

Updates in coccidioidomycosis

**Tucson Medical Center
Health Medical education Program**

December 15, 2023

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Disclosures

No conflicts of interest to disclose



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Objectives

- Overview of clinical presentation and challenges involved with the diagnosis and treatment of Valley fever.
- Methods to improve Valley fever early diagnosis.
- Management of CM patients on BRMs.

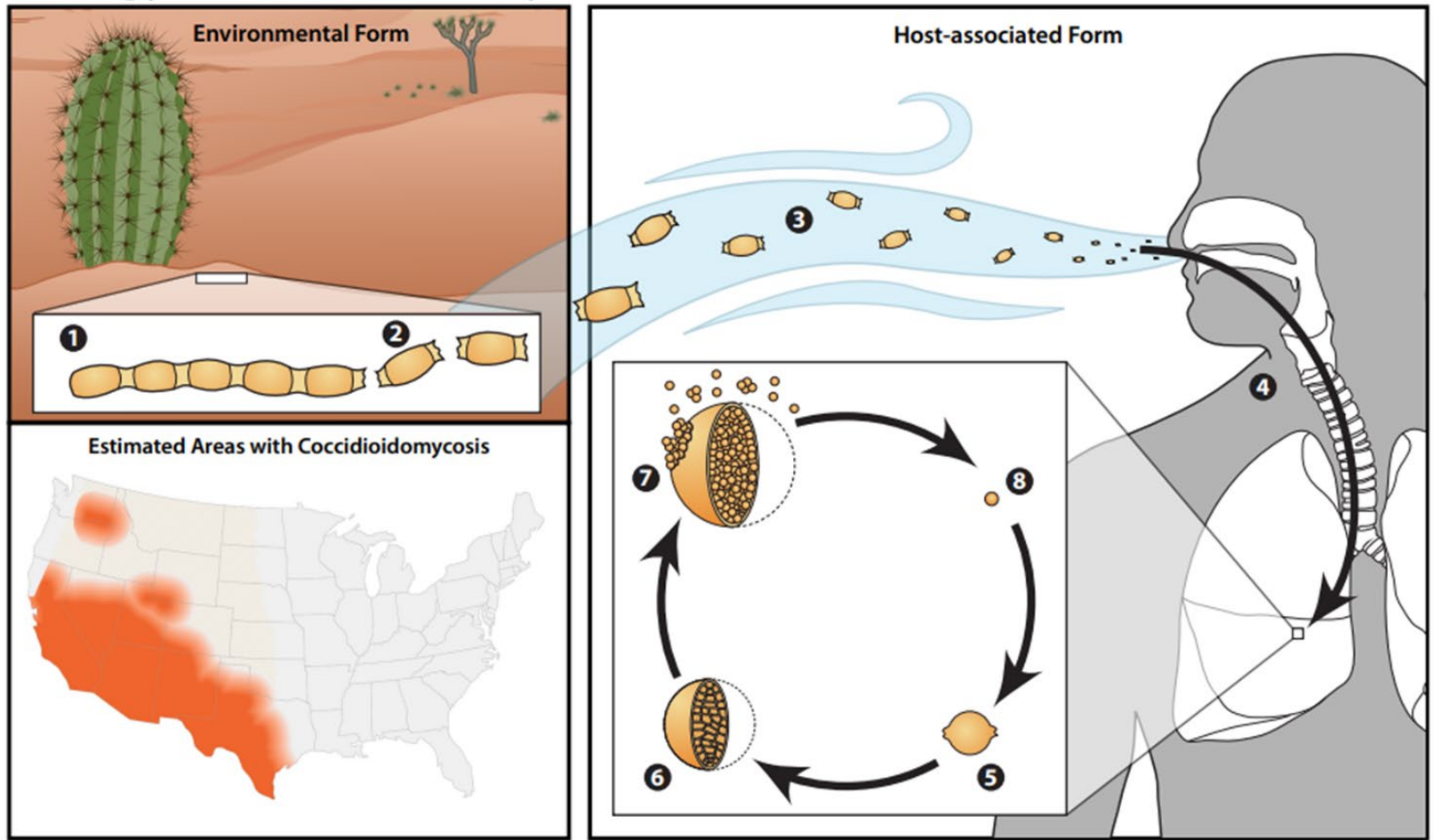


What Is Valley Fever?

- Caused by soil fungi
 - Coccidioides immitis*
 - Coccidioides posadasii*
- Other names:
 - Coccidioidomycosis
 - “COCCI”
- Infection:
 - About 150,000 per year
 - Caused by single spore
- Spectrum of disease
 - Sub-Clinical: 60%
 - “Mild”: 30%
 - Complicated: 10%
- After infection, most persons develop life-long immunity to a second infection



Biology of Coccidioidomycosis



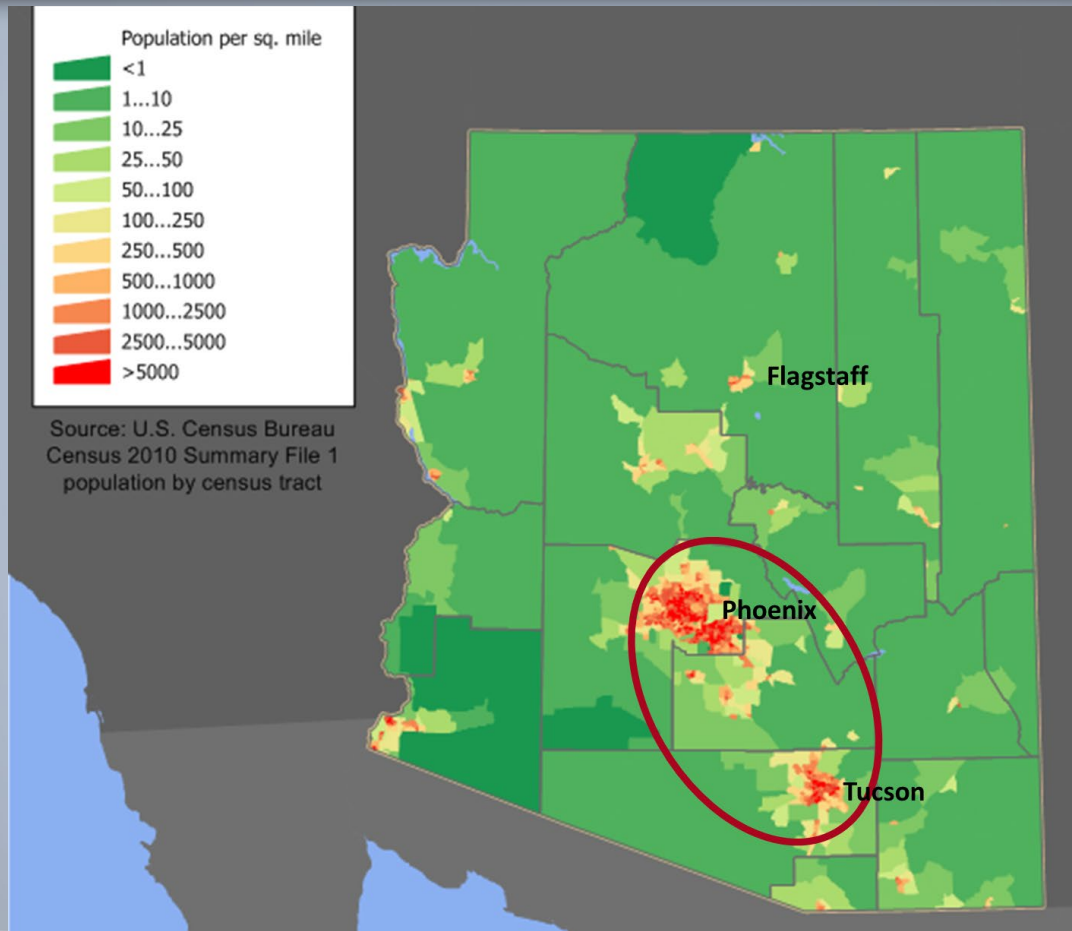
<https://www.cdc.gov/fungal/diseases/coccidioidomycosis/causes.html>

