Sarcoidosis: Current Treatment Perspectives

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Conflict of Interest

- No conflicts of interest to declare for any materials presented in the current talk

Pulmonary Sarcoidosis: Magnitude of problem

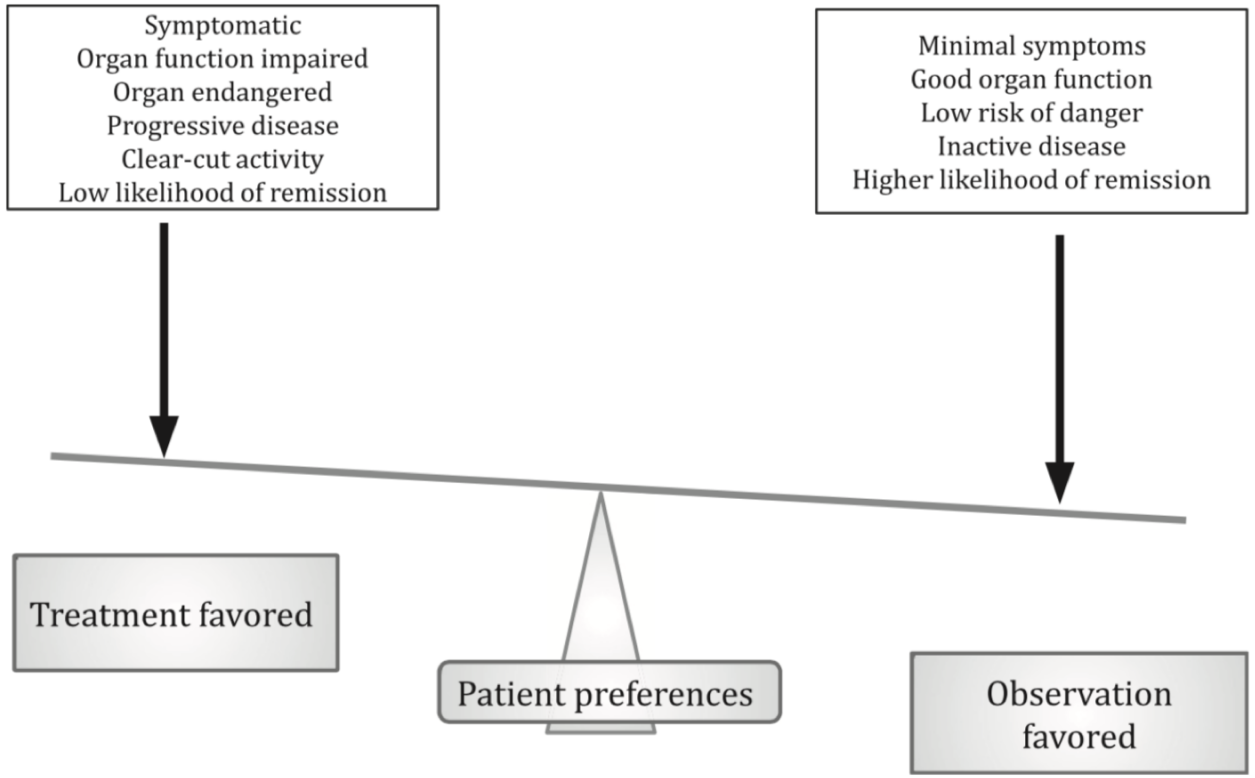
- Pulmonary involvement in 90-95% of cases of sarcoidosis
- Pulmonary sarcoid represents 23-38% of all ILDs

Valerye et al. Clin Chest Med 36 (2015) 631–641

To treat or not to treat

- A dangerous health condition
- Significant worsening of quality of life

- Simply the presence of active sarcoidosis is not always an indication for therapy



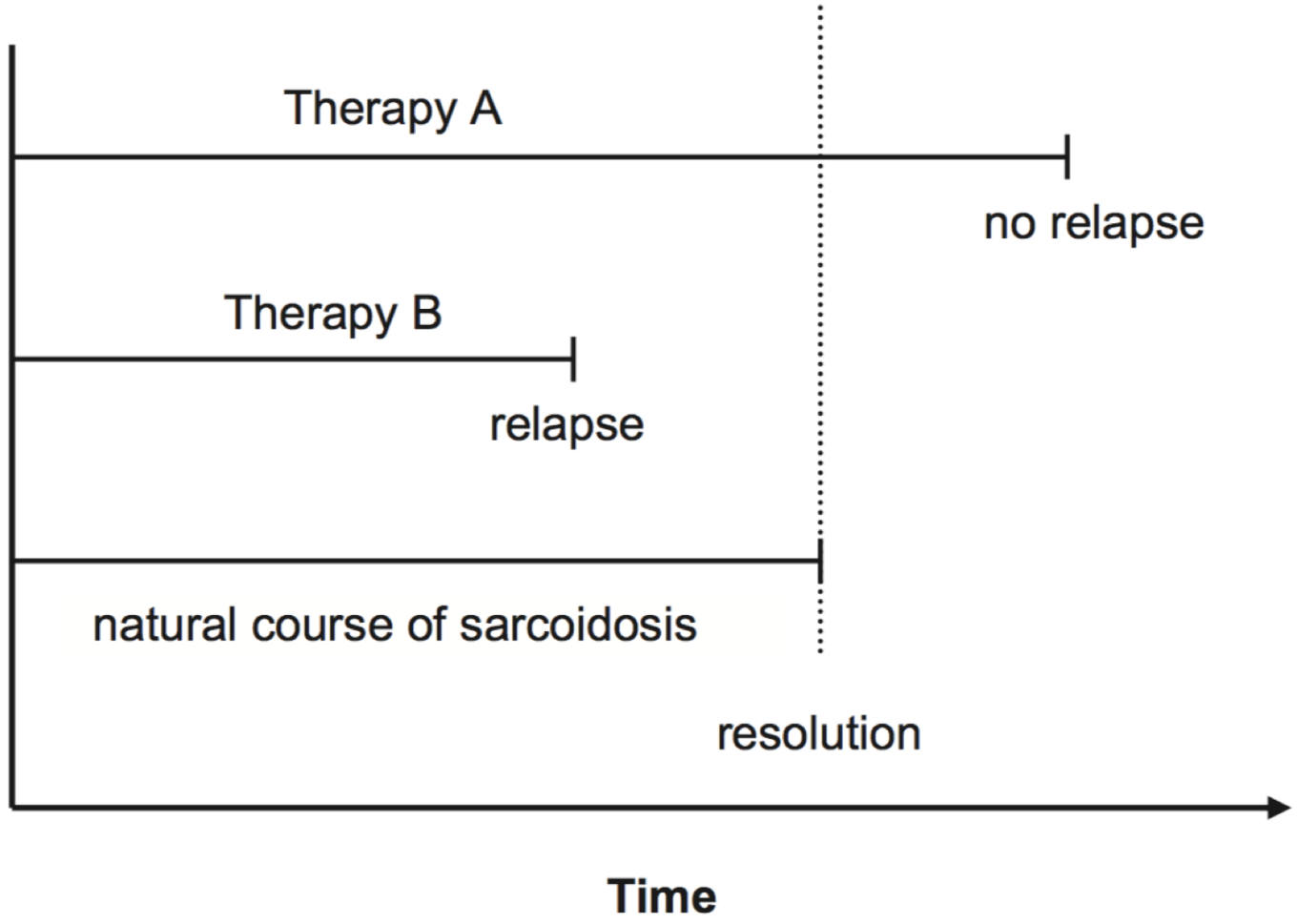
Wijsenbeek et al. Clin Chest Med 36 (2015) 751–767

Quality of life as an indication for treatment

- Pulmonary symptoms may be from an alternative etiology
- Quality of life may be from a previous granulomatous process causing fibrosis which generally does not respond to anti-granulomatous therapy

- Just because the sarcoidosis patient has symptoms does not mean treatment should be instituted

To treat or not to treat



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Non-respiratory indications for treatment of sarcoidosis

Ocular

- Posterior or intermediate uveitis
- Anterior uveitis refractory to topical therapy or with toxicities from topical therapy

Cutaneous

- Disfiguring lesions (patient choice)

Hepatic

- Impaired synthetic function
- Hyperbilirubinemia
- Progressive increase of transaminase levels
- Portal hypertension

Splenic

- Pain or early satiety caused by enlargement
- Cytopenias caused by hypersplenism

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Non-respiratory indications for treatment of sarcoidosis

Cardiac

- Second-degree or third-degree conduction block
- Ventricular dysrhythmias
- Cardiomyopathy

Neurologic

- Any brain or spinal cord involvement
- Granulomatous peripheral nerve disease
- Symptomatic myositis

Bone marrow

- Cytopenias

Endocrine

- Significant hypercalcemia/hypercalciuria
- Nephrolithiasis
- Pituitary sarcoidosis

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Respiratory indications for treatment of sarcoidosis

- Symptomatic pulmonary disease with infiltrates
- Progressive deterioration of pulmonary function tests
- Significant upper respiratory tract sarcoidosis

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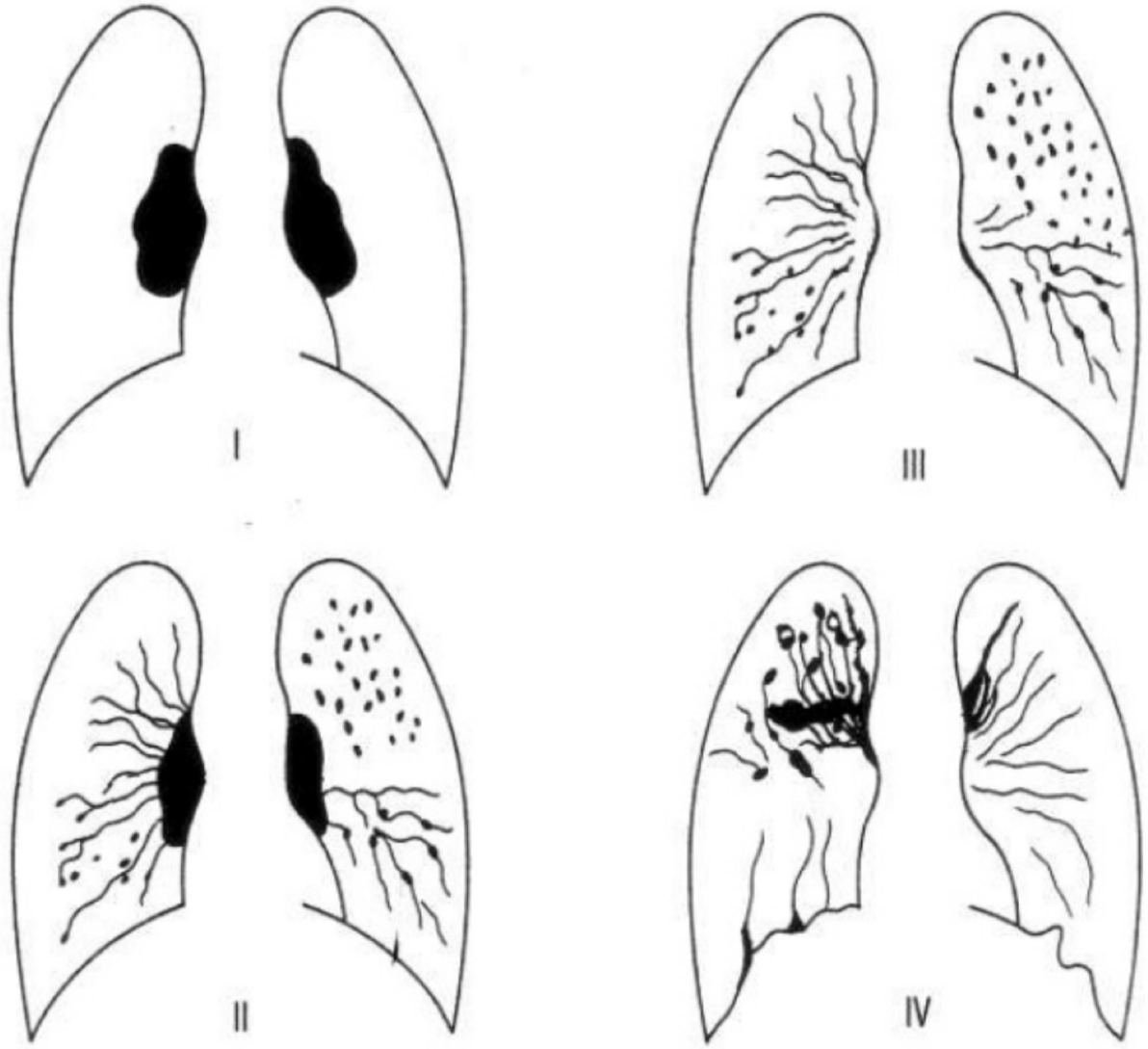
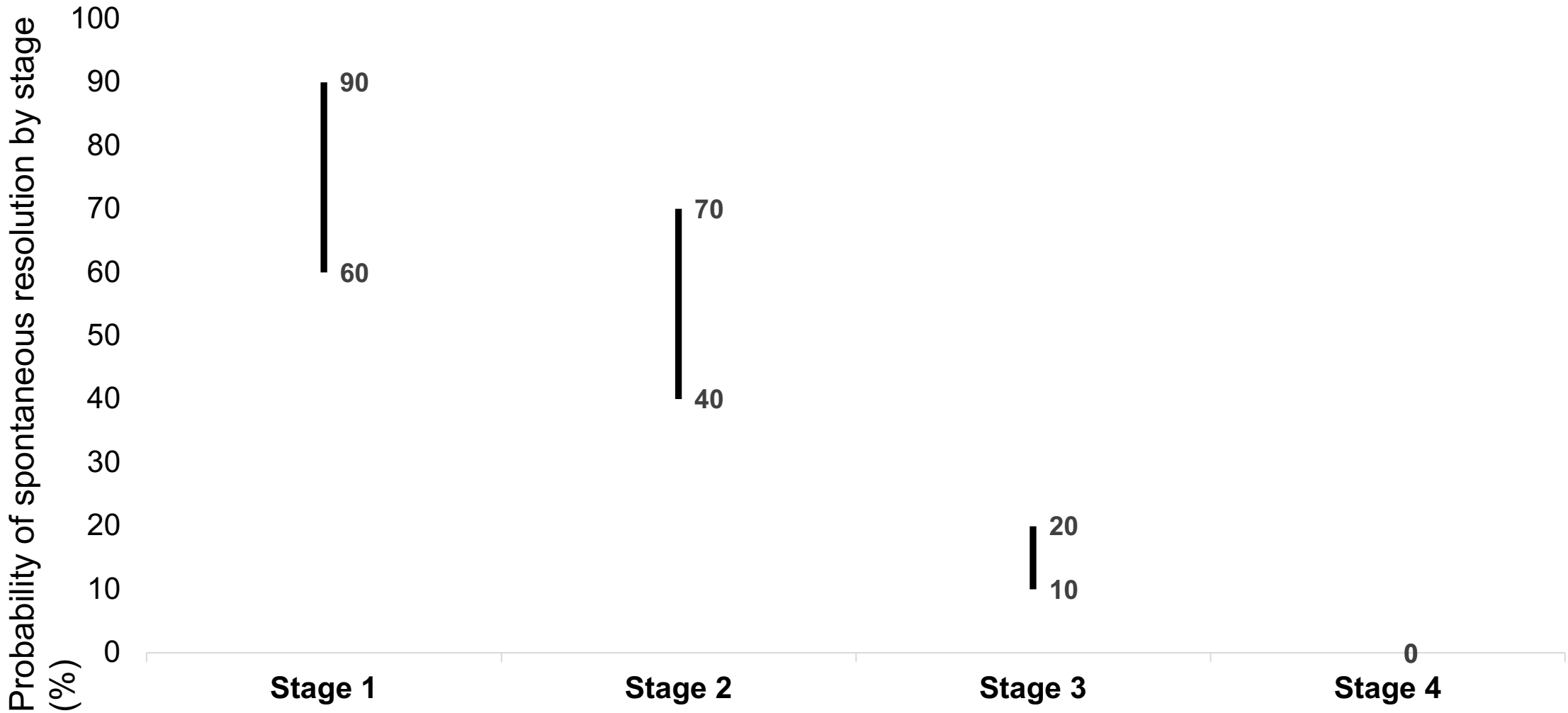
Sarcoid Staging



