoidosis

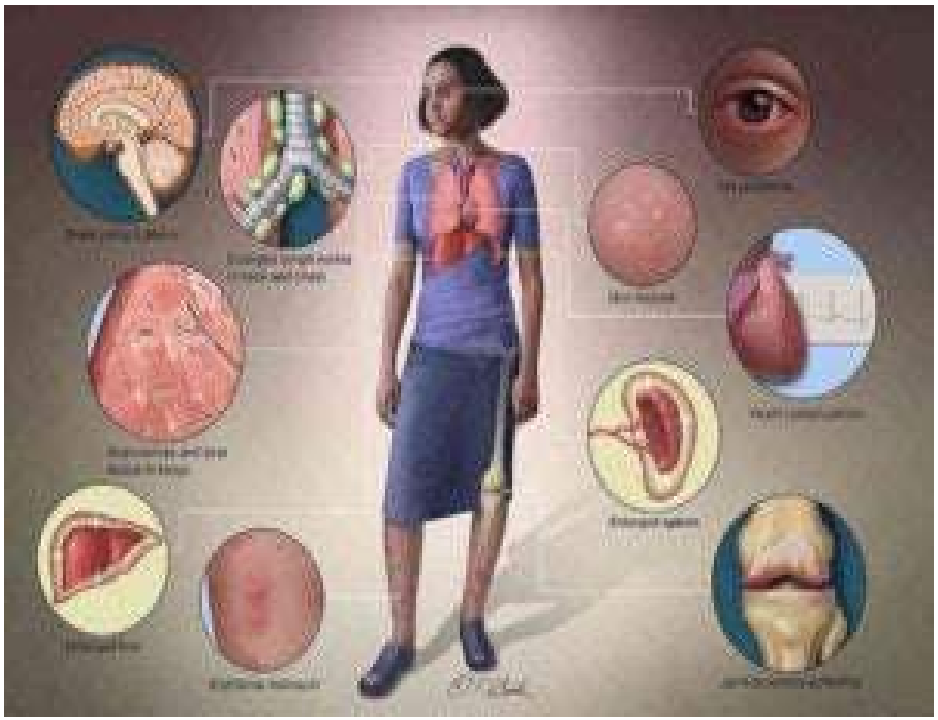
- Histology



  - Epitheloid cells surrounded by lymphocytes & fibroblasts, but devoid of caseation
  - Crystalline or calcified inclusion bodies sometimes seen (Schaumann bodies)



Sarcoid



18

Sarcoid

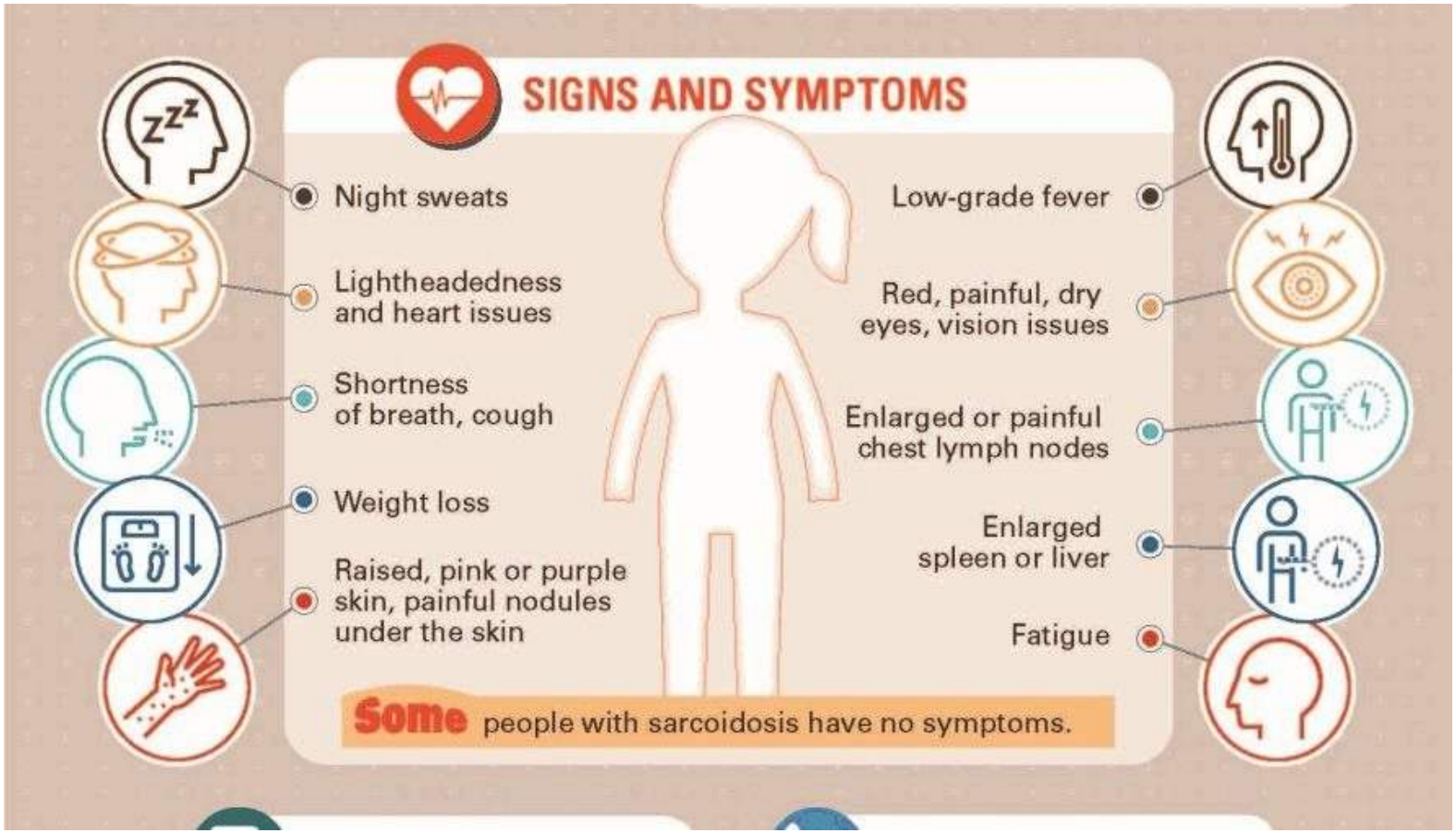
- Affected areas
- Lung
- Skin
- Lymph nodes
- Joines
- Eyes
- Heart
- Nerves/Brain
- Muscles
- Kidneys

