Coccidioidomycosis in Rheumatologic Patients

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The problem

Prevalence of rheumatoid arthritis is 1%

Population of Arizona is 6 million

At least 150,000 new cocci infections yearly

DMARDs and BRMs improve disease outcomes

There are no guidelines for managing cocci in these patients

Studies of cocci in rheumatic disease

Bergstrom et al Arthritis & Rheumatism 2004

1. Chart review 1998-2003

13 cases of cocci in patients taking TNF antagonists

- 12 infliximab (11 with methotrexate)
- 1 etanercept

All had pneumonia

4 had disseminated disease

2 had a prior history of cocci and their disease was thought to represent reactivation

2. Retrospective cohort study 2000-2003

985 patients with RA, JRA, psoriatic arthritis, reactive arthritis

11 developed symptomatic cocci (1%)

- 7/247 on infliximab
- 4/738 on etancercept

Studies of cocci in rheumatic disease

Mertz and Blair Ann NY Acad Sci 2007

- Retrospective chart review 2000-2006
- 854 rheumatology patients
- 16 developed cocci (1.9%)
  - 6 on infliximab
  - 1 on etanercept
  - 2 were disseminated (both articular, neither on TNF inhibitor)
  - 2 were asymptomatic
  - Most common rheumatic dx was RA
- The seasonal pattern and increasing incidence 2000-2006 suggested that most cases were new infections

Studies of cocci in rheumatic disease

Mueller et al American College of Rheumatology 2007

Chart review of 298 patients on BRMs

20 developed cocci (6.7%)

- 13 on infliximab (10.6%)
- 3 on etanercept (2.9%)
- 4 on adalimumab (3.3%)

3 were asymptomatic

4 were disseminated

"Control group" of 225 patients on methotrexate

4 developed cocci (1.3%)

Limitations: capturing the denominator?

Conclusions and questions

There is a significant (1% or higher) incidence of cocci in patients on TNF inhibitors and other drugs for rheumatic diseases

Disseminated disease appears more common than in the general population

How should we manage these patients during and after cocci infection?

Can we resume BRM or DMARD therapy?

Subsequent Therapy of Patients with Biologic Response Modifiers or Disease-Modifying Antirheumatic Drugs after Coccidioidomycosis

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Methods

- Retrospective chart review
  - Developed cocci while on DMARDs or BRMs
  - Seen at least once in a University-affiliated or Veterans Administration outpatient rheumatology clinic in Tucson, Arizona between 2007-2009
  - Charts were reviewed up to June 1, 2011
- Mode of diagnosis, clinical manifestations, antifungal therapy and duration, and management of BRM/DMARDs

Results

485 charts reviewed (344 University, 144 VA)

44 patients developed cocci during treatment with a BRM and/or DMARD

- 6 Asymptomatic
- 29 Pulmonary
- 9 Disseminated
  - Skin: 4
  - Joint: 2 (knee, ankle)
  - Meningitis: 1
  - Lymph node: 1
  - Larynx: 1

