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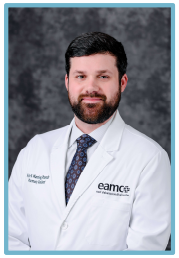
Speaker Introduction

Kyle is a PGY-2 Infectious Diseases pharmacy resident at University of Utah Health. He completed his Doctor of Pharmacy degree at Auburn University Harrison School of Pharmacy in 2020. From 2020 to 2021, he completed his PGY1 training at East Alabama Medical Center in Opelika, Alabama.

Kyle is fascinated by the complexities associated with infectious diseases, and his clinical interests include invasive fungal infections, specifically those involving *Aspergillus* and *Coccidioides* spp.



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HEALTH-SYSTEM PHARMACISTS

Kyle B. Manning
November 6, 2021

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Coccidioidomycosis: No Valley Low Enough

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Disclosure

- Relevant Financial Conflicts of Interest
  - **CE Presenter, Kyle B. Manning, PharmD:**
    - None
  - **CE mentor, Brandon Tritle, PharmD, BCIDP:**
    - None
- Off-Label Uses of Medications
  - Fluconazole (Coccidioidomycosis, treatment and prophylaxis)
  - Itraconazole (Coccidioidomycosis, treatment and prophylaxis)
  - Voriconazole (Coccidioidomycosis, refractory)
  - Posaconazole (Coccidioidomycosis, refractory)
  - Isavuconazole (Coccidioidomycosis, refractory)

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Learning Objectives – Technicians

- List the climate conditions that contribute to an ideal environment for the survival of Coccidioides spp.
- Differentiate the different medications used for the treatment of coccidioidomycosis.
- Recognize common side effects of the antifungal medications used in the treatment of coccidioidomycosis.

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Learning Objectives – Pharmacists

- Examine the changing epidemiology of coccidioidomycosis.
- Identify the clinical manifestations of coccidioidomycosis.
- Interpret primary literature surrounding the medications used in the treatment of coccidioidomycosis.
- Apply evidence-based guideline strategies for the management of coccidioidomycosis based on severity.

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Introduction and Mycology of *Coccidioides*

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Introduction

- First identified in 1892
  - Originally thought to be a parasite
- Coccidioidomycosis is a systemic fungal disease
  - "San Joaquin Valley fever" or "Valley fever"
  - "Desert rheumatism"
  - "Cocci"
- Two known species
  - *Coccidioides immitis* and *Coccidioides posadasii*

Thompson, GR 3rd, et al. Lancet Infect Dis. 2021; S1473-3099(21)00191-2.
Galgiani JN. Coccidioidomycosis: In: Bennett JE. Mandell, Douglas, and Bennett's Principles of Practice of Infectious Diseases, 9e. 2020.

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Mycology

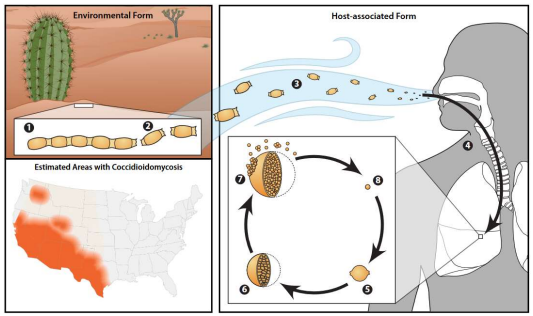

Image source: Centers for Disease Control and Prevention. Coccidioidomycosis: Life Cycle of *Coccidioides*.
Image available at: https://www.cdc.gov/fungal/diseases/coccidioidomycosis/causes.html

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Epidemiology

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Epidemiology

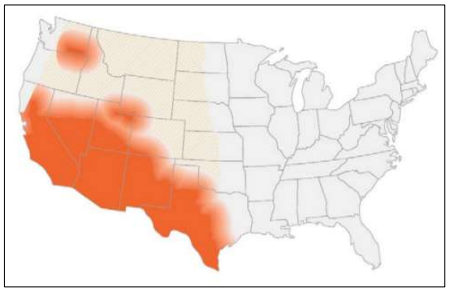

Image source: Centers for Disease Control and Prevention. Fungal Diseases: Valley Fever Maps.

