



LABORATORY OF RESEARCH ON DIABETES

مختبر بحث سكري

« LAREDIAB »

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# Sarcoidosis : An update for internists

AMIWIT 11-LAREDIAB 5  
9-10 December 22

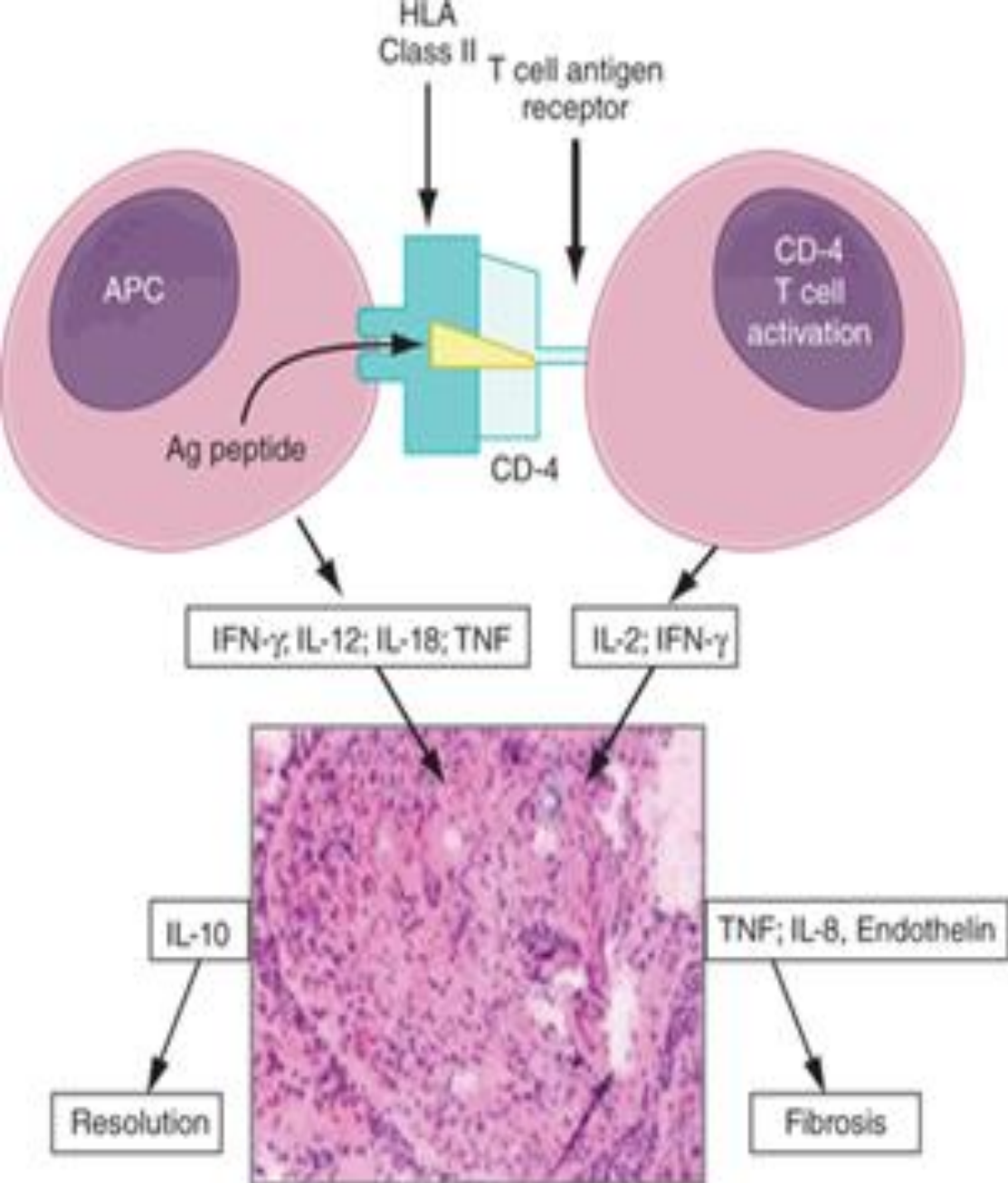
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# Introduction

- Multi organ disease
  - Wide distribution of clinical presentations
    - Some may be diagnostic
- Unknown etiology
  - Pathology supportive but not diagnostic
- Patients have a variable clinical outcome
  - Over a third never require systemic therapy
  - Up to a third need long term treatment
- Recent evidence-based guidelines have been published for diagnosis and treatment





Ocular:  
Uveitis  
Pars planitis  
Optic neuropathy  
Mutton fat keratic precipitates



Neurologic:  
Seventh cranial nerve palsy  
Lymphocytic meningitis  
Gallium enhancing lesion on MRI

Skin:  
Lupus pernio  
Erythema nodosum  
Maculo-papular lesions  
Papules within tattoo

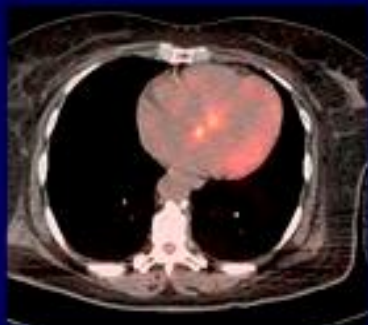


Thoracic:  
Bilateral hilar adenopathy  
Bilateral upper lobe infiltrates  
Perilymphatic nodules on HRCT  
Peribronchial thickening on HRCT  
Lymphocytic alveolitis on BAL

Liver:  
Increased alkaline phosphatase  
Hepatosplenomegaly

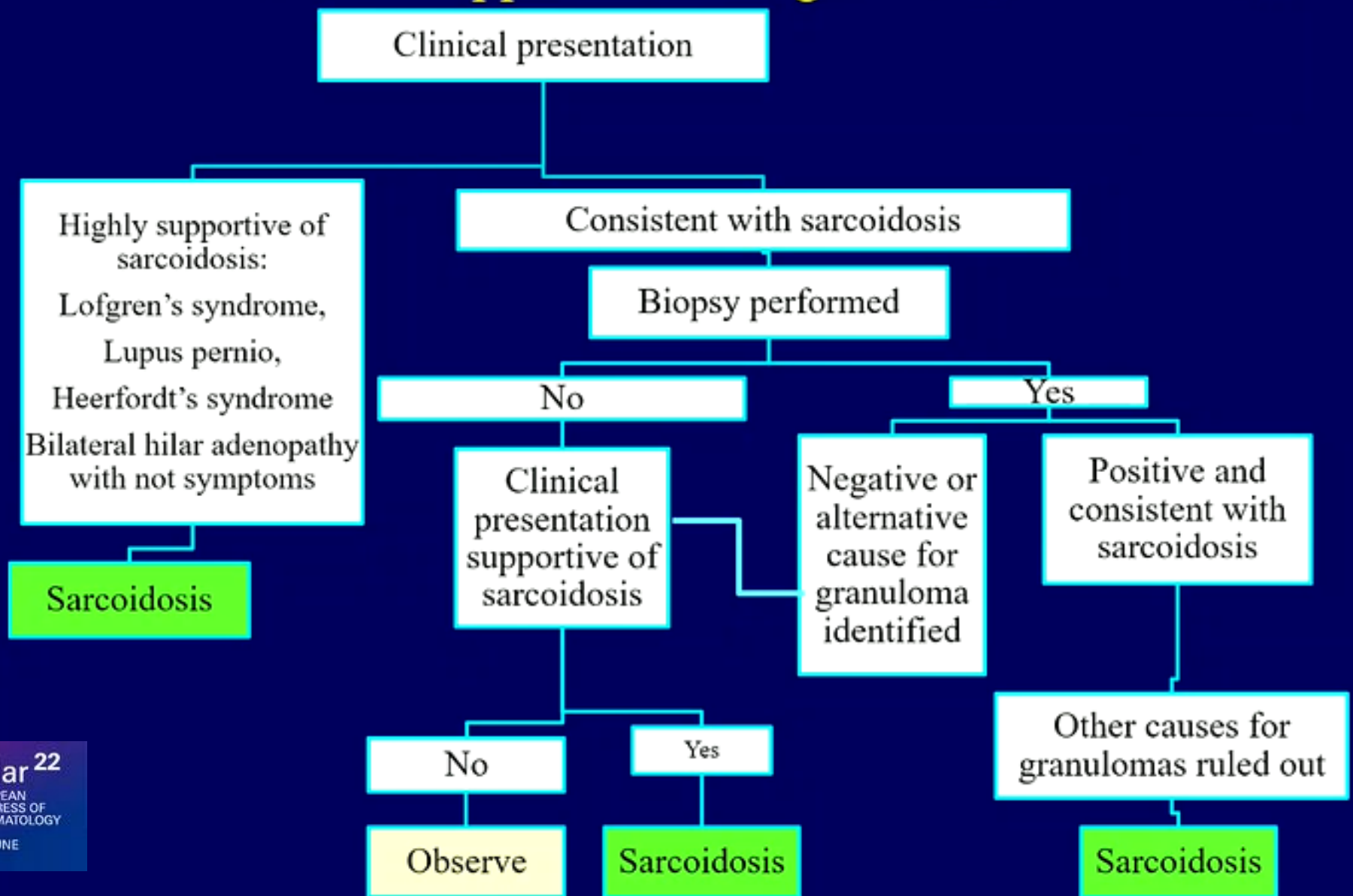


Abnormal calcium metabolism:  
Hypercalcemia or hypercalcuria  
(with or without nephrolithiasis)  
with an increased 1,25-OH  
dihydroxy vitamin D level

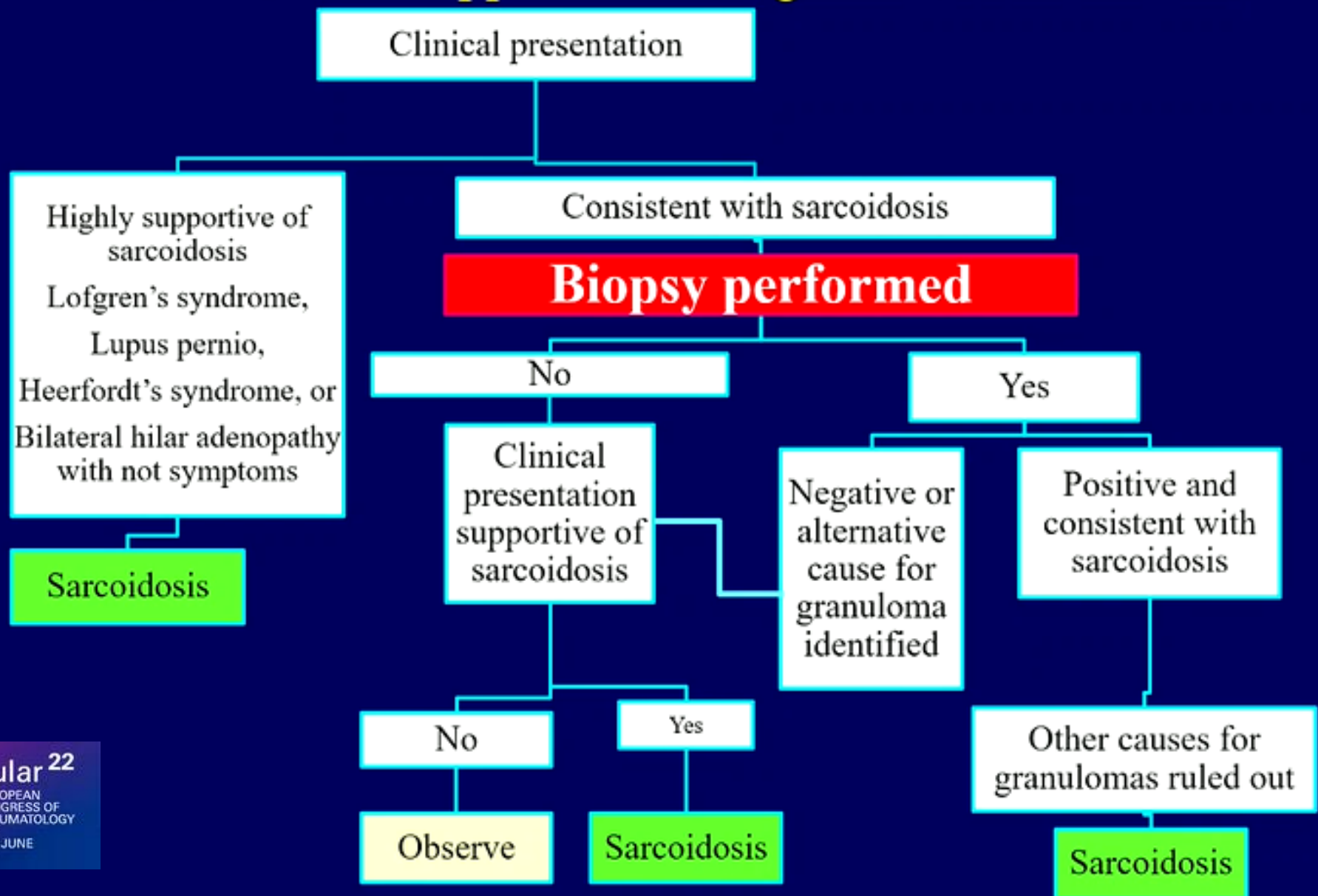


Cardiac:  
PET enhancement of myocardium  
Gallium enhancement of myocardium  
Ventricular arrhythmias  
Cardiomyopathy