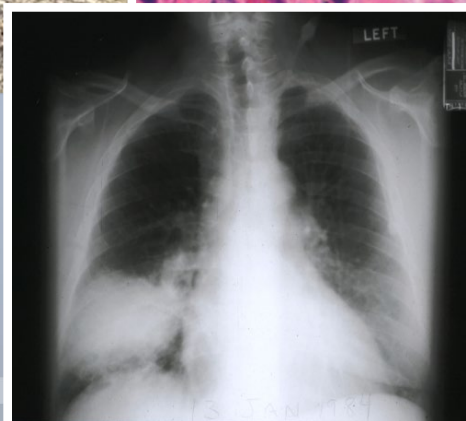
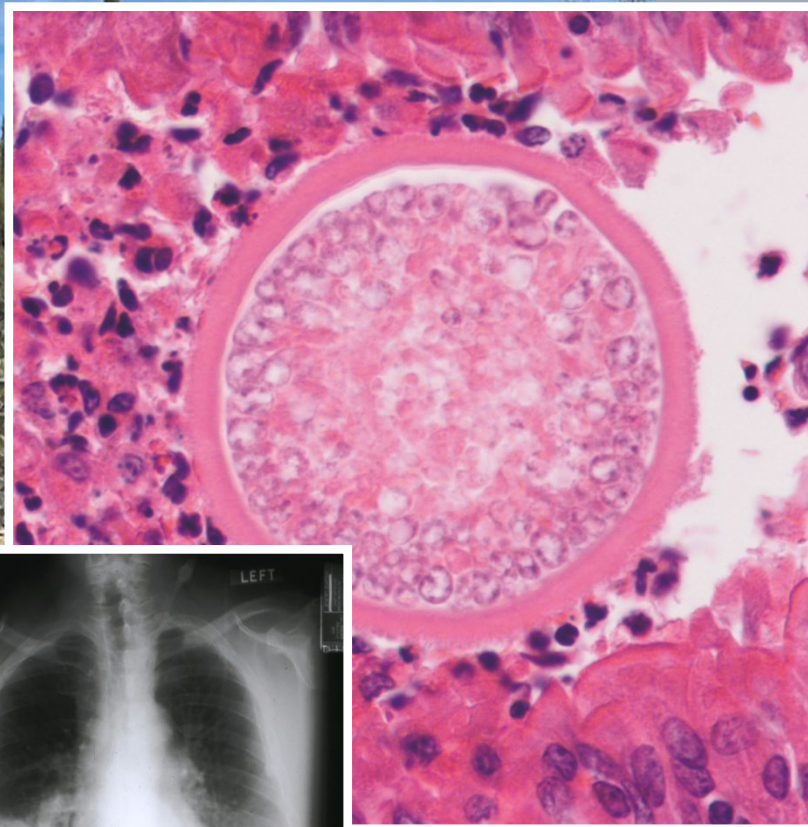


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The Valley Fever Corridor: 2/3 of all U.S. disease occurs here





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Common “Mild” Self-Limited Valley Fever

Signs and Symptoms, < 1 months from exposure:

- Cough, chest pain, fever, weight loss
- Fatigue
- Bone and joint pains (a.k.a. Desert Rheumatism)
- Skin rashes (painful or intense itching)

Course of illness:

- Weeks to months
- 25% of college students are sick for > 4 months
- 50% of workers lose > 2 weeks



Current Clinical Practice for Valley Fever

Arizona CAP

- ~ 25% - 30% due to *Coccidioides*
- BUT

- < 15% are tested for *Coccidioides*

~ 1,000 new AZ medical licenses/year

- 12% received MD in AZ
- 40% no AZ GME

80% didn't know:

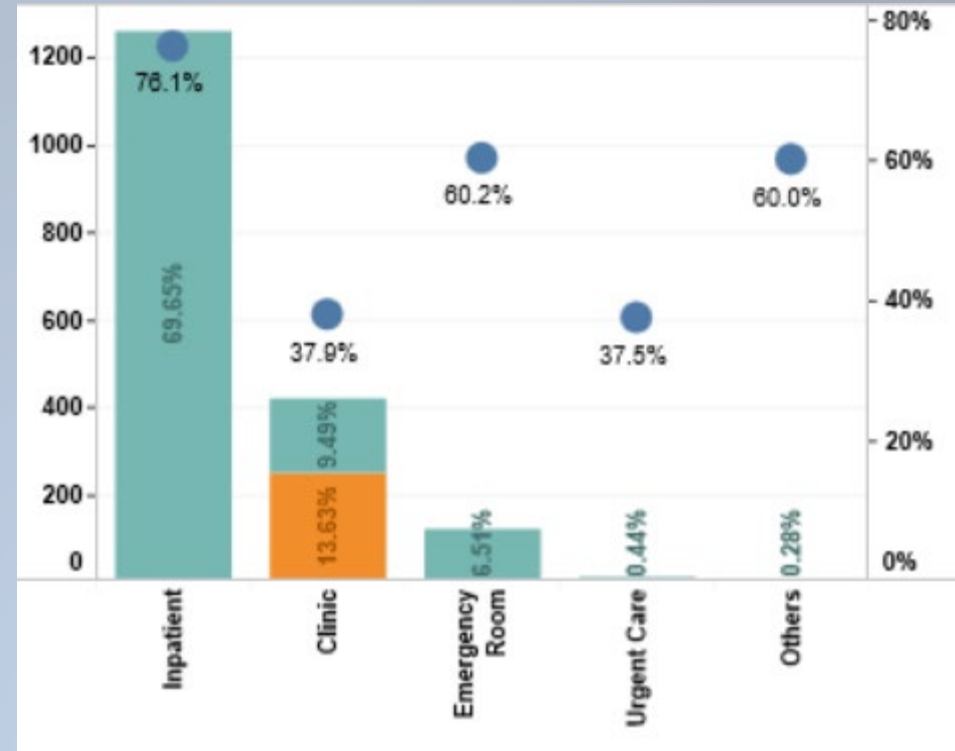
- VF is reportable
- Vaccine does not exist

40% of clinicians are not confident to treat VF



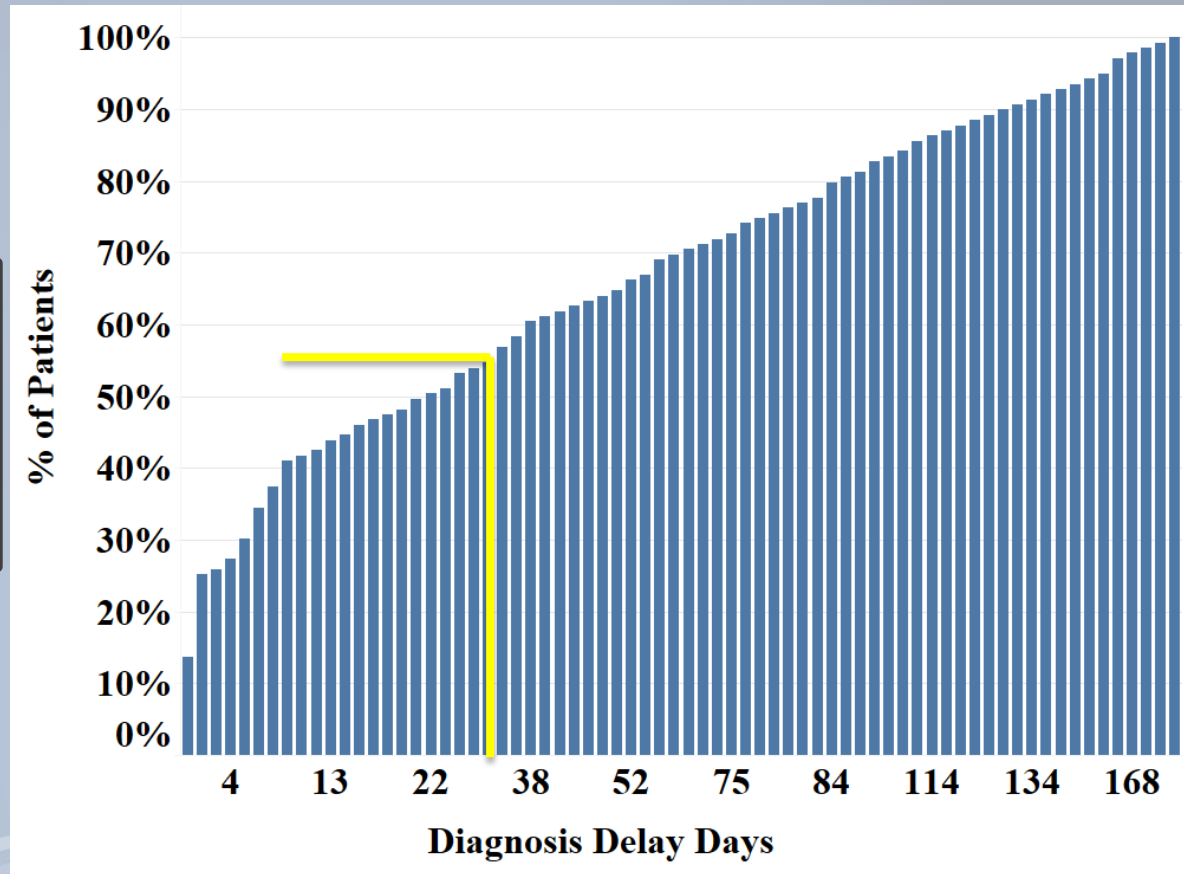
All Cocci Diagnoses in Arizona Banner Health, 2017-19 (YTD)