Who is at Risk?

- Caucasian females
- African American Men and Women
- Auto-immune disorder

- Symptoms:
- Multiple Symptoms
- Sarcoid – but has no symptoms

Symptoms


SIGNS AND SYMPTOMS
Night sweats
Lightheadedness and heart issues
Shortness of breath, cough
Weight loss
Raised, pink or purple skin, painful nodules under the skin
Low-grade fever
Red, painful, dry eyes, vision issues
Enlarged or painful chest lymph nodes
Enlarged spleen or liver
Fatigue
Some people with sarcoidosis have no symptoms.

Patient Case

- 54-year-old woman with chronic mild cough referred from another health care system for sarcoidosis management.
- Rx: Azathioprine 100 mg BID for 5 years.
- PFTs normal.
- Chest imaging: minimal upper lobe chronic fibrotic changes and calcified adenopathy.
- Normal skin exam, ocular exam, serum calcium level, serum creatinine.
- No pathology on record.
- Co-morbidities include hypertension, diabetes, obesity. Patient is an active smoker, ½ pack per day.

Physical Manifestations

Cutaneous Sarcoid

Unusual Variant Sarcoid (cutaneous)

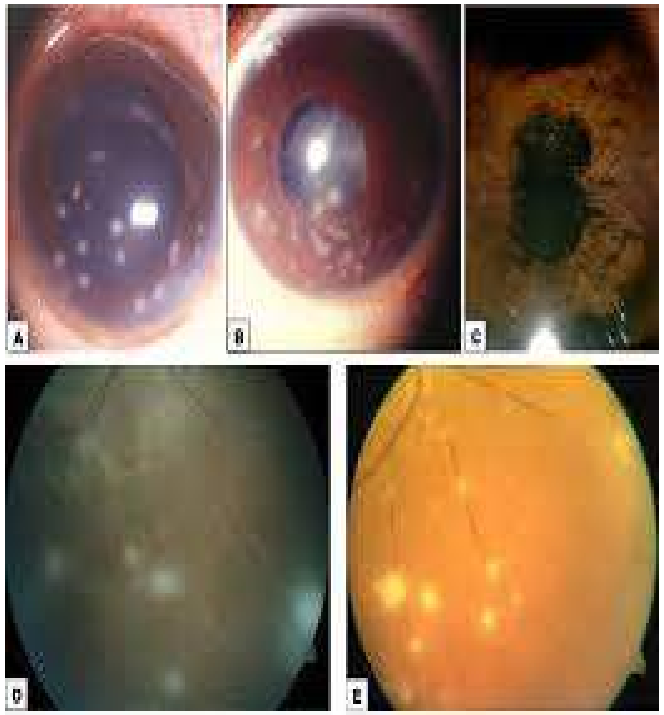
Physical Manifestations

Oral Sarcoid

Oral cutaneous Sarcoid

Physical Manifestations

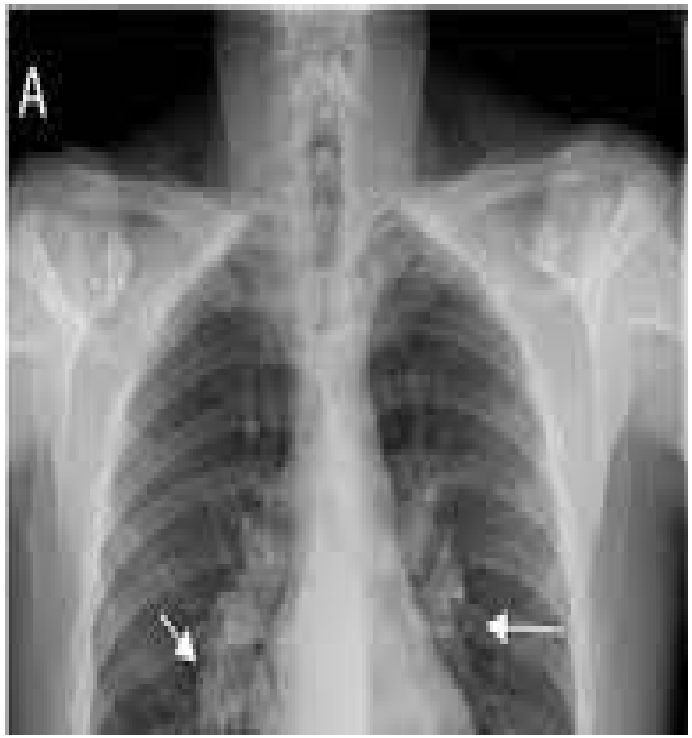
Ocular Sarcoid



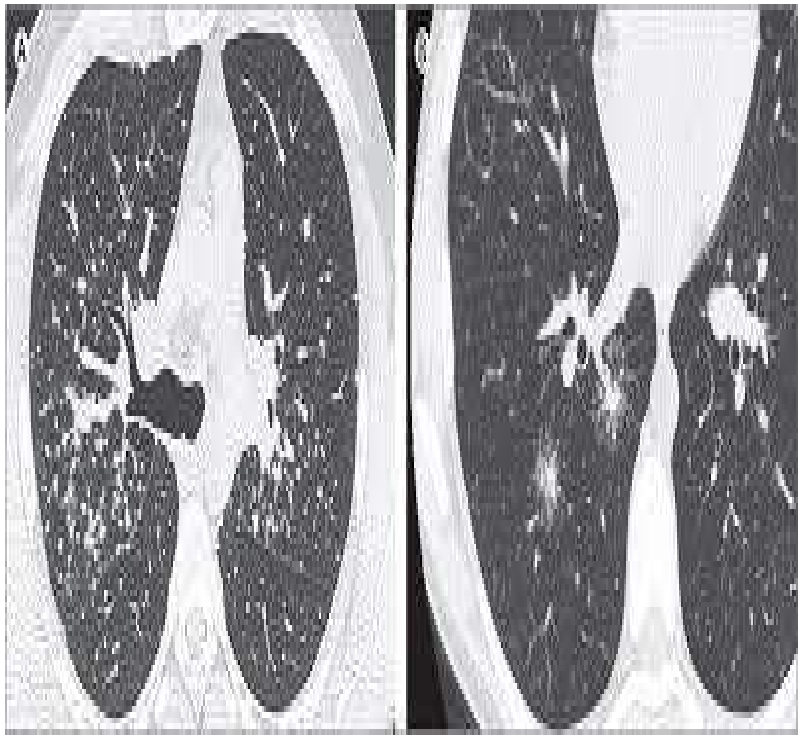
Ocular Sarcoid

Pulmonary Sarcoid

Pulmonary Sarcoid "Pawn symbol"



Pulmonary scarring and nodules



Diagnosing Sarcoid

- Medical History and Exam
- Chest X-Ray
- Pulmonary Function Testing
- Bronchoscopy
- Eye Exam
