Current Therapy: Past and Present Treatment Options

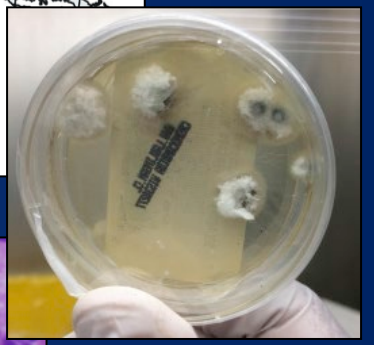
George R. Thompson III MD, FIDSA, FECMM
Professor of Medicine
Division of Infectious Diseases
Department of Internal Medicine
Department of Medical Micro and Immunology
University of California-Davis

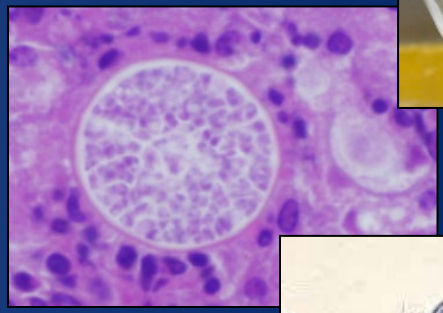
UCDAVIS
UNIVERSITY OF CALIFORNIA

Key Questions

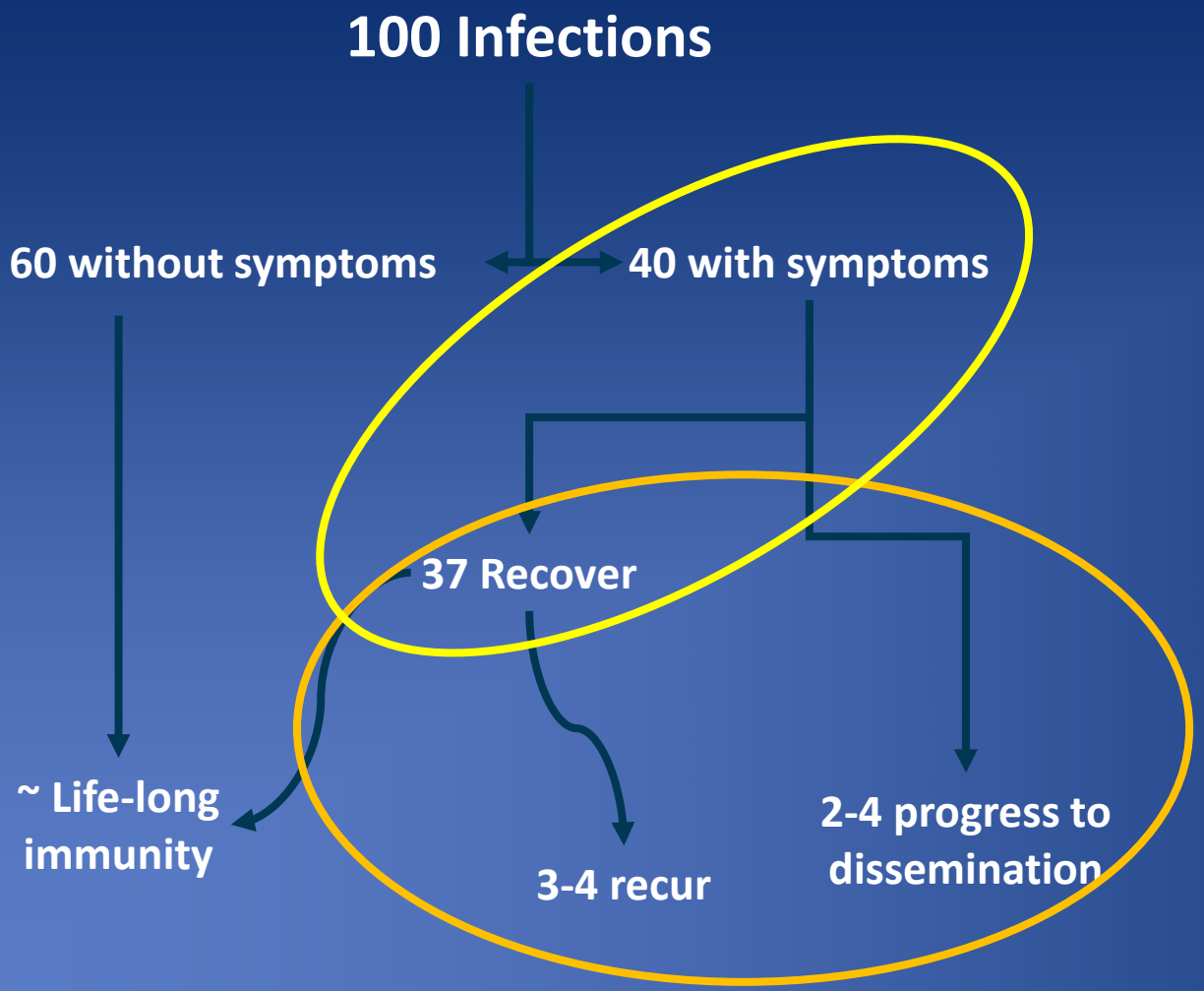
Treatment of Coccidioidomycosis