Only 247 out of 1,812 unique patients (13.6%) who were newly diagnosed as Cocci in primary care clinics (yellow bar)



Delay of Valley Fever Diagnosis

BUMC-P
45% of Diagnoses
Delayed > 1 month



Ginn et al. EID, 2019



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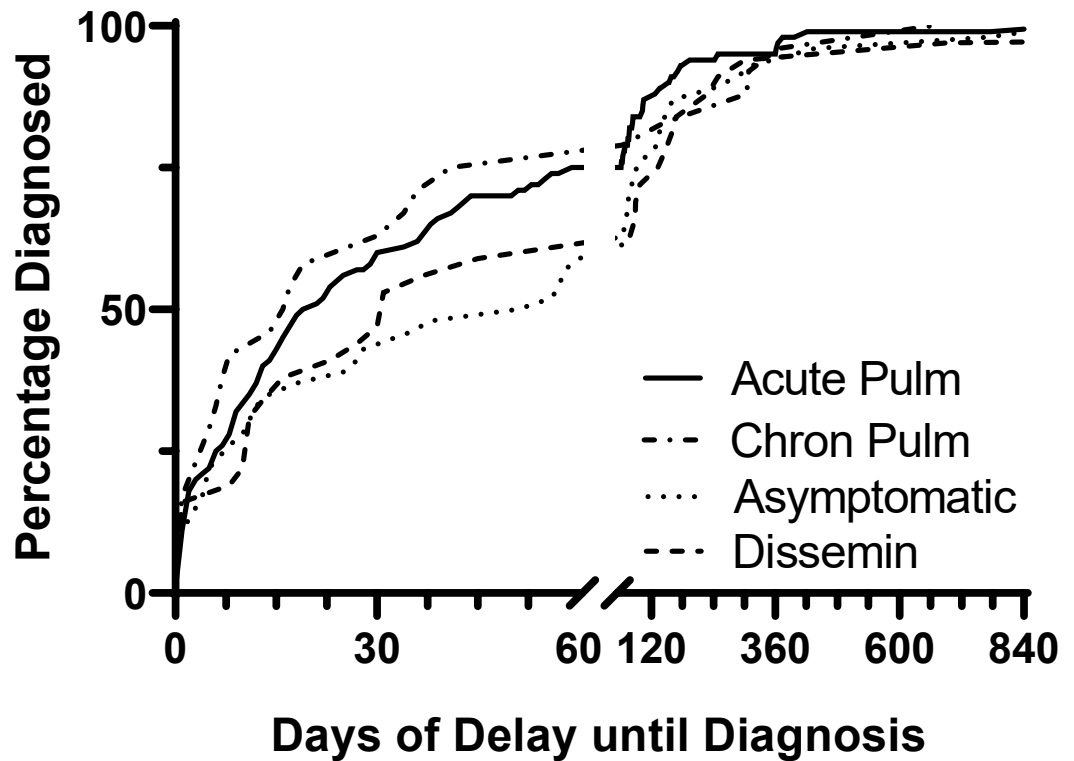


Delay of Valley Fever Diagnosis

BUMC-T
43% of Diagnoses
Delayed > 1 month

Donovan et al. EID, 2019

Figure 1.



What Do Weeks of Delayed Diagnosis Mean?

- Unnecessary anti-bacterial drug use
- Protracted patient anxiety and fear
- Over-utilization CT scans and bronchoscopies, even thoracotomies

Hypothesis: Earlier diagnosis would improve outcomes and reduce cost



Summary of Patients with CAP BMG and BUMG, total 2017-2019YTD

Measure Year	Patients With Initial Diagnosis of Pneumonia	25 % Of Patients With Initial Diagnosis of Pneumonia	Patients With Diagnosis Of Cocci	Patients With Cocci Tests	Patients With Positive Cocci Test Results
2017	837	209	26	26	23
2018	851	213	19	19	13
2019	629	157	12	12	7
Grand Total	2,268	567	57	57	43



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- **Methods to improve Valley fever early diagnosis.**
- Management of CM patients on BRMs.



Valley Fever

(Coccidioidomycosis)

Tutorial for
Primary Care Professionals



Prepared by the
VALLEY FEVER CENTER FOR EXCELLENCE
The University of Arizona



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Primary Care of Coccidioidomycosis

C onsider the diagnosis
O rder the right tests
C heck for risk factors
C heck for complications
I nitiate management



Consider the diagnosis

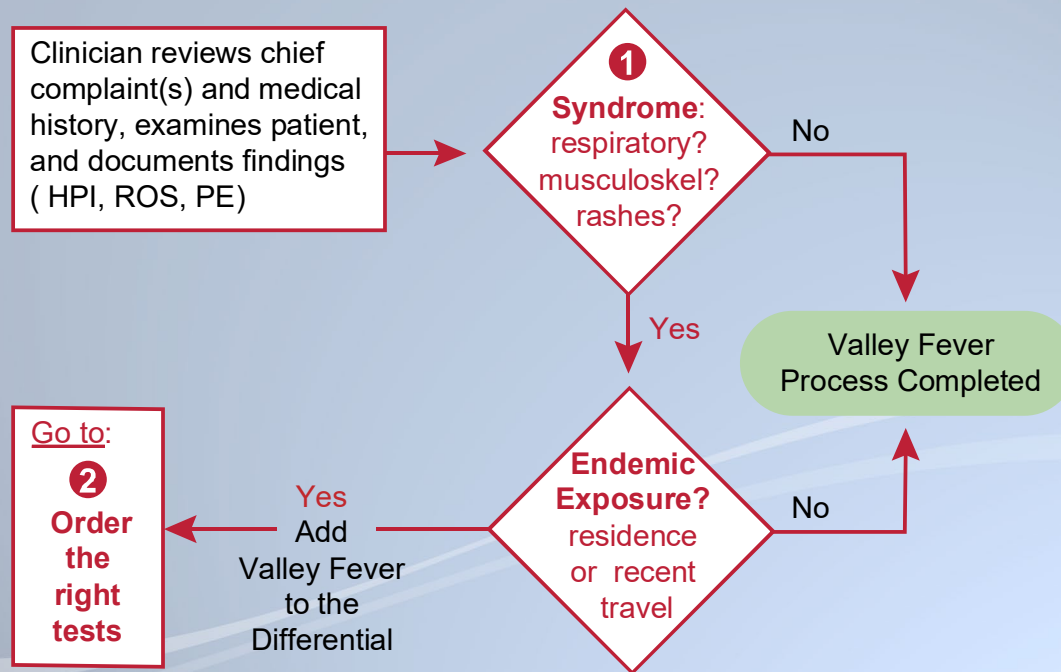
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1 Consider the diagnosis

Respiratory: Previous visit, needs X-ray or antibacterial Rx?

Musc/Skel: More than one week, associated with fever or fatigue.

Rashes: *E. nodosum* or *E. multiforme*



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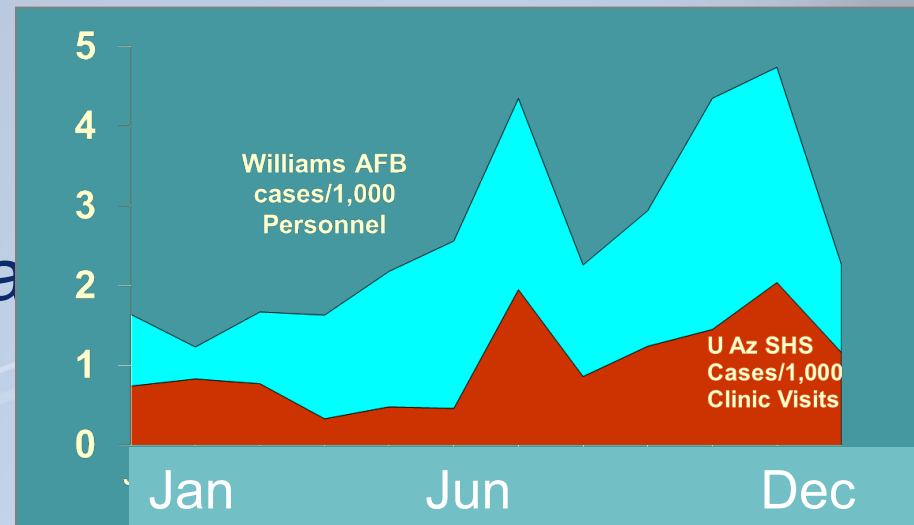
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Consider the diagnosis in Arizona

- In Arizona, Valley Fever is very common. It should be in the differential often.
- More frequent between the monsoons and the winter rains.
- Syndromes:
 - Always in community and
 - Rheumatism.
 - Rashes.

