Cocci in the Immunocompromised Host

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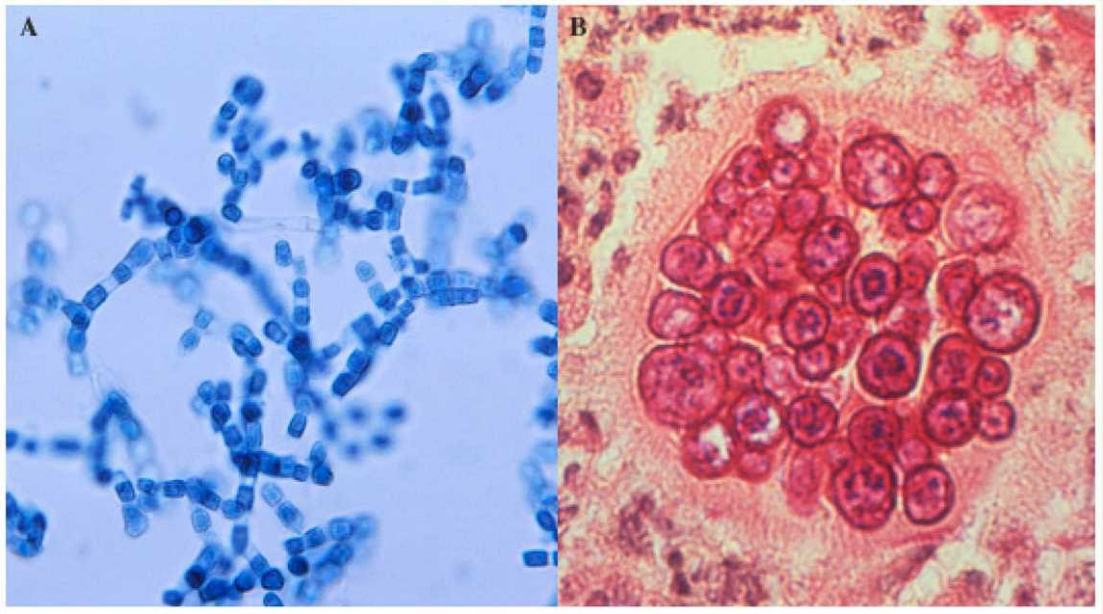
Disclosures

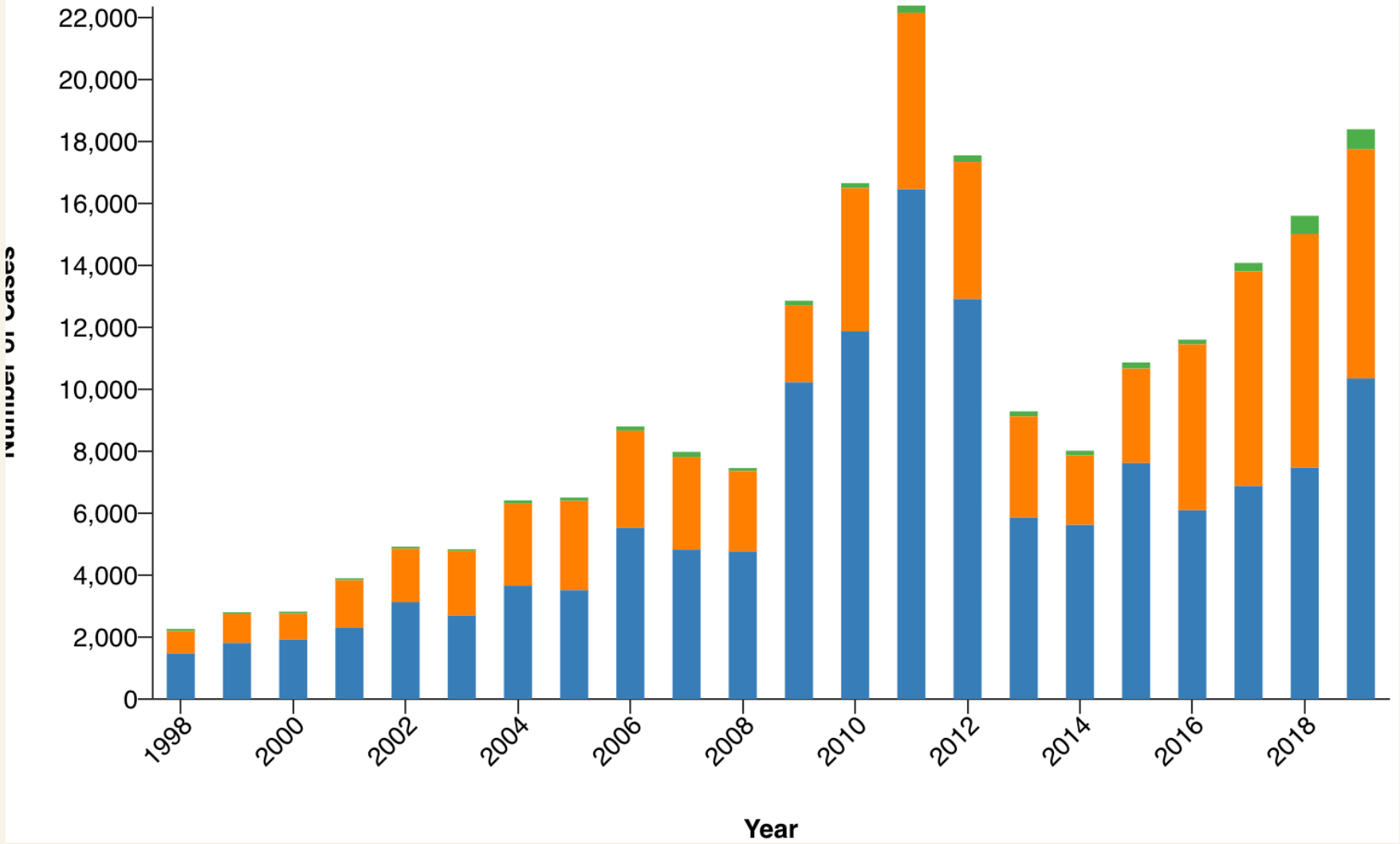
- I have no financial interests or relationships to disclose
- I will be discussing off-label use of the following medications:
  - Posaconazole
  - Isavuconazonium
  - Voriconazole
  - Itraconazole

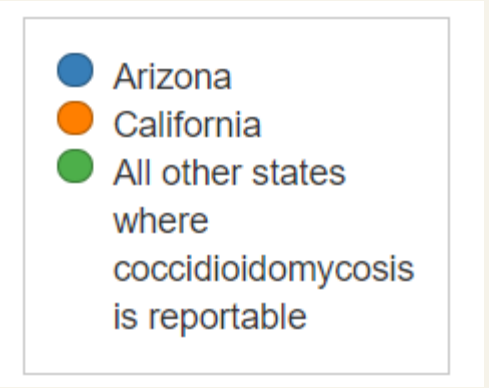


Learning Objectives

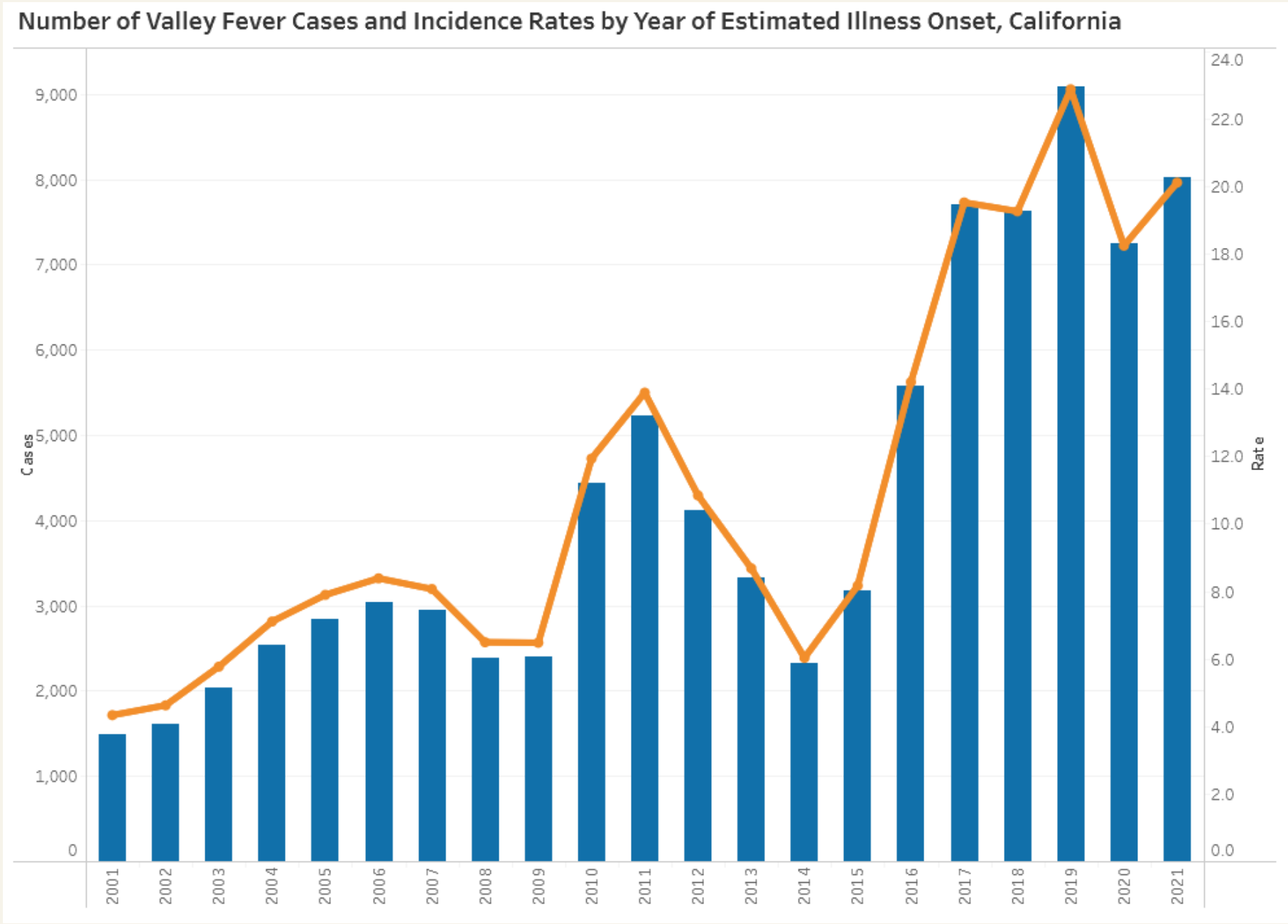
- Understand the impact of immunosuppression on the natural history of cocci
- Review screening and diagnosis of cocci in immunocompromised individuals and solid organ transplant candidates/recipients
- Review management of cocci in immunocompromised patients: prophylaxis and treatment