- Blood Testings – Sarcoid causes elevated levels of Vit D and Angiotensin Converting Factor
- Cat Scan
- Gallium scan
- Pet Scan
- EKG
- Biopsies

Serum Angiotensin-Converting Enzyme Level Is Elevated in Patients With Human Immunodeficiency Virus Infection

MAJ Daniel R. Ouellette, MC, USA; MAJ J. William Kelly, MC, USA; MAJ Gregg T. Anders, MC, USA

• ***Background.*—Serum angiotensin-converting enzyme (ACE) level is elevated in a number of disease states and**

Singer and coworkers[13] measured serum ACE levels in a group of patients with human immunodeficiency virus

Elevated ACE levels in the serum of humans have been reported in a number of disease states, including sarcoidosis,[2,5,6] infectious granulomatous diseases,[7] Gaucher's disease,[8] diabetes mellitus,[9] alcoholic liver disease,[10] and hyperthyroidism.[11] Measurement of the ACE level has been most important clinically in sarcoidosis, where it has been suggested that the degree of elevation correlates with disease activity.[12]

Ouellette et al; Arch Intern Med. 1992; 152:321-324.

Sarcoidosis

The most important question is often "Should I treat?" and not "How do I treat?"

Treatment Indications

No Danger	No Danger, Impaired QOL	Danger
-CXR Only -No symptoms	-Dyspnea -Cough -Mild Skin -Mild joint sx -Stable PFT/CXR	-Prog Resp Sx -Deteriorating PFT/CXR -Ocular Findings -Neurologic -Cardiac -Disfiguring skin -Hypercalcemia

Treatment for Sarcoid

ERS Clinical Practice Guidelines for the treatment of Sarcoid
European Respiratory Journal 2021 58(6): 2004079; DOI: https://doi.org/10.1183/13993003.04079-2020