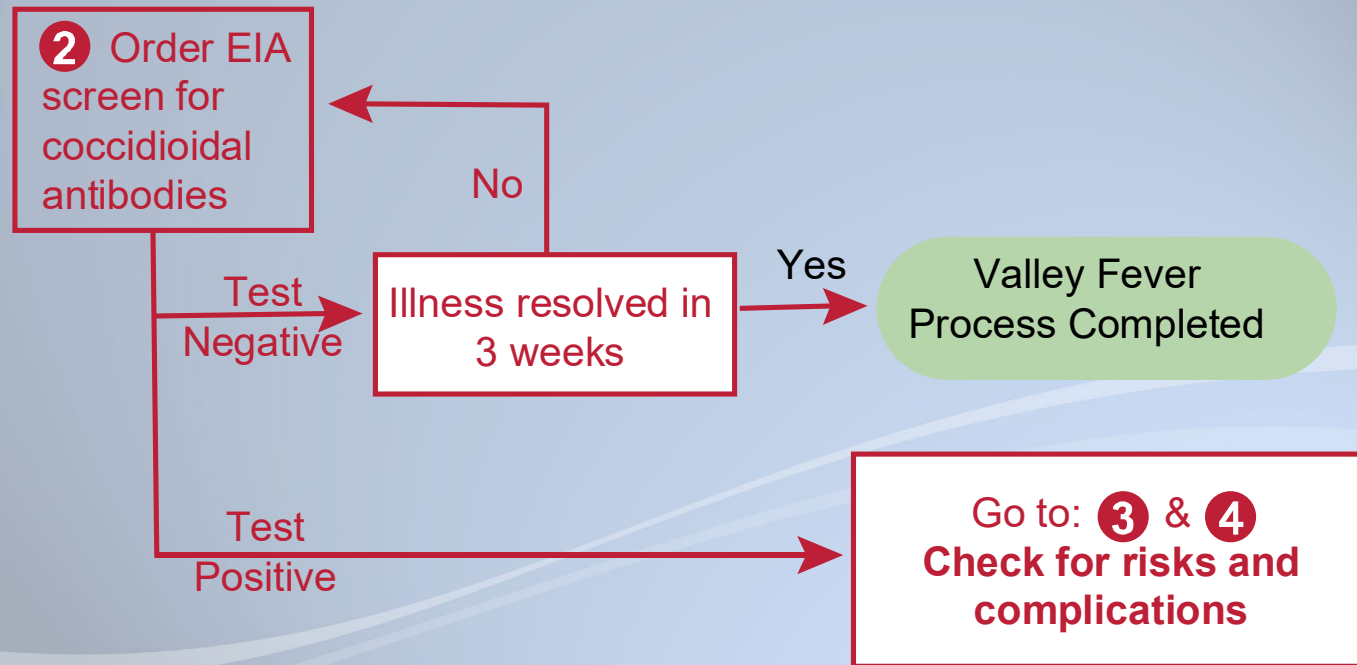


Order the right tests



2 Order the right tests

EIA screen for coccidioidal antibodies with reflex to immunodiffusion and quantitative CF.



Orders the Right Tests: EIA screen for Coccidioidal Antibodies

Enzyme Immunoassay (EIA) test

- **A positive test** is very specific and usually is diagnostic.
- **A negative test** never rules out Valley Fever. Repeated testing improves diagnostic sensitivity.



Check for Risk Factors

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③ Check for Risk Factors

Immunosuppression (HIV, organ recipient, Rheum/GI/Derm response modifier Rx, renal failure)

Diabetes, major cardiac or pulmonary comorbidities, pregnancy



Risk Factors

Pulmonary Complications

- Diabetes mellitus
- Cardio-pulmonary or other co-morbidities (Evidence: “common sense”).

Disseminated Infection

- Major and critical
 - Cell immunodeficiency
 - Pregnancy
- Minor and small effect
 - Males > Females
 - Racial background
 - Adults > Children

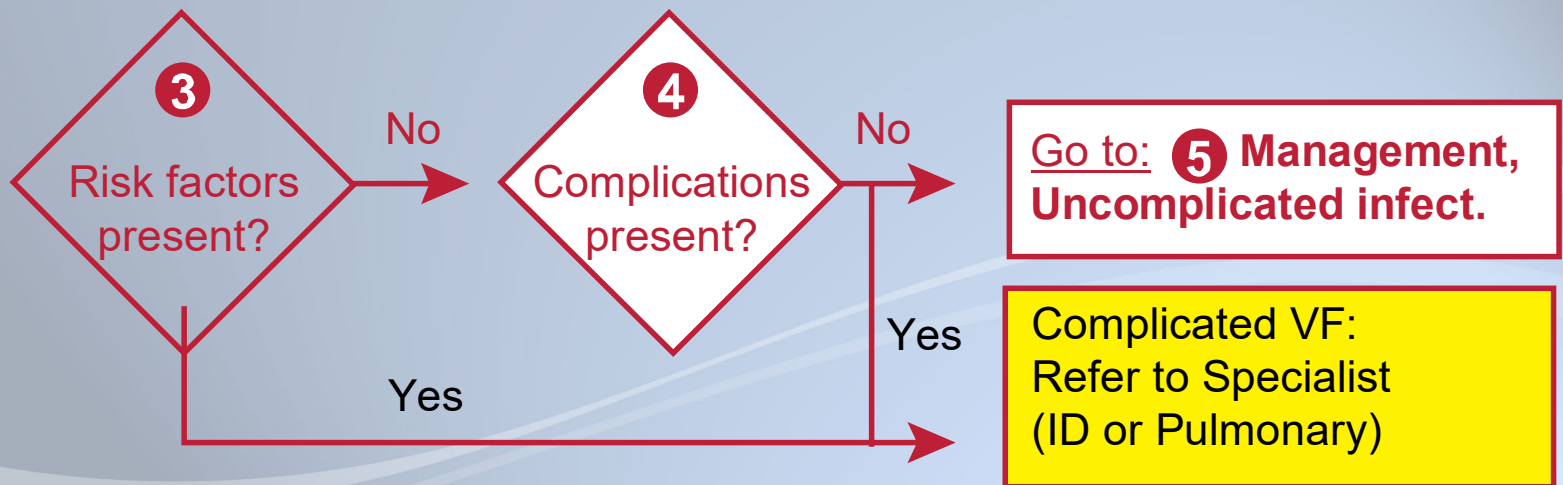


Check for Complications

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④ Check for complications evident by physical exam or imaging

Focal ulceration or skin/soft tissue inflammation.
Asymmetric skeletal pain, joint effusions.
Progressive or unusual headache.

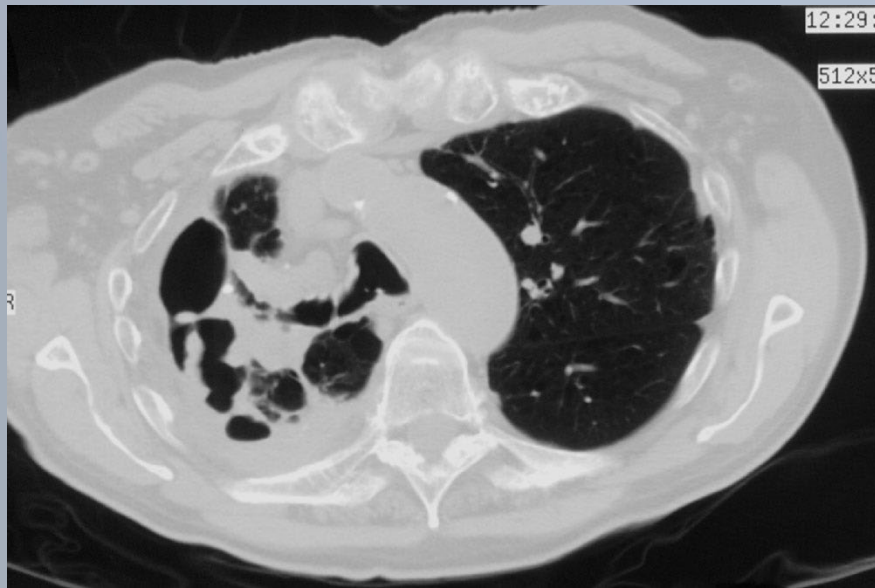


Detecting Complications of Coccidioidomycosis

- Review of Systems: Pain or discomfort
 - Headache
 - Back pain
 - Joint pain or loss of function
- Physical Examination:
 - Skin lesions
 - Subcutaneous fluctuation
 - Joint effusions



Fibro-cavitary Coccidioidomycosis



Complex



Thin-walled



Widely Disseminated Coccidioidomycosis



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Disseminated Coccidioidomycosis



Disseminated Coccidioidomycosis



Disseminated Coccidioidomycosis



Disseminated Coccidioidomycosis



Disseminated Coccidioidomycosis



Check for Complications

- Most complications are focal
- **A review of systems and physical examination will usually detect or exclude the possibility of complications.**
- New focal findings warrant either evaluation or referral for Infectious Diseases or Pulmonary consultation.