Number of reported Valley fever cases





https://www.cdc.gov/fungal/diseases/coccidioidomycosis/statistics.html



https://www.cdph.ca.gov/

Natural history of cocci in immunocompromised – case example

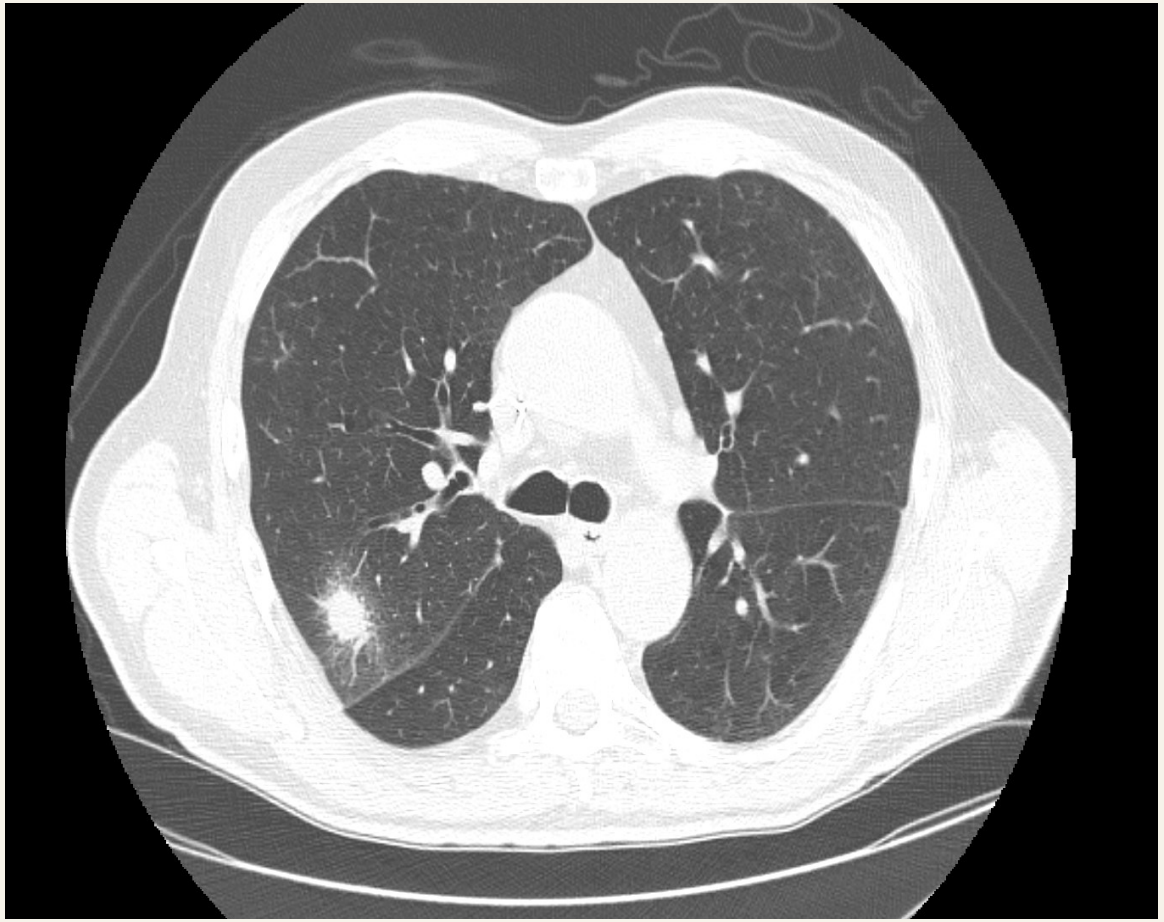
73 y/o M with h/o AML with MDS-related features

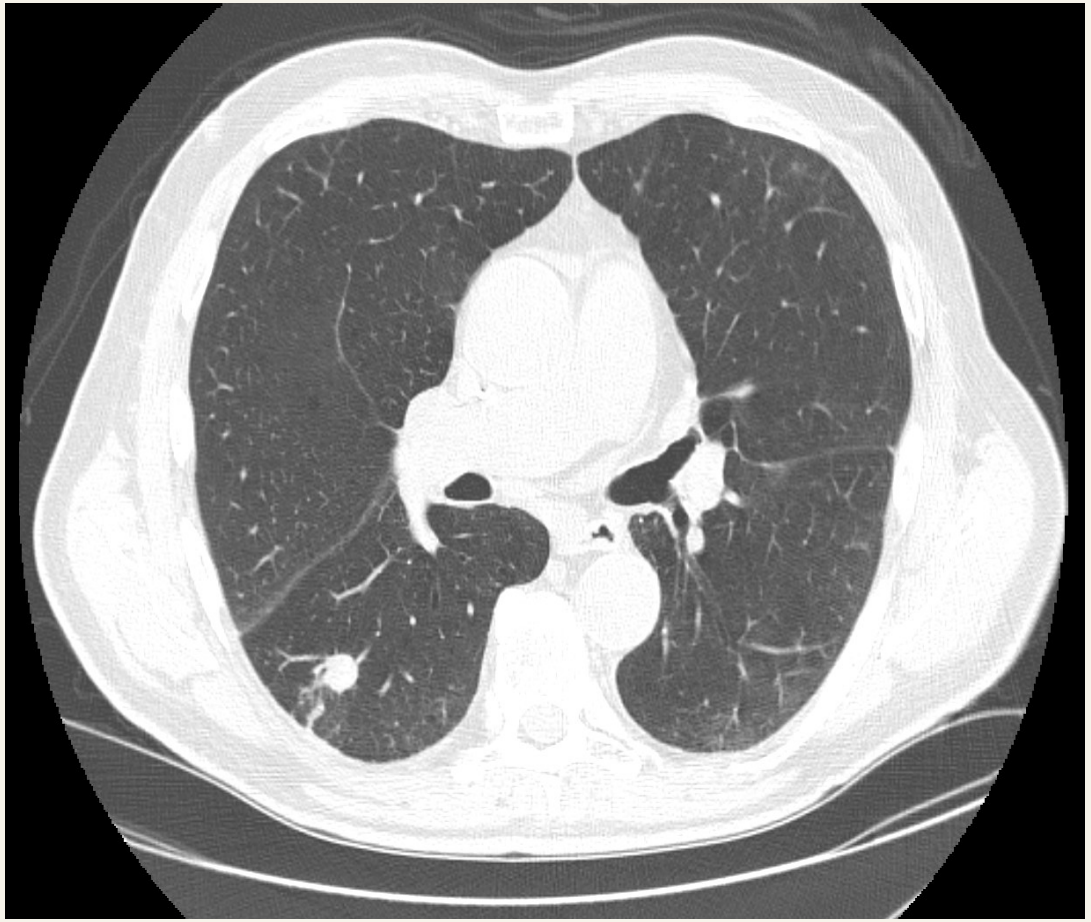
G-CLAC induction Nov 2014, course complicated by:

- Neutropenic fever
- *Moraxella* bacteremia
- Pulmonary nodules

Multani A, et al. Blood Adv. 2019 Nov 26;3(22):3602-3612. PMID: 31743391

November 2014 – 9 months prior to allogeneic SCT





- RUL nodule 1.9 x 1.5 cm with halo
- RLL 1.5 x 1.1.cm nodule partially calcified
- Serum GM 0.06
- Empirical voriconazole started

Multani A, et al. Blood Adv. 2019 Nov 26;3(22):3602-3612. PMID: 31743391

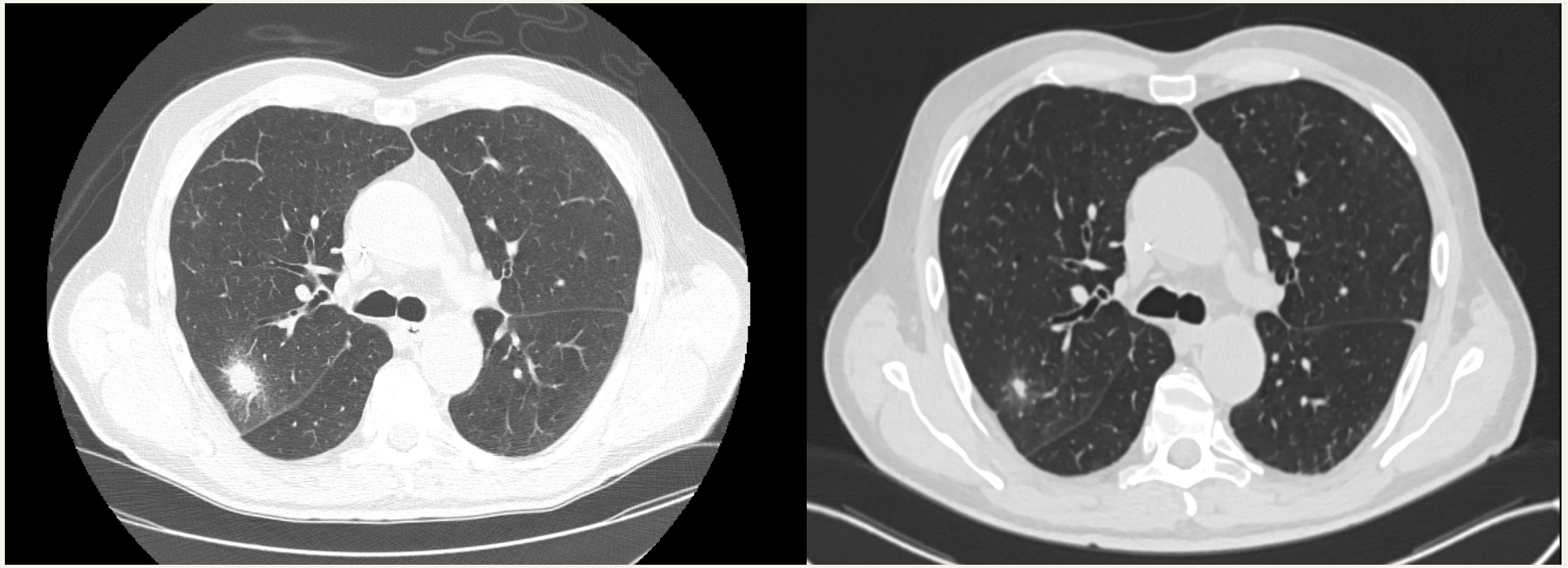
Case

- Dec 2014 - Jan 2015: G-CLAC consolidation x 2 cycles
- May 2015: Non-myeloablative SCT from matched unrelated donor
- CMV D+/R-