# Evidence based approach to diagnosis of sarcoidosis



# Evidence based approach to diagnosis of sarcoidosis





# ACCESS 736 patients

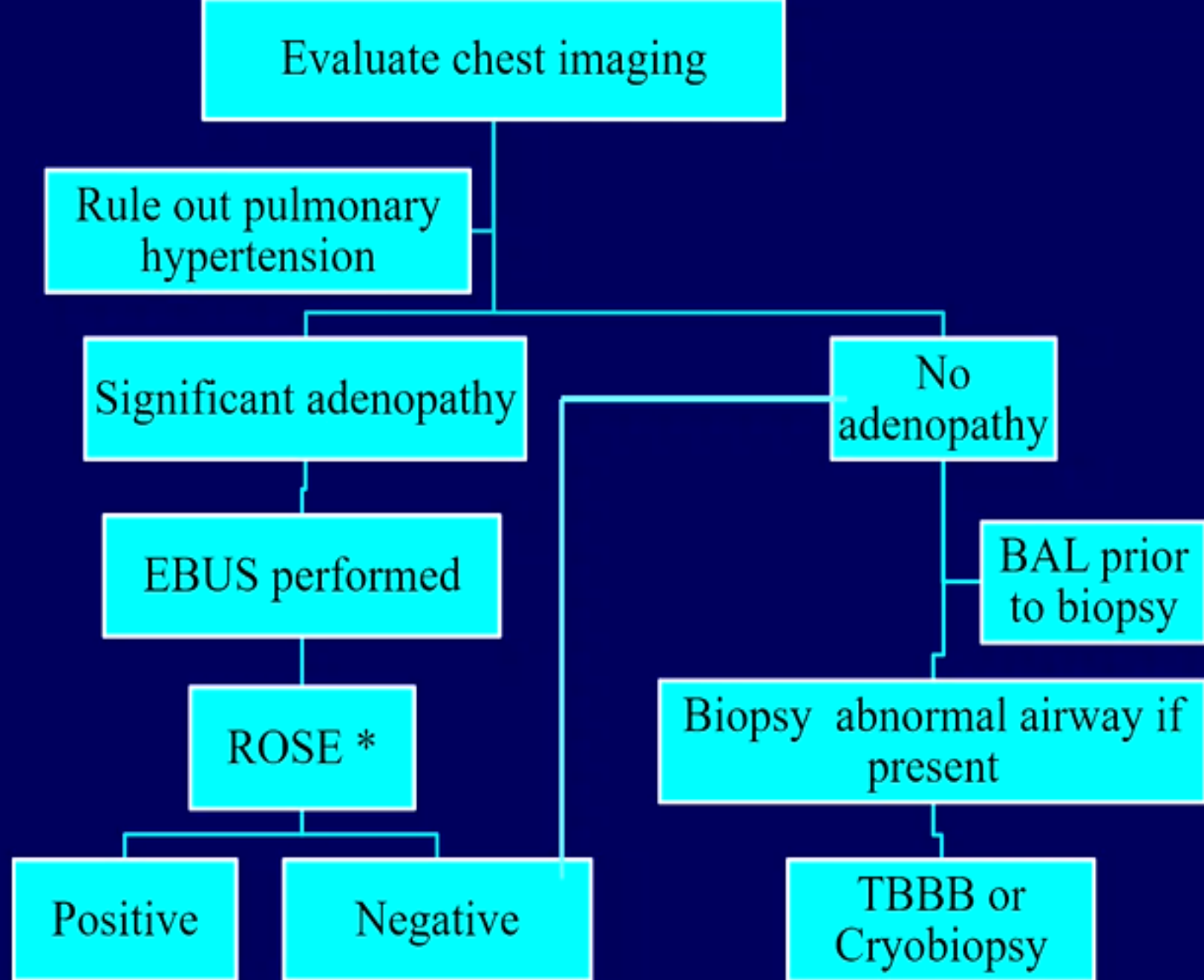
Lung is most common organ sampled to diagnose sarcoidosis

	# Cases	# Biopsied	% Biopsied of number cases
Intrathoracic	699	567	81%
Skin	117	74	63%
Peripheral lymph node	112	61	54%
Otolaryngeal	22	11	50%
Liver	85	19	22%



# Role of Bronchoscopy in Diagnosis of Sarcoidosis

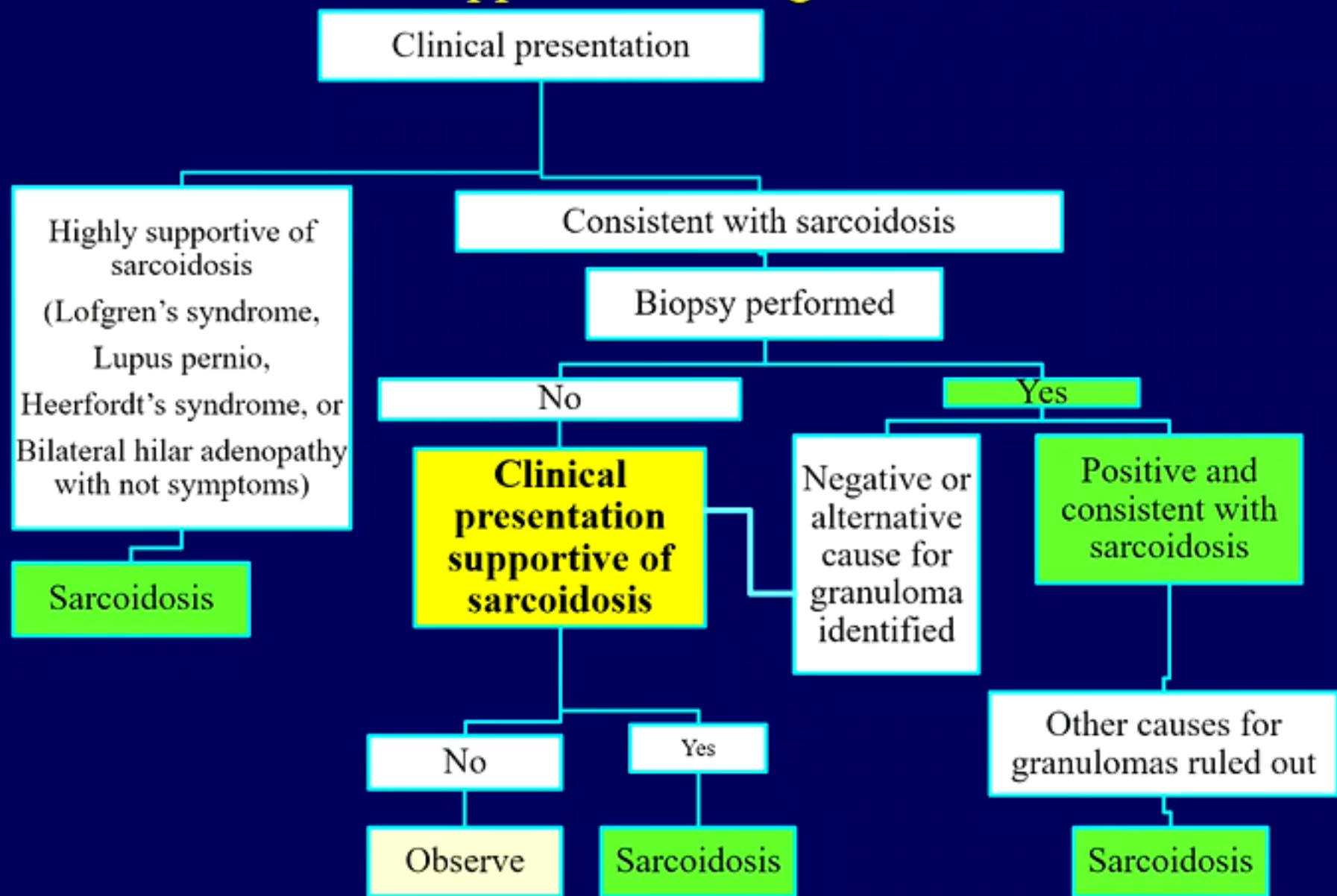
- Biopsy
  - Bronchial biopsy
  - Transbronchial biopsy
  - Cryo biopsy
- Needle biopsy
  - TBNA
  - EBUS
- Bronchoalveolar lavage
- Cultures to rule out other causes of granulomatous diseases