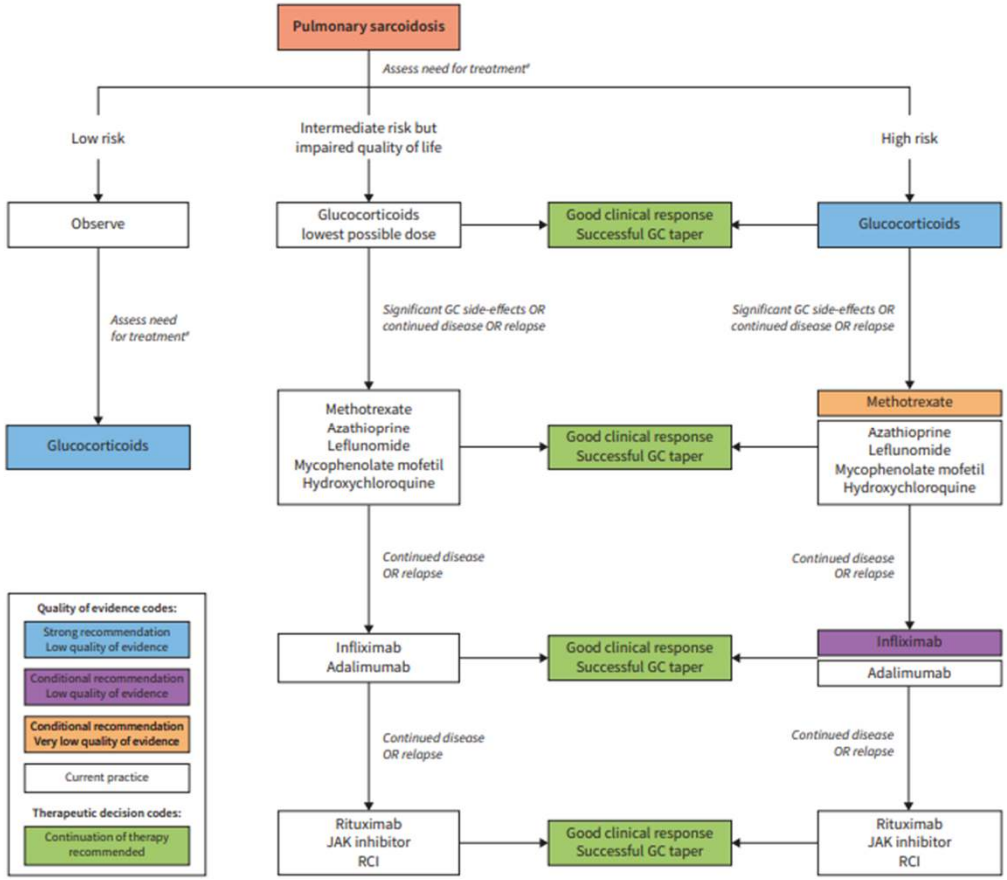
TABLE 2 Immunosuppressive therapies for sarcoidosis

Drug	Usual dosage	Major toxicities	Recommended monitoring	Comments
Prednisone/ prednisolone	Initial 20 mg once a day; follow-up 5–10 mg once a day to once every other day	Diabetes; hypertension; weight gain; osteoporosis; cataracts; glaucoma; moodiness	Bone density; blood pressure and serum glucose	Cumulative toxicity
Methotrexate	10–15 mg once a week	Nausea; leukopenia; hepatotoxicity; pulmonary	CBC, hepatic, renal serum testing	Cleared by kidney, avoid in significant renal failure
Leflunomide	10–20 mg once a day	Nausea; leukopenia; hepatotoxicity; pulmonary	CBC, hepatic, renal serum testing	Cleared by kidney, avoid in significant renal failure
Azathioprine	50–250 mg once a day	Nausea; leukopenia; infections; malignancy	CBC	
Mycophenolate mofetil	500–1500 mg twice a day	Diarrhoea; leukopenia; infections; malignancy	CBC	Less experience in sarcoidosis than other agents
Infliximab or biosimilars[#]	3–5 mg·kg^{-1} initially, 2 weeks later, then once every 4–6 weeks	Infections; allergic reaction	Screen for prior TB; monitor for allergic reactions; contraindicated in severe CHF, prior malignancy, demyelinating neurologic disease, active TB, deep fungal infections	Allergic reactions can be life threatening
Adalimumab[#]	40 mg every 1–2 weeks	Infections	Screen for prior TB; monitor for allergic reactions; contraindicated in severe CHF, prior malignancy, demyelinating neurologic disease, active TB, deep fungal infections	Less toxic than infliximab
Rituximab[#]	500–1000 mg every 1–6 months	Infections	Screen for viral hepatitis; check IgG level with chronic therapy	High risk for viral reactivation; can lead to IgG deficiency
RCI[#]	40–80 units twice a week	Diabetes; hypertension; oedema; anxiety	Monitor glucose and blood pressure	Most of toxicity is on day of injection
Hydroxychloroquine	200–400 mg once a day	Loss of vision	Ocular exams periodically depending on age and renal function	Minimal impact on cardiac and neurologic disease

More details regarding dosages, major toxicities and monitoring are given in supplement S1 in the supplementary material and adapted from prior reports [4, 39–48]. CBC: complete blood count; TB: tuberculosis; CHF: congestive heart failure; RCI: repository corticotropin injection. [#]: use reserved for patients who have failed prior treatments with steroids and/or antimetabolites.