- Post-transplant course complicated by:
- EBV DNAemia without evidence for PTLD → rituximab in June/July 2015

Multani A, et al. Blood Adv. 2019 Nov 26;3(22):3602-3612. PMID: 31743391

Repeat CT – 8 months post-SCT



- Jan 2016 - repeat chest CT: “A 1 cm partially calcified nodule within the RLL is stable to decreased in size.”

- Immunosuppressive therapy dc’d no GVHD
- Voriconazole discontinued

Multani A, et al. Blood Adv. 2019 Nov 26;3(22):3602-3612. PMID: 31743391

Two weeks later …

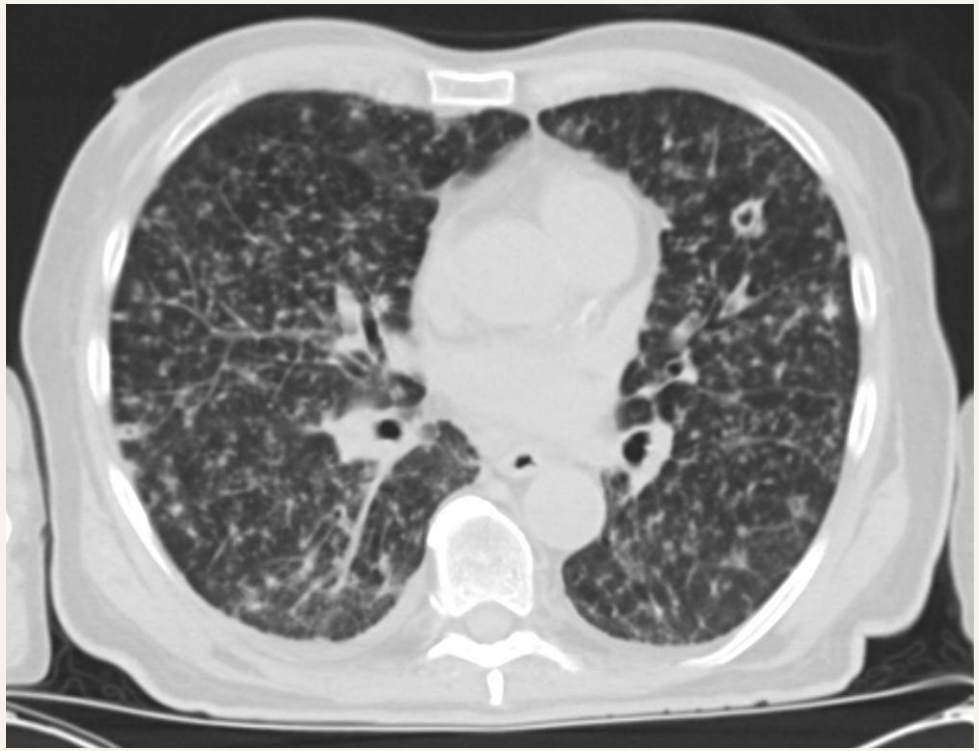
- February 2016: Developed fevers, fatigue, weakness, and cough

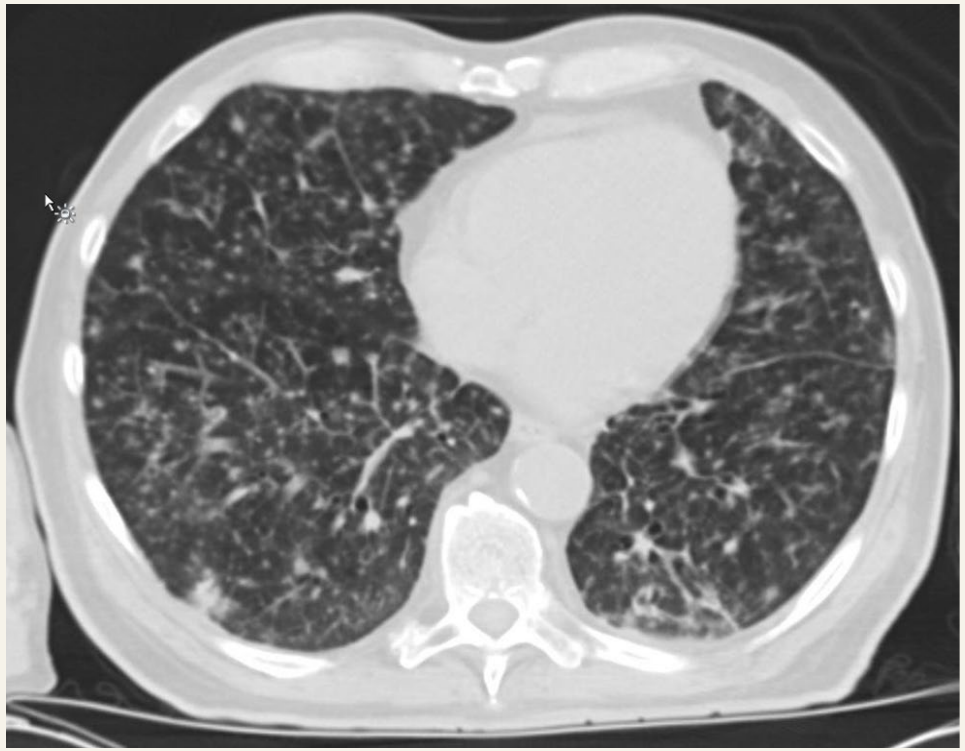
- Admitted to local hospital; noted to have transaminitis and AKI
- Ppx: TMP-SMX, acyclovir (held on admission), rx broad spectrum abx

- HD #6 Transferred to ICU and intubated
- Tx: AmBisome, ganciclovir, levofloxacin, pip-tazo, vancomycin

Multani A, et al. Blood Adv. 2019 Nov 26;3(22):3602-3612. PMID: 31743391

- Cavitary nodules measuring up to 15 mm innumerable scattered noncalcified nodules in both lungs bilaterally



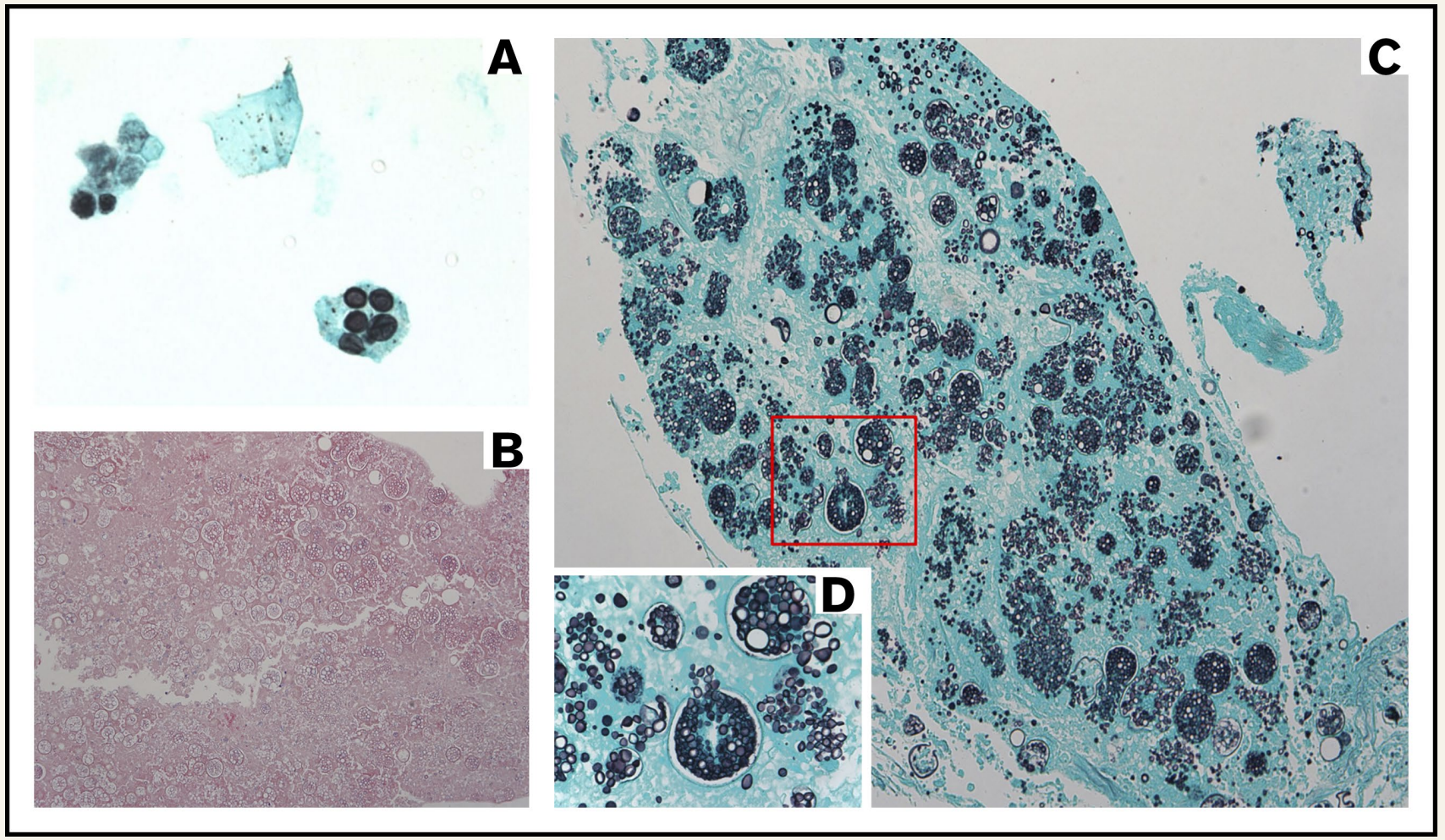


Multani A, et al. Blood Adv. 2019 Nov 26;3(22):3602-3612. PMID: 31743391

Case

- HD #7 ID team consulted:
  - Born in NY and has lived with wife in Paso Robles for 45 years
  - He worked as an analyst and also exported and imported goods from Mexico so traveled there frequently
  - No sick contacts recently
  - They had pet cats but no longer
  - Also used to live on a farm with chickens and horses
  - No known TB exposures