Follow-up Chest X-rays

What to order?

Purposes:

- Identify if infiltrate cavitates.
- Determine if there is a residual nodule (could be confused with cancer in later years)

In most patients, these objectives can be accomplished with simple PA and lateral X-rays; CT scans are usually not needed.



Primary Coccidioidal Pneumonia

Study date:10.26.2011
Study time:11:31.07



Series number:1
Image number:1

WW/WC:4096/2047

KVP:kV
X-ray tube current:mA
Exposure:mAs

October 26



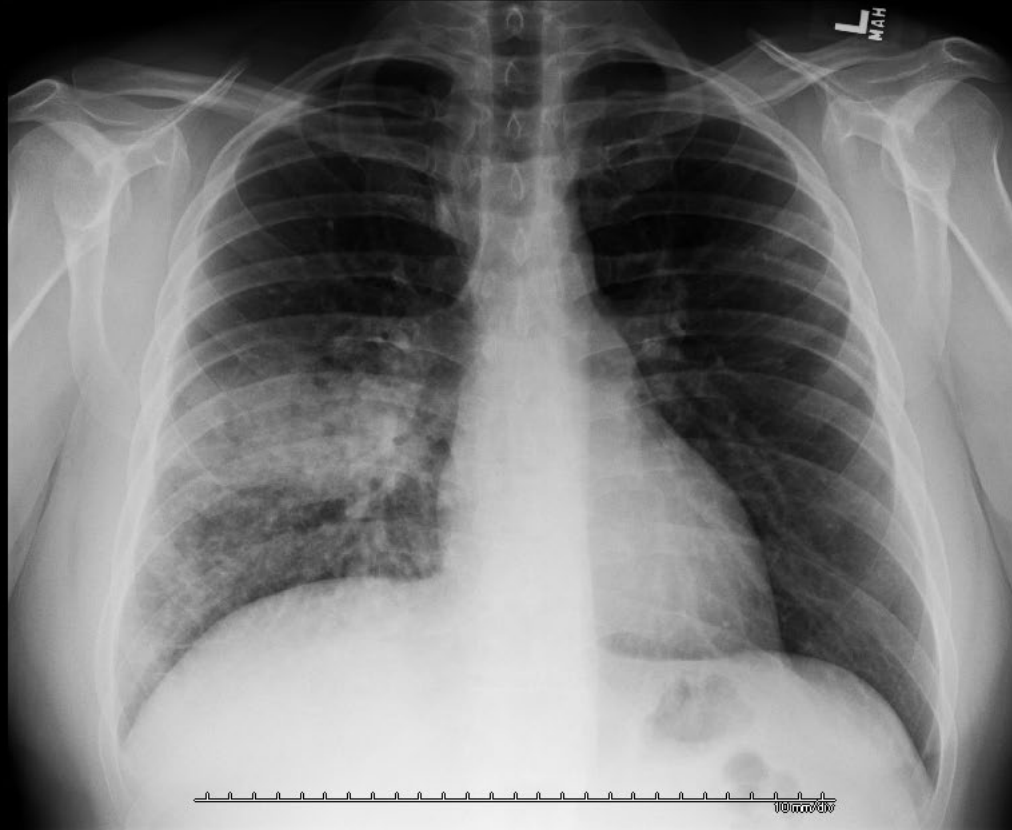
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Primary Coccidioidal Pneumonia

Study date:11.03.2011
Study time:11:44.03

Series number:1
Image number:1



WW/WC:4096/2047

KVP:kV
X-ray tube current:mA
Exposure:mAs

November 3



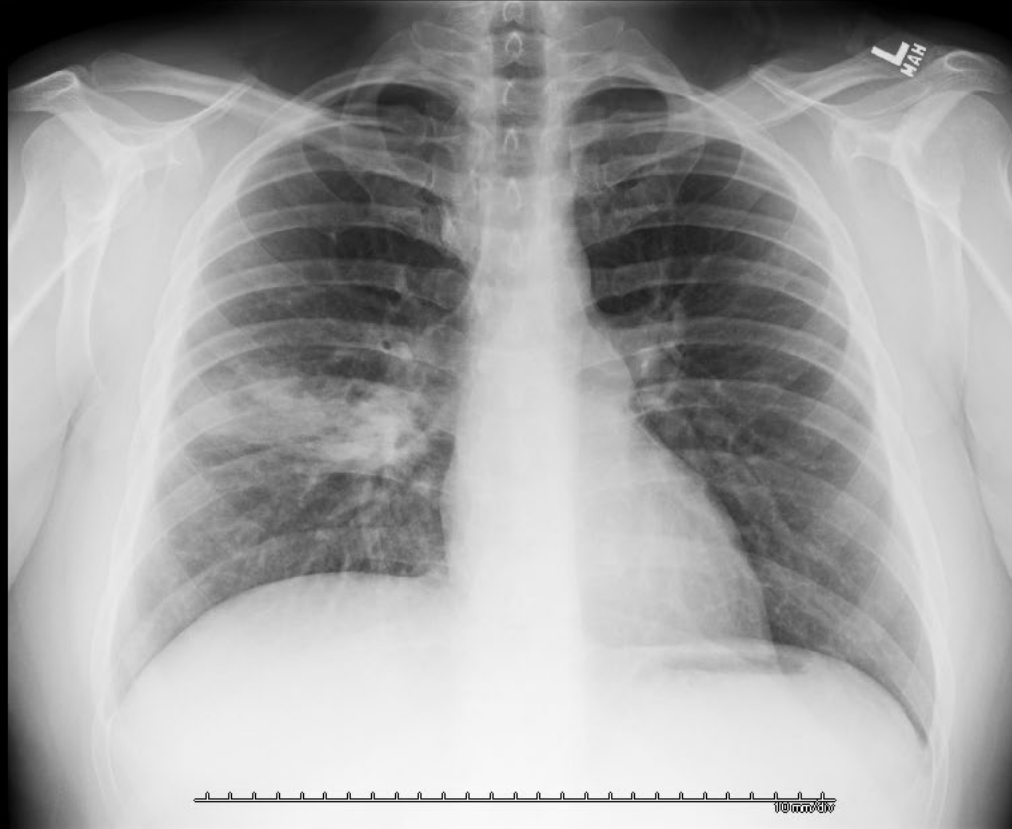
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Primary Coccidioidal Pneumonia