Treatment for Sarcoid

ERS Clinical Practice Guidelines for the treatment of Sarcoid
European Respiratory Journal 2021 58(6): 2004079; DOI: https://doi.org/10.1183/13993003.04079-2020



Patient Case

- 30-year-old black man admitted to hospital with dyspnea, cough, and right upper lobe infiltrate. Symptoms present for several weeks. Reported fever at home.
- Employed by the Post Office; National Guard Reservist. Recently returned from desert warfare training in the Mojave Desert.
- Nonsmoker, negative HIV.
- Chest x-ray and CT demonstrate bilateral hilar adenopathy and right upper lobe airspace disease.

Patient Case

- Physical exam: Normal eye and skin exams.
- Labs: Normal ionized calcium.
- Bronchoscopy: Normal airway exam. EBUS biopsies demonstrate noncaseating granulomas. No organisms identified on the pathologic section.

Self-challenge question: Best answer

1. Start methotrexate, 10 mg weekly.
2. Start prednisone, 40 mg daily.
3. Order a quantiferon gold test, fungal serology; send cocci serology to reference lab.
4. Order a lymphocyte transformation test.

Self-challenge question: Best answer

1. Start methotrexate, 10 mg weekly.
2. Start prednisone, 40 mg daily.
3. **Order a quantiferon gold test, fungal serology; send cocci serology to reference lab.**
4. Order a lymphocyte transformation test.

- **Treatments have side-effects, often not proven to change outcomes, require monitoring.**
- Sarcoidosis is a diagnosis of exclusion.
- Infectious diseases
  - TB
  - Histo
  - Cocci
- Neoplastic diseases
- Environmental and occupational exposures
  - Berylliosis
- Autoimmune and other inflammatory conditions, drugs.

Patient Case

- 28-year-old woman with cough for two months and skin rash for one week. Also notes fevers, fatigue, and sharp chest pain.
- Serum chemistries are normal to include ionized calcium.
- PFTs are normal.
- Tbbx: noncaseating granulomas found.
- Infectious serologies are negative.