Multani A, et al. Blood Adv. 2019 Nov 26;3(22):3602-3612. PMID: 31743391



- (A) BAL specimen with GMS stain demonstrating dark spherical structures, originally misdiagnosed on cytopathology as *P jirovecii*, subsequently determined to *be Coccidioides* endospores. (B) Section of lung with H&E stain demonstrating a mixture of large thick-walled spherules containing variably sized endospores, diagnosed as invasive *C. immitis*. (C) Section of lung showing invasive *C. immitis* as highlighted by GMS stain. (D) Magnification of area outlined in red illustrating multiple ruptured *Coccidioides* spherules releasing endospores into surrounding lung tissue.

PMID: 31743391

Case

- Continued clinical deterioration, passed away HD #12
- *Coccidioides* serologies resulted post-mortem, positive IgG by immunodiffusion and negative by complement fixation
- Autopsy findings were consistent with disseminated coccidioidomycosis, involving the lungs, liver, spleen, and multiple lymph nodes
- Key takeaways: importance of screening/recognition, and need for prophylaxis

Multani A, et al. Blood Adv. 2019 Nov 26;3(22):3602-3612. PMID: 31743391

Coccidioidomycosis in Immunocompromised Patients

- Risk of severe disease with impaired cell mediated immunity
  - At risk for severe pulmonary infection, extrapulmonary dissemination and death
  - Skin/soft tissue, bone, CNS and other

- Risk of reactivation, regardless of time post-infection
  - HIV/AIDS pt in Spain presenting with disseminated cocci 12 years after departing Arizona[1]
  - OHT recipient with brief history of travel (10 days) to Tucson 8 years prior to transplant, died 3 weeks post-txp from reactivation with disseminated cocci [2]

1. Hernandez et al. Eur J Clin Microbiol Infect Dis. 1997;16(8):592. PMID: 9323471.
2. Vartivarian et al Am J Med. 1987 Nov;83(5):949-52. PMID: 3314500.

Coccidioidomycosis in Immunocompromised Patients

- Screening is recommended for anyone at risk:
  - SOT or SCT
  - HIV/AIDS
  - “Biologic immune response modulator” e.g. TNF antagonists
- Prophylaxis necessary for those at risk
- Treatment should **always** be given in these populations with cocci infection
- Indefinite treatment for prevention of relapse is recommended while immunosuppression is ongoing

Coccidioidomycosis in SOT

- Majority of cases occur within the 1st year post-transplant
  - In absence of prophylaxis
- Extra-pulmonary dissemination reported in 30 - 75% of cases historically
- Mortality ~28%, much higher in earlier studies ~ 70%
- Can occur via
  - Reactivation*, De novo infection, Donor transmission
- Donor transmission usually presents early
  - Within 1 month of txp, crucial to notify OPO if suspected for risk mitigation in other recipients

Blair. Ann N Y Acad Sci . 2007 Sep;1111:365-76. PMID: 17363431

Coccidioidomycosis in SOT

- Annual incidence 1.4 – 6.9% in centers from endemic regions without prophylaxis[1]
- UCLA: Cocci seroprevalence among kidney transplant recipients between 2007 – 2016[2]
  - Overall IgG prevalence 1.4%
  - In patients from highly endemic counties (Kern, Fresno, Tulare, Kings, San Luis Obispo) 3.7% IgG +

Prevalence *Coccidioides* EIA IgG/IgM

Test results	*Coccidioides* EIA IgG results N = 2109 N (%)	*Coccidioides* EIA IgM results N = 2109 N (%)
Positive	29 (1.4%)	59 (2.8%)
Indeterminate	7 (0.3%)	28 (1.3%)
Negative	2073 (98.3%)	2022 (95.9%)

1. Miller R, et al. Clin Transplant. 2019 Sep;33(9):e13553. PMID: 30924967
2. Phonphok K, et al. Transpl Infect Dis. 2018 Oct;20(5):e12932 PMID: 29809303

Clinical Manifestations in SOT

- Primary infection or reactivation, disease highly variable
  - SOT patients are more likely to develop disease including pneumonia and disseminated infection
  - Risk of dissemination <1% in IC vs 30-75% in SOT
- Pulmonary involvement
  - Fevers, chills, night sweats, cough, dyspnea, pleurisy
- Extra-pulmonary/disseminated
  - Skin, osteoarticular system, CNS
  - Fungemia very uncommon
- Radiographic findings
  - Lobar consolidation, nodules, mass-like lesions, interstitial infiltrates or cavities
- Eosinophilia 33-50%

Donor Transmission

- Rare, but high mortality
- Published OPTN ad hoc Disease Transmission Advisory Committee (DTAC) experience between 2005-2012
  - Proven or probable donor-derived coccidioidomycosis in 21 recipients from 6 donors (5/6 from OPTN region 5 – AZ, CA, NV, NM, UT)
  - Transmission occurred in 43% of recipients at median 30 days post-SOT
  - Mortality rate 28.5%
  - Survival with preemptive therapy 11/11 (100%) vs 2/7 (28.5%) without, 3 pts without follow-up info (1 expired)
  - Deaths occurred 14-55 days after transplant

Kusne S, et al. Am J Transplant. 2016 Dec;16(12):3562-3567. PMID: 27376472.

Donor Derived Coccidioidomycosis

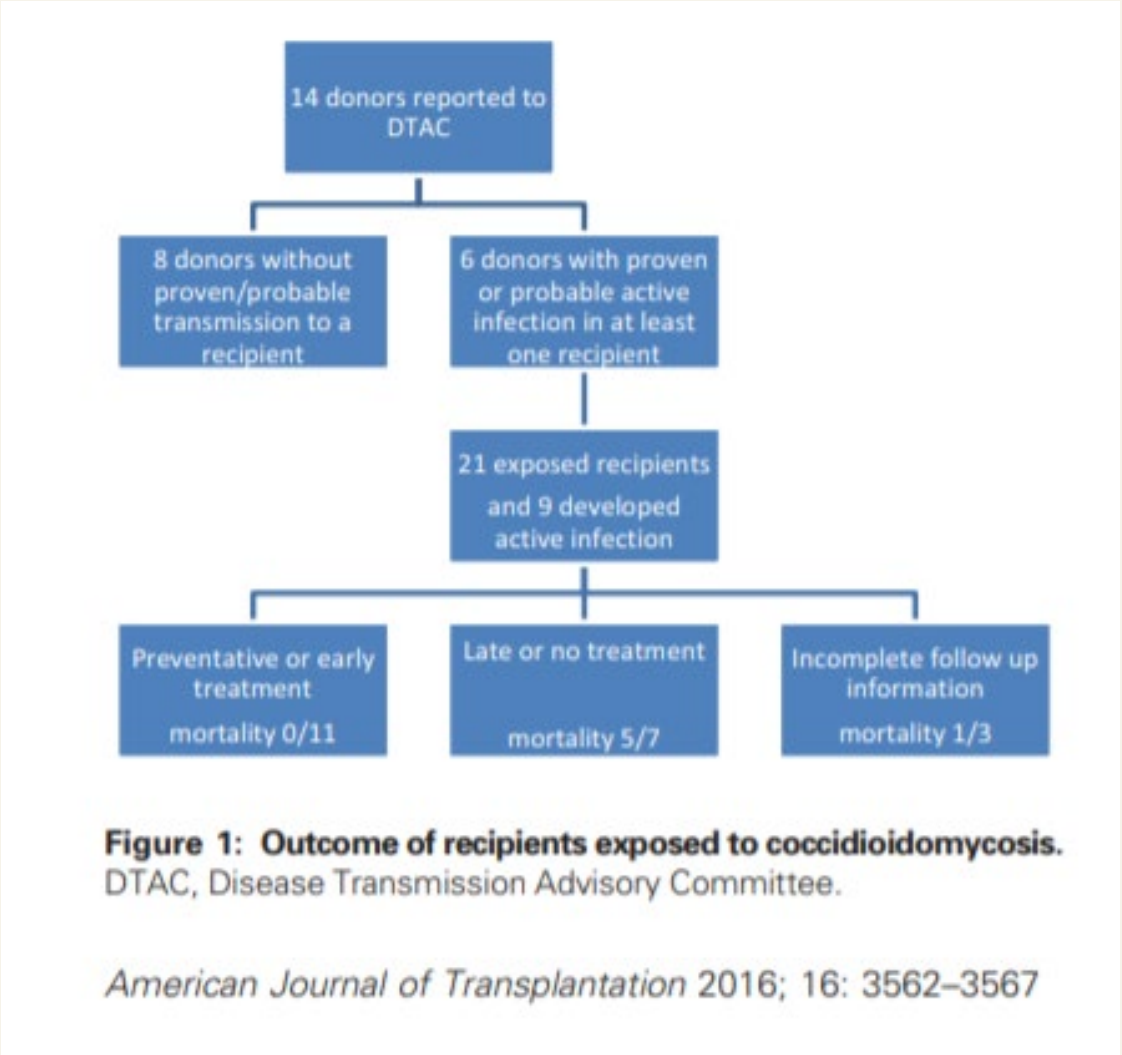


Figure 1: Outcome of recipients exposed to coccidioidomycosis.
DTAC, Disease Transmission Advisory Committee.