- Natural history prior to antifungals
- Early treatment options
- Duration of therapy
- Sequestered Sites
- Toxicity of Current Agents
- Therapeutic Drug Monitoring (TDM)
- Resistance





Natural History: Coccidioidomycosis



Treatment Primary Pulmonary Infection:

To Treat or not – Always treat:

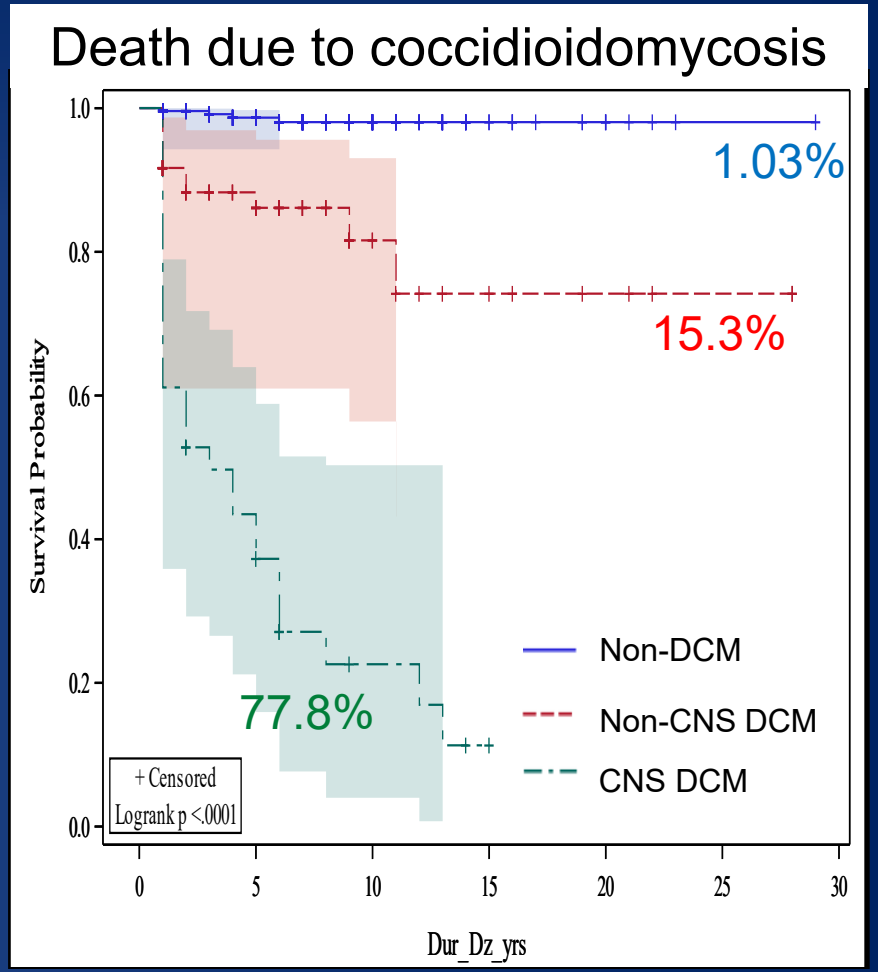
- Immunosuppressed
- Diabetes mellitus
- Cardiovascular disease
- Pregnancy
- Filipino, African-American
- "Exceptionally severe primary infection"