- **Preferential climate:**
  - Low rainfall (12-50 cm per year)
  - Hot summers
  - Mild to moderate winters
  - Alkaline soil

Legend:
- Areas where *Coccidioides* spp are more likely to live
- Areas where *Coccidioides* spp has the potential to live
- Areas where *Coccidioides* spp are rarely found

Valdivia L, et al. Emerg Infect Dis. 2006;12(6):958-962.
Gorris ME, et al. GeoHealth. 2019;3:308-27.
Image available at: https://www.cdc.gov/fungal/pdf/more-information-about-fungal-maps-508.pdf

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Epidemiology

- Centers for Disease Control and Prevention (CDC) 2019 statistics:
  - 18,407 cases of Valley fever reported
  - Mostly in Arizona and California
  - Highest rates in people over 60 years and older
  - Likely under-reported to the CDC due to low testing rates
- In the US, annual incidence is increasing
  - 5.3 cases per 100,000 people in 1998 to 42.6 cases per 100,000 in 2011
- Estimated 200 coccidioidomycosis-associated deaths each year

Centers for Disease Control and Prevention. Valley Fever (Coccidioidomycosis) Statistics. Available at: https://www.cdc.gov/fungal/diseases/coccidioidomycosis/statistics.html

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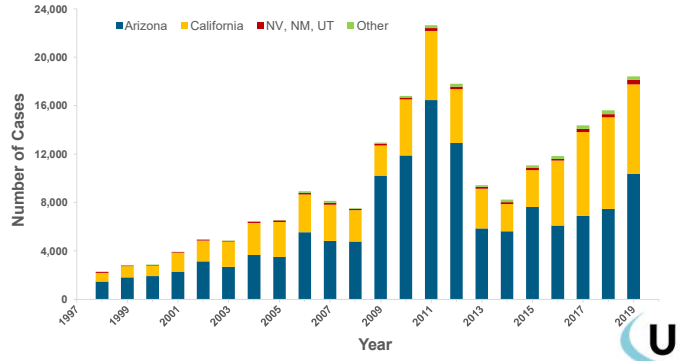
Reported Valley Fever Cases



Created from data available at: Centers for Disease Control and Prevention. National Notifiable Diseases Surveillance System (NNDSS).

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Changing Epidemiology

Changing environmental conditions

Human activity in endemic regions

Changing surveillance

Increasing number of immunocompromised

Clinical awareness

Diagnostic testing

McCotter OZ, et al. Med Mycol. 2019;57(S1):S30-40.

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Pathogenesis

- Very small inoculum for infection
  - Single arthroconidium → respiratory infection
  - If exposure is high, symptoms more likely to appear
  - Not contagious*
    - Extremely rare: a wound infection or through organ transplant
- Truck driver in Hong Kong → extrapulmonary infection
  - Swept out a container from the US
- Brief trips to or through endemic regions
  - Example: changing flights at Phoenix airport

Epidemics of coccidioidomycosis

- Dust storms
- Earthquakes
- Excavation projects
- Drilling

Tang TH, Tsang OT. N Engl J Med. 2011;364(2):e3.
Eckmann BH, et al. Am Rev Respir Dis. 1964;89:175-85.
Dierberg KL, et al. Transpl Infect Dis. 2012;14(3):300-4.

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Pathogenesis

Most affected occupations

Construction and farm workers	Workers in the drilling industry	Military personnel	Inmates and correctional officers

Stockamp NW, et al. Infect Dis Clin North Am. 2016;30:229-46.