Results

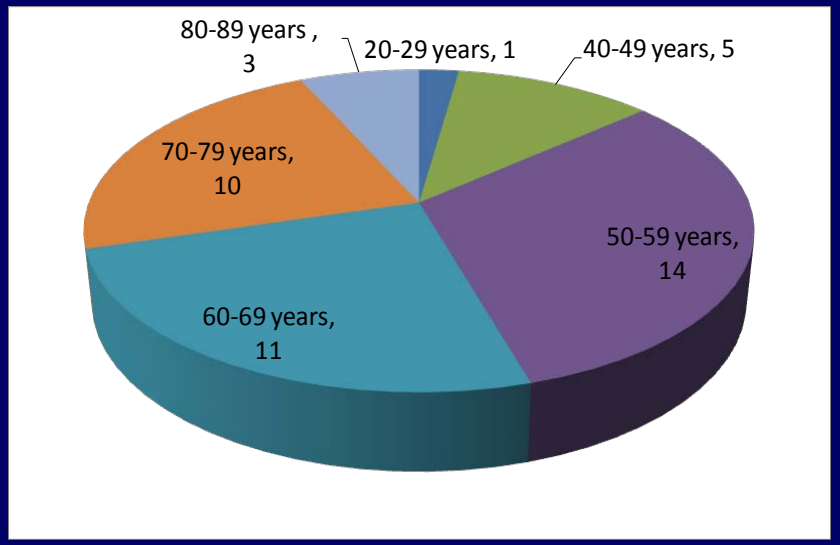
20 Male, 24 Female

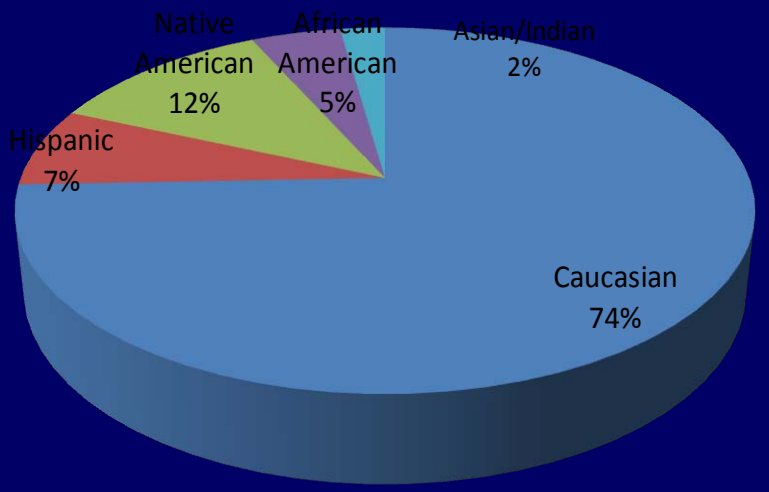
60-79 yrs

Caucasian

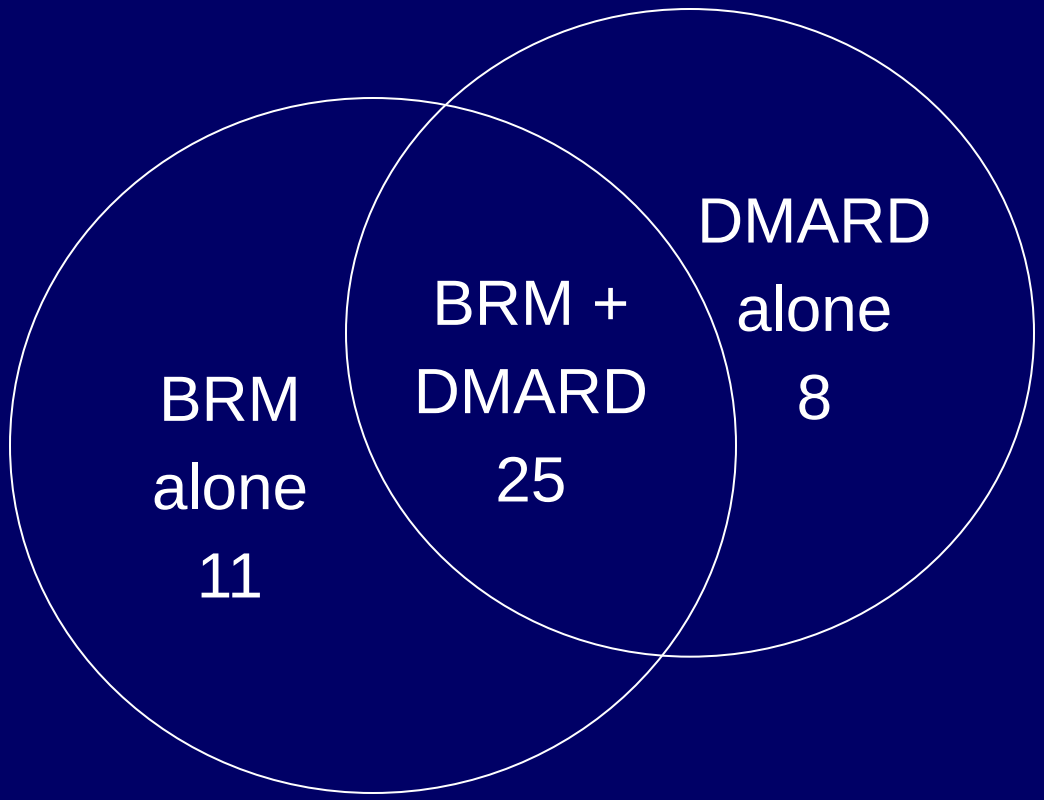
Rheumatoid Arthritis

- 33 RA
- 4 AS
- 3 PsA
- 2 IBD SpA
- 1 SLE
- 1 other





Medications at time of diagnosis



BRMs at time of diagnosis

Most common: Infliximab

Biologic Response Modifier (total)	BRM alone	BRM in combination with DMARD
Infliximab (21)	10	11
Etanercept (6)	1	5
Adalimumab (8)	0	8
Abatacept (1)	0	1