American Journal of Transplantation 2016; 16: 3562–3567

Kusne S, et al. Am J Transplant. 2016 Dec;16(12):3562-3567. PMID: 27376472.

Cocci in patients with hematologic malignancy

- Less data but also associated with higher risk of severe disease, dissemination and death
  - Largest case series is from Mayo AZ, retrospective review of 55 heme malignancy patients between 1987 – 2002 w/ cocci*
  - Most frequent malignancies were NHL, CLL reflecting center demographics; 78% had received chemotherapy
  - 95% pulmonary involvement (40% diffuse), 22% disseminated infection; mortality 38% (15/16 from cocci)
  - Presence of chemotherapy, corticosteroids, CML associated w/ mortality

Blair JE, et al. Arch Intern Med. 2005 Jan 10;165(1):113-7. PMID: 15642886.

Cocci in stem cell transplantation

- Also very limited data, 21 cases reported in literature through 2021
  - Single center review from AZ noted incidence rate of 2.6% in allo SCT
    - Mortality attributable to cocci 45%, although no mortality in cases with onset >2 years post-SCT
  - Several early cases identified, with high rates of dissemination and mortality
    - Due to unrecognized infection present at time of SCT, mortality ~ 50%
  - Majority of reported cases occurred in late post-engraftment period (>100 days post-SCT)
    - 17/19 (89.5%) of patients were not receiving anti-fungal prophylaxis at time of disease

Saling Cf et al. J Fungi (Basel). 2021 Apr 27;7(5):339. PMID: 33925759

Coccidioidomycosis in HIV/AIDS

- Incidence of cocci has declined dramatically in the era of potent ART
  - Early HIV epidemic = high incidence of symptomatic cocci
  - Prospective study of HIV pts in AZ, 25% of study cohort developed active cocci over 41 month period (1988 – 1992)[1]
  - 38% diffuse pulmonary disease, 7.6% extra-pulmonary dissemination, mortality 38.4%
  - Retrospective cohort study from 1995 – 1997, 11.3% of cohort had diagnosis of cocci[2]
  - 4.7% of cohort received cocci diagnosis (incidence rate 0.9%) during study period*
  - 13.8% diffuse pulmonary disease, 6.8% extra-pulmonary, mortality 6.8% none-attributed to cocci
  - Severity of disease seemed to associate with lower CD4, higher HIV VL, and absence of ART; cocci infection associated with lower CD4

1. Ampel NM, et al. Am J Med. 1993 Mar;94(3):235-40. PMID: 8095771
2. Masannat FY, Ampel NM. Clin Infect Dis. 2010 Jan 1;50(1):1-7. PMID: 19995218.)

Cocci in patients on biologic response modifiers "biologics"

- Various agents with different mechanisms of action e.g.
  - Tumor necrosis factor antagonists (anti-TNF) – infliximab, adalimumab, golimumab, certolizumab, etanercept*
  - Cytokine inhibitors ie IL-6 inhibitor tocilizumab
  - T-cell activation inhibitors ie abatacept
  - Frequently given in conjunction with other immunomodulatory medications (DMARDs) ie methotrexate, azathioprine, etc
- Associated with increased risk of infection with opportunistic pathogens ie mycobacterial infection, histoplasmosis
- TNF- α, interferon-γ pathway important in immune response to cocci

Table 2. Available biologic response modifiers.

Generic name	Brand name	Mechanism	Properties	Coccidioidomycosis reported
Infliximab	Remicade	Chimeric mAb against TNF-α (mouse Fc, human V)	Half-life, 10 days; antibodies against TNF-α cause Mtb reactivation in mice	Yes
Adalimumab	Humira	Fully human mAb against TNF-α		Yes
Certolizumab	Cimzia	Pegylated humanized Fab fragment of mAb against TNF-α	No Fc portion, so ADCC or complement activation is not induced	Yes[43]
Golimumab	Simponi	Fully human IgG1k mAb against TNF-α	Does not induce ADCC or complement activation	Yes[43]
Etanercept	Enbrel	Soluble bivalent TNF receptor	Half-life, 4 days; does not induce ADCC	Yes
Abatacept	Orencia	Soluble CTLA-4 fused to Fc (inhibits costimulation for T-cell activation)	Half-life, 13 days; does not exacerbate Mtb in mice; modified Fc does not induce ADCC or complement activation	Yes
Ustekinumab	Stelara	Human mAb that binds IL-12 and IL-23	Crohn disease and psoriasis; needed for maintenance of Th17 cells?	No
Tocilizumab	Actemra	mAb to IL-6 receptor	Needed for maintenance of Th17 cells?	No
Tofacitinib	Xeljanz	JAK1 and JAK3 inhibitor	Reduces IL-6 and IL-17; reduces MMP	No
Vedolizumab	Entyvio	Human mAb to integrin	Inhibits T-cell migration across endothelium	No

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; Fab, antibody-binding fragment; Ig, immunoglobulin; IL, interleukin; JAK, janus kinase inhibitor; mAb, monoclonal antibody; MMP, matrix metalloproteinase; Mtb, mycobacterium tuberculosis; Th17, T-helper 17; TNF, tumor necrosis factor.

Blair JE, et al. Med Mycol. 2019 Feb 1;57(Supplement_1):S56-S63. PMID: 29669037.

Cocci in patients on biologic response modifiers "biologics"

- Retrospective studies examining cocci in pts with inflammatory arthritis, incidence of symptomatic cocci 1- 1.9% (29 pts total)[1,2]
  - Higher incidence with infliximab – 2% at 1 year, 12% at 5 years
  - RR with infliximab comparison to other anti-TNF 5.23 (1.54 – 17.7, $p<0.1$)
  - Dissemination in 20.6%, mortality 7.6% (1 death attributable to cocci, unrecognized ante-mortem)
- In one study majority of patients were eventually able to resume biologic safely[3]

1. Bergstrom L. et al. Arthritis Rheum. 2004 Jun;50(6):1959-66. PMID: 15188373.
2. Mertz LE, Blair JE. Ann N Y Acad Sci. 2007 Sep;1111:343-57. PMID: 17363440.
3. Taroumian S, et al. Arthritis Care Res (Hoboken). 2012 Dec;64(12):1903-9. PMID: 22745051.

Clinical outcomes in various states of IS

	Immuno-competent	SOT	SCT	Heme malignancy	HIV/AIDS	Biologic response modifiers
Incidence of symptomatic disease*	--	1.4 – 6.9%	2.6%*	--	0.9%	1 – 1.9%
Severe pulmonary disease	--	33 – 37.5%	63.6%	40%	13.8%	--
Extra-pulmonary dissemination	<1%	30%	26.3%	22%	6.8%	~20%
Mortality	<1%	~30%	45%	38%	--	~3.5% or less

Takeaways

- Immunocompromised patients are more likely to develop symptomatic infection, severe disease, disseminated infection and death
  - Disease can occur via reactivation of latent infection, or with induction of immunosuppression with unrecognized active infection → severe infection
    - E.g. unrecognized donor-transmission, conditioning chemotherapy with active infection
- Anti-fungal prophylaxis effectively mitigates disease
- Treatment in immunocompromised patients is always necessary
- If history of infection, treatment duration is indefinite as long as immunosuppression is ongoing
  - Or if not infected, prophylaxis recommended as long as there is ongoing exposure (ie residence in endemic area)

Case

55 yoF with PMH significant for CML with transformation to ALL, type 2 DM, history of LTBI (s/p treatment ~ 35 ya), referred to ID for evaluation of a cavitary pulmonary nodule.

PMH:

CML - Diagnosed 5/2018 → ALL crisis 8/2018, BCR-ABL + on imatinib

Case

- Lived in Porterville, CA for 40 years, born in Michoacan, Mexico
- Before illness worked 15 years as agricultural fieldworker in California central valley
- No pets at home, no chickens. Lives with husband, children
- No tobacco, EtOH, no drug use
- Last travel to Mexico was 20 years
- Hx + PPD, diagnosed during pregnancy (35 years) and recalls taking medication for several months after pregnancy