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Clinical Manifestations

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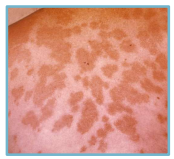
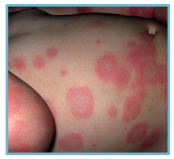
Clinical manifestations

- Incubation period is 1-3 weeks
- Asymptomatic or very mild symptoms (~60%)
- Clinical illness (~40%)
  - General: Fever, arthralgia, myalgia, night sweats, fatigue
  - Pulmonary: cough, chest pain, dyspnea
  - Other: rash, weight loss of 5-10% of total body weight, hemoptysis
- Extra-pulmonary dissemination (≤1%):
  - Skin, bones, central nervous system (CNS)
  - Destructive ulcerative lesions
- Symptoms may take weeks to months to resolve



Erythema nodosum



Erythema multiforme

Galgiani JN, et al. Valley Fever (Coccidioidomycosis). Valley Fever Center for Excellence. 2016.

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High risk groups – severe disease

- Immunocompromised
  - Advanced HIV, transplant recipients, corticosteroids, immunosuppressants
- African and Filipino ancestry
- Age > 65 years old
- Diabetes mellitus
- Underlying cardiopulmonary conditions
- High Coccidioidal complement fixation titer (>1:16)

Galgiani JN, et al. Valley Fever (Coccidioidomycosis). Valley Fever Center for Excellence. 2016.

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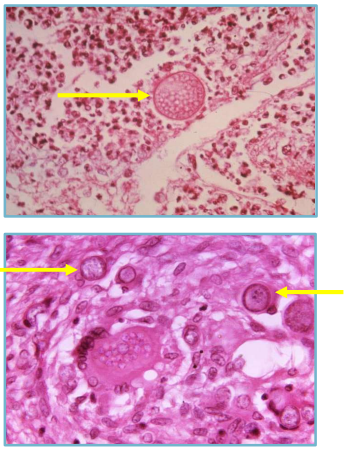
Diagnosis



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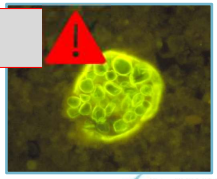
Diagnosis

- Direct microscopic examination of secretions
- Cultures
- Histopathology
- Imaging
- Latex testing
- Coccidioidal antigen detection
- Skin testing

WARNING: HAZARDOUS
Alert micro lab if suspected



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Galgiani JN. Coccidioidomycosis: In: Bennett JE. Mandell, Douglas, and Bennett's Principles of Practice of Infectious Diseases, 9e. 2020.

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Diagnosis

- Serological testing
  - Enzyme-linked immunoassay (EIA)
  - Immunodiffusion (ID)
  - Complement fixation (CF)
    - Titers > 1:16 increase the possibility of disseminated disease
    - Repeat every 12 weeks during care
    - May be used to detect reactivation of coccidioidomycosis

- Typically, see serum IgM production within 1-3 weeks of symptom onset
  - Followed by IgG production 4-8 weeks later

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Thompson, GR 3rd, et al. Lancet Infect Dis. 2021; S1473-3099(21)00191-2.
Galgiani JN, et al. Valley Fever (Coccidioidomycosis). Valley Fever Center for Excellence. 2016.

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Review

- *Coccidioides* spp prefer desert climates
- Small inoculum → infection
- Incidence of coccidioidomycosis is increasing
  - Several hypotheses exist for cause(s)
- Majority of cases: asymptomatic or mild symptoms
- Common symptoms: fatigue, fever, cough, dyspnea, arthralgias
- Certain populations are high-risk for severe disease
- CF titers: useful for evaluating response in acute infection or reactivation

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Audience Response Question

Q1: Choose the ideal climate for the survival of *Coccidioides* spp from the following:

A. High rainfall, warm temperatures year-round, acidic soil

B. Moderate rainfall, humid summers with mild winters, neutral pH soil

C. Low rainfall, hot summers with moderate winters, alkaline soil

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Audience Response Question

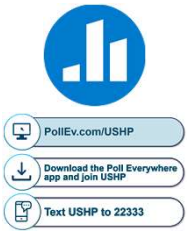
Q2: By year 2100, due to changing climate conditions, cases of coccidioidomycosis are expected to:

A. Increase up to 25%

B. Increase up to 50%

C. Remain about the same

D. Decrease by 25%



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Audience Response Question

Q3: Which of the following are common clinical manifestations of coccidioidomycosis? (Select all that apply)