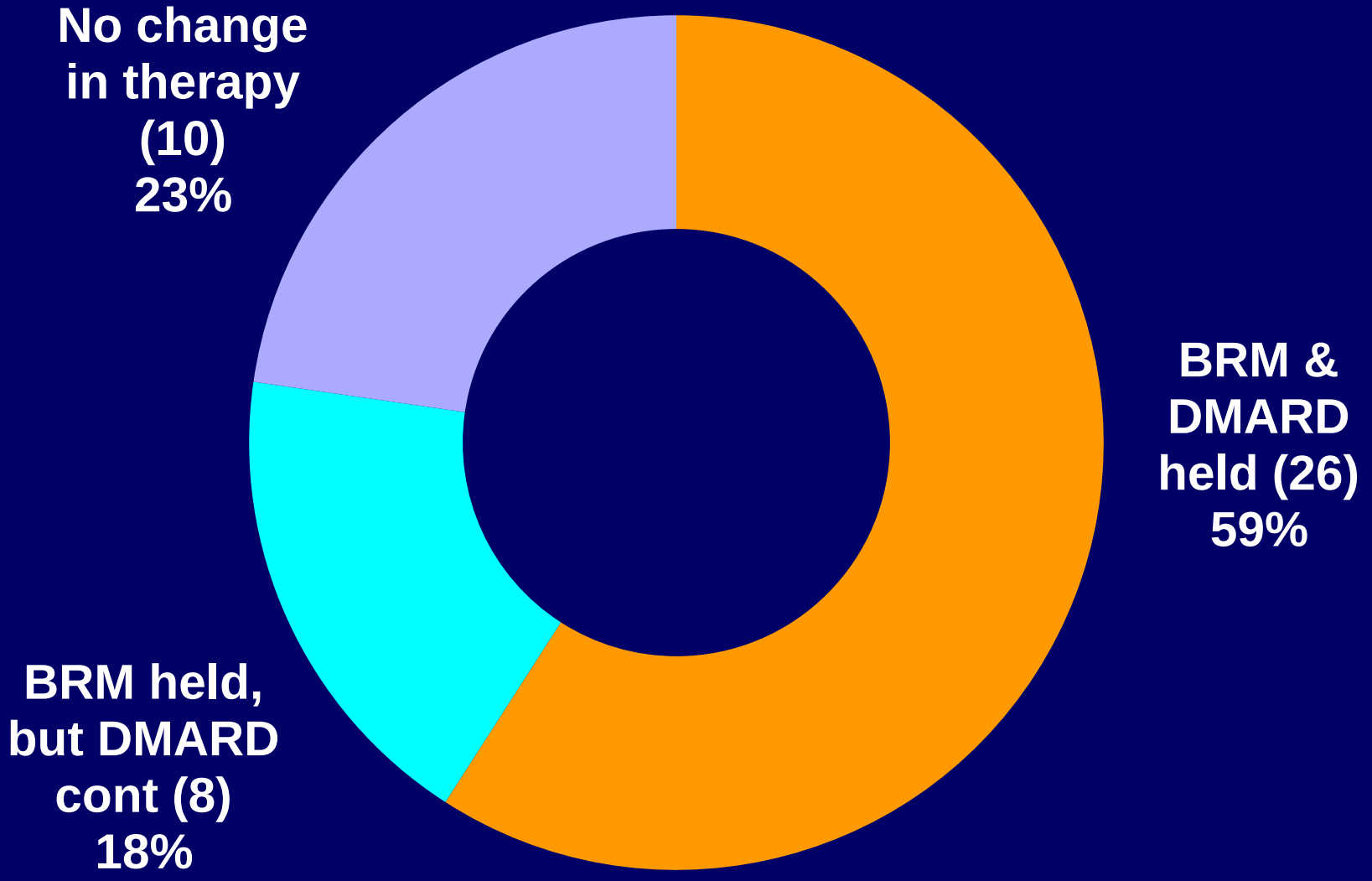
No particular agent seemed to be associated with dissemination