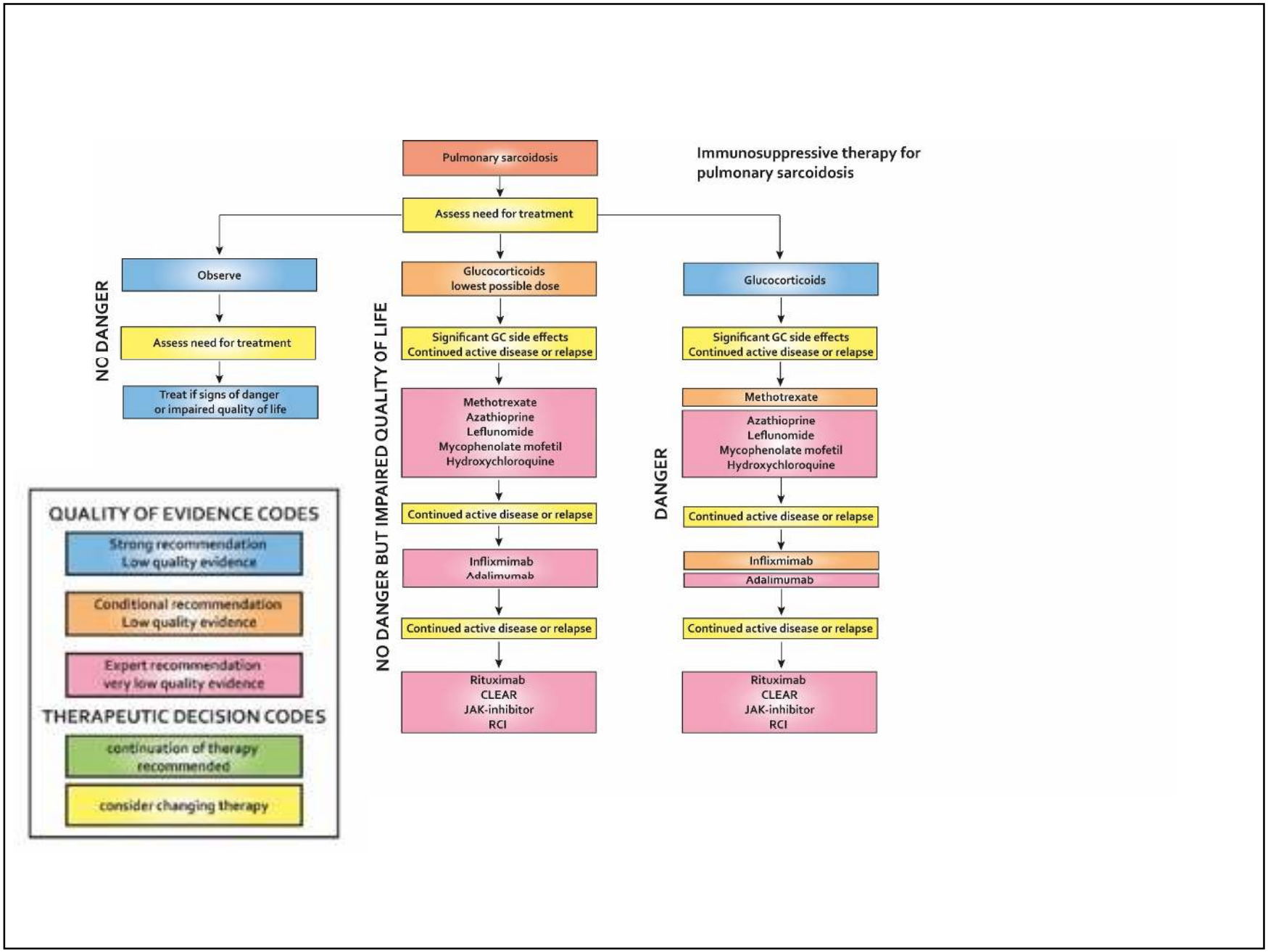
Patient Case

Patient Case

- Diagnosis:
- Danger Level:
  - No Danger
  - No Danger, Impaired QOL
  - Danger
- Treatment Choice:

Patient Case

- Diagnosis: Pulmonary sarcoidosis
- Danger Level:
  - No Danger
  - No Danger, Impaired QOL
  - Danger
- Treatment Choice:
  - Prednisone. Consider 20mg daily for several weeks, monitor course, as initial therapy.


Immunosuppressive therapy for pulmonary sarcoidosis
Pulmonary sarcoidosis
Assess need for treatment
NO DANGER
Observe
Assess need for treatment
Treat if signs of danger or impaired quality of life
NO DANGER BUT IMPAIRED QUALITY OF LIFE
Glucocorticoids lowest possible dose
Significant GC side effects Continued active disease or relapse
Methotrexate
Azathioprine
Leflunomide
Mycophenolate mofetil
Hydroxychloroquine
Continued active disease or relapse
Infliximab
Adalimumab
Continued active disease or relapse
Rituximab
CLEAR
JAK-inhibitor
RCI
DANGER
Glucocorticoids
Significant GC side effects Continued active disease or relapse
Methotrexate
Azathioprine
Leflunomide
Mycophenolate mofetil
Hydroxychloroquine
Continued active disease or relapse
Infliximab
Adalimumab
Continued active disease or relapse
Rituximab
CLEAR
JAK-inhibitor
RCI
QUALITY OF EVIDENCE CODES
Strong recommendation Low quality evidence
Conditional recommendation Low quality evidence
Expert recommendation very low quality evidence
THERAPEUTIC DECISION CODES
continuation of therapy recommended
consider changing therapy

Patient Case

- 40-year-old man with biopsy confirmed sarcoidosis 5 years ago presenting with peripheral edema and dyspnea.
- Treated 5 years ago with 6 months of prednisone.
- BNP 1200 pg/mL, ionized calcium level 1.6 mmol/L.
- CXR: prominent vascular pattern, Kerley B lines, small bilat. effusions, hilar adenopathy, upper lobe mild bronchiectasis and airspace disease.
- ECHO: 25% LVEF
- Cardiac PET: positive for sarcoid-like inflammatory changes.