Treatment of Complicated Infection:

- Chronic pulmonary infection
- Dissemination
- Long courses required for some

Natural History: Relapse or Chronic Infection

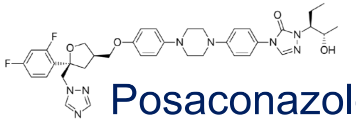
- Most complications occur within a few weeks to months of onset of infection:
  - Approximately 5% to 10% of patients develop pulmonary sequelae
  - Less than 1% of patients develop extrapulmonary disease (dissemination).
    - Skin
    - Bone
    - Brain
    - Any site!
- Patients may already have complications at diagnosis.
- A careful review of symptoms and a physical examination usually is sufficient to detect possible complications.

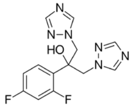


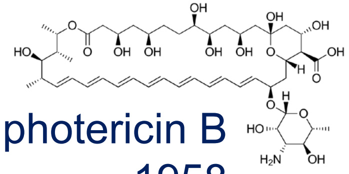
Bays, Thompson, Galgiani. ***Clin Infect Dis*** 2021, 73(11):e3814-e3819.

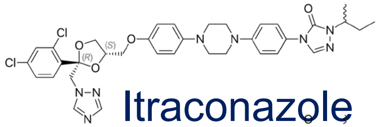
Treatment Options

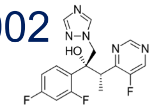
FDA approved treatment:
Amphotericin B
Ketoconazole