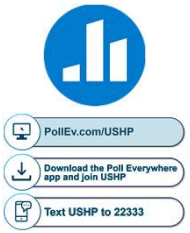
A. Fever

B. Weight loss

C. Night Sweats

D. Asymptomatic

E. Chest pain



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Coccidioidomycosis: Management

- Assessment of the need for intervention
- Selection of antifungal agent
- Choice of surgical intervention for destructive lesions

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Therapy

- Individualized decision to treat
  - Antifungals typically not required for most mild infections in immunocompetent patients
  - Most patients control their infection without long-term sequelae

Populations warranting treatment
High-risk groups for severe disease: immunocompromised, African or Filipino ancestry, > 65 y/o, diabetes mellitus, underlying cardiopulmonary conditions, CF titer > 1:16
High-risk chest infections • Extensive chest disease: involvement of most of one lung or portions of both • Debilitating disease: weight loss >10%, intense night sweats >3 weeks, inability to work • Persistent disease: symptoms lasting >2 or 3 months
Any extrapulmonary disease (e.g., bone, joint, skin, CNS)

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Galgiani JN, et al. Clin Infect Dis. 2016;63:e112-146.

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Treatment

Blair JE, et al. (2014)	
Intervention	Patients receiving vs. not receiving antifungals
Population	n=36 pts with mild pulmonary coccidioidomycosis
Design	Prospective 24-week observational study
Outcomes	• Primary: time to achieve a 50% decrease in symptom score • Secondary: time to 100% symptom resolution and time to full attendance at work

Results	• **No statistical differences found in any endpoints**
	  • Median times from onset to 50% reduction and to complete symptom resolution for patients in treatment and nontreatment groups were 9.9 and 9.1 weeks, and 18.7 and 17.8 weeks, respectively
	  • Median times to full return to work were 8.4 and 5.7 weeks, respectively

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Blair JE, et al. Emerg Infect Dis. 2014;20(6):983-990.

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Therapy

Azoles

- Fluconazole, itraconazole
- Posaconazole, voriconazole, isavuconazole

→ Interferes with fungal cytochrome P450 activity, which interrupts the conversion of lanosterol to ergosterol, inhibiting cell membrane function

Polyenes

- Amphotericin B (AmB)

→ Binds to ergosterol which alters cell membrane permeability, causing leakage of cell components

Surgical intervention

- Video-assisted thoracoscopic surgery (VATS)

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Galgiani JN, et al. Clin Infect Dis. 2016;63:e112-146.

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Treatment – Acute Pulmonary Infection

- **Mild infection (high-risk groups or immunocompromised patients):**
  - **First line:** Fluconazole 400 or 800 mg PO daily or itraconazole 200 mg PO BID
- **Mild infection (immunocompetent): No treatment; monitor and follow up**
  - If decision is made to treat, consider fluconazole 400 mg PO daily or itraconazole 200 mg PO BID
- **Severe or rapid progressing infection: Liposomal AmB 3-5 mg/kg/day**
  - De-escalate to oral azole upon clinical improvement (typically for 3-6 months)
- **Durations vary based on the individual's clinical response**
  - Resolution of symptoms, infiltrate(s), and stabilized inflammatory markers
  - Immunocompromised typically require 3-6 months of treatment
  - Immunocompetent usually require 6 to 12 weeks of antifungals, if treated

Galgiani JN, et al. Clin Infect Dis. 2016;63:e112-146.
Thompson, GR 3rd, et al. Lancet Infect Dis. 2021; S1473-3099(21)00191-2.

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Treatment – Chronic Pulmonary Infections

PULMONARY NODULE OR ASYMPTOMATIC CAVITY IN PATIENTS WITHOUT IMMUNOSUPPRESSION	• Monitor without treatment

SYMPTOMATIC CAVITARY COCCIDIOIDAL PNEUMONIA	• Azole therapy for ≥ 1 year (regardless of immune status)
	  • Either fluconazole 400 mg/day or itraconazole 200 mg twice daily
	• If cavities are present for > 2 yrs or recurrence
	  • Consider surgical options

RUPTURED CAVITY	• Resection + decortication + oral azole • AmB in refractory cases or rapid deterioration

Galgiani JN, et al. Clin Infect Dis. 2016;63:e112-146.
Thompson, GR 3rd, et al. Lancet Infect Dis. 2021; S1473-3099(21)00191-2.