DMARDs at time of diagnosis

Most common: Methotrexate (MTX) alone or in combination

DMARD (total)	DMARD alone	In combination with BRM
Methotrexate (26)	5	21
Azathioprine (5)	3	2
Leflunomide (2)	0	2

Initial BRM/DMARD Management

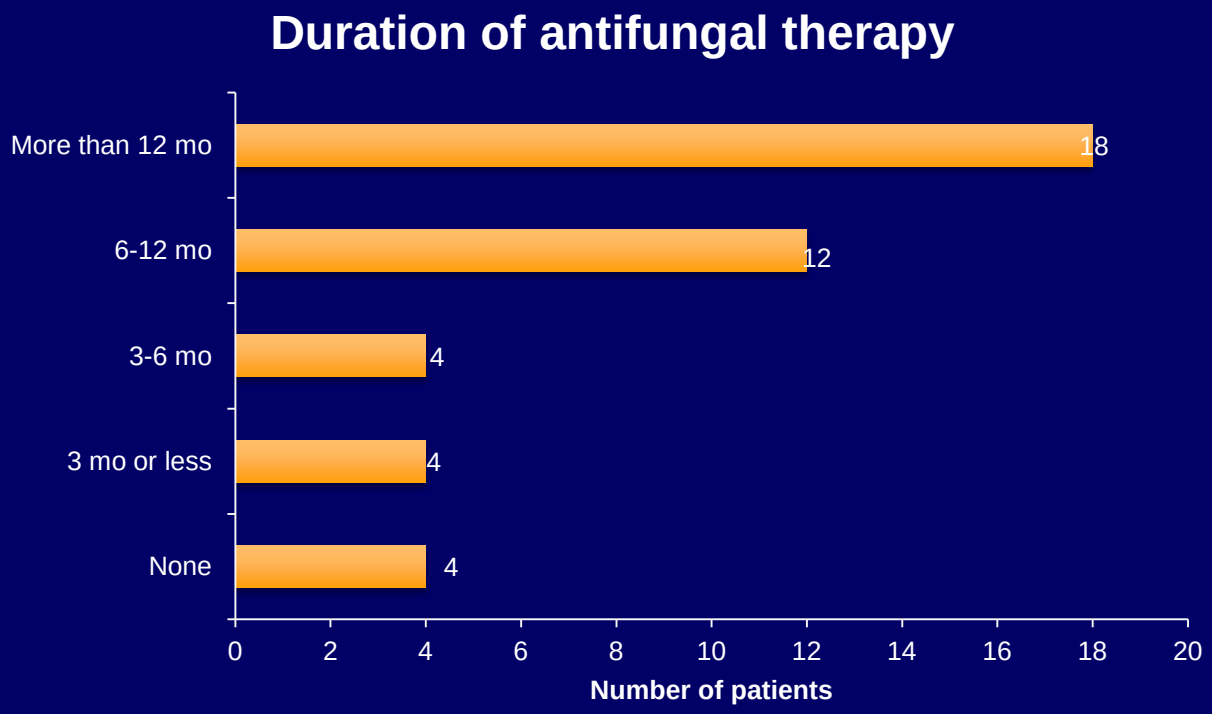


Initial Antifungal Therapy

All but 3 patients had antifungal therapy initiated for 3 months or longer (fluconazole 400 mg/day)

Median duration was 12 months

Range 0 – 96 months



Subsequent BRM/DMARD Management

Follow-up data were available for 38/44 patients

33/38 patients had resumed or continued BRM and/or DMARD

- 23 restarted BRM +/- DMARD; 10 DMARD alone
- Disseminated disease:
  - 4 BRM + DMARD
  - 4 DMARD alone
- 5 patients did not restart BRM/DMARD: remission of rheumatic disease (4), dissemination (1)

No complications from cocci to date (median f/u 30 mo)

BRM/DMARD Rationale

- BRM/DMARD continued at time of initial infection
  - Cocci asymptomatic
  - Active rheumatic disease
- BRM/DMARD later restarted
  - Active rheumatic disease

Time to Restart DMARD/BRM

DMARD

- Range: 0-48 months
- Median: 1 month

BRM

- Range: 0-72 months
- Median: 10 months

Antifungal Therapy

- 16/33 received BRM/DMARD WITH antifungal therapy
  - 5 DMARD alone
  - 11 BRM +/- DMARD
- 17/33 received BRM/DMARD WITHOUT antifungal therapy
  - 5 DMARD alone
  - 12 BRM +/- DMARD