ROSE: Rapid On Site Evaluation

Madar K, et al. J Bronchology Interv Pulmonol 2017; 24(1):48-58

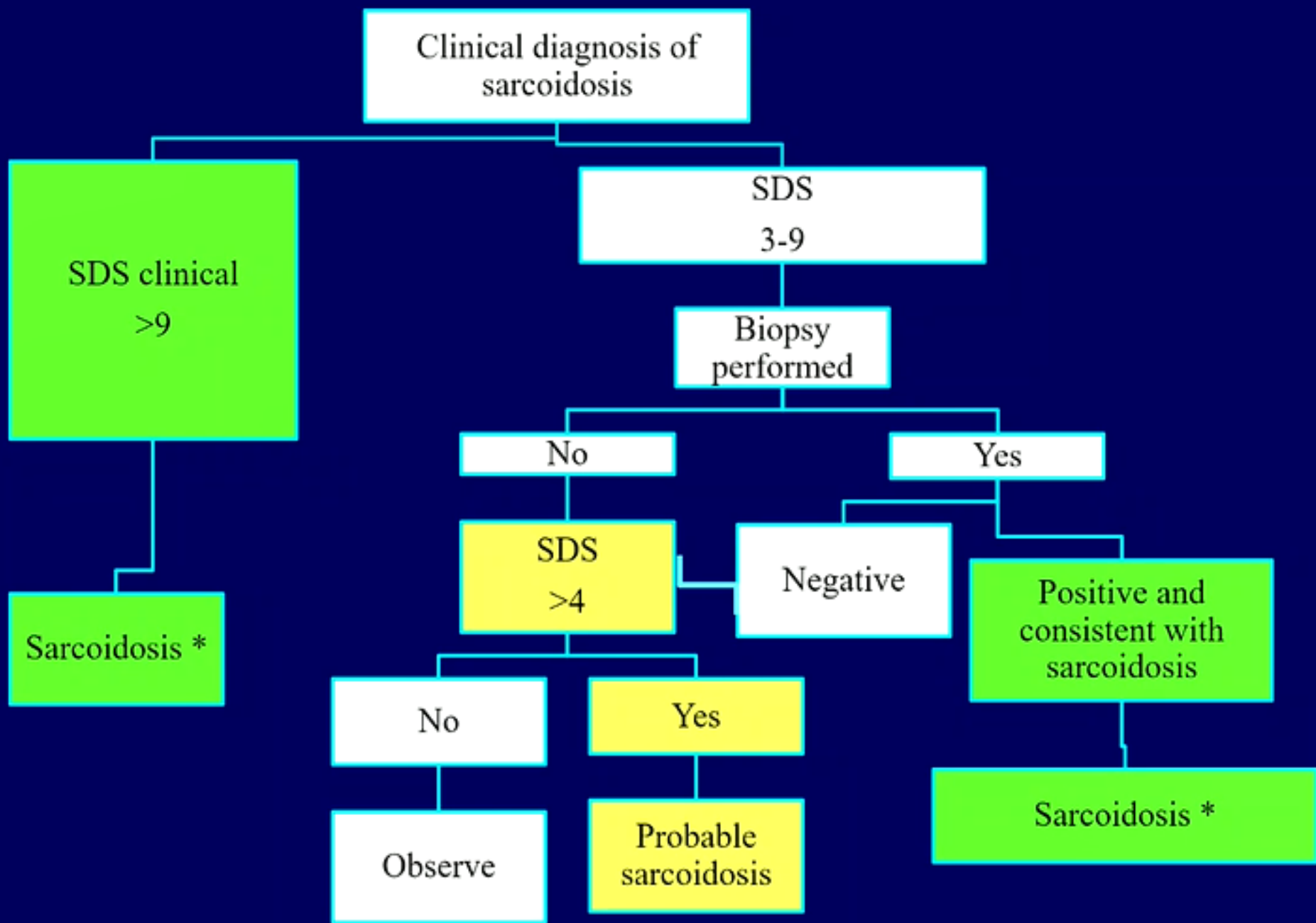
# Evidence based approach to diagnosis of sarcoidosis



# Sarcoidosis Diagnostic Score

- Scoring system based on identifying individual organ involvement using WASOG criteria (Judson MA, et al. Sarcoidosis VDL 2014; 31:19-27)
  - 3 points for each organ with highly probable organ involvement
  - 2 points for probable organ involvement
- Scoring system was developed at one institution
  - 980 patients
    - 553 with sarcoidosis
- Validated with a multi-center, multi-national study





\*In patients with beryllium exposure, ANCA, or CVID, sarcoidosis can not be

## Well's Law:

Only treat sarcoidosis to avoid danger or improve quality of life





EUROPEAN RESPIRATORY JOURNAL  
ERS OFFICIAL DOCUMENTS  
R.P. BAUGHMAN ET AL.

## ERS clinical practice guidelines on treatment of sarcoidosis

Robert P. Baughman<sup>1</sup>, Dominique Valeyre<sup>2</sup>, Peter Korsten <sup>3</sup>, Alexander G. Mathioudakis <sup>4</sup>,  
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Dominique Israel-Biet<sup>10</sup>, Jan C. Grutters<sup>11,12</sup>, Marjolein Drent <sup>11,13,14</sup>, Daniel A. Culver<sup>15</sup>,  
Francesco Bonella <sup>16</sup>, Katerina Antoniou<sup>17</sup>, Filippo Martone<sup>18</sup>, Bernd Quadder<sup>19</sup>, Ginger Spitzer<sup>20</sup>,  
Blin Nagavci<sup>21</sup>, Thomy Tonia<sup>22</sup>, David Rigau<sup>23</sup> and Daniel R. Ouellette<sup>24</sup>

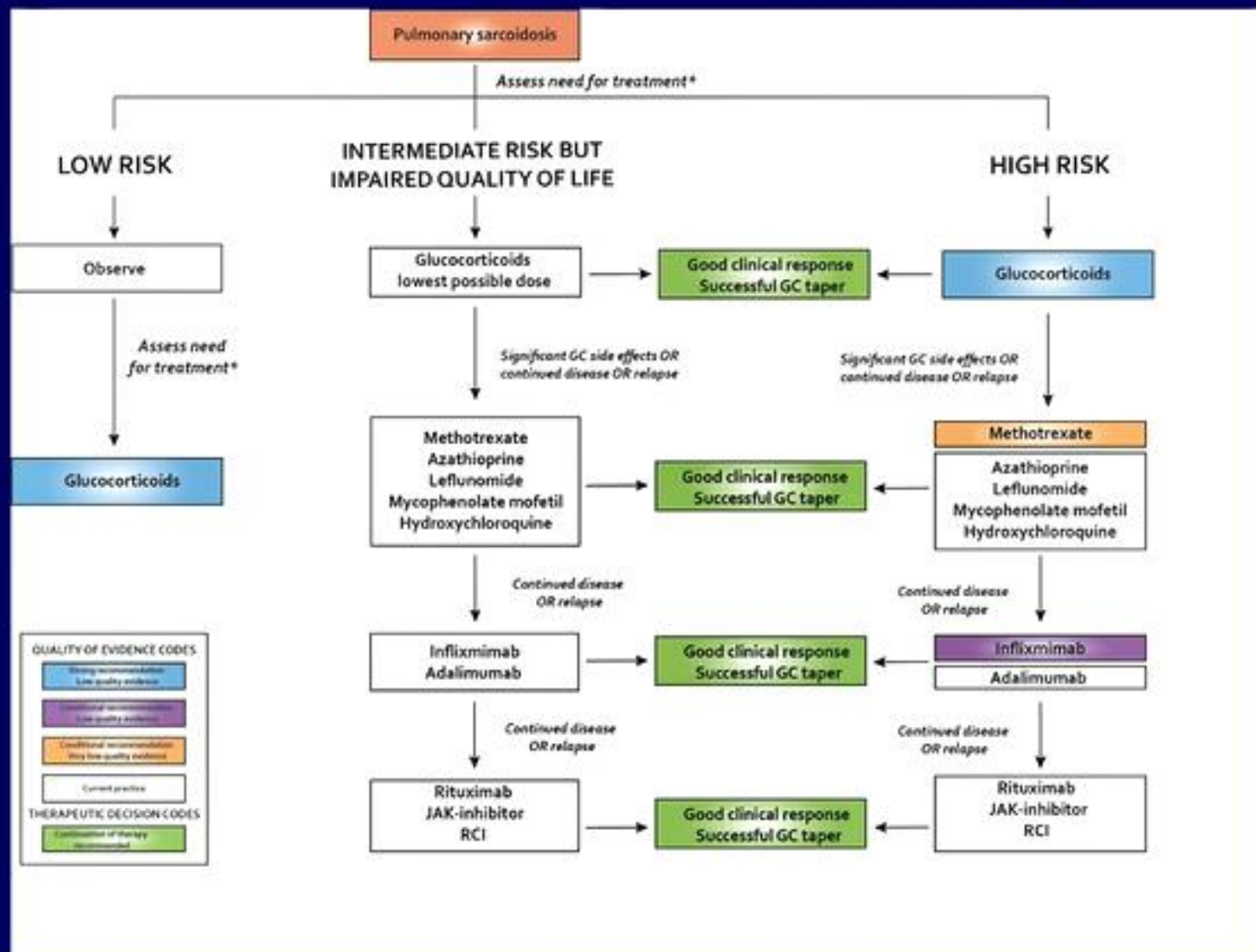
TABLE 1 Task Force recommendations

PICO question	Recommendations
1) In patients with pulmonary sarcoidosis, should glucocorticoid treatment be used <i>versus</i> no immunosuppressive treatment?	<ul style="list-style-type: none"> <li>For untreated patients with major involvement from pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis, we recommend the introduction of glucocorticoid treatment to improve and/or preserve FVC and QoL. (<i>Strong recommendation, low quality of evidence.</i>)</li> </ul>
2) In patients with pulmonary sarcoidosis, should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?	<ul style="list-style-type: none"> <li>For patients with symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids and have continued disease or unacceptable side-effects from glucocorticoids, we suggest the addition of methotrexate to improve and/or preserve FVC and QoL. (<i>Conditional recommendation, very low quality of evidence.</i>)</li> <li>For patients with symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued disease, we suggest the addition of infliximab to improve and/or preserve FVC and QoL. (<i>Conditional recommendation, low quality of evidence.</i>)</li> </ul>
3) In patients with cutaneous sarcoidosis, should glucocorticoid treatment be used <i>versus</i> no immunosuppressive treatment?	<ul style="list-style-type: none"> <li>For patients with cutaneous sarcoidosis and cosmetically important active skin lesions which cannot be controlled by local treatment, we suggest oral glucocorticoids be considered to reduce skin lesions. (<i>Conditional recommendation, very low quality of evidence.</i>)</li> </ul>
4) In patients with cutaneous sarcoidosis, should one add other immunosuppressive treatment when treatment with glucocorticoids has not been effective?	<ul style="list-style-type: none"> <li>For patients with cutaneous sarcoidosis who have been treated with glucocorticoids and/or other immunosuppressive agents and have continued cosmetically important active skin disease, we suggest the addition of infliximab compared to no additional treatment to reduce skin lesions. (<i>Conditional recommendation, low quality of evidence.</i>)</li> </ul>