Decision to treat sarcoidosis: Probability of spontaneous resolution



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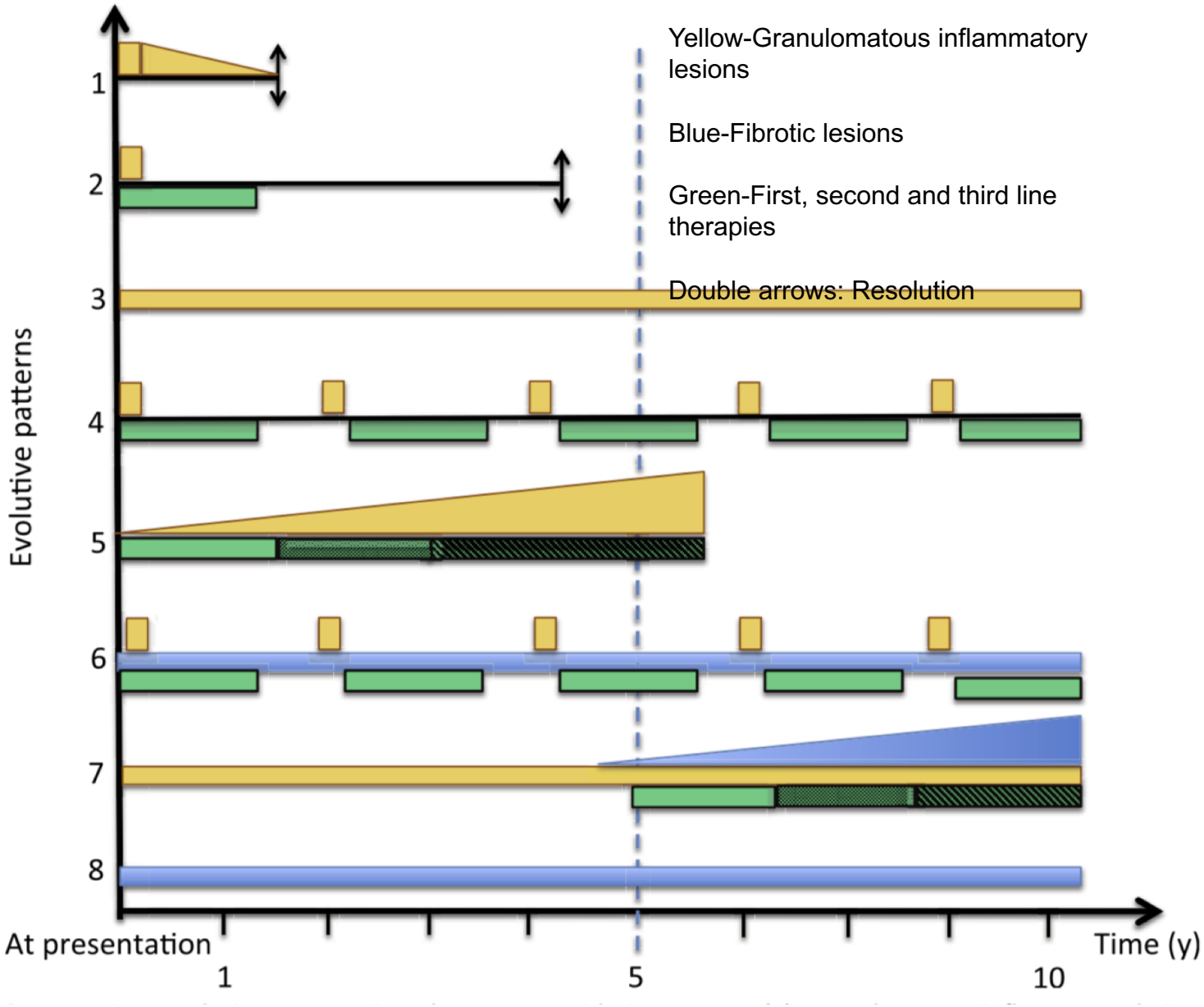
Patterns of disease evolution



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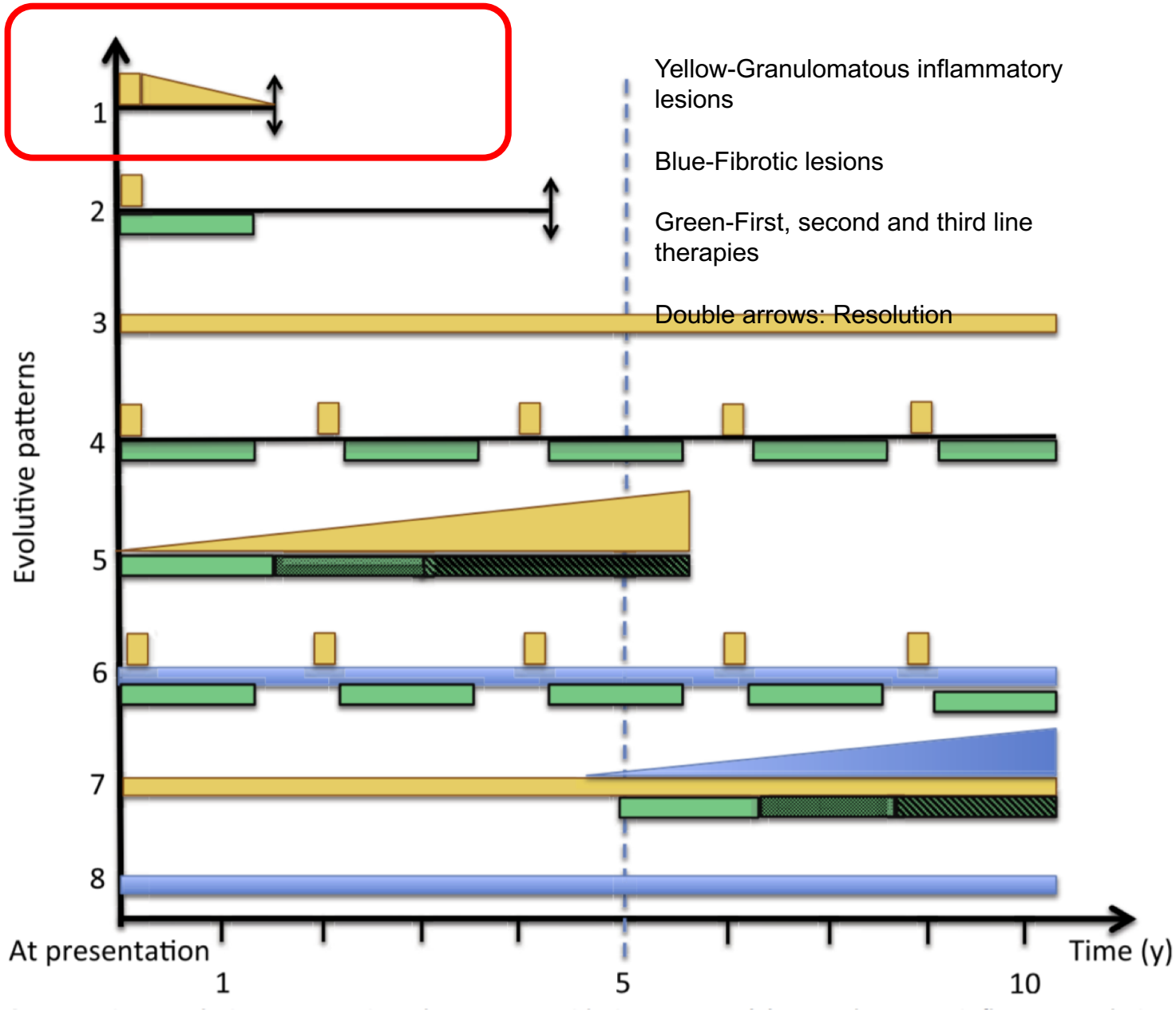
Patterns of disease evolution

- Usually asymptomatic or few symptoms
- Usually Stage I or II
- Disease spontaneously remits without treatment in < 5 years



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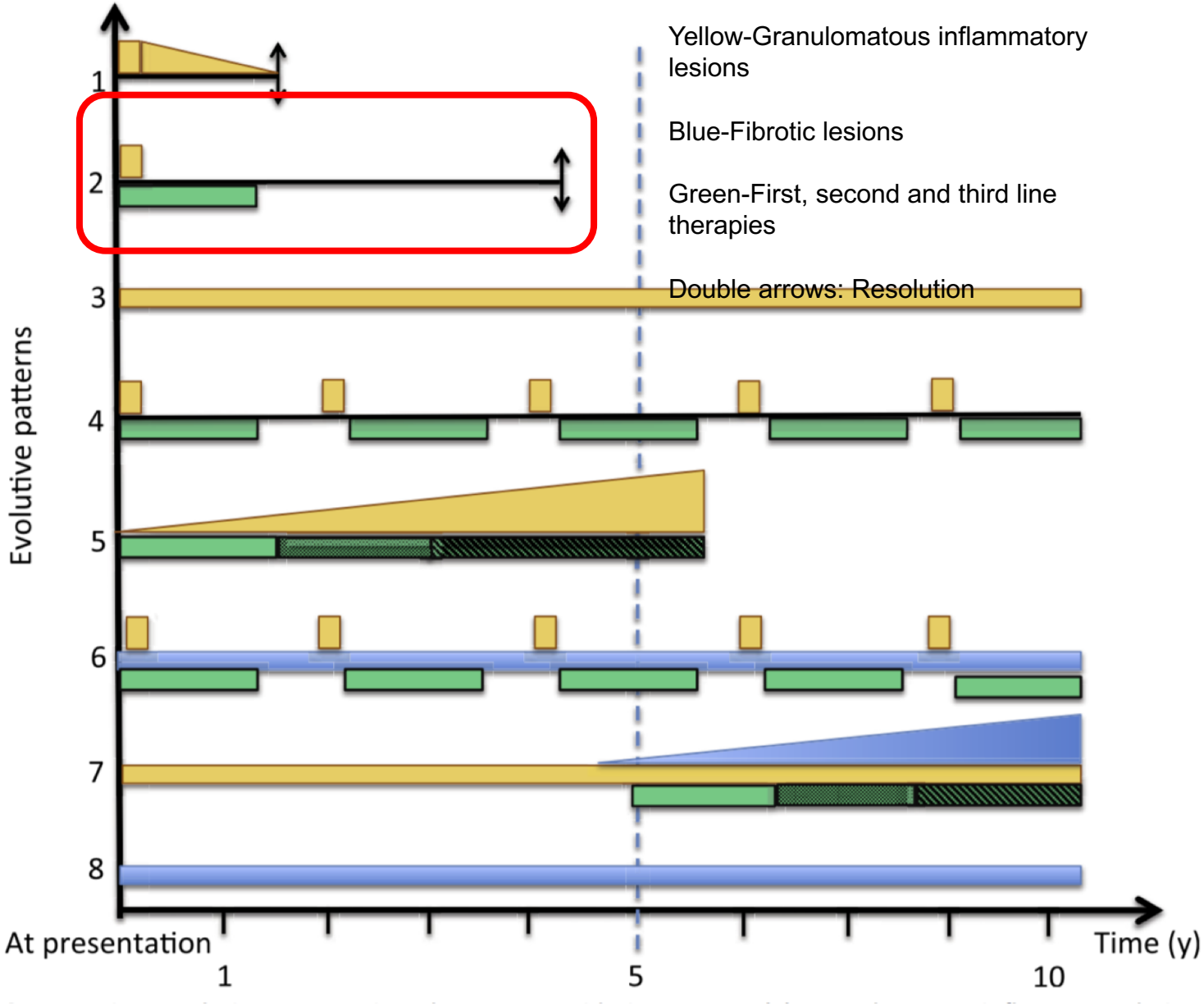
Patterns of disease evolution