Study date:11.14.2011
Study time:14:39.29

Series number:1
Image number:1



WW/WC:4096/2047

KVP:kV
X-ray tube current:mA
Exposure:mAs

November 14

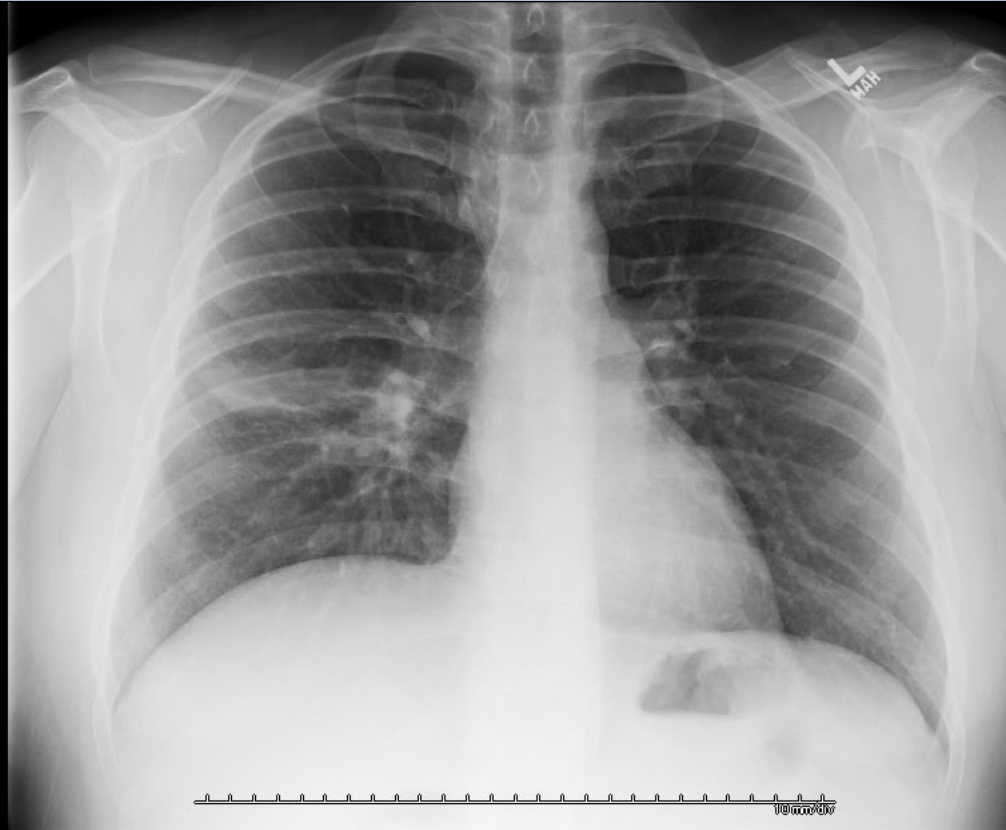


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Primary Coccidioidal Pneumonia

Study date:12.15.2011
Study time:14:38.55



Series number:1
Image number:1

WW/WC:4096/2047

KVP:kV
X-ray tube current:mA
Exposure:mAs

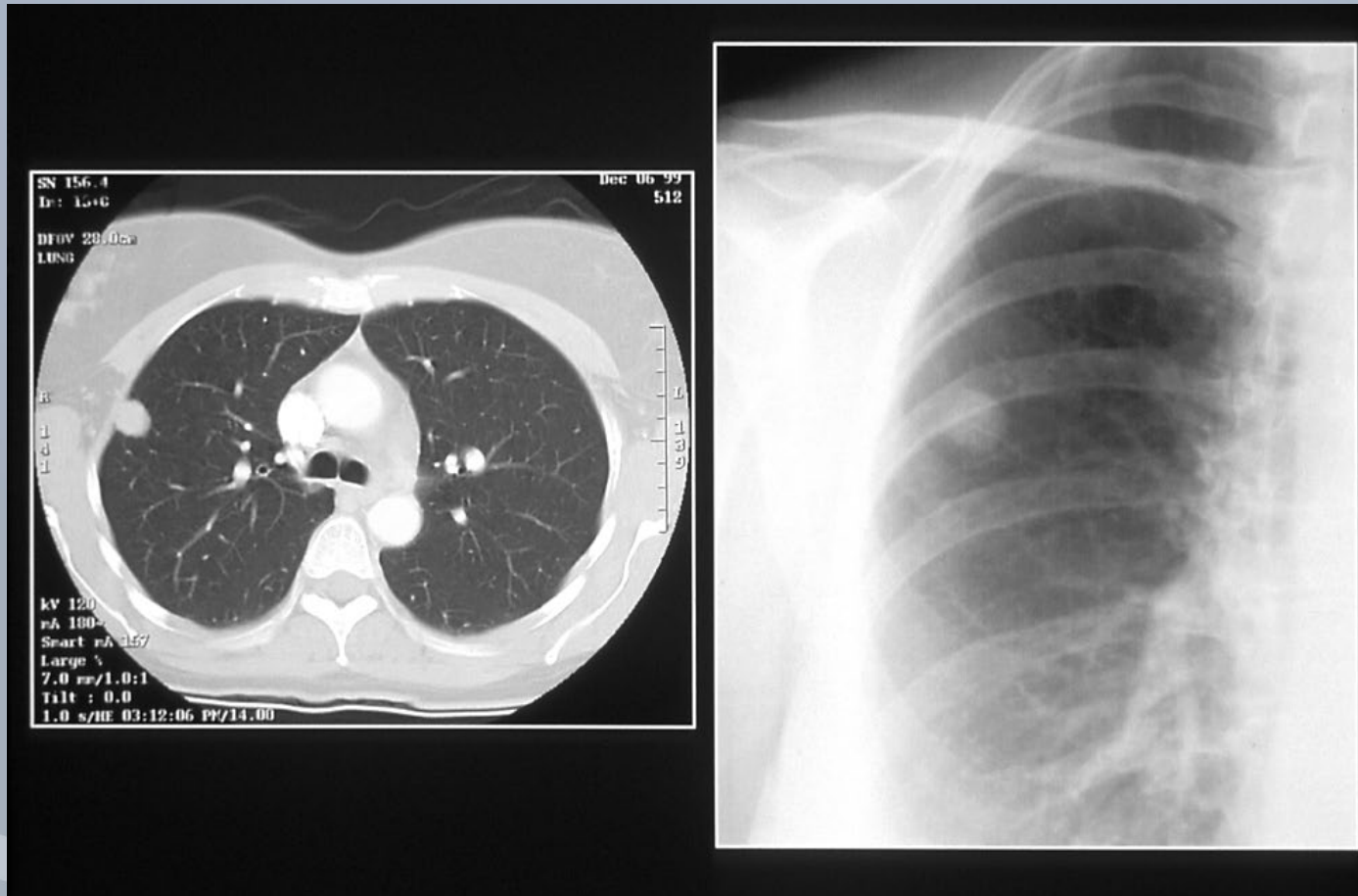
December 15



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Peripheral Coccidioidal nodule



Follow-up Coccidioidal Serology

How do they help?

- As patients improve, titers generally decrease
- The decrease typically occurs over several months, occasionally even slower.
- If titers increase, re-evaluate for possible complications.
- Titers are a marker, not a disease



Follow-up Coccidioidal Serology How do they help?

Clinical Infectious Diseases

Comparison of a Novel Rapid Lateral Flow Assay to Enzyme Immunoassay Results for Early Diagnosis of Coccidioidomycosis

Fariba M. Donovan,^{1,2} Ferris A. Ramadan,³ Sher A. Khan,³ Apoorva Bhaskara,² William D. Lainhart,^{2,4} Aneesh T. Narang,⁵ Jarrod M. Mosier,² Katherine D. Ellingson,³ Edward J. Bedrick,³ Michael A. Saubolle⁵ and John N. Galgiani^{1,2}

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Fatigue: Often the Last Symptom Typical Problem

- Primary coccidioidal pneumonia diagnosed serologically in an otherwise healthy active person.
- Over several weeks, weight returns to normal, fever resolves and pulmonary symptoms gone. ESR becomes normal. CF low or neg.
- However, patient complains of profound inability to carry out normal activities.
- How should this be managed?



Potential Causes of Fatigue

- In some, striking deficit in O₂ utilization (VO₂ peak <10% of predicted)*
- Physical deconditioning because of decreased activity.
- Lack of experience by the patient with subacute or chronic disability.
- Patient with excessive expectations of own performance.



Management Strategies for fatigue

- **Exclude objective evidence of tissue destruction or focal lesions.**
- **Patient Education**
 - Prolonged fatigue common and resolves
 - No evidence of permanent damage
 - Deconditioning and unrealistic expectations
- **Patient Actions**
 - Keep a journal
 - Refer patient to Physical Therapist for reconditioning
- **Antifungal drugs? May or May Not be Helpful**



Clinical Infectious Diseases

IDSA GUIDELINE



OXFORD

2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis

John N. Galgiani,¹ Neil M. Ampel,² Janis E. Blair,³ Antonino Catanzaro,⁴ Francesca Geertsma,⁵ Susan E. Hoover,⁶ Royce H. Johnson,⁷ Shimon Kusne,³ Jeffrey Lisse,⁸ Joel D. MacDonald,⁹ Shari L. Meyerson,¹⁰ Patricia B. Raksin,¹¹ John Siever,¹² David A. Stevens,¹³ Rebecca Sunenshine,^{14,15} and Nicholas Theodore¹⁶