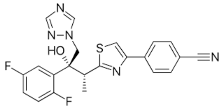

Posaconazole
2006


Fluconazole
1990


Amphotericin B
1958


Itraconazole
1992

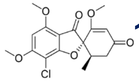
Voriconazole
2002


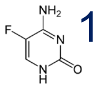

Isavuconazole
2015

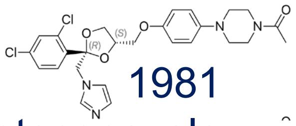
L-AMB 1997

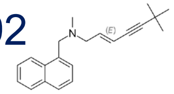
SUBA-itraconazole 2018

1950 1960 1970 1980 1990 2000 2010 2020

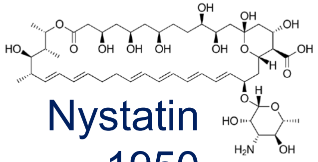
Griseofulvin

1959

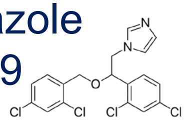
Flucytosine

1971


1981
Ketoconazole

Terbinafine
1992


Caspofungin 2001
Micafungin 2005
Anidulafungin 2006


Nystatin
1950

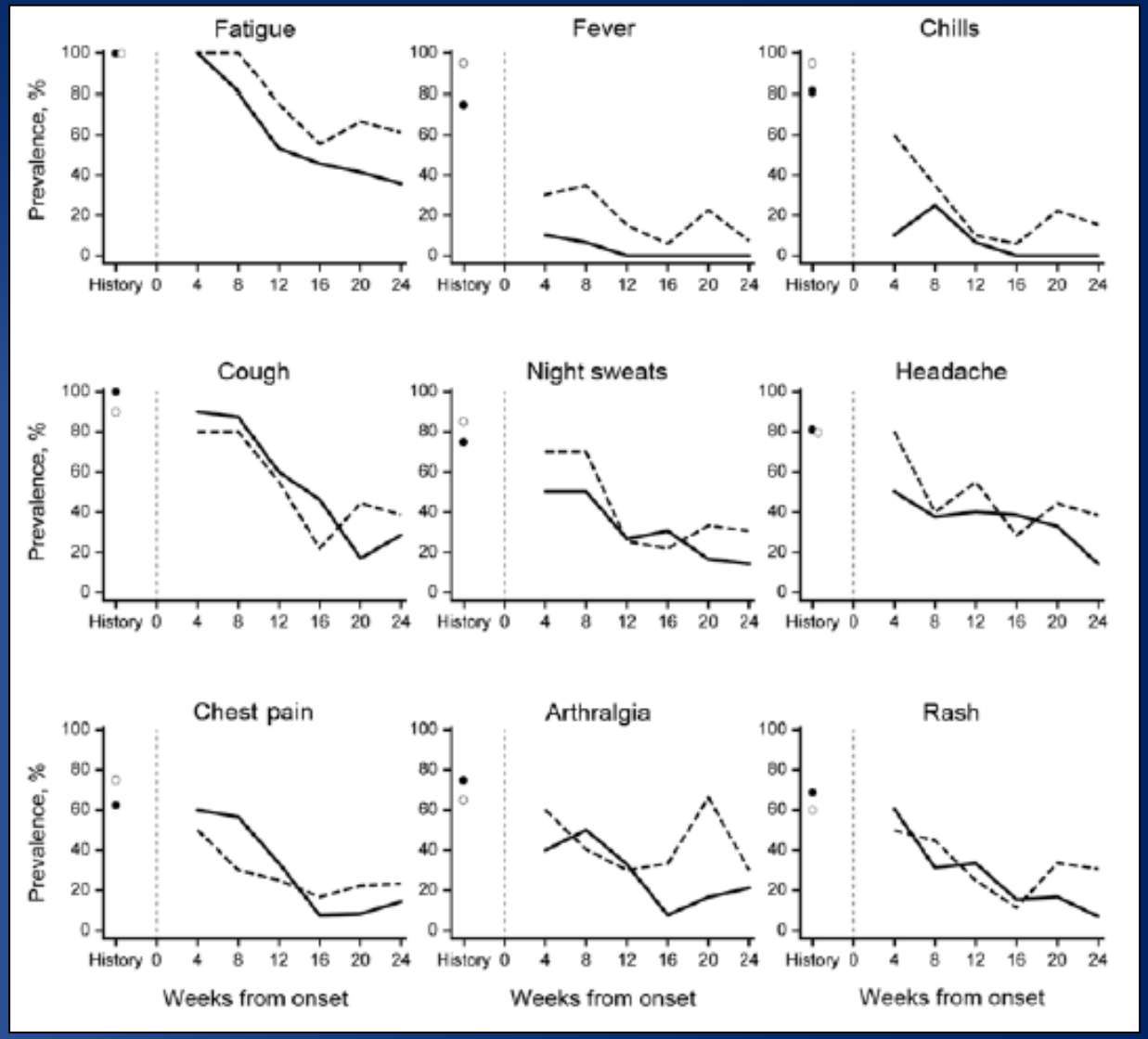
Miconazole
1979


Treatment

Highly Individualized

Primary Pulmonary Infection:

- Treatment: Range from none to fluconazole/itraconazole 3-6 months
- Treatment may not change duration of symptoms
- Does not prevent dissemination