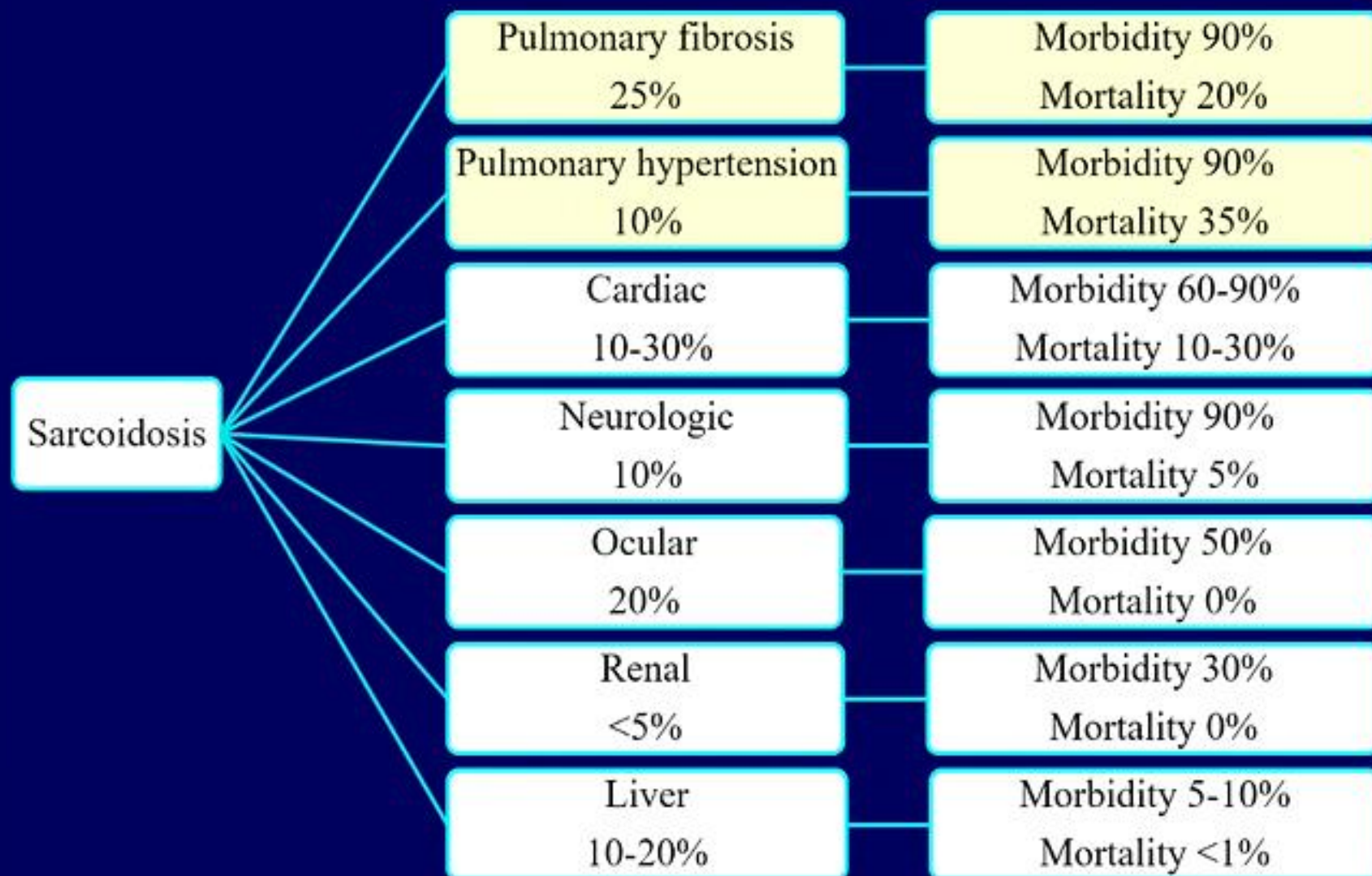


- 5) In patients with clinically relevant cardiac sarcoidosis, should glucocorticoids with or without other immunosuppressives *versus* no immunosuppression be used?
- For patients with evidence of functional cardiac abnormalities, including heart block, dysrhythmias or cardiomyopathy, we recommend the use of glucocorticoids (with or without other immunosuppressives). (*Strong recommendation, very low quality of evidence.*)
- 6) In patients with neurosarcoidosis, should immunosuppressive treatment be used *versus* no immunosuppressive treatment?
- For patients with clinically significant neurosarcoidosis, we recommend treatment with glucocorticoids. (*Strong recommendation, very low quality of evidence.*)
  - For patients with neurosarcoidosis that have been treated with glucocorticoids and have continued disease, we suggest the addition of methotrexate. (*Conditional recommendation, very low quality of evidence.*)
  - For patients with neurosarcoidosis that have been treated with glucocorticoids and a second-line agent (methotrexate, azathioprine, mycophenolate mofetil) and have continued disease, we suggest the addition of infliximab. (*Conditional recommendation, very low quality of evidence.*)
- 7) In patients with sarcoidosis-associated fatigue, should immunosuppressants, neurostimulants, exercise or other treatments be used *versus* no treatment for fatigue?
- In patients with sarcoidosis who have troublesome fatigue, we suggest a pulmonary rehabilitation programme and/or inspiratory muscle strength training 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 programme, we suggest the use of *D*-methylphenidate or armodafinil for 8 weeks to test its effect on fatigue and tolerability. (*Conditional recommendation, low quality of evidence.*)
- 8) In sarcoidosis patients with small-fibre neuropathy, should immunosuppressants or intravenous immunoglobulin be prescribed *versus* no treatment?
- No recommendations were made for this PICO question due to a lack of sufficient evidence.