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Clin Infect Dis, 2016



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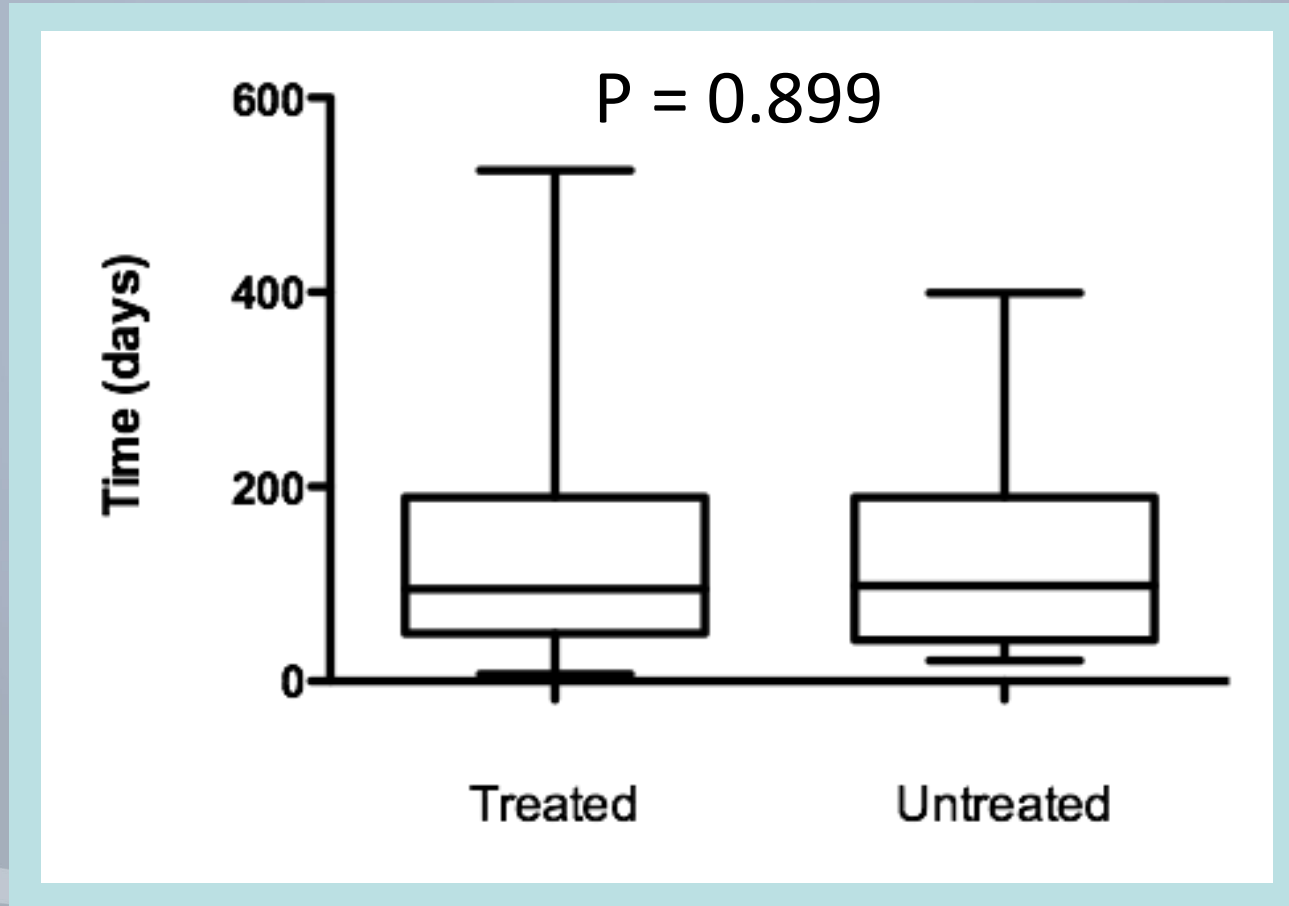
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2016 IDSA Guidelines Treatment of Coccidioidomycosis

“It should be emphasized that no randomized trials exist to assess whether antifungal treatment either shortens the illness of early uncomplicated coccidioidal infections or prevents later complications.”



Median days to $\geq 50\%$ decline in total clinical score



Outcome of Subjects (> 1 month follow-up)

- 50 not treated
 - Median follow-up: 3.1 years
 - All without complications
- 51 treated
 - Median follow-up: 2.9 years
 - 38 off-therapy and without complications
 - 5 remained on treatment
 - 8 had relapses
 - 5 with pulmonary disease
 - 3 with extrapulmonary dissemination
 - Relapses occurred up to 2 years after stopping treatment



The Valley Fever Tool Kit

www.vfce.arizona.edu

Support Resources Training Resources

- Process Flow pocket guide.
- Wall posters and patient educational brochures
- Nurse Practitioner referral support? (proposed)
- EMR alerts? (only if wanted by the clinicians)
- Webinar Overview
- Primary Care Tutorial
- Powerpoint presentation online
- CME presentations at individual clinical practices.



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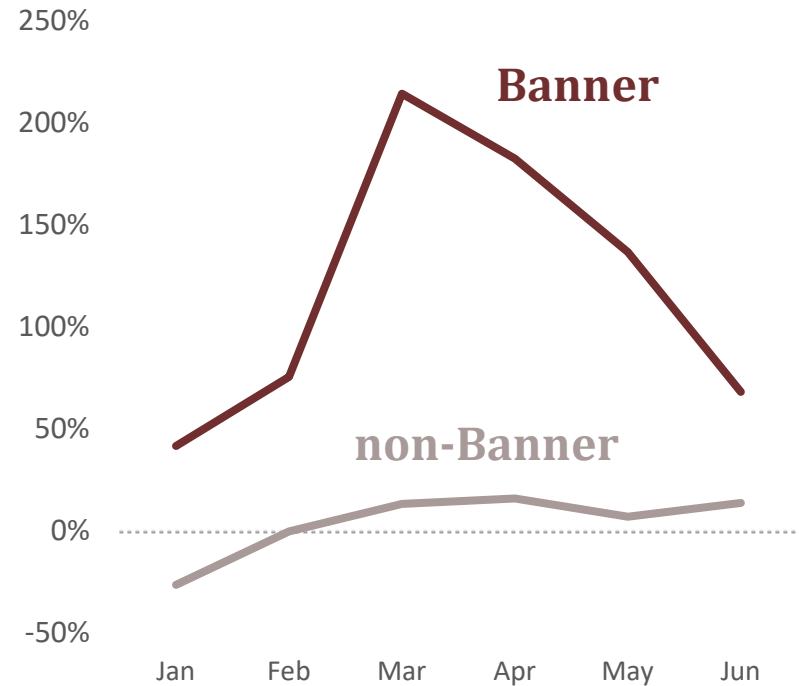
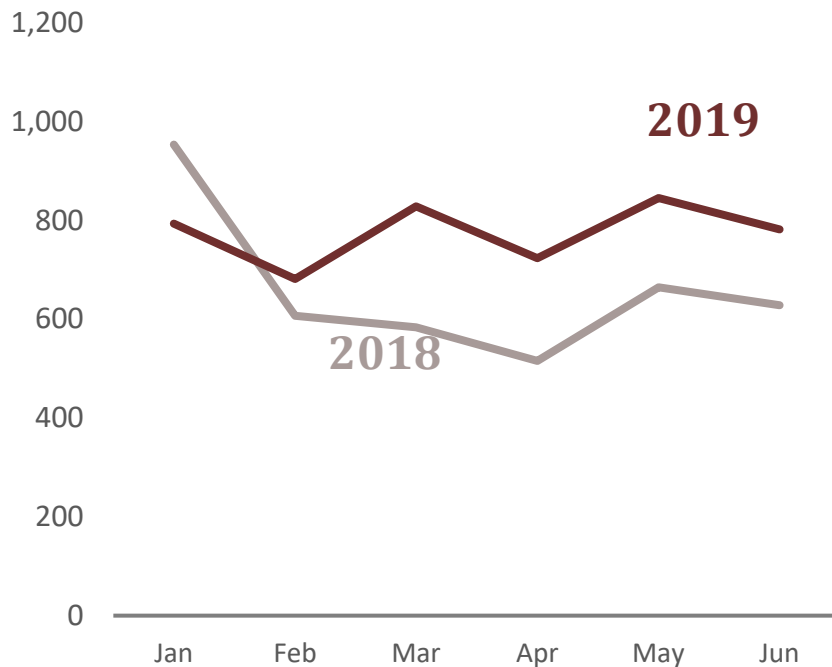


Potential impact of the Banner Training on Arizona cocci surveillance data

Arizona Department of Health Services Preliminary Analysis, 7/30/19.

Reported cases have been elevated for most of **2019** year-to-date compared to **2018**.


Monthly percent change from 2018 to 2019 in cases from **Banner** and **non-Banner facilities**.