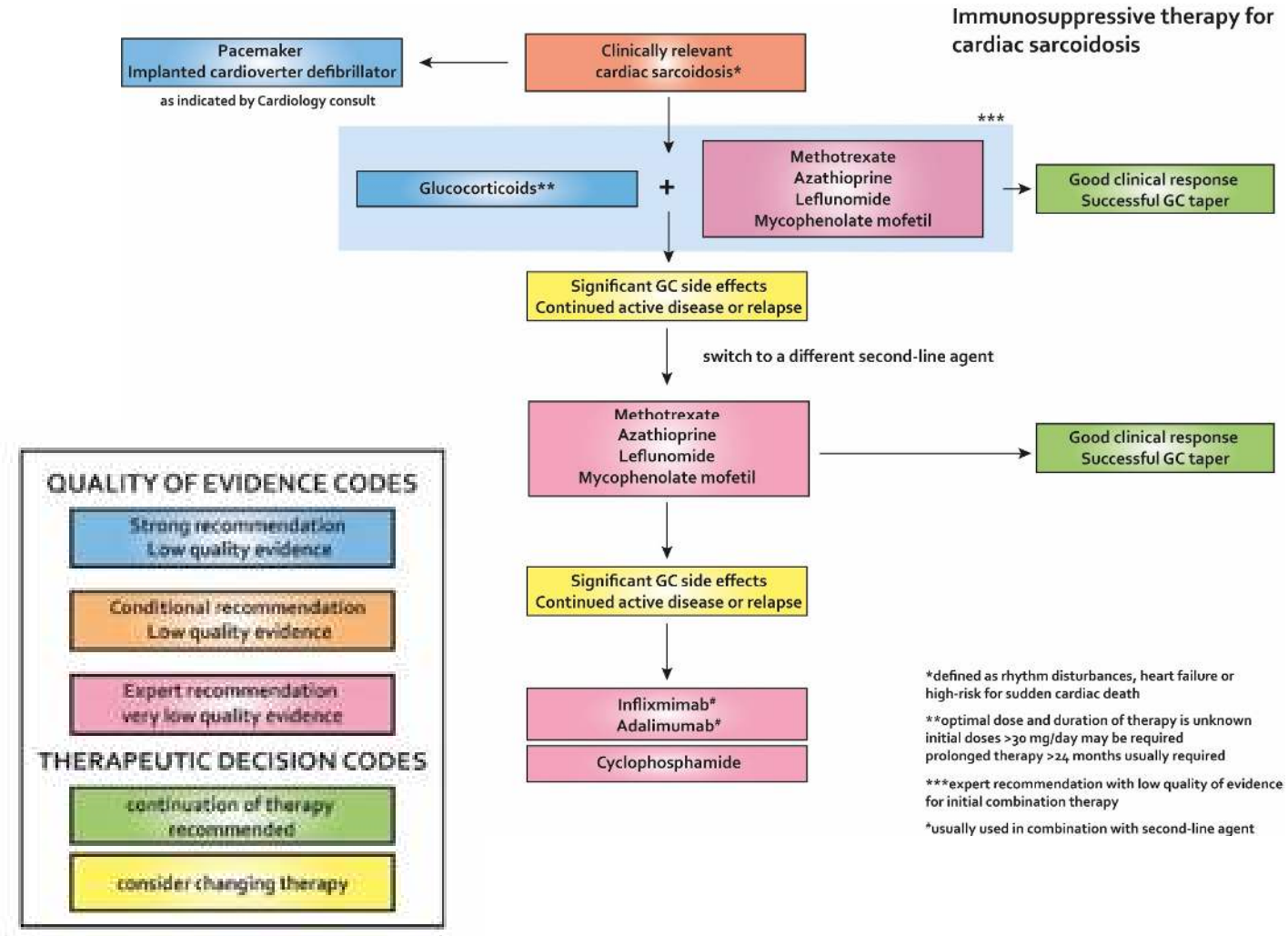
42

Patient Case

- Diagnosis:
- Danger Level:
  - No Danger
  - No Danger, Impaired QOL
  - Danger
- Treatment Choice:

Patient Case

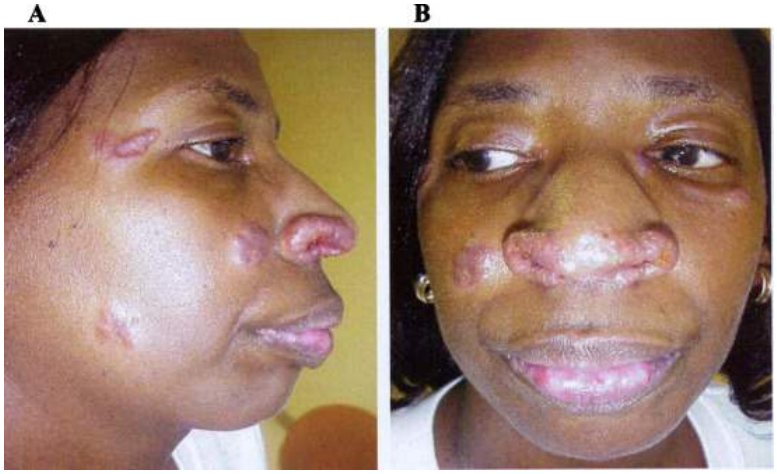
- Diagnosis: Cardiac Sarcoidosis with multisystem involvement
- Danger Level:
  - No Danger
  - No Danger, Impaired QOL
  - Danger
- Treatment Choice:
  - AICD
  - Prednisone 40 mg daily
  - Consider combination Rx with MTX


Immunosuppressive therapy for cardiac sarcoidosis
Pacemaker
Implanted cardioverter defibrillator
as indicated by Cardiology consult
Clinically relevant cardiac sarcoidosis*
***
Glucocorticoids**
+
Methotrexate
Azathioprine
Leflunomide
Mycophenolate mofetil
Good clinical response
Successful GC taper
Significant GC side effects
Continued active disease or relapse
switch to a different second-line agent
Methotrexate
Azathioprine
Leflunomide
Mycophenolate mofetil
Good clinical response
Successful GC taper
Significant GC side effects
Continued active disease or relapse
Infliximab#
Adalimumab#
Cyclophosphamide
QUALITY OF EVIDENCE CODES
Strong recommendation
Low quality evidence
Conditional recommendation
Low quality evidence
Expert recommendation
very low quality evidence
THERAPEUTIC DECISION CODES
continuation of therapy recommended
consider changing therapy
*defined as rhythm disturbances, heart failure or high-risk for sudden cardiac death
**optimal dose and duration of therapy is unknown
initial doses >30 mg/day may be required
prolonged therapy >24 months usually required
***expert recommendation with low quality of evidence for initial combination therapy
#usually used in combination with second-line agent

45

Patient Case

- 35-year-old woman with facial rash. Bx confirmed sarcoidosis.
- Failed topical steroids, oral prednisone, and MTX.
- Normal PFT, echo, i-cal.