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Treatment – Extrapulmonary Infection

- Any extrapulmonary infection warrants treatment
- Skin and soft tissue (immunocompetent and immunocompromised)
  - **First line agents: fluconazole or itraconazole**
    - Fluconazole 400-800 mg IV/PO daily or itraconazole 200 mg PO BID
- Bone and joint infections (immunocompetent and immunocompromised)
  - **Non-severe: Itraconazole is preferred over fluconazole**
    - Itraconazole 200 mg BID or fluconazole 800 mg/day
  - **Severe: AmB x3 months, then long-term azole**
    - AmB once daily in hospital setting, followed by three times weekly to complete 3 months
  - **Surgical intervention may be required**

Galgiani JN, et al. Clin Infect Dis. 2016;63:e112-146.
Thompson, GR 3rd, et al. Lancet Infect Dis. 2021; S1473-3099(21)00191-2.

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Treatment – Fluconazole vs. Itraconazole

Galgiani JN, et al. (2000)	
Interventions	Superiority of fluconazole 400 mg daily vs. itraconazole 200 mg BID
Population	n=198 pts with chronic pulmonary, soft tissue, or skeletal coccidioidal infections
Design	Randomized, double-blind, placebo-controlled trial
Results	Neither fluconazole or itraconazole showed statistically superior efficacy • At 12 months, 57% and 72% of pts responded to fluconazole and itraconazole, respectively • Difference, 15 percentage points (CI: 0.003–30 percentage points); *P* = 0.05
Subgroup analysis	**Response in patients with skeletal infections at 12 months:** • 37% (10/27) of patients in the fluconazole group compared to 70% (16/23) of patients in the itraconazole group, *P* = 0.03

Galgiani JN, et al. Ann Intern Med. 2000;133:676-686.

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Treatment – Coccidioidal Meningitis

- **Fluconazole – preferred initial agent**
  - 400-1200 mg IV/PO daily (most initiate at ≥ 800 mg/day)
  - Suppressive, not curative
    - Suppressive azole therapy for life regardless of immune status
- Treatment failure in patients with CM:
  - Switch to another oral azole or initiate intrathecal AmB
  - If switching to itraconazole, posaconazole, or voriconazole:
    - Recommended to monitor antifungal drug levels for therapeutic purposes

Galgiani JN, et al. Clin Infect Dis. 2016;63:e112-146.
Thompson, GR 3rd, et al. Lancet Infect Dis. 2021; S1473-3099(21)00191-2.
Ho J, et al. Clin Infect Dis. 2017;64(4):519-24.

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Treatment – Murine study

Kamberi P, et al. (2007)	
Interventions	Oral therapy with fluconazole, itraconazole, or cyclodextrin (control) at doses of 10, 25, or 50 mg/kg twice daily was given for 12 days (from day 3 of infection)
Design	Murine model
Outcomes	Survival, histologic analysis, short-term organ clearance, fungal burdens
Results	• At 50 mg/kg, itraconazole and fluconazole were equivalent in survival and clearing fungi from brain and kidney • At 10 and 25 mg/kg, itraconazole prolonged survival compared to fluconazole (P < 0.05 and 0.01, respectively) • At 10 mg/kg, itraconazole was more effective in clearing lungs and kidneys (P< 0.05 and P< 0.001, respectively) • At 50 mg/kg, itraconazole was superior to fluconazole in clearing fungi from the spinal cord and lungs (P< 0.05)
Conclusions	• Overall, itraconazole was more efficacious on a mg/kg basis but similar to fluconazole at high doses

Kamberi P, et al. Antimicrob Agents Chemother. 2007;51(3):998-1003.

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Treatment

- Major exceptions to fluconazole as the preferred initial antifungal:
  - Bone and joint infections
  - Life- or limb-threatening infections
  - Infection during pregnancy

Galgiani JN, et al. Clin Infect Dis. 2016;63:e112-146.