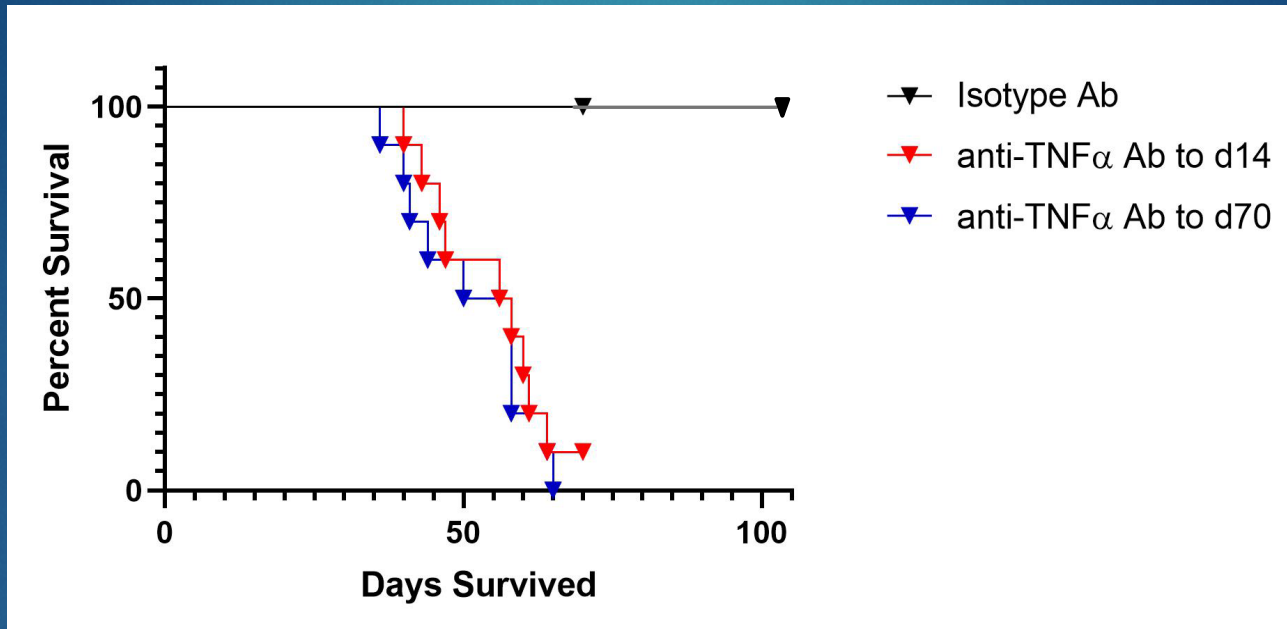
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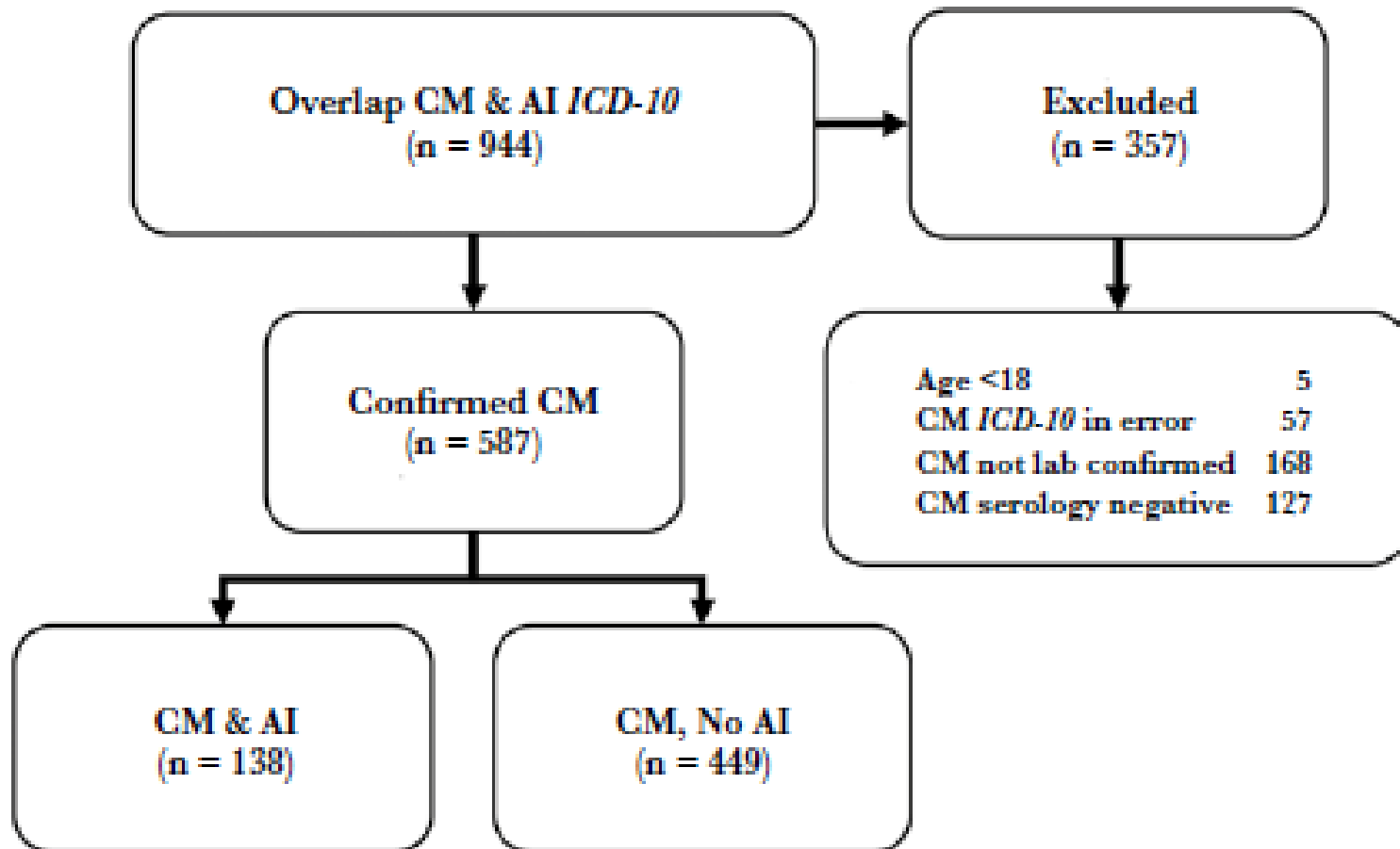


- 
- **An increasing number of BRMs used for autoimmune diseases such as RA pose further risk for endemic mycosis.**
 - **Some patients on BRMs handle CM poorly.**
 - **The risk of DCM rises as much as 150-fold in some immunosuppressed patients (Cohen, 1982).**
 - **Clinical question:
Is it safe to use BRMs in CM-endemic regions?**

Early TNF α blockade has deleterious effect on mice survival



Evaluating the CM risk in patients on BRMs:



Evaluating the CM risk in patients on BRMs

- Male sex was associated with more CM ($P = 0.003$)
- African ancestry were 3 times more likely than those with European ancestry to develop DCM ($P < .001$).
- Comparing CM+/AI+ ($n = 138$) with CM+/AI- ($n = 449$) patients, there were **no** significant differences in CM clinical presentations.
- Patients receiving BRMs had **2.4 times** more DCM compared to pulmonary CM (PCM).

Evaluating the CM risk in patients on BRMs

Table 4. Comparison of Biologic Response Modifier Used in Pulmonary and Disseminated Coccidioidomycosis Among Patients With Autoimmune Disease

Clinical Presentation	BRM		No BRM		PValue*
	No.	(%)	No.	(%)	
PCM	17	(65.4)	58	(85.3)	.045**
DCM	9	(34.6)	10	(14.7)	
Total [‡]	26	(100)	68	(100)	

Abbreviations: BRM, biologic response modifier; DCM, disseminated coccidioidomycosis; PCM, pulmonary coccidioidomycosis.

*Total of 94 patients identified with both PCM/DCM presentation and autoimmune syndrome.

**Fisher exact test was used to evaluate categorical groups.

***Statistically significant difference between coccidioidomycosis-positive groups.

Summary

- Banner Health and the UA Valley Fever Center for Excellence are changing the way Arizona clinicians recognize and manages patients with Valley Fever.
- Central to this change will be the expanded roll of primary care clinicians in earlier diagnosis and management of uncomplicated Valley Fever.



Thank-You

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For more information:

<http://vfce.arizona.edu/toolkit>