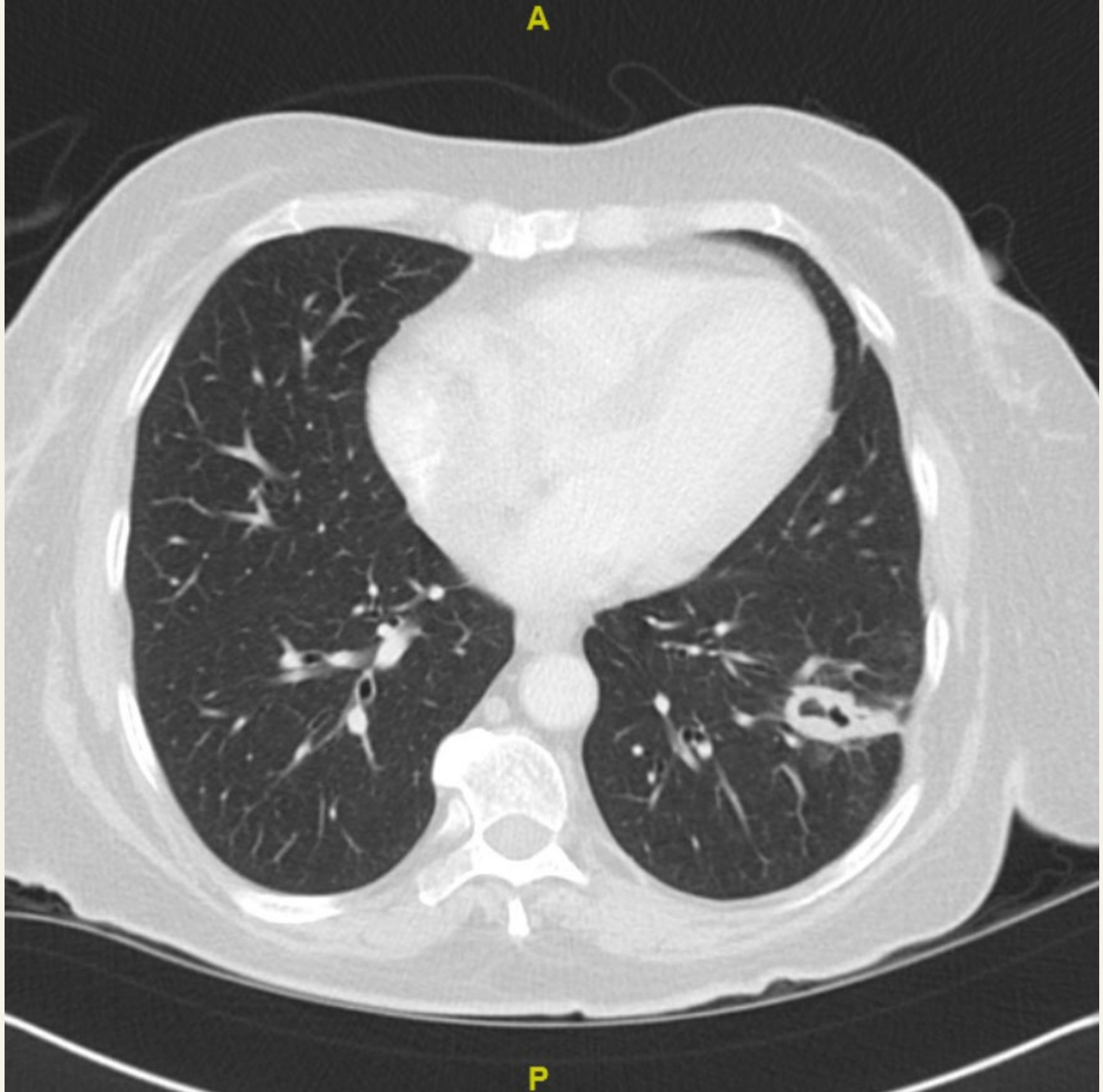

NEVADA
Sacramento
San Francisco
San Jose
Las Vegas
Los Angeles
San Diego

Case

Hospitalized in Bakersfield December 2018 with neutropenia, nausea and LLL pneumonia radiographically; recalls that she had been experiencing cough, fever and night sweats at that time

- 12/2018 *Cocci* IgM/IgG EIA negative
- Started on empiric fluconazole

Now referred in April 2019 for ID evaluation of a cavitary pulmonary nodule in setting of potential need for allogeneic SCT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Approach to screening and diagnosis

Does this patient have cocci?

What further testing is recommended?

Case - Repeat Serologic Testing

	2 4/11/2019 1319
Cocci IgG EIA	<0.150 *
Cocci IgM EIA	<0.150 *
Coccidioides Ab CF...	1:2 *
Coccidioides Ab ID	Negative *
ASPERGILLUS AG EIA	<0.50 *
Cryptococcal Ag Bld	Negative

- May have also considered bronchoscopy for BAL culture, *Coccidioides* antigen, PCR + biopsy

Case Resolution

- Continued on fluconazole, increased to treatment dose (400 mg PO qday)
- Recommended deferral of allogeneic SCT pending radiographic improvement
- Subsequently based on ALL characteristics decision made independently to defer allogeneic SCT for time being

Diagnostic test performance in SOT for symptomatic coccidioidomycosis

Table 1: Characteristics of 27 solid organ transplant recipients with proven or probable active coccidioidomycosis

Characteristic	No. (%)[1]
Age, mean (range), y	55 (36–74)
Male sex	19 (70)
Transplant type	
Kidney	14 (52)
Liver	13 (48)
Donor type	
Living	10 (37)
Deceased donor	17 (63)
Infection type	
Pulmonary[2]	23 (85)
Disseminated[3]	4 (15)
Active coccidioidomycosis definition	
Proven	12 (44)
Probable	15 (56)
Immunosuppression at diagnosis[4]	
Tacrolimus	23 (85)
Mycophenolate preparations	19 (70)
Sirolimus	2 (7)
Cyclosporine	0 (0)
Thymoglobulin	1 (4)
Prednisone >10 mg/day	2 (7)
Prednisone ≤10 mg/day	6 (22)

[1]Values are number (percentage) unless indicated otherwise.
[2]This includes one patient who had coccidioidal empyema after rupture of a coccidioidal cavity in the lung.
[3]Sites of dissemination: tendon (n = 1), wrist (n = 1), liver (n = 1) and meninges (n = 1).
[4]Numbers total >27 and percentages total >100% because some patients were taking more than 1 medication.

Table 1. Sensitivity of serologic testing for coccidioidomycosis in transplant recipients.[a]

Method	First test positive, %	Second test positive, %
EIA IgM	28	32
EIA IgG	56	64
ID IgM	21	29
ID IgG	38	38
CF titer	28	36
Any positive	77	92

Abbreviations: CF, complement fixation; EIA, enzyme immunoassay; ID, immunodiffusion; Ig, immunoglobulin.
[a]The first test was typically performed at the first presentation to medical evaluation for signs/symptoms of clinical illness, and the second test was typically performed 2 to 4 weeks later.
Adapted from Mendoza and Blair.[41] Used with permission.

Table 3: Summary of culture, histology, cytology and PCR results among solid organ transplant recipients with active coccidioidomycosis

Type of text	No. of cultures positive/no. tested (%)
Culture[1]	
Respiratory specimen[2]	9/17 (53)
Tissue biopsy or swab[3]	4/7 (57)
Pleural fluid	1/2 (50)
Any positive culture[4]	14/26 (54)
Other tests	
Cytology[5]	3/10 (33)
Tissue pathology[6]	6/8 (75)
Rapid PCR[7]	3/5 (60)

PCR = polymerase chain reaction.
[1]Nine patients had ≥2 cultures performed.
[2]Respiratory specimens included induced or expectorated sputum (3/7 tests were positive), bronchial washings (3/3 tests positive), bronchoalveolar lavage specimens (3/5 tests positive), endotracheal culture (0/1 tests positive),and protected catheter brushing (0/1 tests positive).
[3]Positive results: Wrist tissue and swab were both positive (n = 1 each); lung tissue (n = 1); and left index finger tissue (n = 1). Negative results: Abdominal tissue (n = 1); lung (n = 1); and maxilla (n = 1).
[4]Respiratory, tissue biopsy or swab, or pleural fluid culture.
[5]Positive results: Induced sputum (n = 1) and bronchoalveolar lavage (n = 2). Negative results: Pleural fluid (n = 1); bronchoalveolar lavage (n = 3); cerebrospinal fluid (n = 2); and protected catheter brush bronchial wash (n = 1).
[6]Positive results: Synovium/bone/capsule of right wrist (n = 1 each); left index finger (n = 1); and lung (n = 2). Negative results: Lung (n = 2).
[7]Specimens included bronchoalveolar lavage (2/3 positive); induced sputum (1/1 positive); and cerebrospinal fluid (0/1 positive).

1. Mendoza N. Blair JE. Am J Transplant. 2013 Apr;13(4):1034-1039. PMID: 23399074.
2. Blair JE, et al. Med Mycol. 2019 Feb 1;57(Supplement_1):S56-S63. PMID: 29669037.

Diagnostic test performance in SOT varies by assay

Table 1. The spectrum of sensitivity and specificity of coccidioidomycosis diagnostic tests in SOT recipients.

Diagnostic Test	Sensitivity	Specificity	Comments	Refernces
Serology Miravista * Meridian IMMY	 87% 40–70% 40–70%	 90% 95% 95%	Different enzyme immunoassays have varying degrees of reported sensitivity and specificity.	[12,29–31]
(1–3) Beta-d-glucan (serum)	44–57%	Unknown	Serum (1–3) Beta-d-glucan is not specific to coccidioidomycosis.	[32,33]
Coccidioides Galactomannan Antigen (serum)	50%	95%	*Coccidioides* Galactomannan antigen has high sensitivity in CSF but lower sensitivity in blood and urine samples, except for cases of severe disease.	[34,35]
Coccidioides spp. culture	50%	100%	Sensitivity of the fungal culture is dependent on the obtained sample and microbiology laboratory.	[22]
Coccidioides spp. pathology	50%	100%	Sensitivity of the histopathology is dependent on the obtained sample, burden of disease, and pathologist expertise.	[22,23]
Coccidioides spp. PCR	70–90%	100%	Very promising technology but lacks real-world data and is likely sample-dependent.	[36–38]

PCR, polymerase chain reaction; CSF, cerebrospinal fluid; IMMY, Immuno Mycologics, Inc, Norman, OK, USA.
* Based on a study that evaluated the sensitivity and specificity of antibody tests in various immunosuppressed patients.

Zangeneh TT, Al-Obaidi MM. J Fungi (Basel). 2023 Apr 26;9(5):513. PMID: 37233224

Diagnostic test performance in immunocompromised patients with coccidioidomycosis

Table 2. Seropositivity among 62 immunocompromised hosts with serologic confirmation of coccidioidomycosis detected by various serologic tests

Category of immunosuppression	Type of serologic testing, no. (%)							
	EIA (IgM and IgG)		CF		ID (IgM or IgG or both)		Any test	
	Tested	Positive	Tested	Positive	Tested	Positive	Tested	Positive
Hematologic malignancy (N = 14)	12	4 (33)	10	6 (60)	6	1 (17)	12	8 (67)
Cancer and chemotherapy, nonhematologic (N = 19)	18	13 (72)	18	12 (67)	15	9 (60)	19	18 (95)
HIV infection (N = 4)	4	1 (25)	3	2 (67)	3	2 (67)	4	3 (75)
Organ transplantation (N = 7)	7	5 (71)	6	2 (33)	3	0 (0)	7	5 (71)
Rheumatologic illness (N = 13)	11	9 (82)	10	6 (60)	8	4 (50)	11	10 (91)
Other ICH illness* (N = 11)	10	9 (90)	10	10 (100)	8	6 (75)	10	10 (100)
All patients†	57	38 (67)	52	35 (67)	40	21 (53)	58	49 (84)
Healthy patients tested ≤ 1 y after symptom onset (N = 261)	244	212 (87)	252	188 (75)	248	180 (73)	261	247 (95)

CF, complement fixation; EIA, enzyme immunoassay; ICH, immunocompromised; ID, immunodiffusion; HIV, human immunodeficiency virus.