- Usually few symptoms
- Usually Stage I or II
- Need short course of treatment (< 1 year)
- Disease remits in < 5 years



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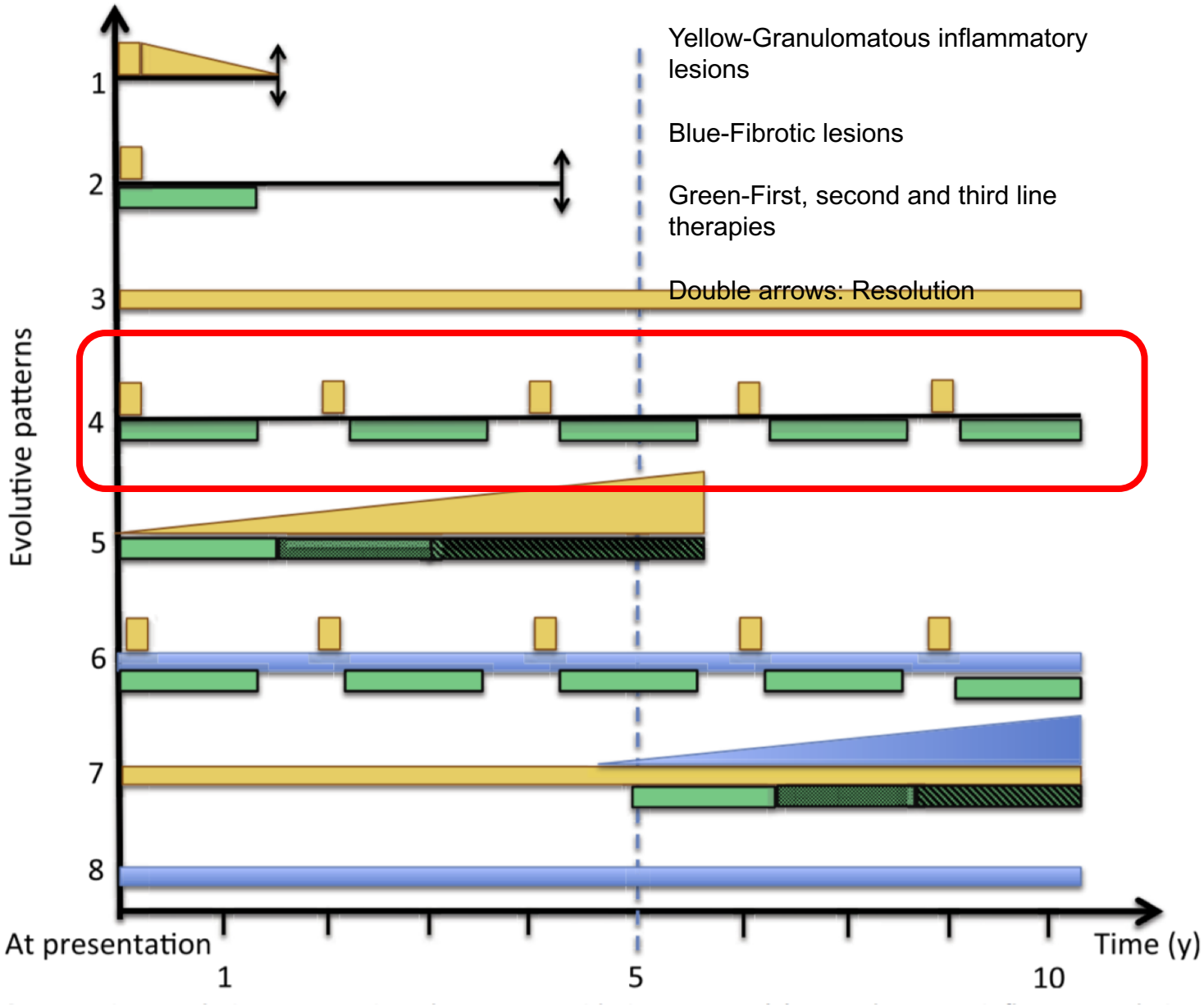
Patterns of disease evolution

- Symptomatic disease
- Iterative relapse during dose reduction or withdrawal of therapy
- Without significant fibrosis



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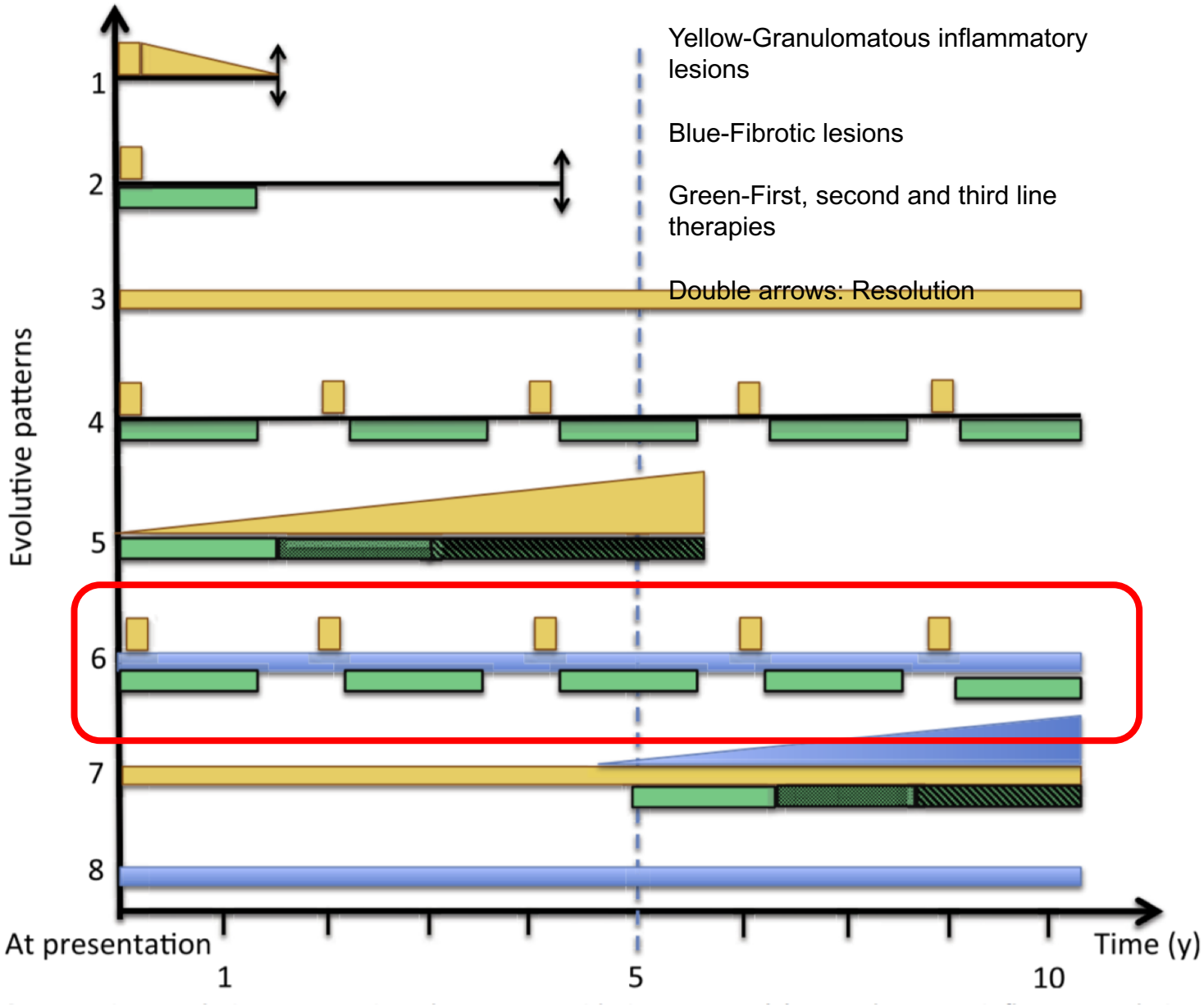

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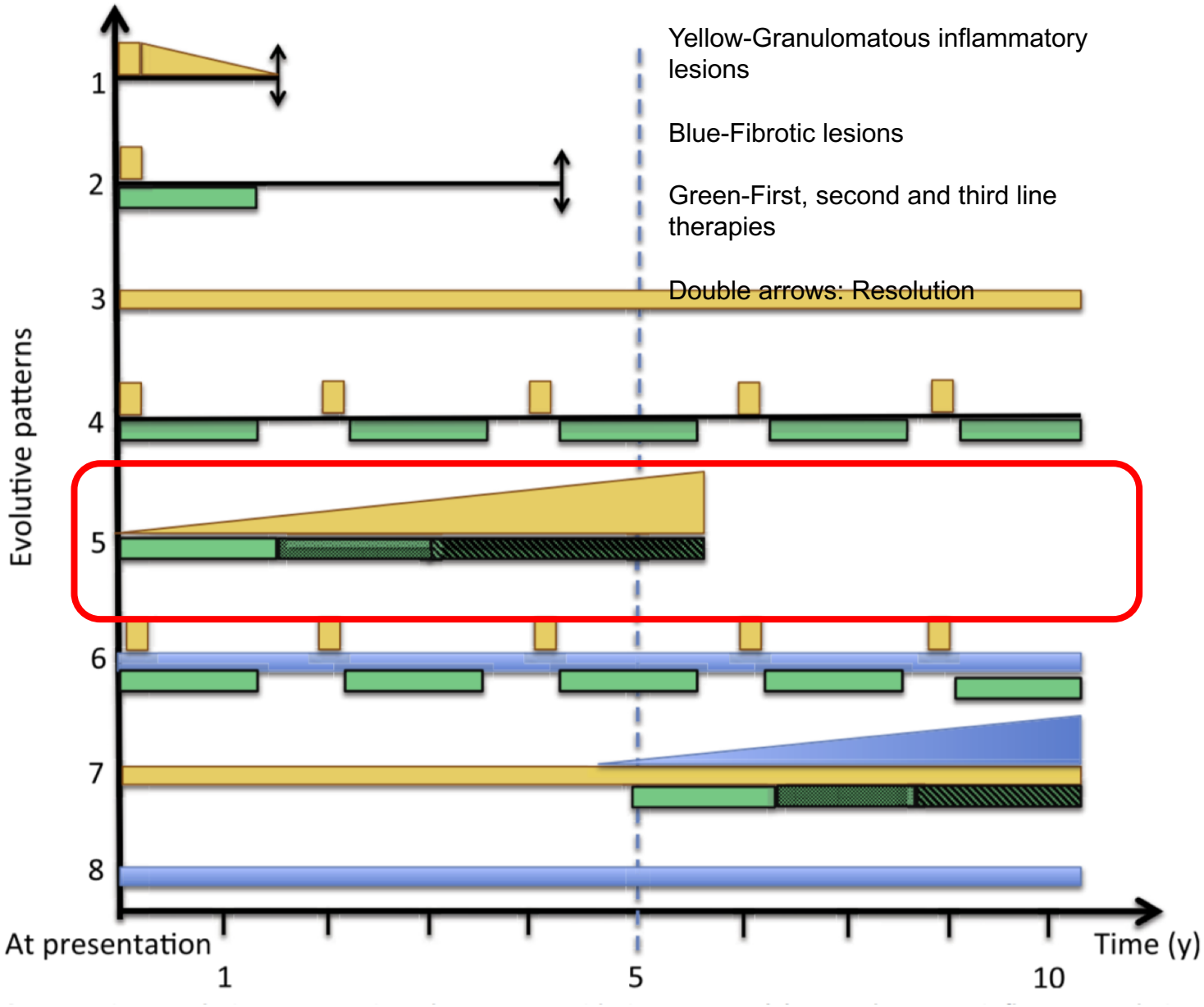
Patterns of disease evolution