# European Respiratory Society Evidence Based Recommendations for Treatment of Pulmonary Sarcoidosis

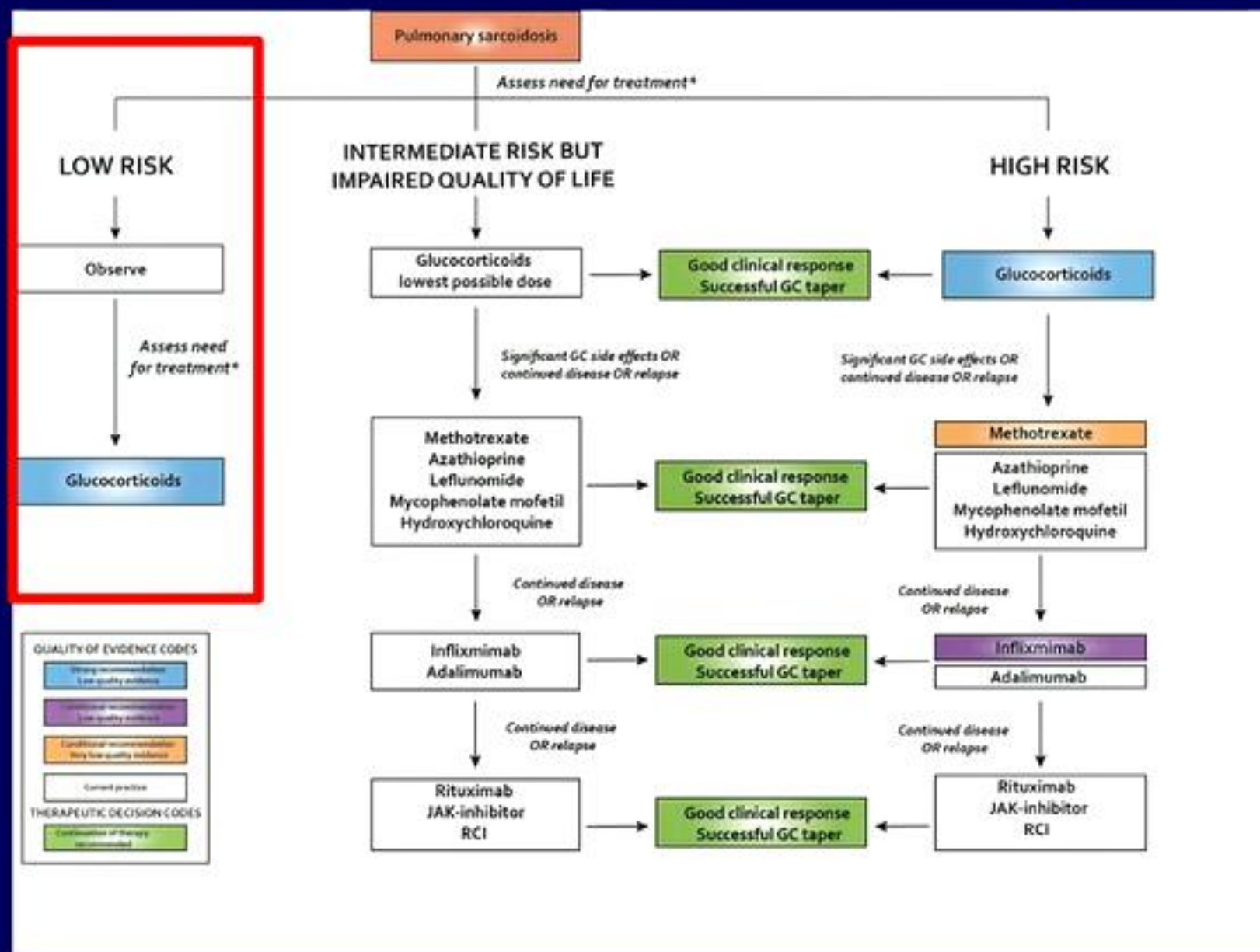


# Morbidity and Mortality of Advanced Sarcoidosis



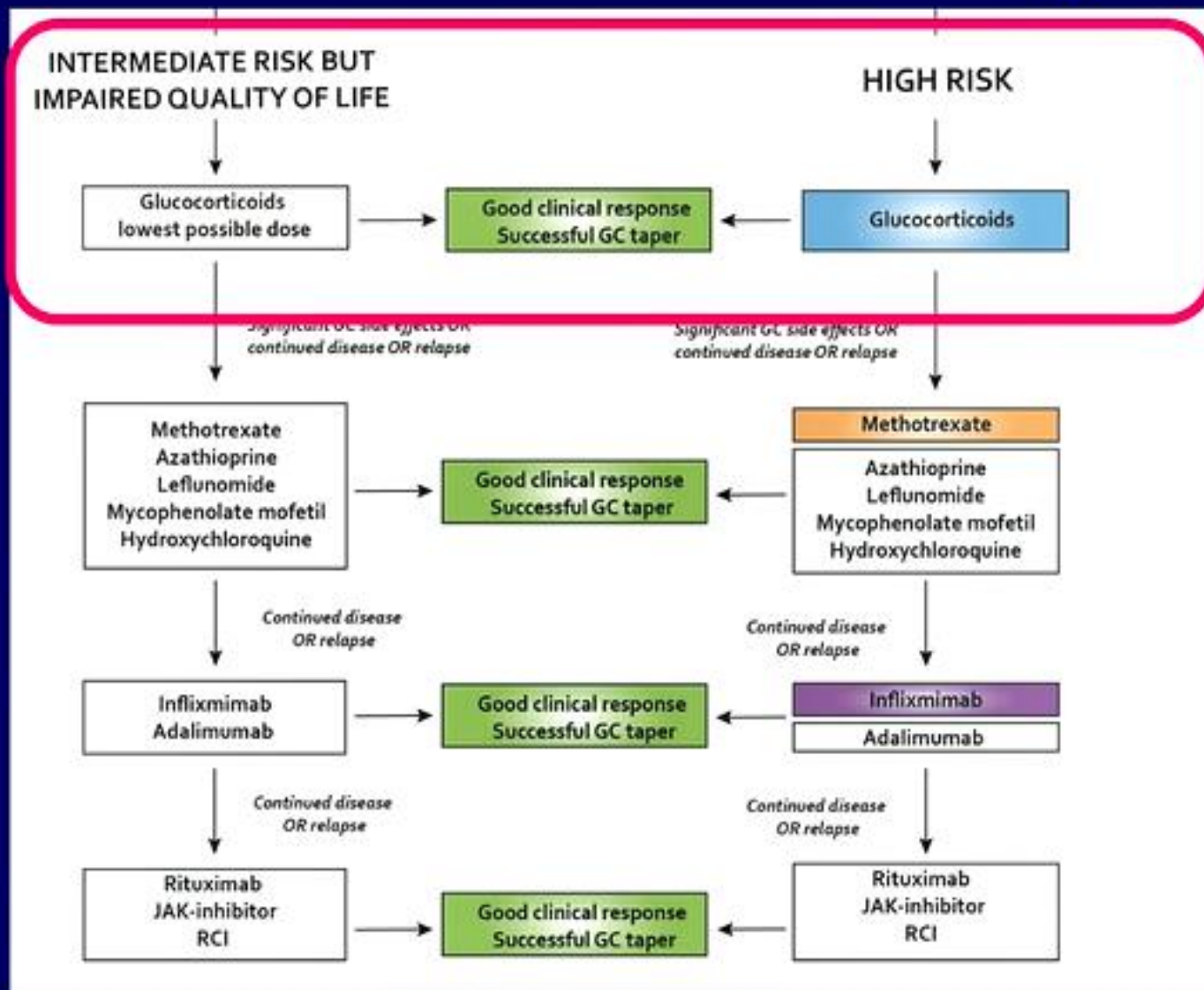


# European Respiratory Society Society Based Recommendations for Treatment of Pulmonary Sarcoidosis

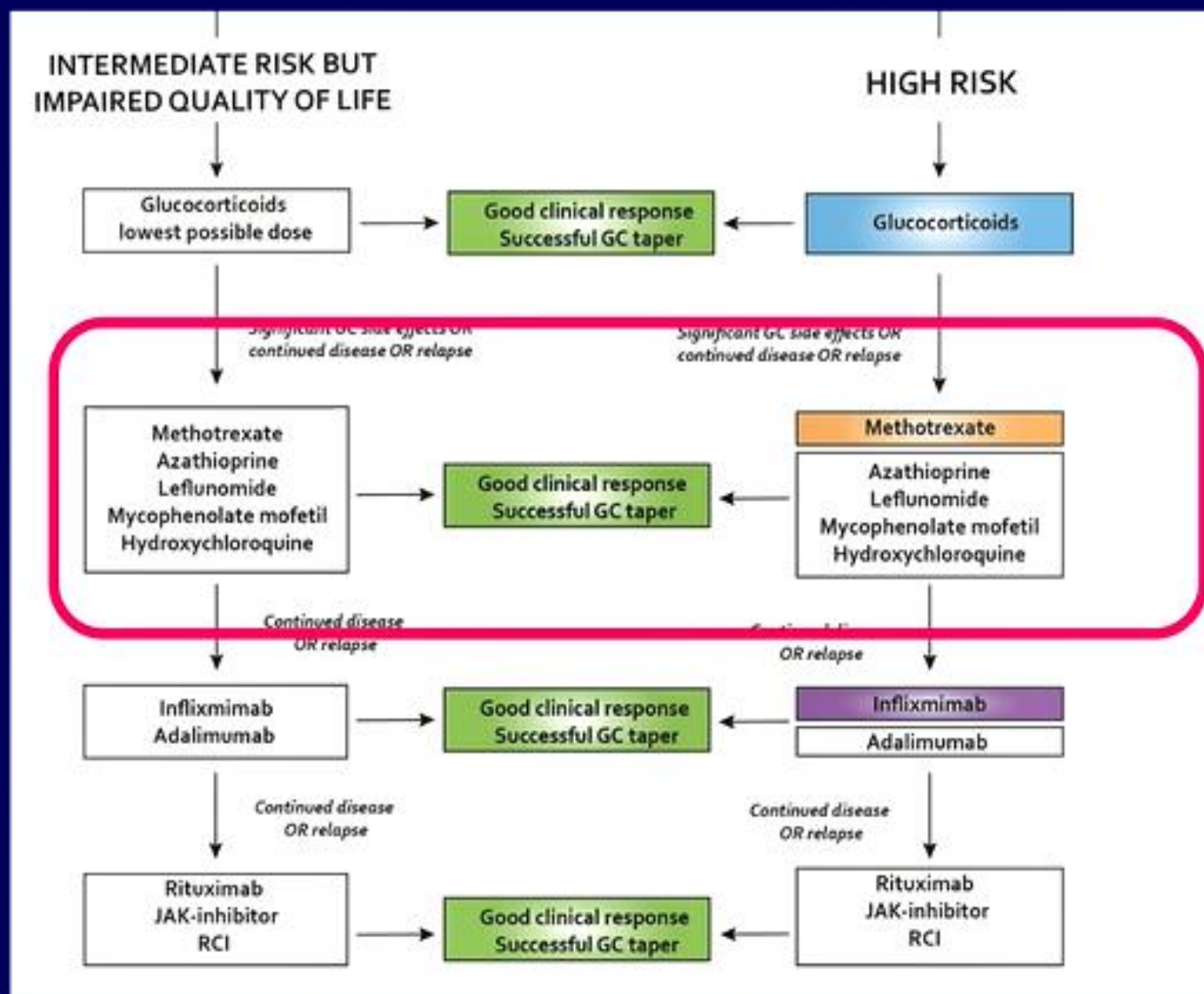




# European Respiratory Society Evidence Based Recommendations for Treatment of Pulmonary Sarcoidosis

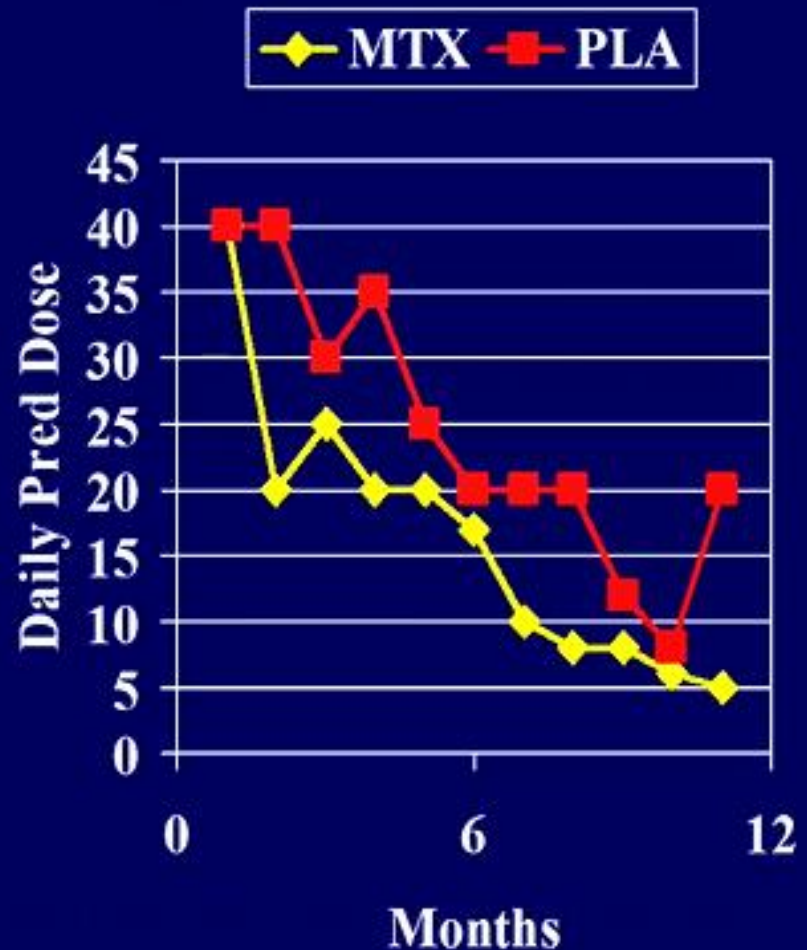


# European Respiratory Society Evidence Based Recommendations for Treatment of Pulmonary Sarcoidosis



# Steroid Sparing Effect of Methotrexate for Acute Sarcoidosis

- Methotrexate patients had a significant lower prednisone dose in the last six months of study.
- This was associated with significantly less weight gain for patients on MTX



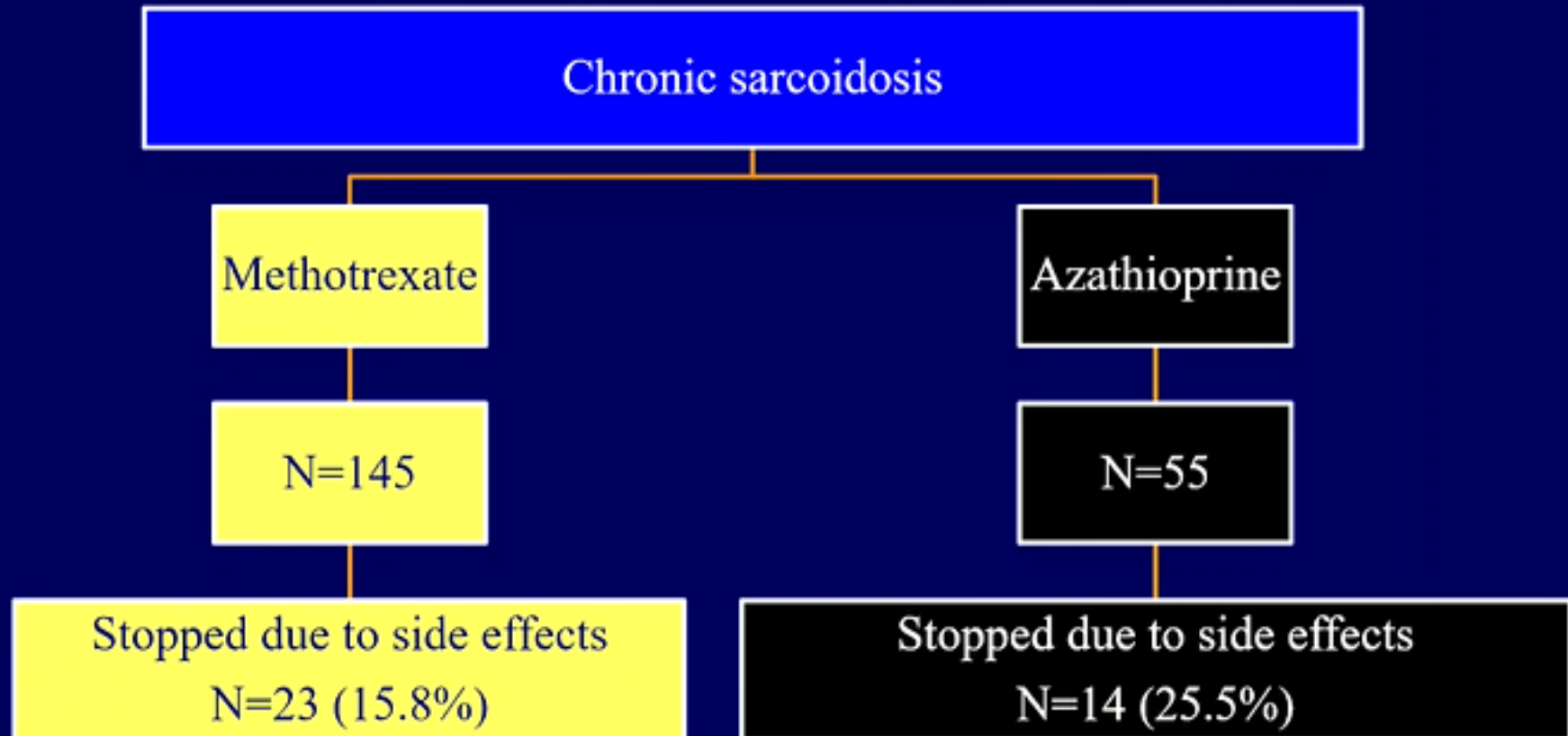


# Methotrexate vs Azathioprine

- Retrospective study of treatment of these agents as steroid sparing agents
- Two sites employing different therapy
  - One site: Methotrexate
  - Other site: Azathioprine