Antifungal Therapy Rationale

- Continuing antifungal while on BRM/DMARD:
  - Persistent positive serologies
  - Dissemination
- Stopping antifungal while on BRM/DMARD:
  - Negative serology
  - Adverse reaction

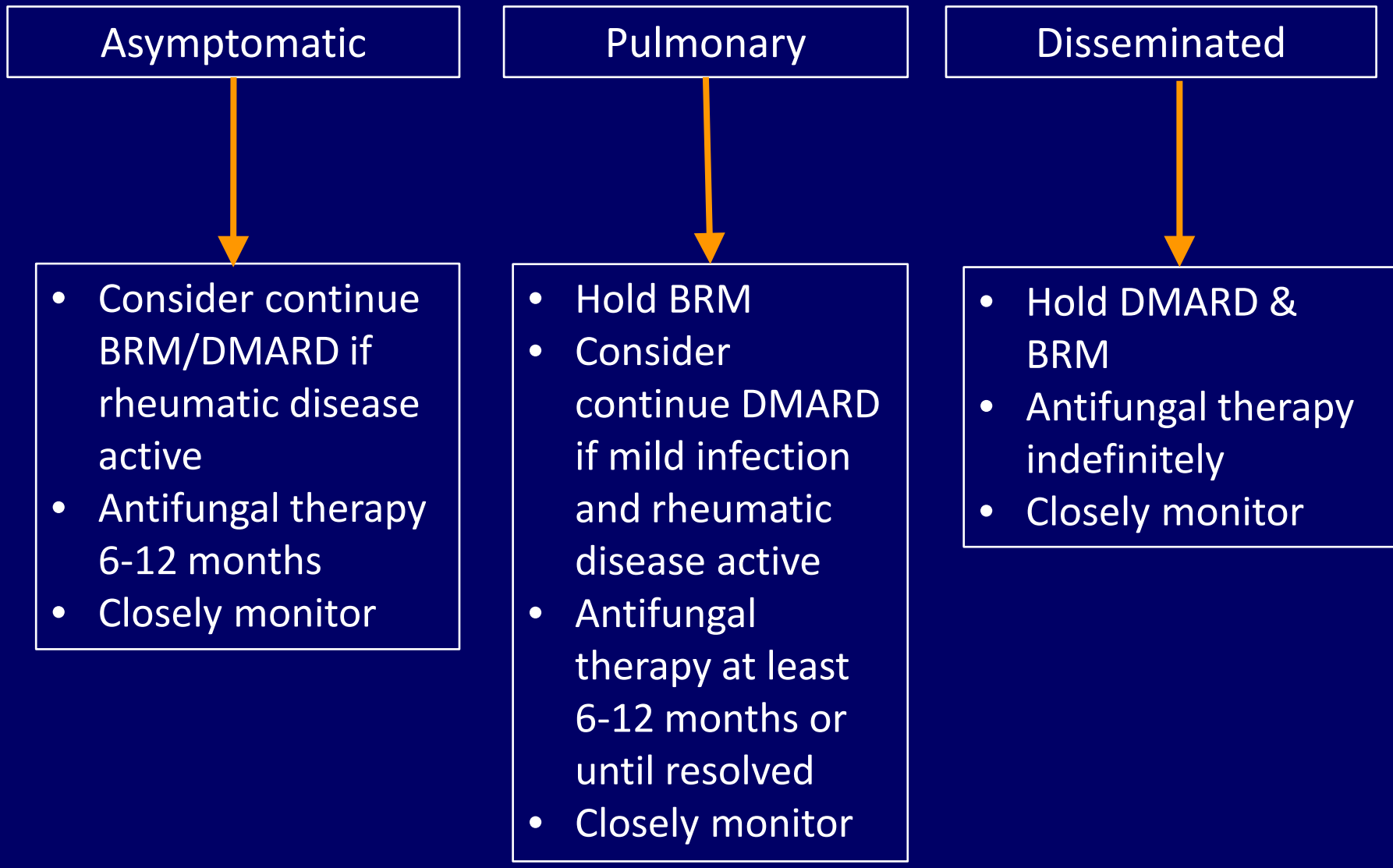
A Proposed Algorithm

Cocci can be serious infection in patients on BRM/DMARDs

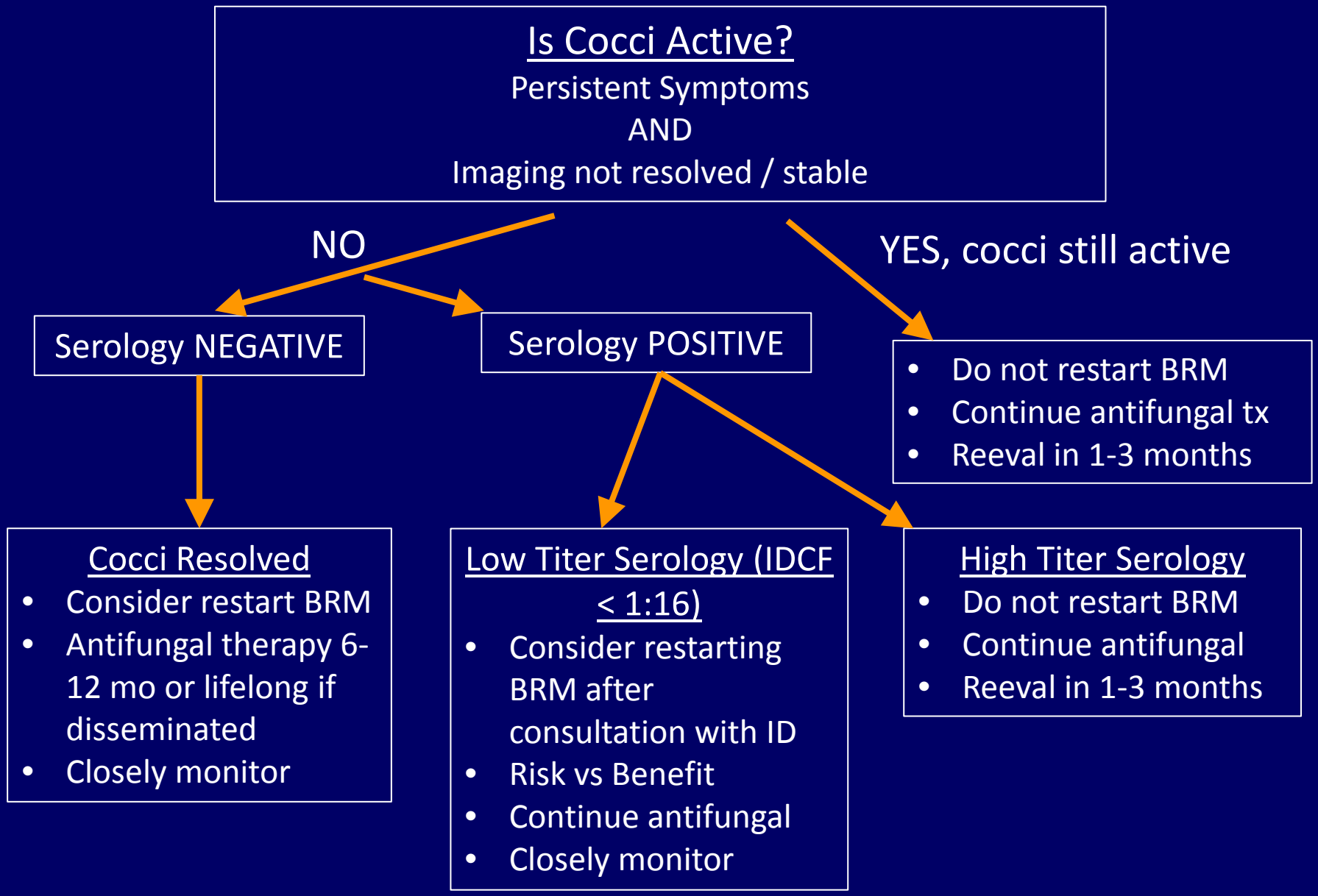
How do I manage the initial infection?

Can I resume BRM/DMARD therapy?

Initial Cocci Infection



Subsequent BRM Therapy



Conclusions

- Treating with a BRM and/or DMARD after cocci infection appears to be safe in some patients
- All patients should receive initial antifungal therapy; however concomitant antifungal when resuming BRM/DMARD must be an individualized decision
- Larger studies with longer follow up are indicated to further characterize the relationship between BRM/DMARD therapy and this endemic fungal infection