- Symptomatic disease
- Progressive, and resistant to one or several treatments
- Without significant fibrosis



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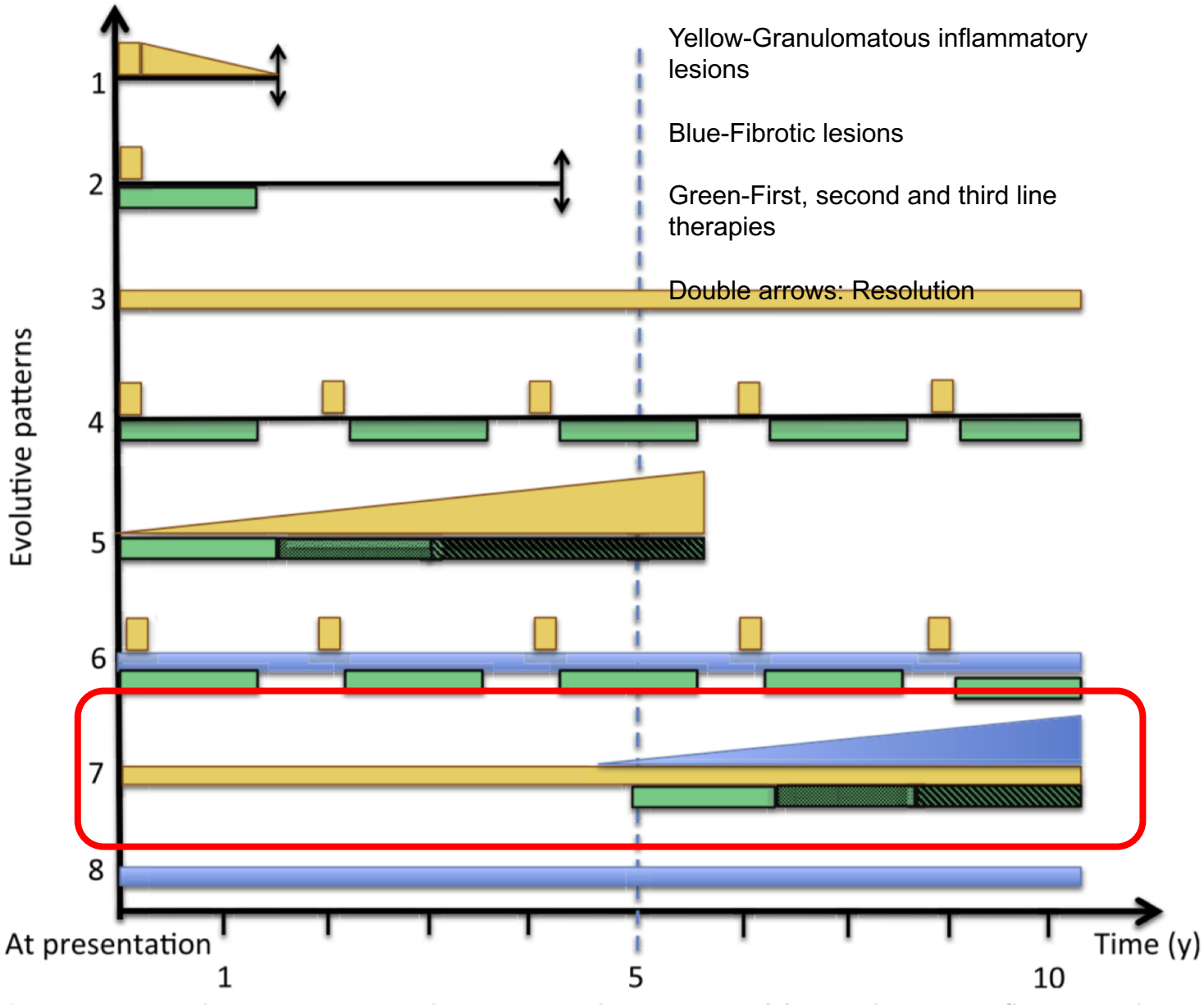
Patterns of disease evolution

- Symptomatic disease
- Progressive, and resistant to one or several treatments
- With significant and progressive fibrosis



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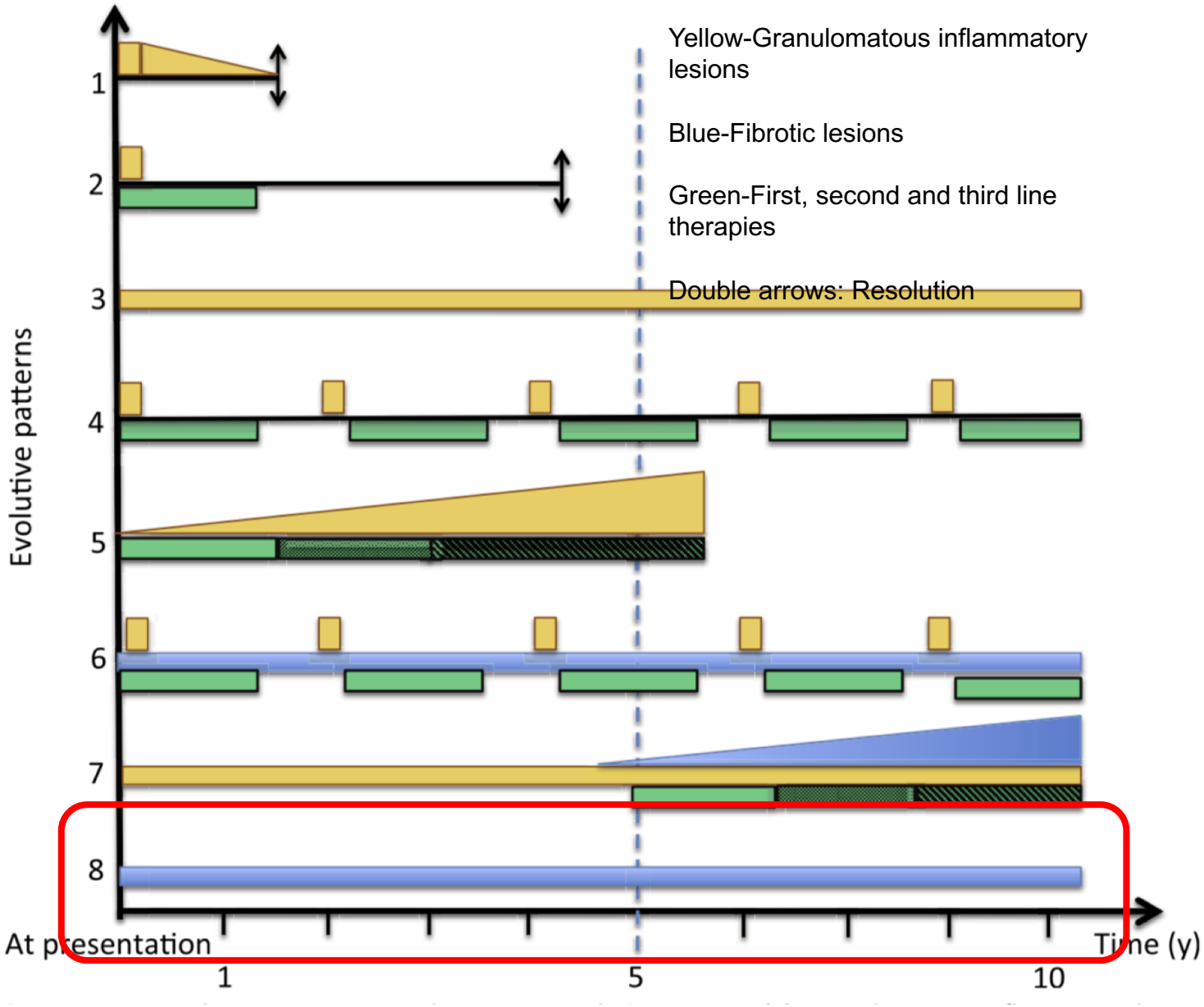
Patterns of disease evolution

- Variable amounts of fibrosis
- No disease activity
- No progression



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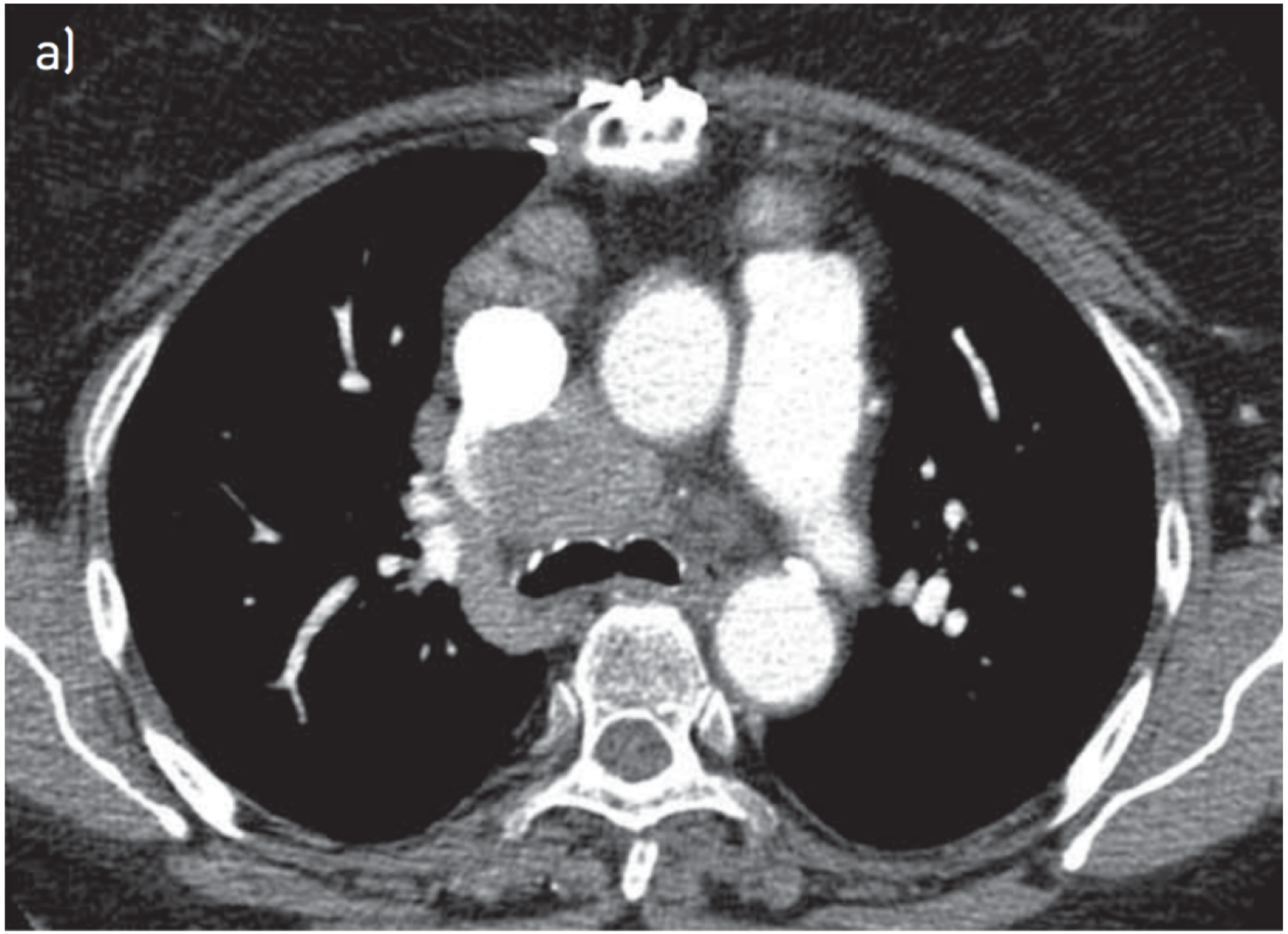
To treat or not to treat