*Patients with other causes of immunocompromise include 3 inflammatory bowel disease (1 taking infliximab), 2 autoimmune blood dyscrasias (hemolytic anemia and idiopathic thrombocytopenic purpura) taking prednisone, 1 autoimmune polyneuropathy, and 5 taking corticosteroids long-term for sarcoid, cough, other pulmonary diseases (chronic obstructive pulmonary disease, interstitial pulmonary fibrosis, or normal interstitial pneumonia).

†Six patients have 2 immunosuppressive illnesses and are represented in each category.

Blair JE, et al. Mycopathologia. 2006 Nov;162(5):317-24. PMID: 17123029

Key points for diagnosis

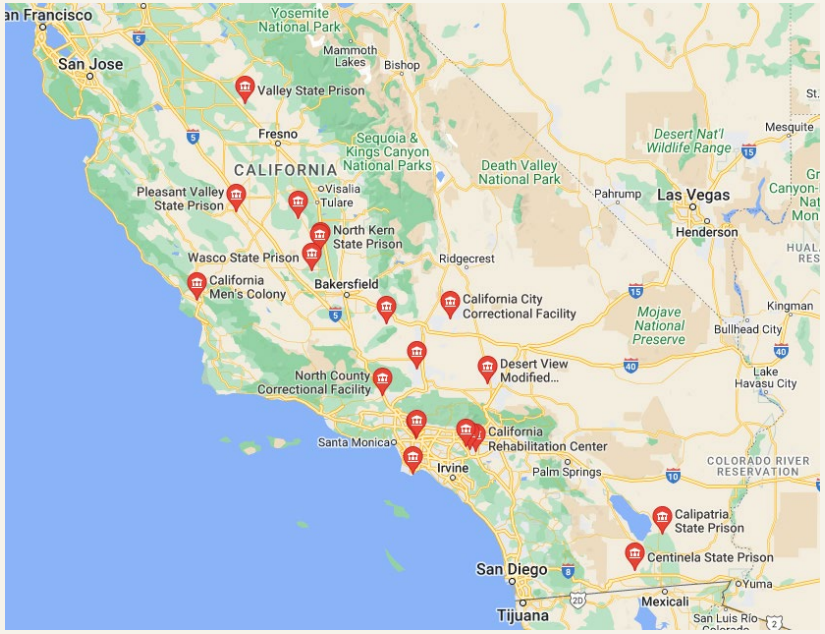
- Sensitivity of serologic testing is lower in immunocompromised individuals
  - Performing multiple different serologic methods concurrently increases sensitivity
    - If concerned for active cocci in SOT check: coccidioides EIA IgM/IgG, ID and CF Ab
    - Culture and low threshold for tissue invasive testing to establish diagnosis
    - Incorporate antigen and/or PCR testing (blood, urine plus relevant site = BAL, CSF)
  - If negative initially, convalescent serology should be repeated in 4-6 weeks
- Given limitations of diagnostics in IC patients, high clinical index of suspicion and judgement of risk is critical

Pre-transplant evaluation or if planning for IS

- Obtain history:
  - Residence in endemic areas
  - Remote history of residence or travel in endemic areas
  - Frequent travel or work in endemic area
  - Review behavioral/occupational risk factors that may increase risk

Risk Factors for Exposure – recipient and donor

- Travel to or residence in endemic area
- Occupational risk factors, jobs involving soil disruption:
  - E.g. Construction, Agricultural worker, Military, Firefighter
- Recreational risk factors
  - Horseback riding, off-road motor biking, four wheeling, etc
- Hx of incarceration in California
  - Several reported outbreaks in CA state prisons[1]



Wheeler C, et al. Emerg Infect Dis. 2015 Jan;21(1):70-5. PMID: 25533149

Pre-transplant evaluation or if planning for IS

- Evaluation
  - Cocci EIA IgG as screening for asymptomatic individuals
    - Be wary of false positive if isolated *Coccidioides* EIA IgM and low pre-test suspicion
  - CXR and/or CT chest if significant epidemiologic risk
  - Assessment for prior diagnosis or symptoms compatible with prior history of infection
    - Ask - “Have you ever been diagnosed with or treated for valley fever?”

Cocci endemic areas in California

2017 Incidence Rate by County (per 100,000)

North Los Angeles county:
Palmdale, Lancaster, Santa Clarita, Canyon country, western SF valley

Ventura county:
Simi Valley, Moorpark

North San Bernadino county:
Victorville, Apple Valley

North Santa Barbara county:
Santa Maria, Lompoc

From CA DPH

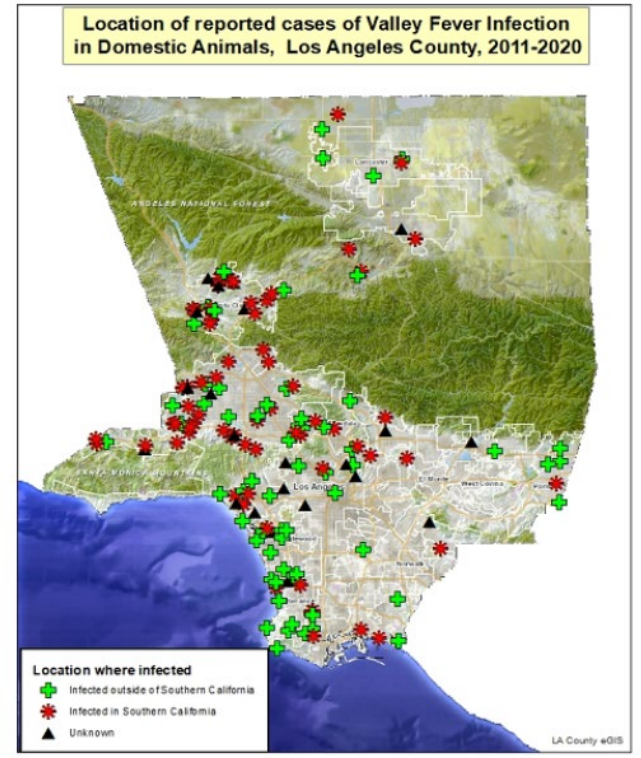
Local Epidemiology and Gray Zones

- North Los Angeles county, SF Valley and Santa Clarita

TABLE 1.—*Coccidioidin Surveys in Southern California Areas*

Area	Total No. Tested	Total No. Positive	Per Cent Positive	Prev. Residence in Coccid. Area		No Residence in Known Coccid. Area	
				No.	Per Cent +	No.	Per Cent +
Probation Camps:							
No. 4 Saugus	100	14	14	31	20	69	12
No. 3 Calabasas	78	6	8	25	25	53	0
No. 5 Azusa	60	4	7	27	14	33	3
High Schools:							
Banning and Palm Springs	74	15	20	21	21	53	17
Canoga Park	441	65	15	82	24	359	13
Newhall	85	9	11	20	30	65	5
Los Angeles	220	9	4	38	16	182	1.6
Total	1,058	122	11.5				