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Fluconazole treatment failure

- Consider switching to another azole:
  - Itraconazole
  - Posaconazole
  - Voriconazole
  - Isavuconazole (not extensively studied in coccidioidomycosis)
- Consider switching to amphotericin B (AmB) if rapidly progressing infection
  - AmB deoxycholate (0.5-1.5 mg/kg daily)
  - Liposomal AmB (3-5 mg/kg daily)

Galgiani JN, et al. Clin Infect Dis. 2016;63:e112-146.

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Fluconazole

- Good oral bioavailability (>90%); available IV/PO
- Distribution
  - Body tissues and fluids: urine, eyes, skin, saliva, sputum, and nails
  - CSF penetration: 50-94% of plasma serum concentration
- Metabolism and Excretion
  - Partial metabolism
  - Both metabolite (11%) and unchanged drug (60-80%) excreted in urine
- Dosed aggressively in coccidioidomycosis
  - To reduce potential for treatment failure

Fluconazole

- Common ADRs – **generally well tolerated**
  - GI intolerance: bloating, N/V, anorexia
  - Reversible alopecia (seen at doses > 400 mg/daily)
  - Transaminase elevations
- Numerous drug-drug interactions
  - Potent inhibitor CYP2C19 and 2C9
  - Moderate inhibitor of 3A4 (dose-dependent)
  - Rifampin and other inducers
  - Immunosuppressants (tacrolimus)

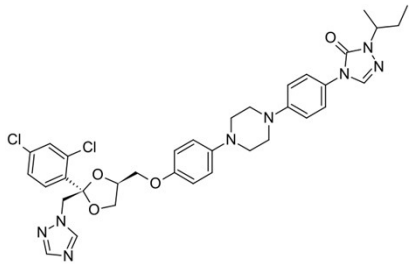
Itraconazole

- Variable oral absorption
- Poor CNS and urinary distribution
- No renal or hepatic dose adjustments necessary
- More drug interactions and side effects than fluconazole
- Boxed warning: congestive heart failure
  - Negative inotropic effects

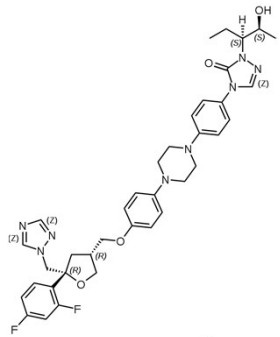
Absorption
Capsules: • Requires acidic pH • Avoid H2RAs or PPIs • Administer with meals
Solution: • Unaffected by gastric pH • Administer on an empty stomach
SUBA®-itraconazole (capsules): • More reliable absorption • PPI: Basic environment ↑ absorption • Expensive

SUBA® = Super BioAvailable

Azoles



Itraconazole



Posaconazole

Posaconazole

- Potential role as salvage therapy
- Potent activity vs. *Coccidioides* in murine and in vitro studies
  - ≥ 200 times as potent as fluconazole and ≥ 50 times as potent as itraconazole in reducing fungal burden in nonmeningeal coccidioidomycosis in a murine model
- Successfully used in disseminated nonmeningeal cases refractory to other azoles and AmB
- Limited evidence in CM
  - Case report in 2011: 2 patients had symptomatic and laboratory improvement and 1 patient with previously unresponsive CM had clinical improvement.

Lutz JE, et al. Antimicrob Agents Chemother. 1997;41(7):1558-61.
Stevens DA, et al. CHEST. 2007;132(3):952-58.
Kim MM, et al. Clin Infect Dis. 2011;53:1060-6.
Schein R, et al. Clin Infect Dis. 2011;53:1252-4.