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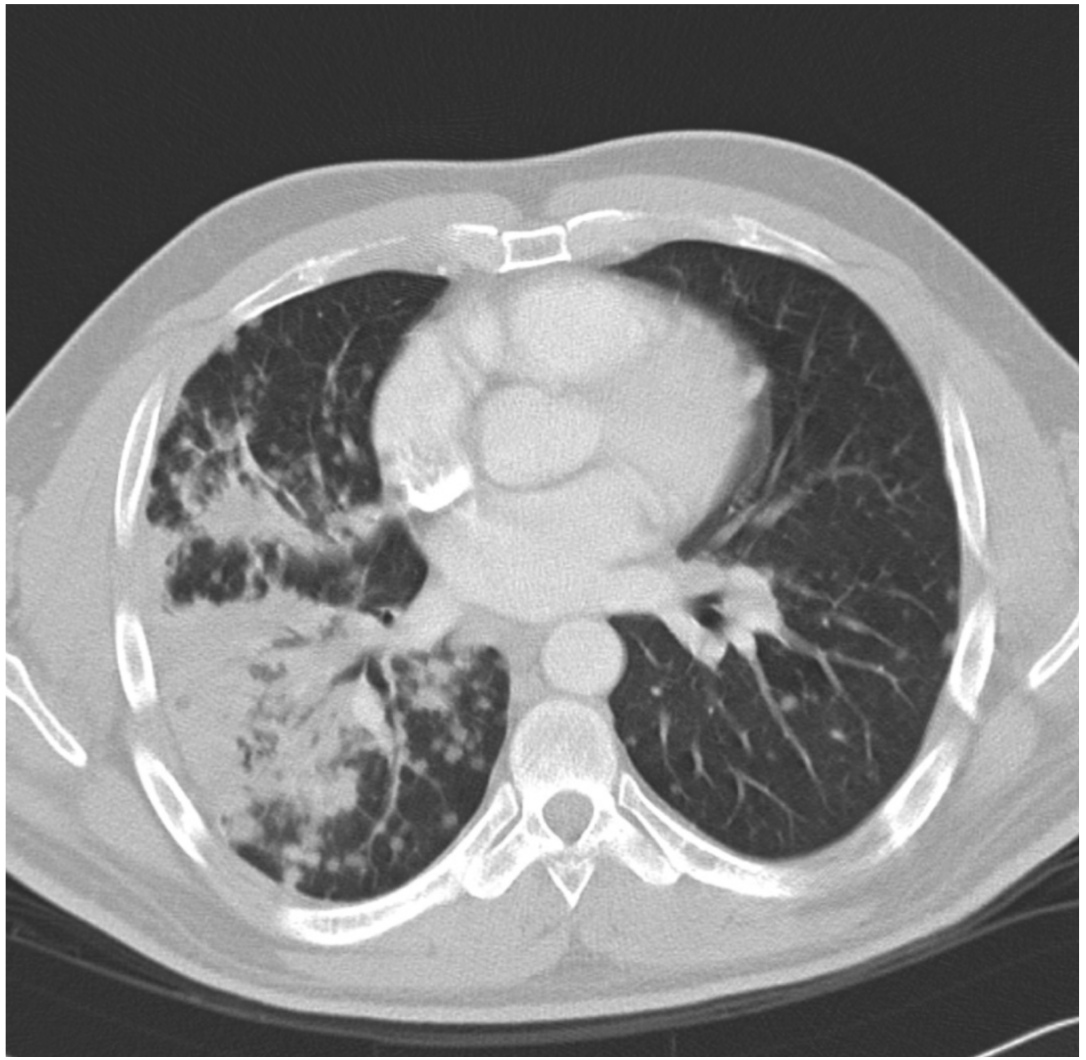

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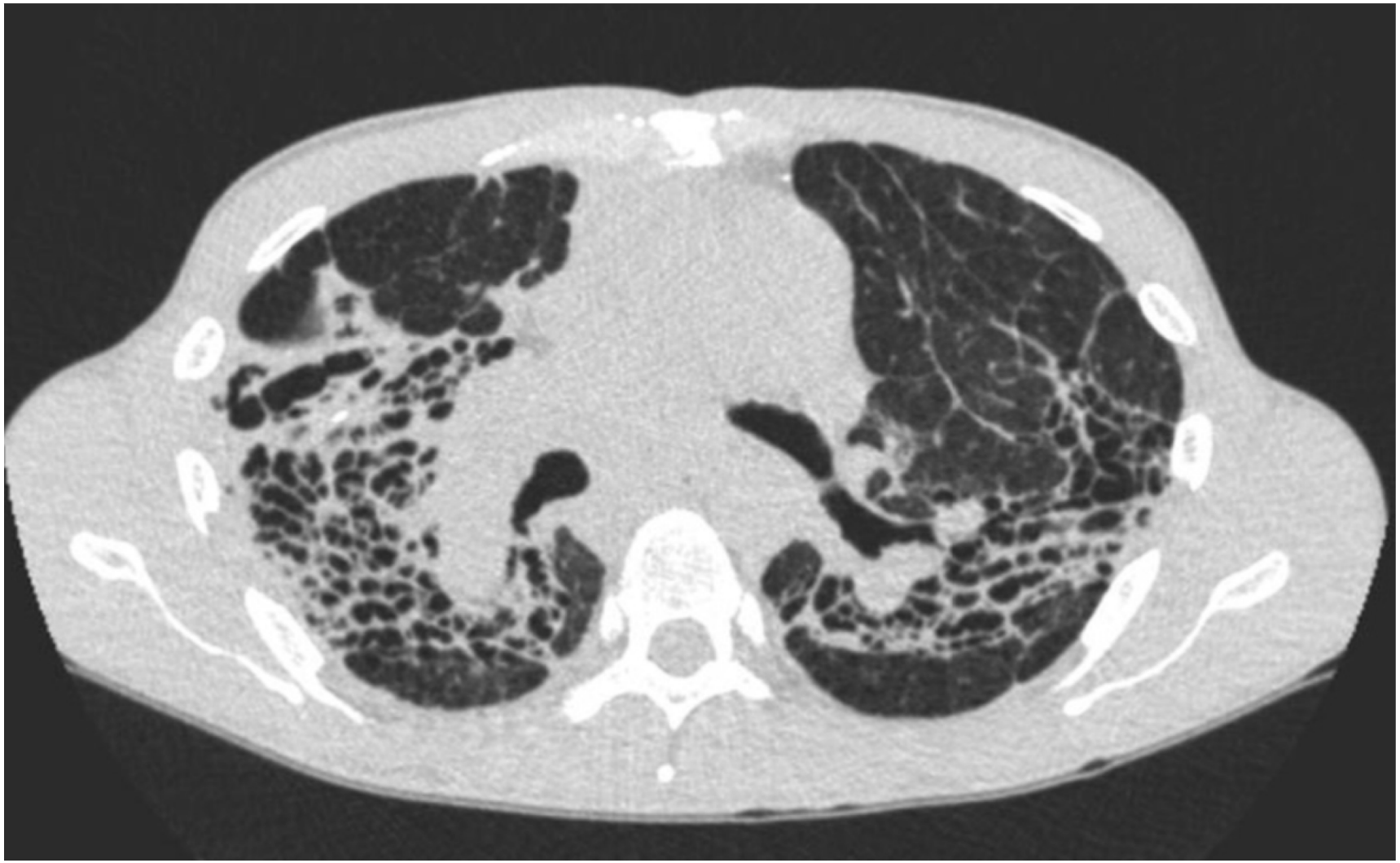

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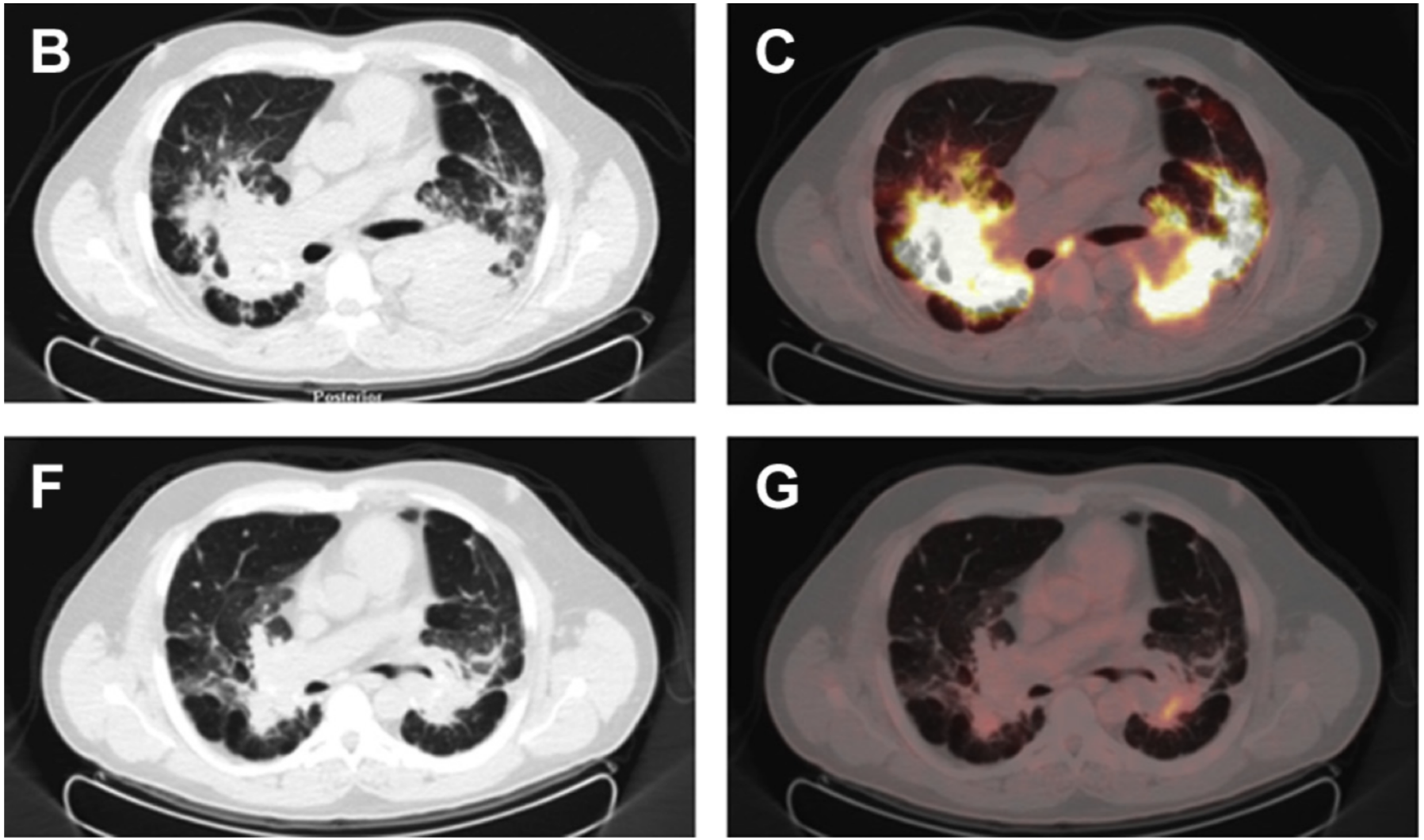
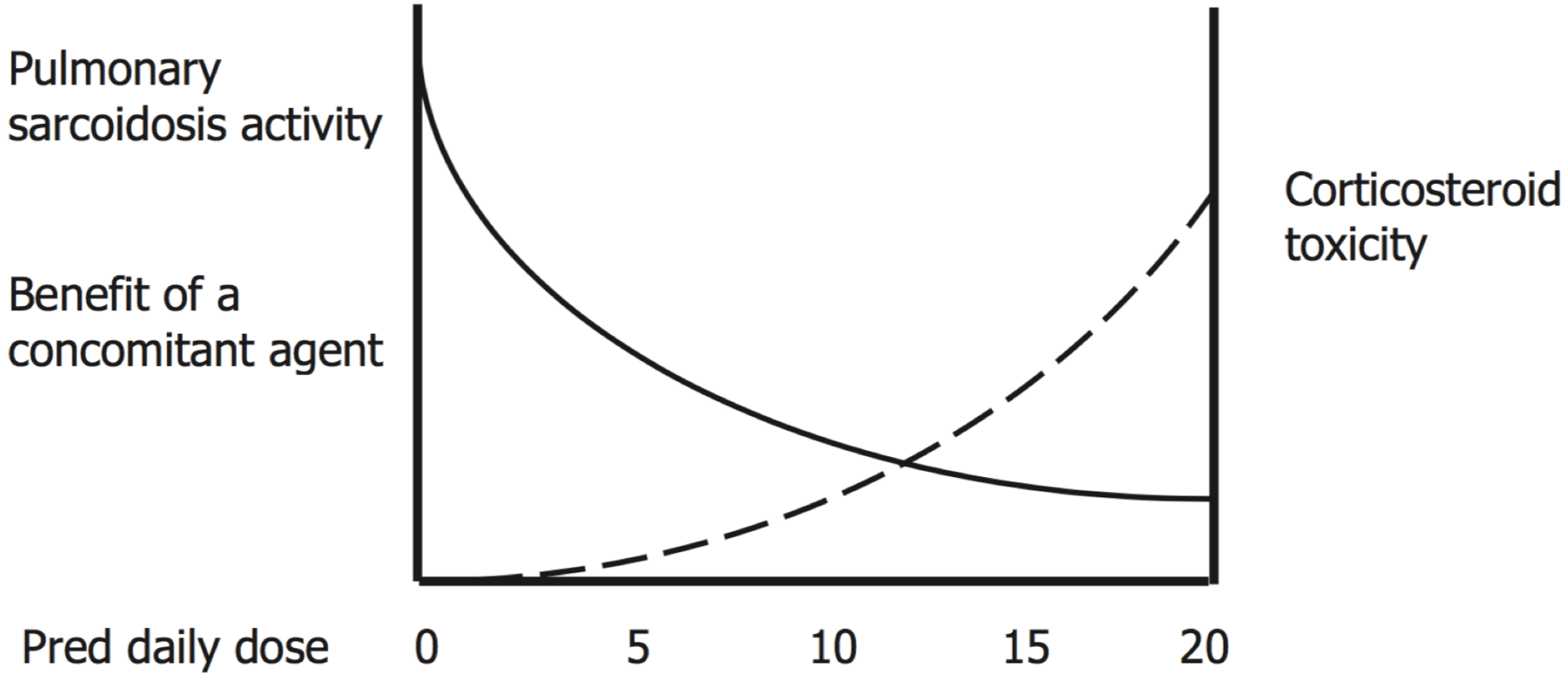