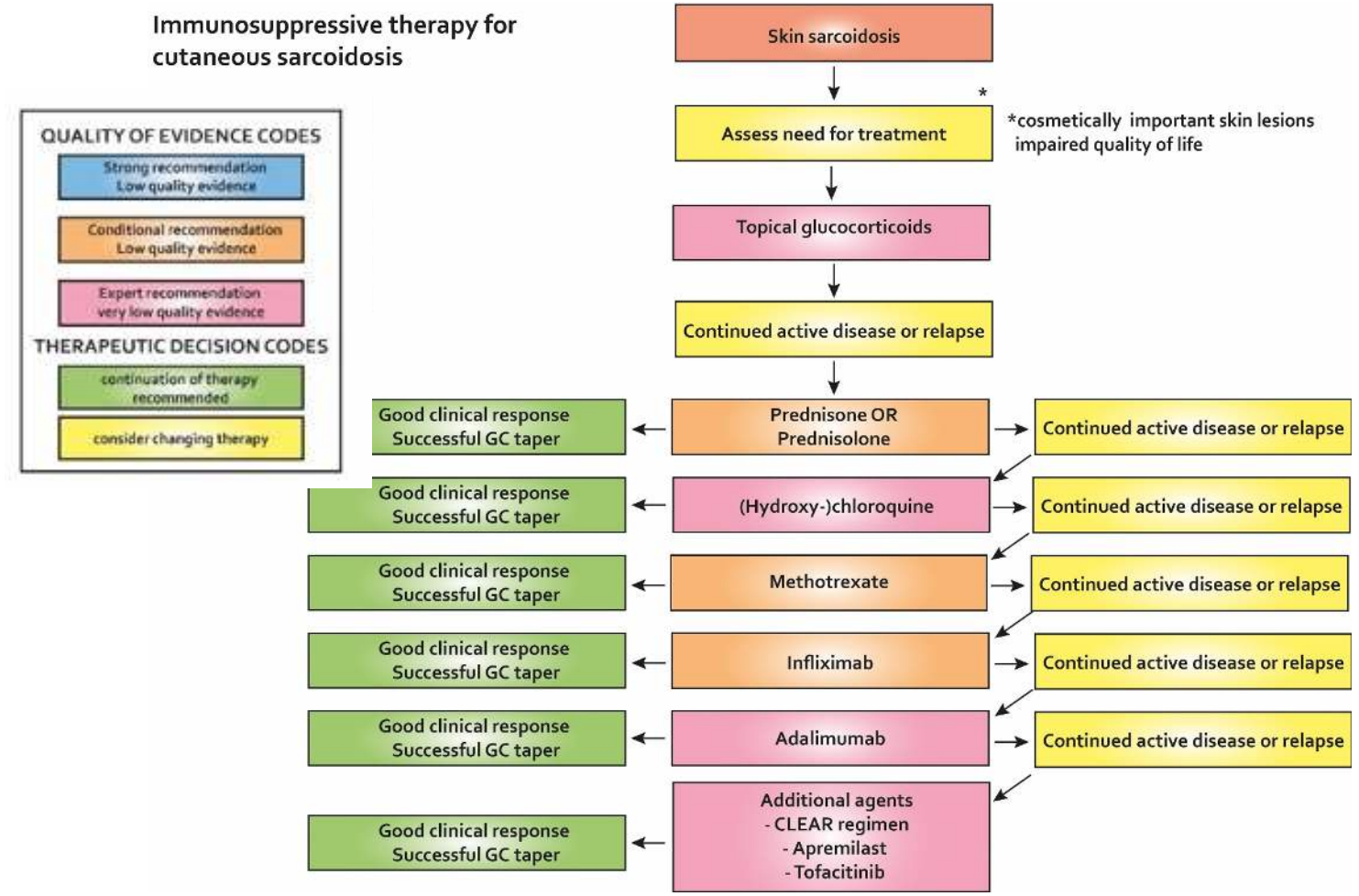
Lupus pernio

Patient Case

- Diagnosis:
- Danger Level:
  - No Danger
  - No Danger, Impaired QOL
  - Danger
- Treatment Choice:

Patient Case

- Diagnosis: Cutaneous sarcoidosis
- Danger Level:
  - No Danger
  - No Danger, Impaired QOL
  - Danger
- Treatment Choice:
  - Infliximab 3 mg/kg


Immunosuppressive therapy for cutaneous sarcoidosis
QUALITY OF EVIDENCE CODES
Strong recommendation Low quality evidence
Conditional recommendation Low quality evidence
Expert recommendation very low quality evidence
THERAPEUTIC DECISION CODES
continuation of therapy recommended
consider changing therapy
Skin sarcoidosis
Assess need for treatment
*
*cosmetically important skin lesions impaired quality of life
Topical glucocorticoids
Continued active disease or relapse
Prednisone OR Prednisolone
Good clinical response Successful GC taper
Continued active disease or relapse
(Hydroxy-)chloroquine
Good clinical response Successful GC taper
Continued active disease or relapse
Methotrexate
Good clinical response Successful GC taper
Continued active disease or relapse
Infliximab
Good clinical response Successful GC taper
Continued active disease or relapse
Adalimumab
Good clinical response Successful GC taper
Continued active disease or relapse
Additional agents
- CLEAR regimen
- Apremilast
- Tofacitinib
Good clinical response Successful GC taper

Sarcoidosis Management

- Treat for definite indications
- Monitor for adverse effects
- Stop therapy and re-assess
- Assess patient “danger”
- Use algorithms with recommended agents
- Invite your friends to the party (subspecialty consultation)
- Be open to novel mechanisms of disease in the future

International Sarcoidosis Guideline Panel

Lausanne, Switzerland - April 24, 2017

Thank You – Questions