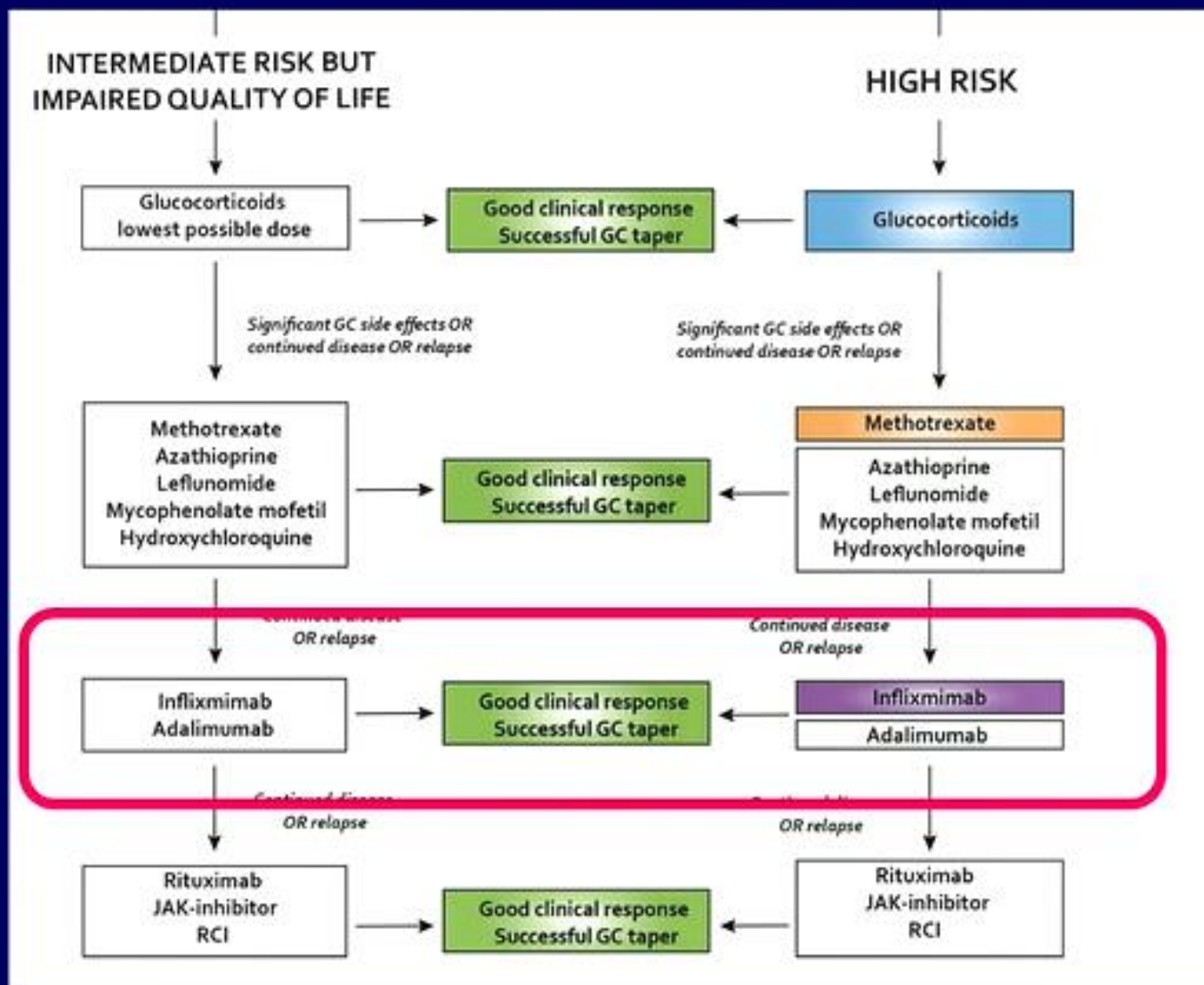


# Comparison of Methotrexate to Azathioprine



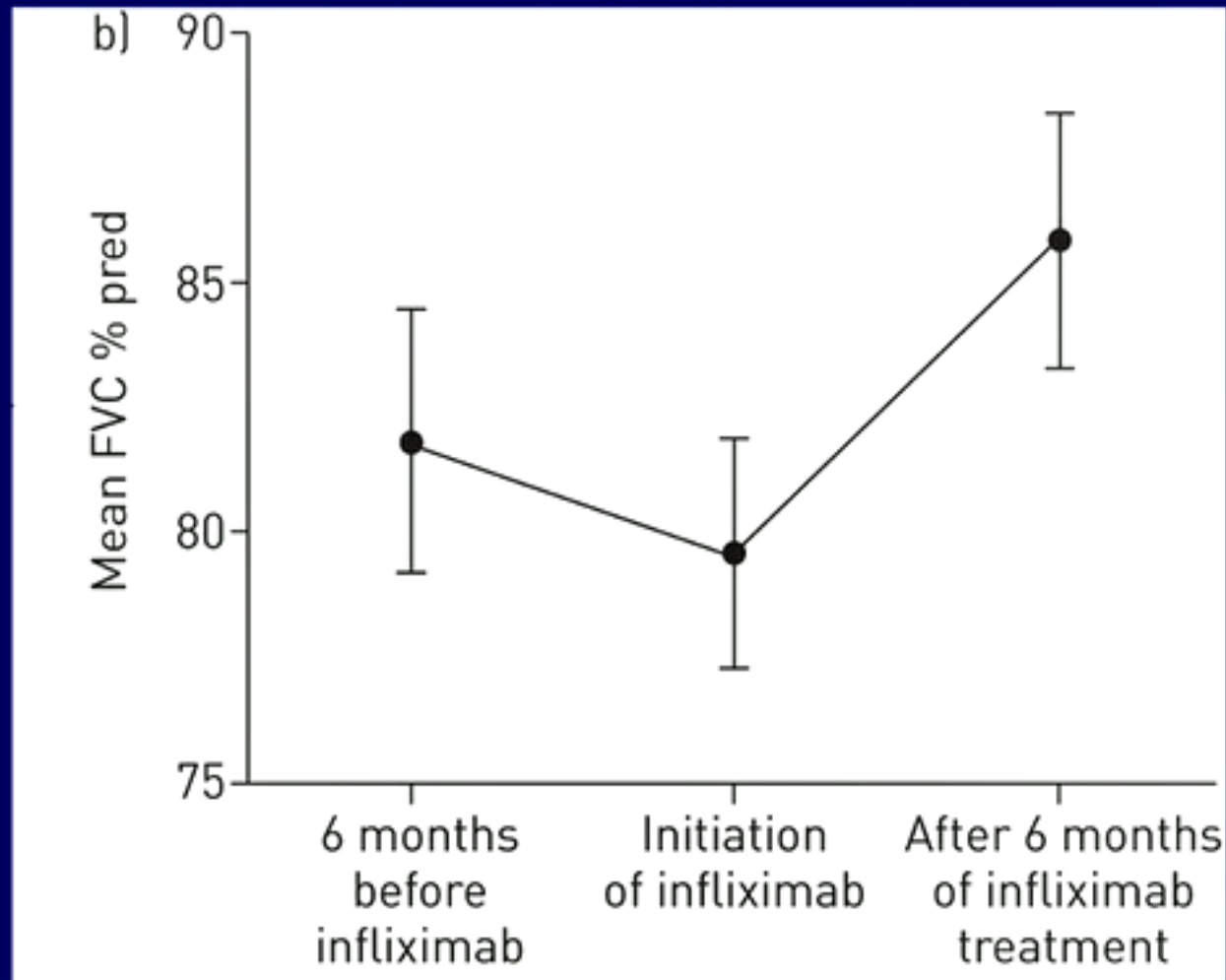
- Reduction of dose of prednisone mean 10 mg over first year, similar for both treatments
- Improvement in FVC of 95 ml/year, no difference between groups
- More likely to discontinue azathioprine, usually due to infection,  $p=0.01$

# European Respiratory Society Evidence Based Recommendations for Treatment of Pulmonary Sarcoidosis



# Infliximab treatment for 26 weeks

## 48 patients studied



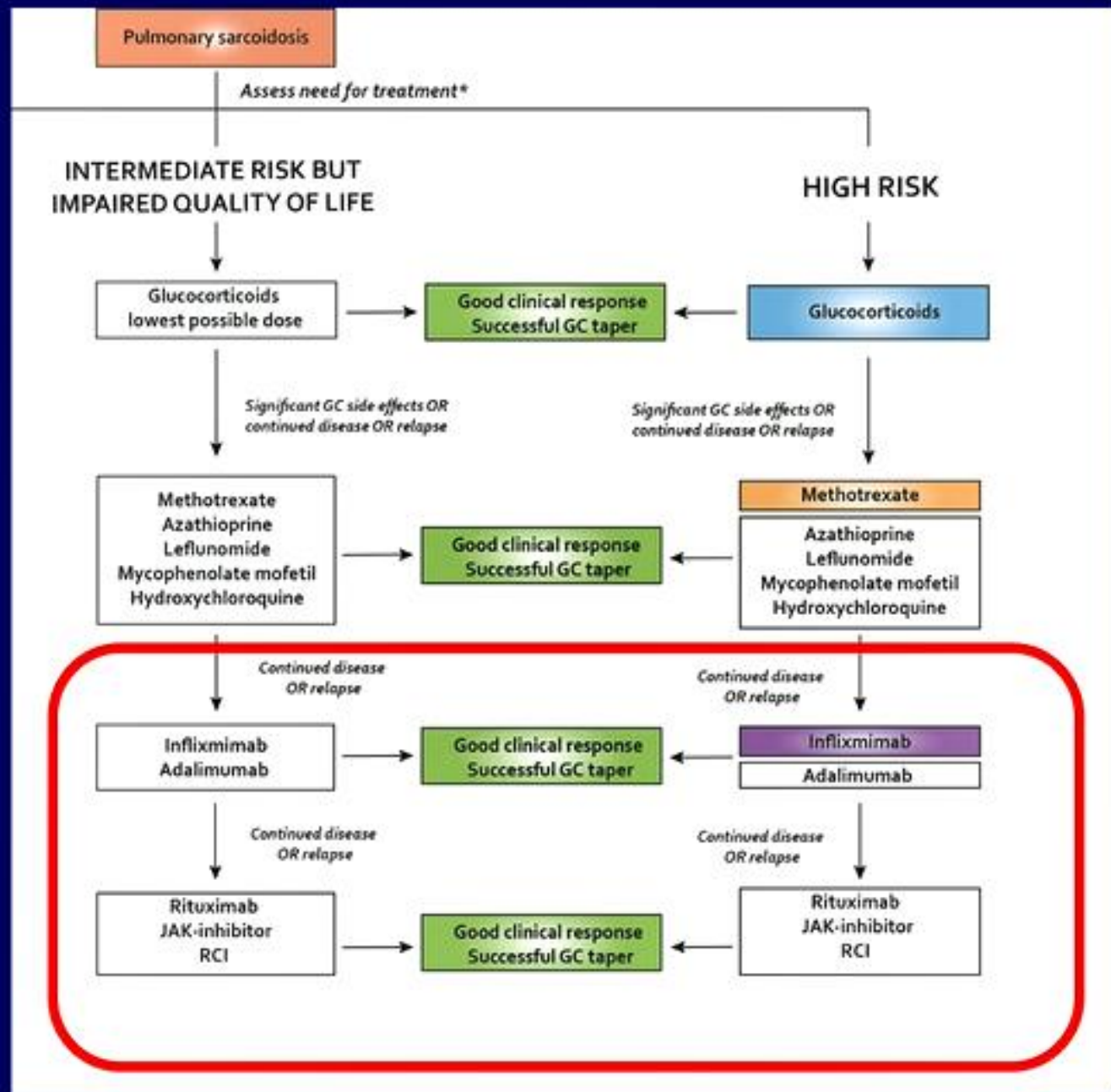
# Who should be considered for infliximab therapy?

- Chronic advanced pulmonary disease
- Evidence for ongoing inflammation
  - Elevated CRP
  - Increased soluble IL-2 receptor
  - Positive PET scan
- Lupus pernio
- Neurologic disease
- Refractory eye disease



# Not all anti-TNF agents are the same

- Etanercept less effective
  - TNF receptor antagonist
  - Limited benefit in treating progressive pulmonary disease
    - Utz JP et al. Chest 2003; 124(1):177-185.
  - No different from placebo in treating eye disease
    - Baughman RP et al. Chest 2005; 128(2):1062-1067.
- Golimumab showed no improvement in pulmonary disease
  - Judson MA et al. Eur Respir J 2014; 44:1296-1307.