CORTICOSTEROIDS FOR SARCOIDOSIS

Corticosteroids: Dosage



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Lesions which generally respond to steroids (Estimated frequency % in clinical practice)

- Sudden death, severe arrhythmia, severe left ventricular dysfunction from cardiac sarcoidosis (1%)
- Optic neuritis (<5%)
- Severe neurosarcoidosis (<1%)
- Vitamin D dysregulation causing renal failure, severe nephrolithiasis (<1%)

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Lesions which generally do not respond to steroids (Estimated frequency % in general clinical practice)

- End-stage fibrocystic sarcoidosis (FVC<50% of predicted) (<5%)
- Sarcoidosis-associated pulmonary hypertension (5%)
- Hemoptysis from pulmonary mycetoma (<1%)
- Upper airway obstruction (<1%) (usually not, and surgical correction required)
- Endobronchial airway obstruction (<1%) (usually not)

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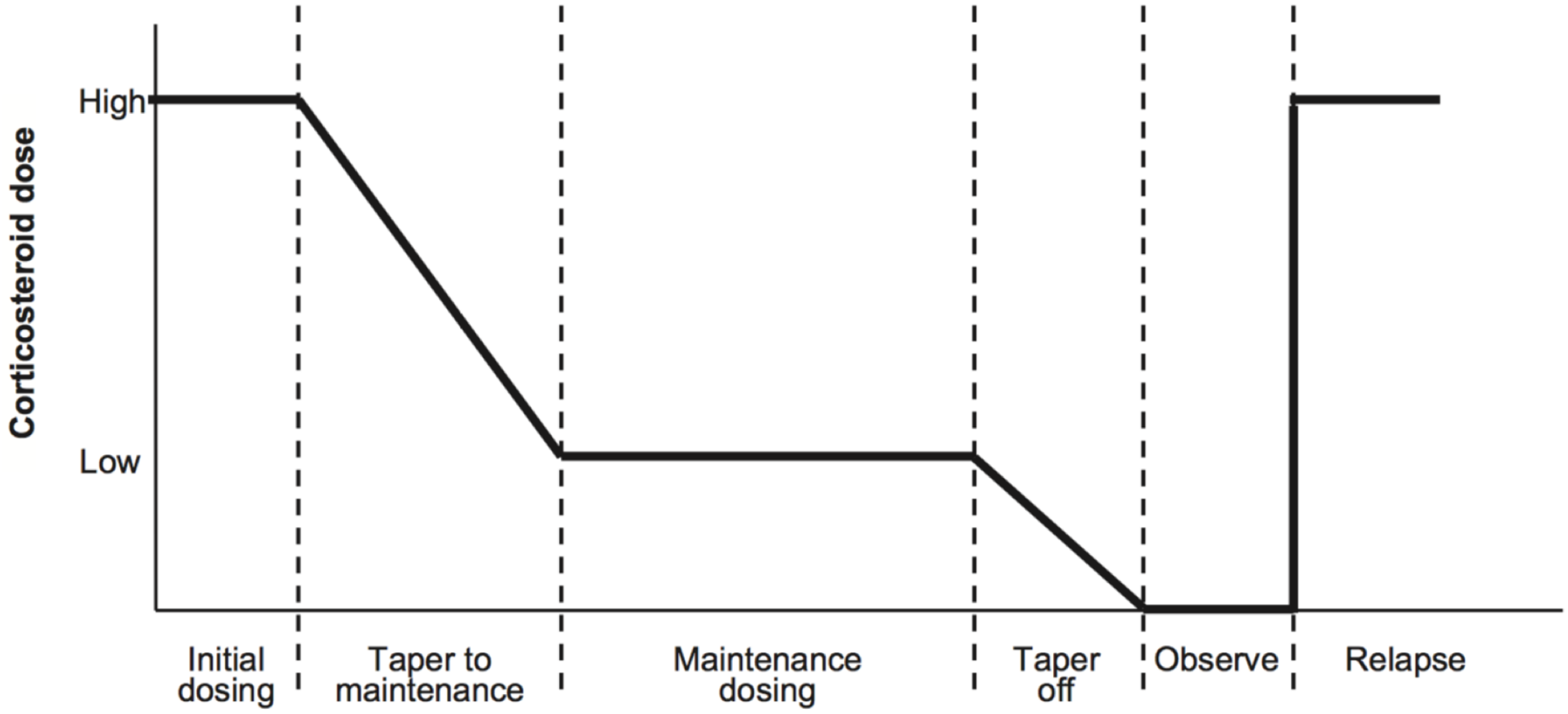
Treat vs. Observation for “acute” disease

- Mixed data
- Some studies showing benefit vs others showing harm
- Relatively small and uncoltrolled studies
- No study has shown clear cut long term benefits in treating acute sarcoidosis
  - 80% of Lofgren syndrome patients treated with steroids had persisting disease at 2 years vs 37% of nontreated patients(Grunewald et al. AJRCCM 2009)
  - BTS study in Stage II and III sarcoidosis treated with steroids for 18 months showed lower incidence of radiographic fibrosis and lower prevalence of dyspnea (Gibson et al. Thorax 1996)
  - Finnish study double blind randomized to steroids vs observation. Steroid treated group had more resolution of radiologic findings and less relapse for Stage II and III but not Stage I. (Pientinalho et al. Chest 2002)(small study with baseline difference between groups)

Corticosteroids in the treatment of sarcoidosis: ATS/ERS/WASOG Consensus Statement



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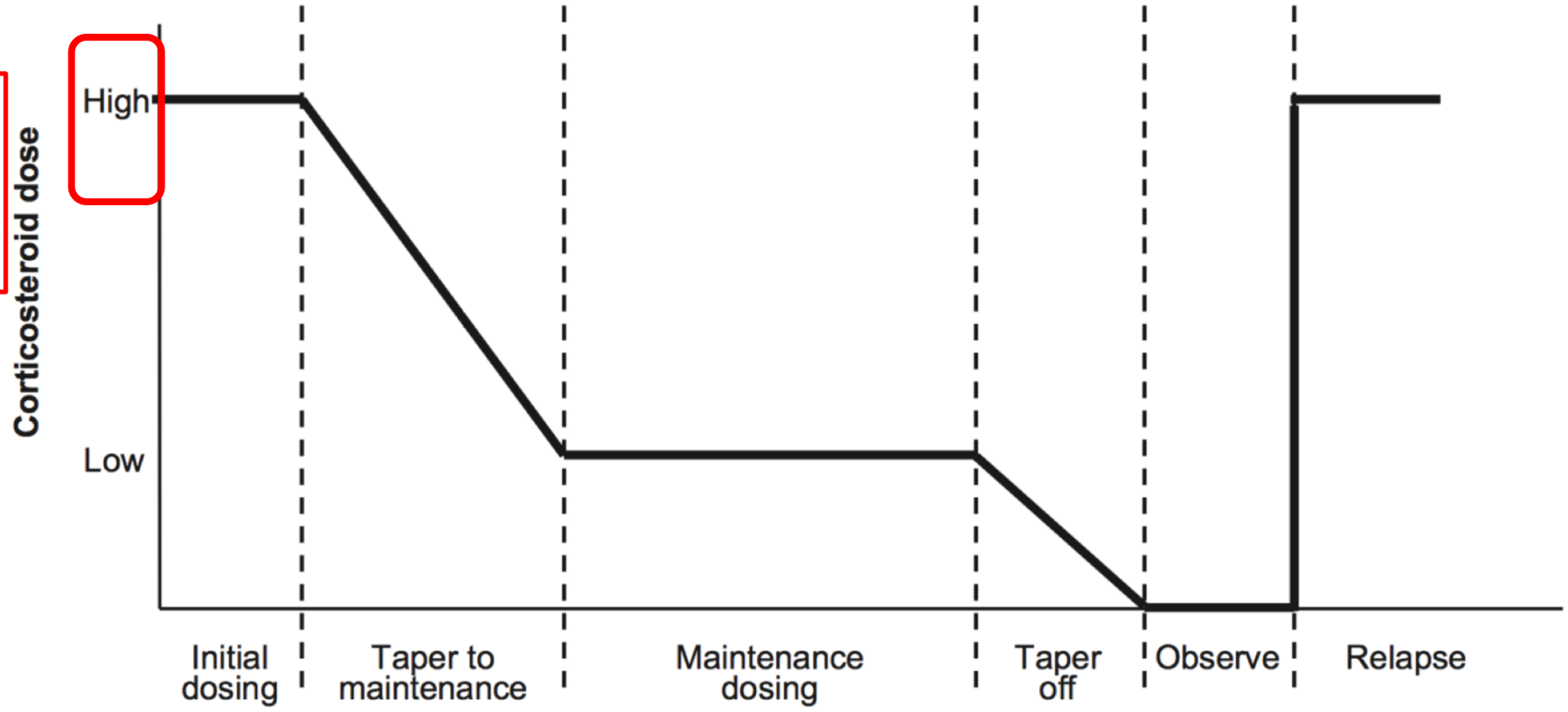
20-40 mg /day Prednisone equivalent dose



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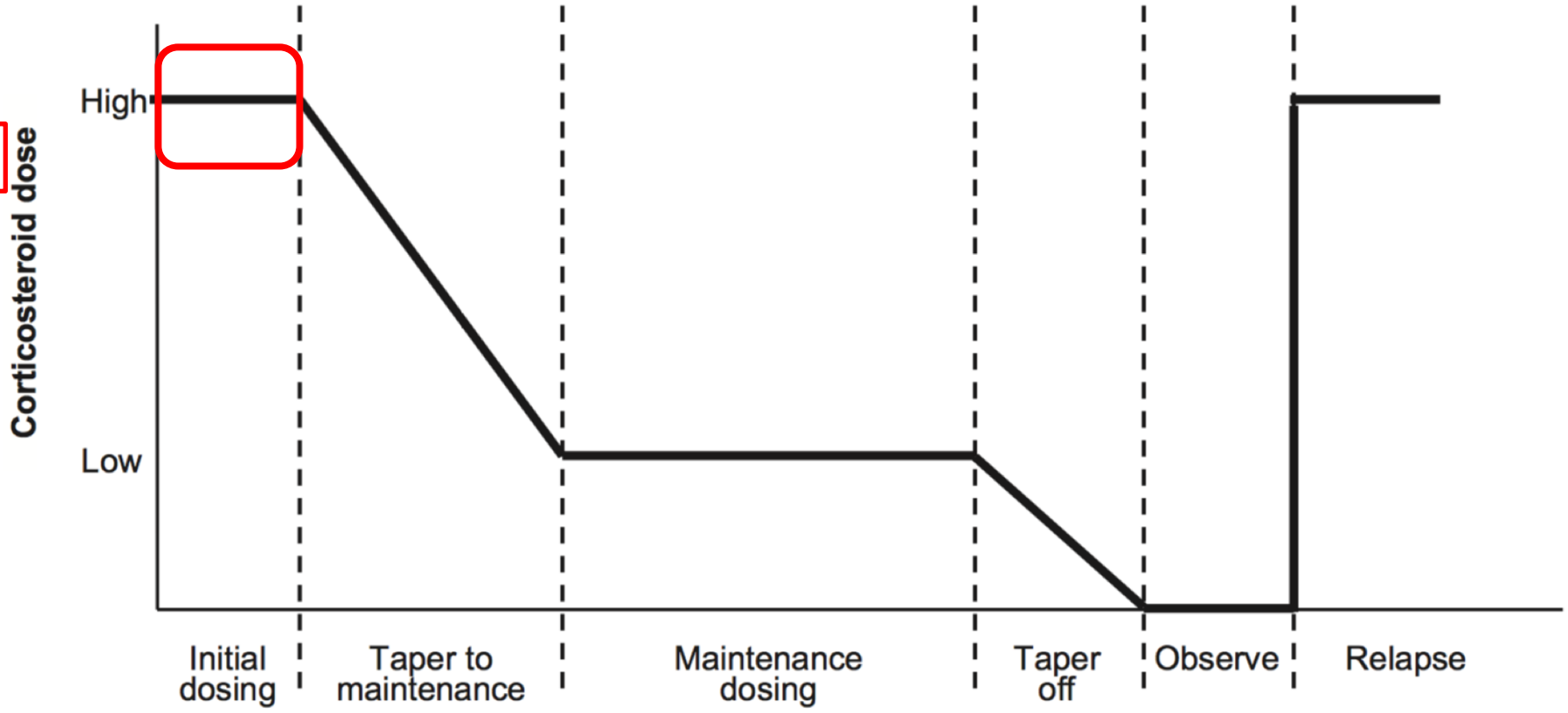
1-3 months