Kessel JF et al. Calif Med. 1950 Oct;73(4):317-21. PMID: 14772654

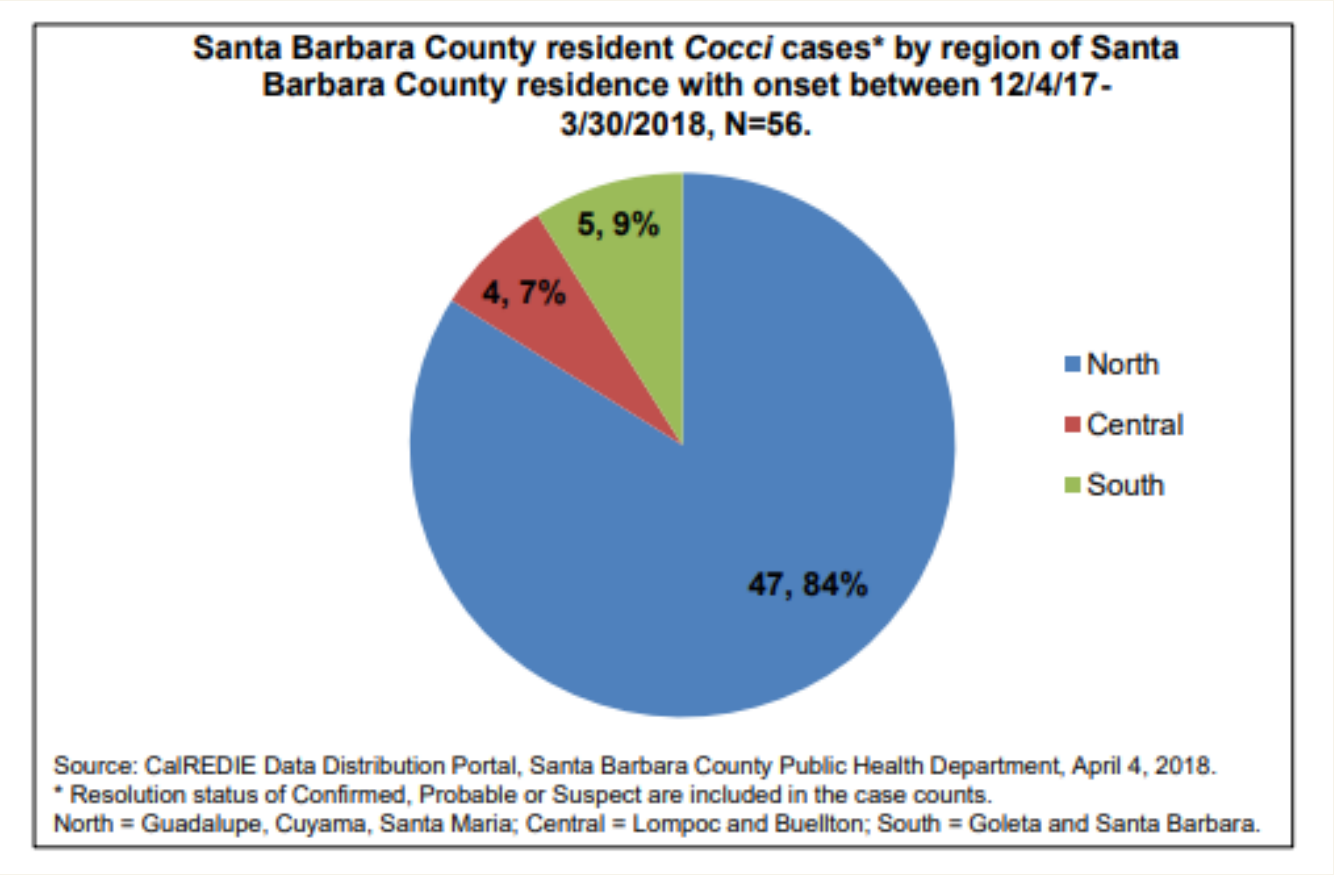


LAC DPH

Dust clouds in Santa Susana mountains after 1994 Northridge earthquake

Local Epidemiology and Gray Zones

- North Santa Barbara county



Santa Barbara DPH

Universal prophylaxis vs pre-emptive management for SOT in cocci endemic areas

- Prior to implementation of screening and azole prophylaxis in SOT
  - Incidence of coccidioidomycosis in pts from endemic areas = 4-9% per year
  - Dissemination and mortality rates as high as 75%, 72% respectively[1]
- Targeted prophylaxis strategy (pre-emptive management) vs universal prophylaxis for 12 months
  - Cumulative incidence 2-3%, 10 patients total with 2 deaths [2]

TABLE 2. Coccidioidal Characteristics of All Study Patients

Characteristic	Group: Targeted Prophylaxis (n = 349)	Group: Universal Prophylaxis (n = 143)	*P* Value
Residence in an endemic area	325 (93.1%)	119 (83.2%)	0.001
Before transplantation			
Asymptomatic seropositivity	26 (7.4%)	27 (18.9%)	0.001
Coccidioidomycosis	11 (3.2%)	10 (7%)	0.08
1 year after transplantation			
Asymptomatic seroconversion	8 (2.3%)	0	0.11
Coccidioidomycosis	10 (2.9%)	0	0.04

1. Blair JE, et al. Med Mycol. 2019 Feb 1;57(Supplement_1):S56-S63. PMID: 29669037.
2. Kahn A, et al. Liver Transpl. 2015 Mar;21(3):353-61. PMID: 25482428.

Prevention

- Universal azole prophylaxis is recommended for all organ transplant recipients living in endemic areas

- If seronegative pre-transplant
  - Fluconazole 200 mg daily
  - 6 -12 months post-transplant or indefinite, practice at UCLA is indefinite as long as residing within endemic area

1. Miller R, et al. Clin Transplant. 2019 Sep;33(9):e13553. PMID: 30924967

Prevention

- If seropositive pre-transplant
  - Fluconazole 400 mg daily for 12 months post-transplant
  - Transition to 200 mg daily indefinitely if clinical/laboratory inactive

- If history of pre-transplant coccidioidomycosis
  - Fluconazole 400 mg daily for 12 months post-transplant
  - Transition to 200 mg daily indefinitely if clinical/laboratory inactive
  - Consider serological monitoring with cocci CF titers, if azole is ever discontinued pre-emptive monitoring is strongly recommend

1. Miller R, et al. Clin Transplant. 2019 Sep;33(9):e13553. PMID: 30924967

Mitigating donor transmission

- Allograft from donor with history of cocci or seropositive donors
  - Provide preemptive azole therapy
  - Lung transplant recipients should receive lifelong azole therapy
    - Fluconazole 400 mg daily indefinitely if not on other azole therapy
  - Non-lung SOT should receive at least 6-12 months
    - Fluconazole 400 mg daily
    - Consider step down to 200 mg afterwards
    - If azole discontinued at 12 months, clinical and serological monitoring is recommended
  - If extra-pulmonary dissemination in donor
    - Fluconazole 400 mg daily indefinitely for lung and non-lung SOT

Singh N, et al. Am J Transplant. 2012 Sep;12(9):2414-28.PMID: 22694672.

Prevention in SCT recipients

- No guidelines given limited amount of data – personal opinion
  - Evaluation should be performed similar to SOT ie obtain history about residence, risk and pre-SCT screening
  - Allogeneic SCT – majority of patients will be on mold-active azole while receiving GVHD prophylaxis or treatment
  - Autologous SCT – less likely to remain on anti-fungal prophylaxis after initial engraftment period
  - Patients with history of cocci or seropositive = fluconazole 400 mg qday (if not on azole) for at least 12 months or as long as on immunosuppression
  - Seronegative patients in endemic area = fluconazole 200 mg qday (if not on azole) for at least 12 months or as long as on immunosuppression

Singh N, et al. Am J Transplant. 2012 Sep;12(9):2414-28.PMID: 22694672.

Screening & prophylaxis for cocci in HIV/AIDS

- Uncontrolled HIV replication & CD4 count <250 cells/uL associated with lack of adequate coccidioidal cellular immune response
  - Associated with more severe disease and worse outcomes
- Universal prophylaxis is not recommended
- Annual screening is recommended for patients with HIV living in cocci endemic regions
  - Serology and chest radiography annually
- Antifungal therapy recommended if clinical evidence of cocci or isolated seropositive and CD4 <250 cells/uL
  - Continue indefinitely at least until CD4 >250,cells/uL

Galgiani JN, et al. Clin Infect Dis. 2016 Sep 15;63(6):e112-46. PMID: 27470238.

Screening & prophylaxis for cocci w/ biologics

- Recommendation to screen patients prior to initiation of biologic therapy
- Clinical follow-up to monitor signs & symptoms is recommended
- Routine prophylaxis and serological screening not currently recommended per IDSA guidelines

Galgiani JN, et al. Clin Infect Dis. 2016 Sep 15;63(6):e112-46. PMID: 27470238.

Key points

- Disease related to cocci is preventable, but requires appropriate recognition of risk, screening for presence of infection, and prophylaxis
- Primary prophylaxis should be continued for at least 12 months post-SOT
  - Personally advocate for indefinite prophylaxis if ongoing risk of *de novo* infection based on area of residence
- Secondary prophylaxis should continue indefinitely until immunosuppressive state is resolved

Treatment of immunocompromised patients

- Treatment for active cocci is always recommended
- Treatment guidelines are otherwise the same as for immunocompetent individuals
  - Acute pulmonary cocci = fluconazole 400 mg qday
  - Severe pulmonary or disseminated cocci = ambisome followed by transition to fluconazole, consider high dose fluconazole
  - Personal practice, low threshold to use posaconazole or isavuconazonium
- High risk of relapse following discontinuation of antifungal therapy
  - Requires indefinite azole for prevention of relapse while immunosuppression is ongoing

Galgiani JN, et al. Clin Infect Dis. 2016 Sep 15;63(6):e112-46. PMID: 27470238.

Special considerations for treatment in SOT

- Be wary of drug-drug interactions with azole anti-fungals
  - CYP450 inhibition with all azoles → increased calcineurin inhibitor (tacrolimus, cyclosporine) levels
  - Voriconazole is particularly problematic due to variable and dynamic pharmacokinetics
    - non-linear pharmacokinetics, auto-induction
  - Itraconazole can also be challenging due to variable absorption
  - Therapeutic drug monitoring highly recommended
  - Necessary to counsel patients to not discontinue azole without notifying transplant team as this can precipitate rejection (from subtherapeutic CNI levels)

Special considerations for treatment in SOT

- Increased risk of squamous cell carcinoma with voriconazole
  - Incidence of squamous cell skin cancer in SOT is 65 – 250 times higher than general population at baseline[1]
  - Exposure to voriconazole is associated with further 2.6 fold increase in SCC
  - In SOT recipients we generally avoid voriconazole if possible because of this issue

1. Euvrard S et al. N Engl J Med. 2003 Apr 24;348(17):1681-91. PMID: 12711744.
2. Williams K, et al. Clin Infect Dis. 2014 Apr;58(7):997-1002. PMID: 24363331

Extended Spectrum Triazoles for Refractory Coccidioidomycosis

TABLE 2 Number of MIC values for each antifungal agent tested at specific concentrations

Agent	Total (*n*)	No. of values at MIC (μg/ml) of:												
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64
AMB	397	–[a]	8	28	81	174	68	27	9	2	0	0	–	–
FLU	581	–	–	–	9	11	13	20	26	58	228	170	24	22
ITR	486	–	34	41	81	120	178	27	1	1	2	1	–	–
POS	377	–	40	59	113	128	33	2	1	0	0	1	–	–
VOR	499	–	40	168	196	67	16	6	3	1	2	0	–	–
AFG	19	1	1	8	6	1	1	0	0	0	1	–	–	–
CFG	172	1	26	24	72	17	2	5	1	4	20	–	–	–
MFG	50	1	5	21	18	4	0	0	0	0	1	–	–	–

[a]–, Not tested.

215/581 (37.3%) >=16 ug/ml.

Thompson GR 3rd, et al. Antimicrob Agents Chemother. 2017 Mar 24;61(4):e02634-16. PMID: 28096163

Summary

- Treatment is always indicated for immunocompromised pts
- Be cognizant of drug-drug interactions
- Fluconazole is first line for uncomplicated infection
- For severe (life threatening) disease amphotericin B is recommended (+/- concurrent azole) → azole once stable
- For severe or refractory cases consider extended spectrum triazole (posaconazole, isavuconazonium, itraconazole, voriconazole)
    - *in vitro* data suggests possibly superior but lacks conclusive clinical outcomes data

Thank You

Questions?

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