# Third Line Drugs for Sarcoidosis recommended ERS Guidelines 2021

Agent	Mechanism of Action	Studies supporting usage	GRADE recommendation	Case by case recommendation
Infliximab	Anti-TNF monoclonal antibody	DBPC trial pulm/skin	Pulmonary disease	Neurologic Cardiac
Adalimumab	Anti-TNF monoclonal antibody	DBPC trial skin		Pulmonary, neurologic, cardiac
Rituximab	B cell depletion	Open label prospective trial		Pulmonary
RCI	MCRs	Open label prospective agent		Pulmonary
JAK-2		Case reports		Pulmonary



# University of Cincinnati

## Comparison of Third Line

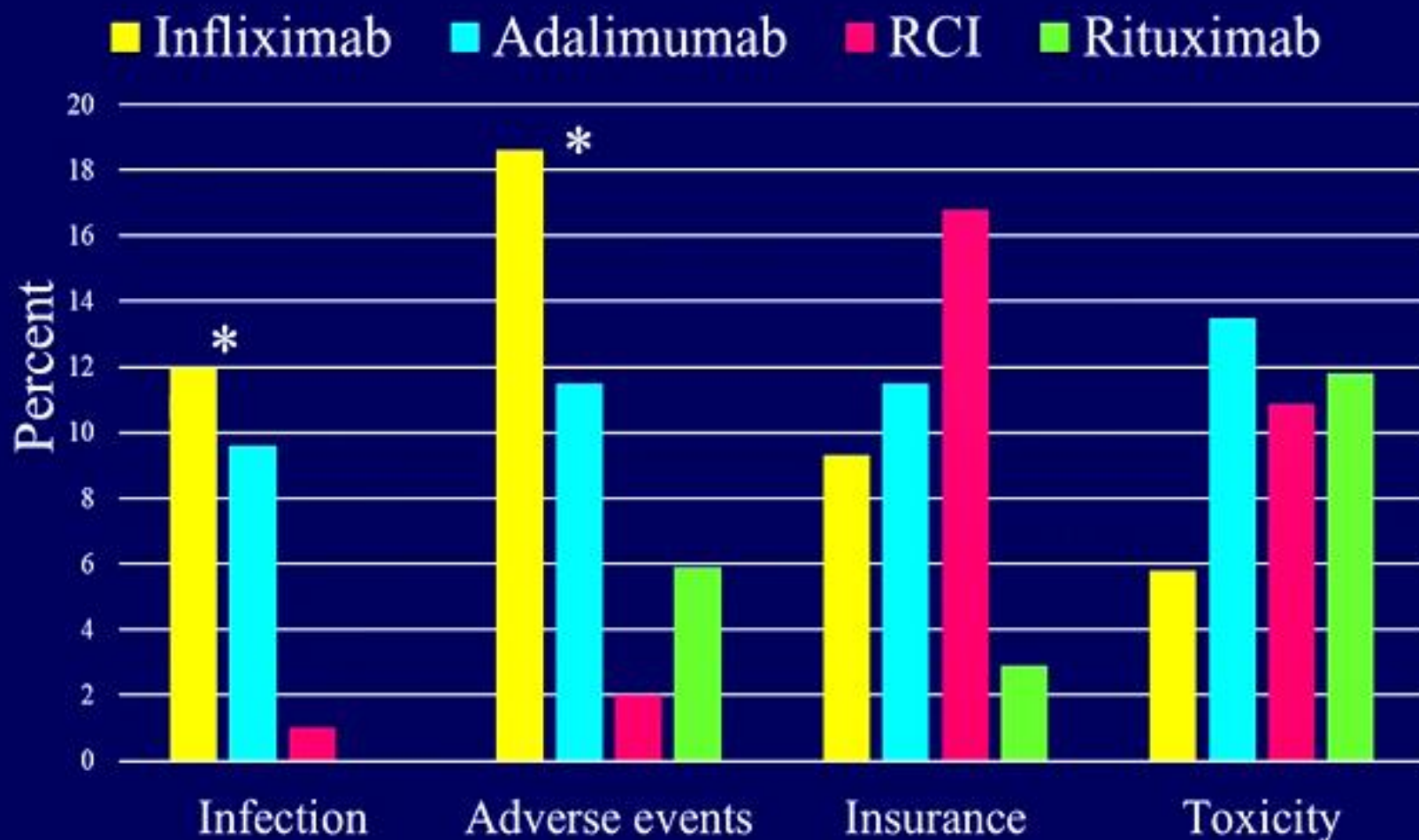
	<b>Number treated</b>	<b>Total Discontinued</b>
<b>Infliximab</b>	258	142 (55.0%)
<b>Adalimumab</b>	52	30 (57.7%)
<b>RCI</b>	101	43 (42.6%)
<b>Rituximab</b>	34	10 (29.4%) §

\*number (percent) of those treated with specific regimen

§ Differences between treatments, Chi square=11.959, p=0.0075



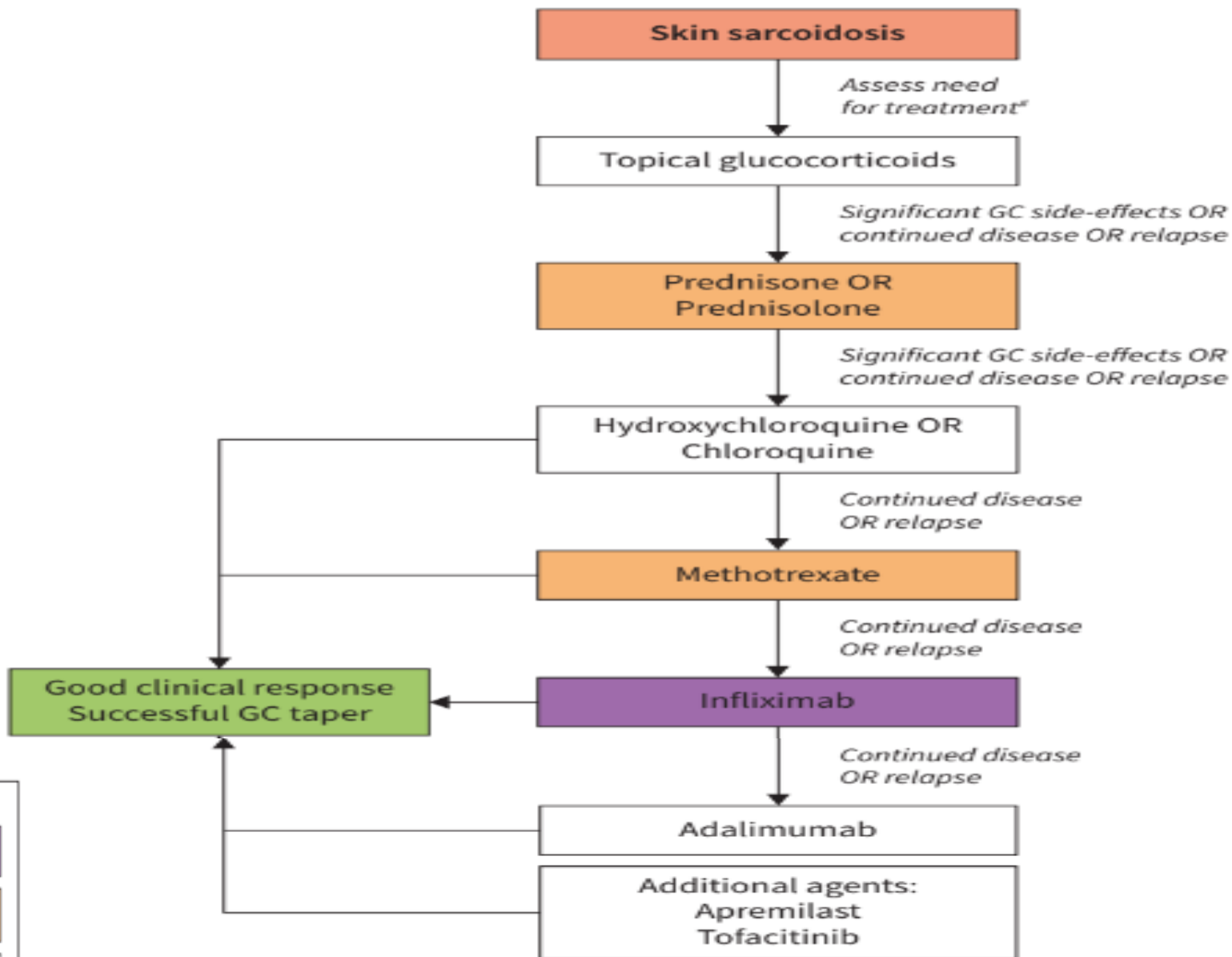
# Reasons for drug discontinuation



\* For both Infection and Adverse Events,  $p < 0.01$

## Other recommendations from ERS include

- Skin involvement
- Cardiac involvement
- Neurologic involvement
- Sarcoidosis associated fatigue
- Sarcoidosis associated small fiber neuropathy