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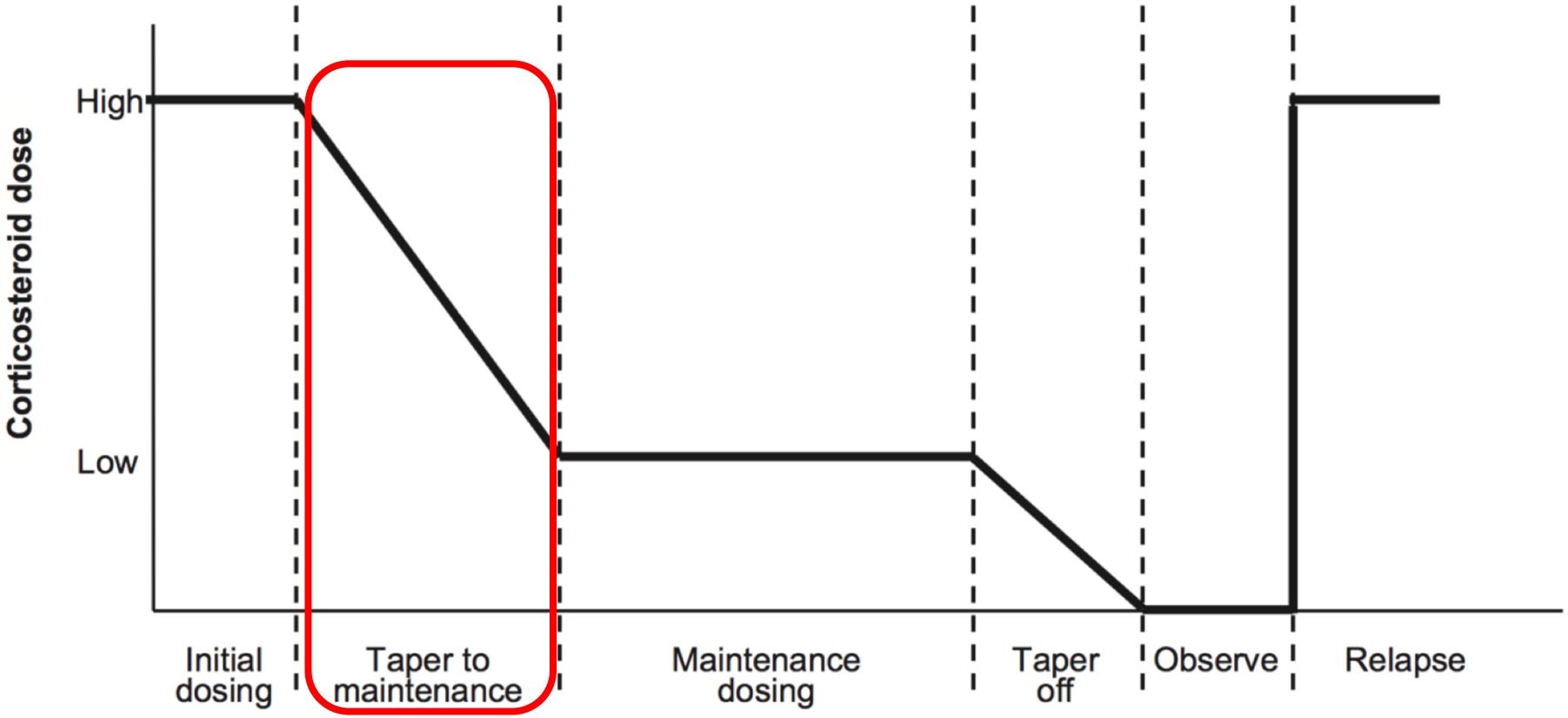
5-10 mg/day prednisone equivalent dose



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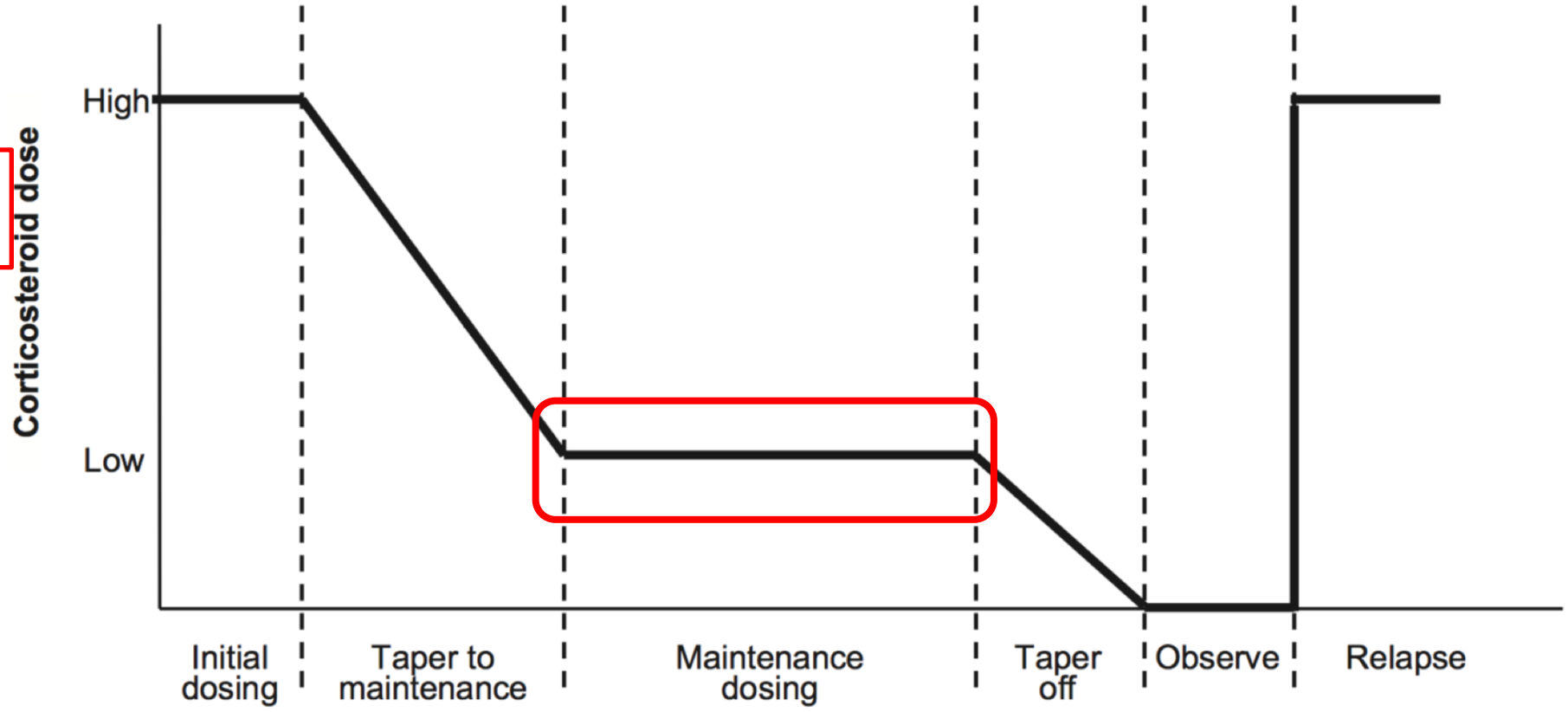
1 year (5-10 mg/day)



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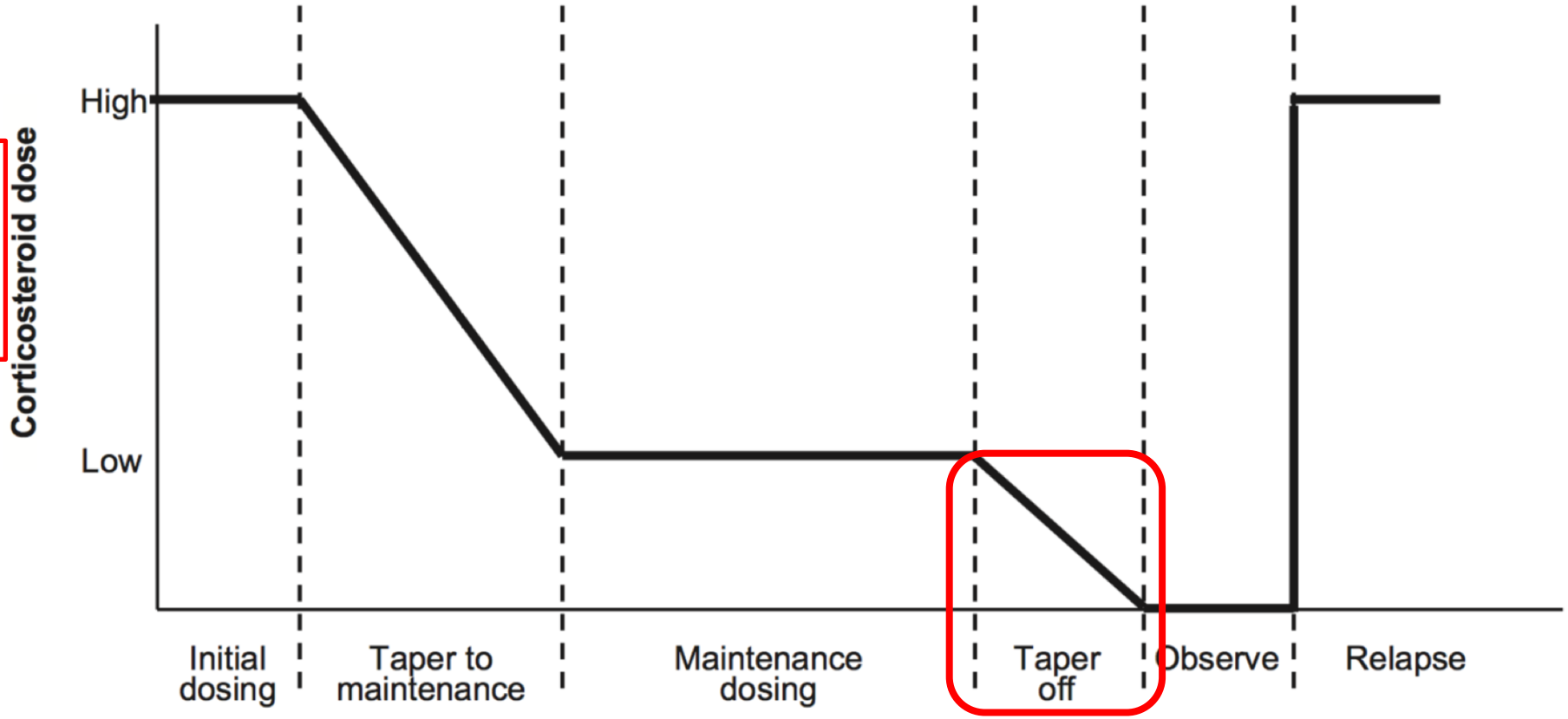
Individualize based on specific response



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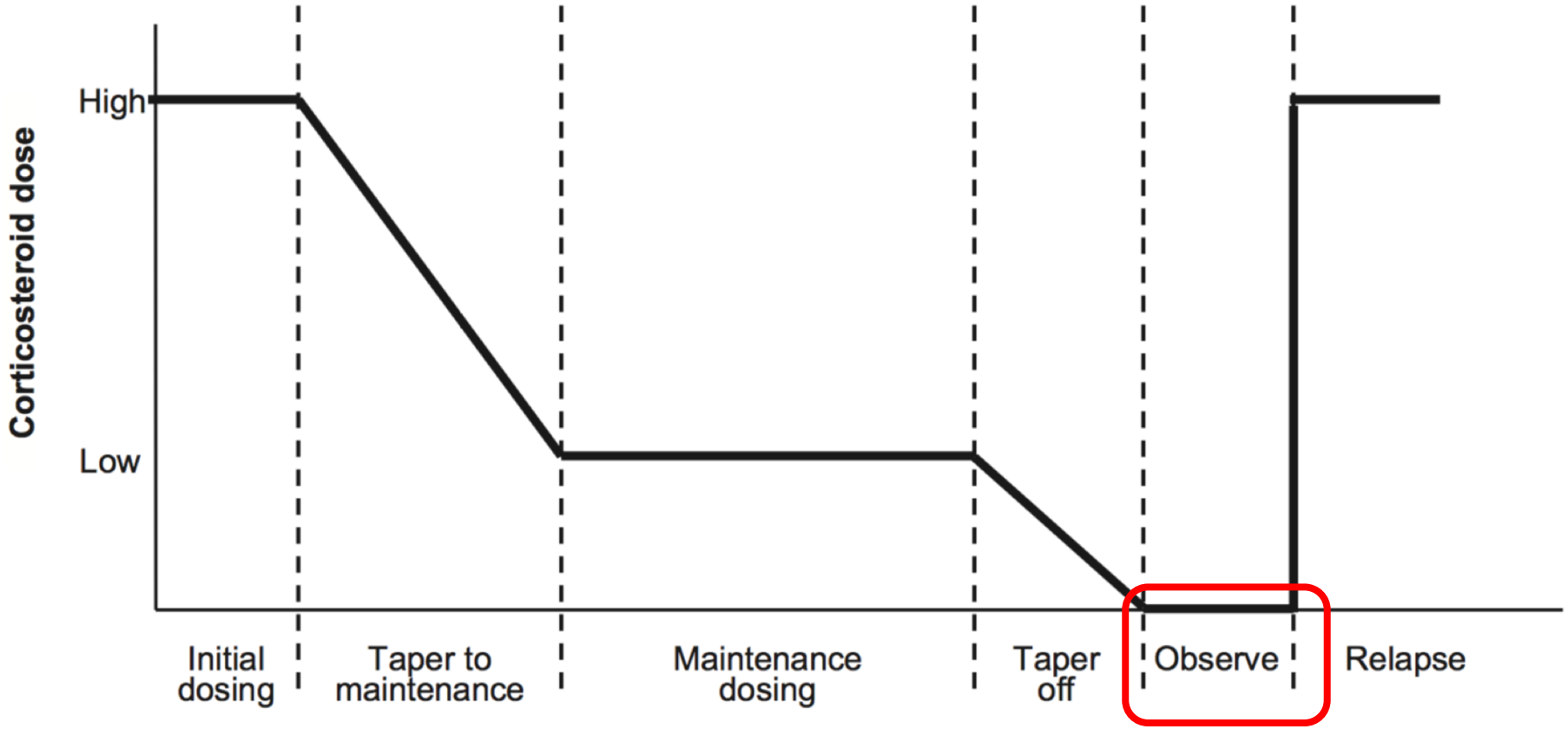