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Amphotericin B

Formulations	Routes	Dose	Infusion time (minimum)
Conventional (deoxycholate)	IV, IT	0.7 – 1 mg/kg/day (max: 1.5 mg/kg)	4-6 hrs
Lipid Complex	IV	3 – 5 mg/kg/day	2 hrs
Liposomal	IV	3 – 5 mg/kg/day	2 hrs

- High rates of infusion-related reactions: fever, rigors, hypotension
  - Pre-medicating can help with reactions
- Can extend infusions over 12 to 24 hours to improve tolerability
- Improved safety with lipid formulations

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Review – Initial therapies

Condition/Severity	Preferred	Alternative(s)
Acute Pulmonary Infection		
Mild cases (immunocompetent)	No treatment recommended†	--
Severe/rapidly progressing	AmB	--
High-risk/immunocompromised	Fluconazole or itraconazole	--
Chronic Pulmonary Infection		
Asymptomatic nodule/cavity	No treatment recommended	--
Symptomatic	Fluconazole or itraconazole	AmB, posaconazole, voriconazole
Ruptured cavity	Fluconazole or itraconazole	AmB, posaconazole, voriconazole
Extrapulmonary Infection		
Skin and soft tissue	Fluconazole or itraconazole	AmB, posaconazole, voriconazole
Bone and joint (mild-moderate)	Itraconazole > fluconazole	AmB, posaconazole, voriconazole
Bone and joint (severe)	AmB +/- surgery	--
CNS (meningitis)	Fluconazole	↑ fluconazole dose, switch azoles, or initiate IT AmB

†Fluconazole or itraconazole if decision is to treat

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Preventive Strategies: Special At-risk Populations

- Organ transplantation recipients
  - In endemic areas without active coccidioidomycosis:
    - Fluconazole 200-400 mg daily for 6-12 months post-transplant
  - With previous active coccidioidomycosis should receive:
    - Fluconazole 200-400 mg daily
    - Continued indefinitely or until withdrawal of immunosuppressive therapy
- Patients with HIV living in endemic regions
  - Antifungal prophylaxis is not recommended.
- Exposed personnel
  - Ex: lab workers
  - Benefits of prophylaxis not proven
  - May consider fluconazole or itraconazole (400 mg PO daily) for 6 weeks

Galgiani JN, et al. Clin Infect Dis. 2016;63:e112-146.

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Conclusion

- *Coccidioides* spp are endemic to the southwestern United States
- Coccidioidomycosis likely remains under-reported
- Clinical presentation often resembles community-acquired pneumonia
- Fluconazole and itraconazole are the mainstay of therapy
- Posaconazole, voriconazole, isavuconazole are options in salvage therapy
- Amphotericin B is an option in life- or limb-threatening cases
- Most coccidioidal infections resolve without long-term sequelae

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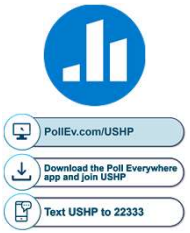
Audience Response Question

Q4: Which antifungal is the preferred antifungal for a majority of coccidioidomycosis cases?

A. Fluconazole
B. Itraconazole
C. Amphotericin B
D. Voriconazole
E. Posaconazole



USHP

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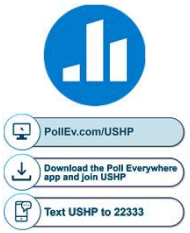
Audience Response Question

Q5: Which antifungal medication is most associated with infusion-related reactions?

A. Fluconazole
B. Itraconazole
C. Amphotericin B
D. Voriconazole
E. Posaconazole



USHP

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Audience Response Question

Q6: Which antifungal showed trends of slightly greater efficacy when compared to fluconazole 400 mg PO daily for skeletal coccidioidal infections?

A. Itraconazole 200 mg PO BID

B. Voriconazole 200-300 mg PO BID

C. Posaconazole 300 mg PO daily

D. Amphotericin B (liposomal) IV 3-5 mg/kg/day

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Audience Response Question

Q7: Which of the following would be the most appropriate agent to use for a pregnant patient (gestational age: 8 weeks) with acute pulmonary coccidioidomycosis?

A. Fluconazole 400-1200 mg PO daily

B. Itraconazole 200 mg PO BID

C. Amphotericin B (liposomal) IV 3-5 mg/kg/day

D. Voriconazole 200-300 mg PO BID

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Coccidioidomycosis: No Valley Low Enough

CE Code: (USHP will fill in)

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