**Quality of evidence codes:**

Conditional recommendation  
Low quality of evidence

Conditional recommendation  
Very low quality of evidence

Current practice

**Therapeutic decision codes:**

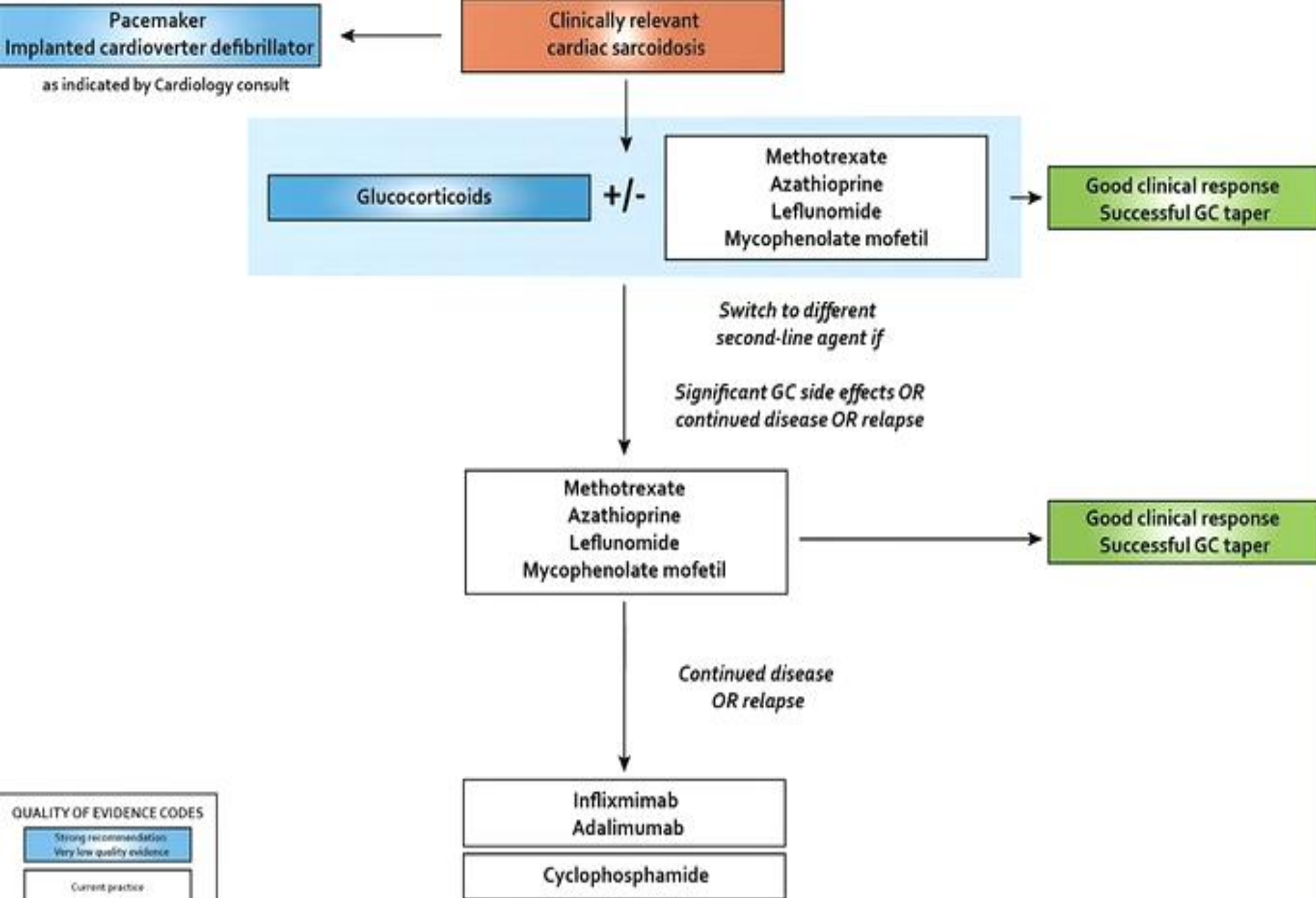
Continuation of therapy  
recommended



**First Report of use of Infliximab for sarcoidosis:  
before and after three months of Infliximab**





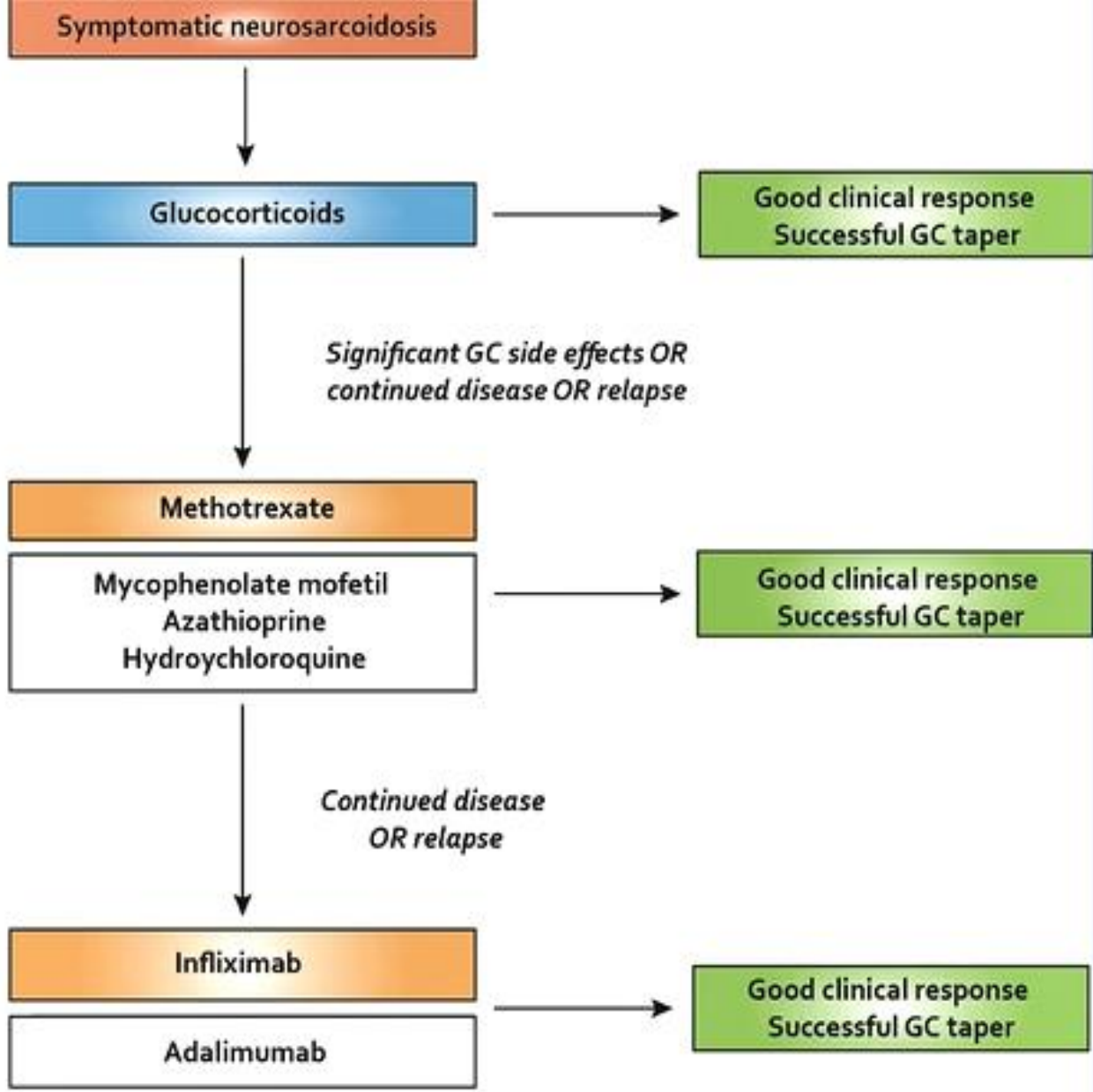


**QUALITY OF EVIDENCE CODES**

- Strong recommendation  
Very low quality evidence
- Current practice

**THERAPEUTIC DECISION CODES**

- Continuation of therapy  
recommended



**QUALITY OF EVIDENCE CODES**

Strong recommendation  
Very low quality evidence

Conditional recommendation  
Very low quality evidence

Current practice

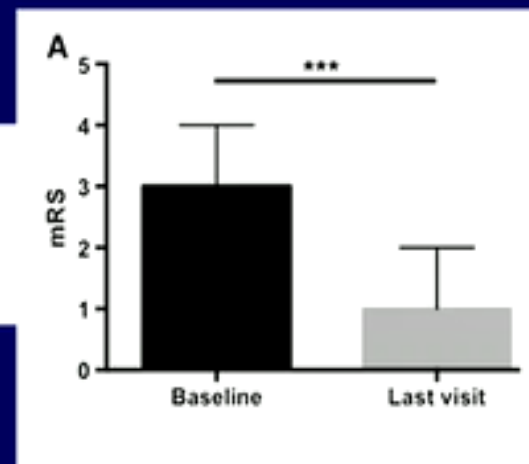
**THERAPEUTIC DECISION CODES**

Continuation of therapy  
recommended

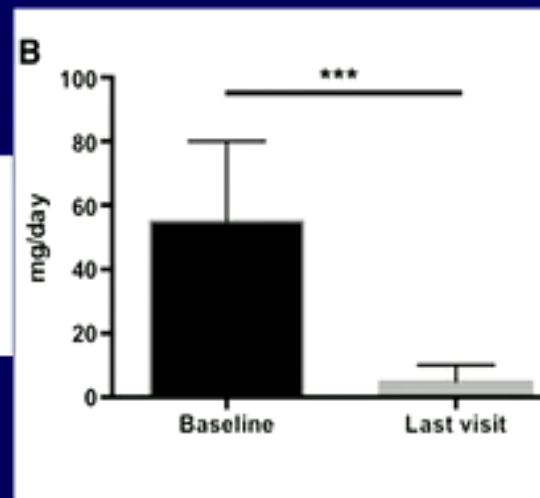
# Infliximab in neurosarcoidosis

- 18 patients studies
- At 6 months of therapy
  - Complete remission 6 (33%)
  - Partial remission 10 (56%)
  - Stable disease 2 (11%)
- Median follow-up time was 20 months (range 6–93)
- Significant improvement of modified Rankin score (mRS) and prednisone dose

**Functional status, mRS**



**Daily prednisone dose**



Sarcoidosis-associated fatigue\*

No response to treating ongoing symptomatic sarcoidosis

Exercise training  
Inspiratory muscle training

Good clinical response

Continued symptoms

Armodafinil  
D-Methylphenidate

Good clinical response

Continued symptoms

Low-dose  
Glucocorticoids  
and/or  
Methotrexate

**QUALITY OF EVIDENCE CODES**

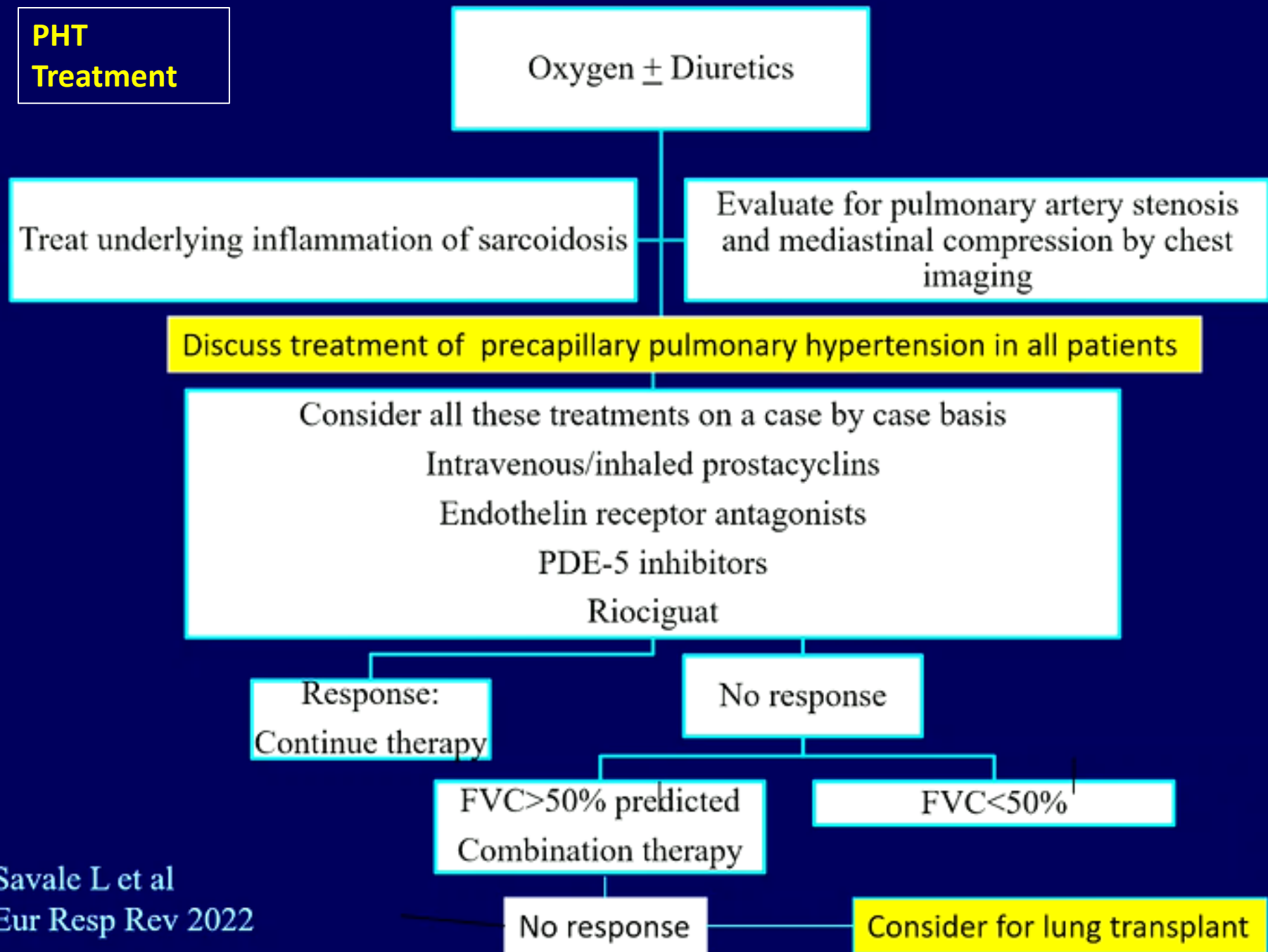
- Conditional recommendations  
Low quality evidence
- Current practice

**THERAPEUTIC DECISION CODES**

- Continuation of therapy recommended



**PHT  
Treatment**



# Conclusion

- Diagnosis of sarcoidosis is a combination of clinical features and biopsy
- Several agents are available for treating the inflammation seen in sarcoidosis
- A step wise approach to therapy seems appropriate
- Treatment for advanced disease should include both anti-inflammatory and other treatments