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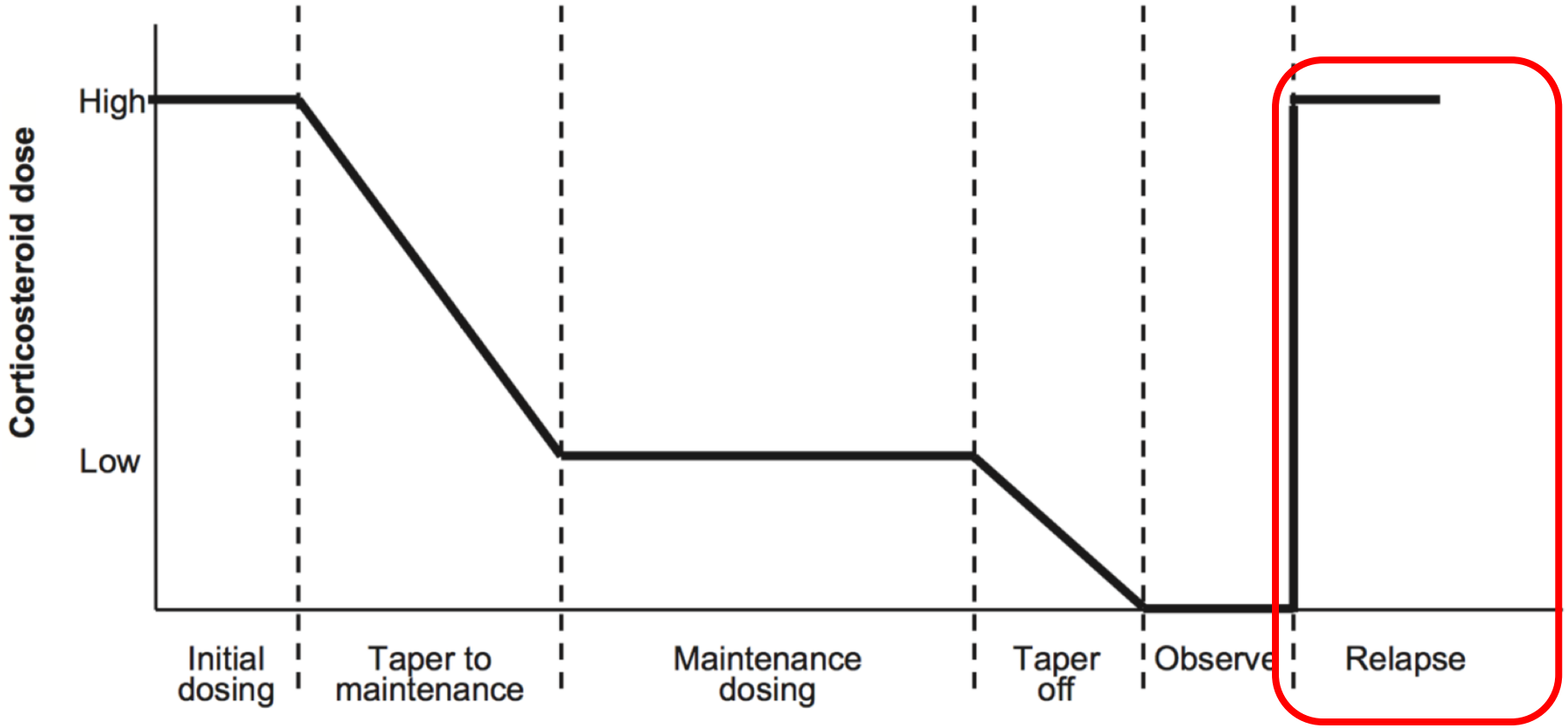

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Corticosteroids: Other considerations

- Bone health
- PJP Prophylaxis

Inhaled corticosteroids

- Not routinely indicated
- Consider as monotherapy in patient with Stage II patients with significant cough but no significant physiologic impairment
- As add-on therapy to oral steroids as an oral steroid sparing agent
- (Inhaled steroids are not free of systemic side effects)

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Corticosteroids: Other dose considerations

Cardiac sarcoidosis

- Asymptomatic cardiac lesions need not always be treated
- 30-40 mg/day prednisone equivalent starting dose adequate for most
- Consider higher dose for life threatening ventricular arrhythmia

Skin sarcoidosis

- 20-60 mg/day prednisone equivalent for highly disfiguring lesions
- Lower end of dosing preferable

Neurosarcoidosis

- 40-80 mg/day prednisone equivalent

Musculoskeletal sarcoidosis

- 20-30 mg/day prednisone equivalent

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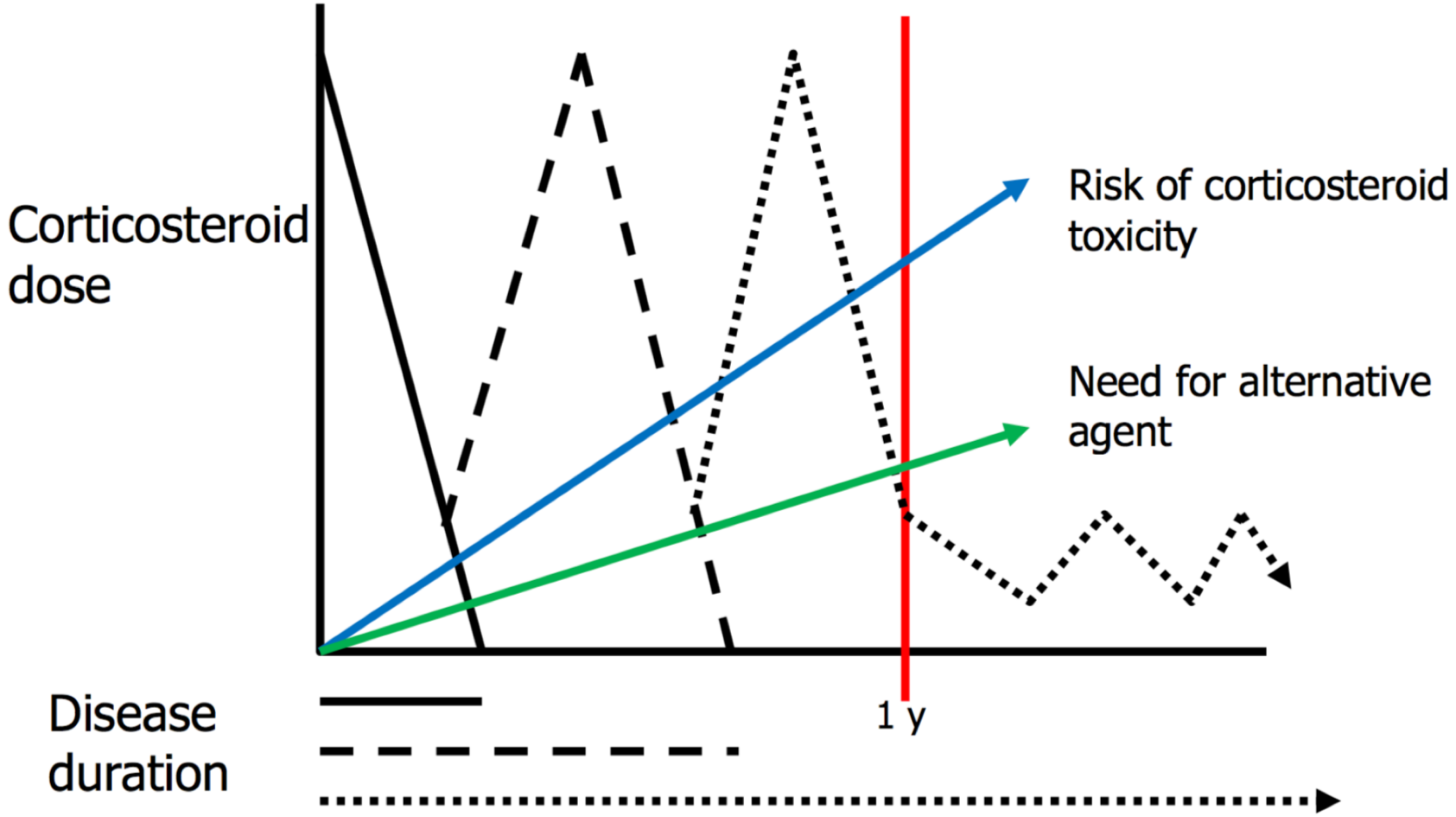
When to add a steroid sparing agent



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Steroid sparing agents in sarcoidosis

- Methotrexate
- Azathioprine
- Mycophenolate
- Leflunomide
- Hydroxychroloquine
- Cyclosporine
- Cyclophosphamide
- “Biologics”
  - Infliximab
  - Others

Methotrexate

- Generally considered the fist line DMASD (Disease Modifying Anti-Sarcoid Drugs)
- Guidelines derive mostly from observational studies, consensus and expert opinion rather than evidence based recommendations stemming from large prospective studies

Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: Cremers et al. Curr Opin Pulm Med2013; 19:545–

Methotrexate: Indications

- Steroid refractory disease
- Presence of side effects of corticosteroids
- First line as a MTX/Steroid combination
  - Neurosarcoidosis
  - Cardiac sarcoidosis
  - Diabetic patients or those with increased BMI
- Rarely, monotherapy as first line

Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: Cremers et al. Curr Opin Pulm Med2013; 19:545–

Methotrexate: Initial dosage

- Generally, 5-15 mg weekly
- Higher doses more effective but more toxic
- Starting dose varies
  - Start at 5 mg weekly
  - Escalate by 5 mg weekly every 1-3 months
- More rapid escalation more effective but more toxic
- More than 20 mg weekly not recommended

Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: Cremers et al. Curr Opin Pulm Med2013; 19:545–

Methotrexate: Concomitant folate use

- Folate reduce GI and liver toxicity without limiting efficacy
- At least 5 mg / weekly dose recommended
- Options
  - 5 mg /week
  - 7 mg /week
  - 1 mg/day
- We use 1mg/day on all days except for the day patient takes methotrexate

Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: Cremers et al. Curr Opin Pulm Med2013; 19:545–

Methotrexate: Pre administration workup

- CBC with differential count
- Liver function testing
  - AST, ALT, ALP, Bili
- Creatinine
- HIV
- Hepatitis B/C serologies
- MTb testing: Interferon Gamma Release Assay (IGRA)

Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: Cremers et al. Curr Opin Pulm Med2013; 19:545–

Methotrexate: Looking for contraindications before starting

- Significant renal disease (GFR < 30ml/min)
- Leucocytopenia (WBC Count < 3.0 k/ml)
- Thrombocytopenia (Plt count < 50 k/ml)
- Significant drug or alcohol use
- Abnormal LFTs not attributable to sarcoidosis

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Methotrexate: Monitoring for toxicity

- CBC
- Creatinine, LFTs
- Every 3-6 weeks until stable dose reached
  - › We monitor every 4 weeks
- Every 1-3 months thereafter
- Testing interval can be extended to every six months after stabilization
  - › We extend it to every 2 months after 1 year

Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: Cremers et al. Curr Opin Pulm Med2013; 19:545–

Methotrexate: GI Side effects

- Nausea, mucositis
- Splitting dose as long as total dose is ingested in 12 hours

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Methotrexate: Elevated LFTs while on it

- Elevated LFTs are relatively common in sarcoid patients on MTX, and many of it attributable to hepatic sarcoid (9% at 1 yr, 14% at 2 yrs)
- Severe liver disease from MTX toxicity is uncommon
- Degree of LFT elevation or number of positive tests do not confidently predict probability of developing severe liver disease
- No consensus on how to manage elevated LFTs
- Always look for other causes
  - Alcohol, NSAIDs, NASH etc.
- < X 2 ULN LFT elevation
  - OK to monitor closely and individualize decisions
- X 2 – X 4 ULN LFT elevation
  - Consider discontinuing MTX
- > X 4 ULN
  - Discontinue

Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: Cremers et al. Curr Opin Pulm Med2013; 19:545–

Methotrexate: Duration of therapy

- No studies with long term follow up data to conclusively determine the long term safety profile of MTX for sarcoidosis patients
- Discontinuation rate because of complications small
- 68% of sarcoid experts did not put an upper limit to the duration of therapy
- We re-evaluate the risks/benefits of continued therapy for each patient individually on each visit, and definitely beyond 2 years

Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: Cremers et al. Curr Opin Pulm Med2013; 19:545–

Methotrexate: Pregnancy and children

- Both male and female patients should contraception while on MTX
- Discontinue MTX at least 3 months prior to planned pregnancy, for men and women
- Discontinue if pregnant

Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: Cremers et al. Curr Opin Pulm Med2013; 19:545–

Questions ?

“It's tough to make predictions, especially about the future.”
(Yogi Berra)