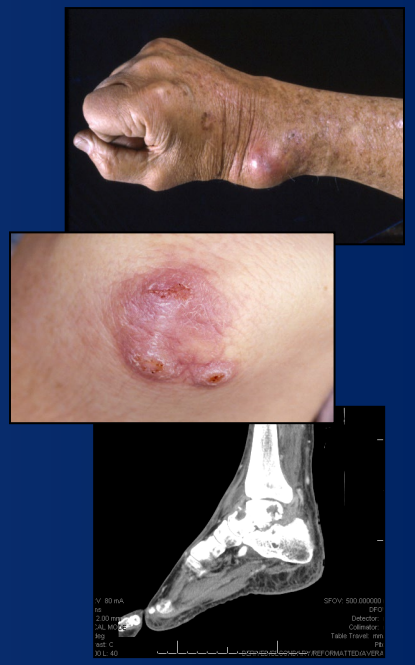
Blair et al. ***Emerg Inf Dis***. 2014 Jun; 20(6): 983–990.
Ampel et al. ***CID*** 2009; 48:172–8

Treatment

Highly Individualized – consideration of sequestered sites

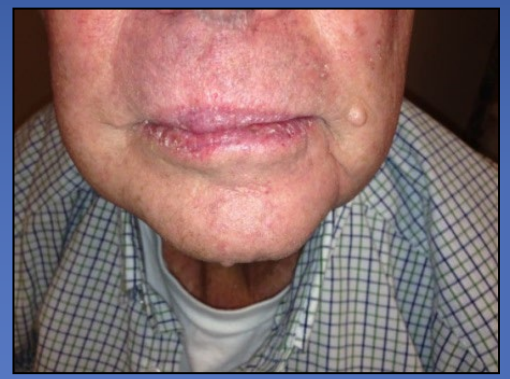
Complicated disease

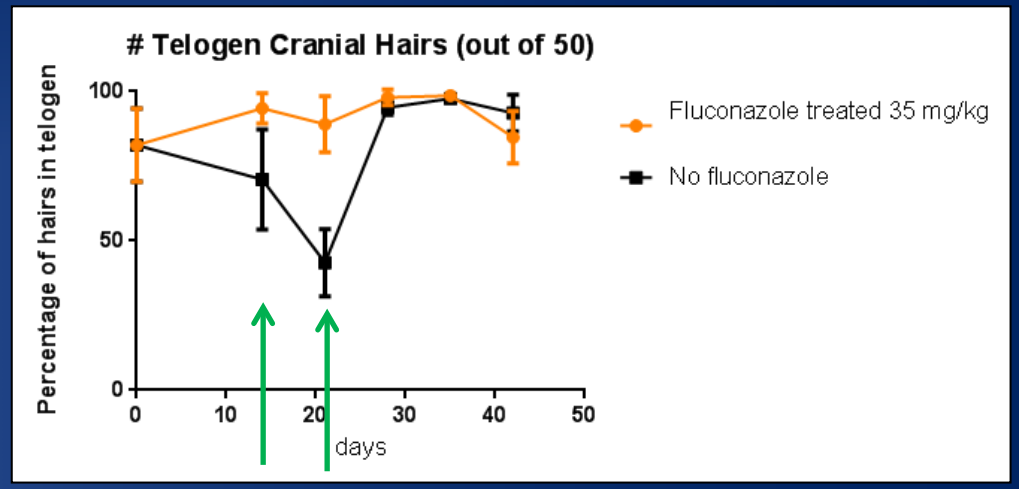
- Severe Disease: Combination Amphotericin B plus triazole
- Chronic Pulm Infection: chronic triazole - **years**
- Cutaneous: chronic triazole, give trial off therapy +/- 2 **years**
- Joint/Bone: chronic triazole, give trial off therapy +/- 2 **years**
- Spine or Meningitis: chronic triazole, **life-long therapy**
  - Refractory meningitis: Intrathecal amphotericin B for months
- Organ Transplant: **life-long therapy**



Treatment: Toxicity (Fluconazole)

- Fluconazole toxicity?
- Alopecia, cheilitis, dry skin
  - Generally well tolerated, even at doses > 800 mg/day; for many life-long therapy
  - Eval of >300 patients on fluconazole for > 30 days: 50% discontinued secondary to toxicity
- Change to itra/posa/or stop – ~14-21 days to resolution of skin toxicity, ~90 days to resolution of alopecia



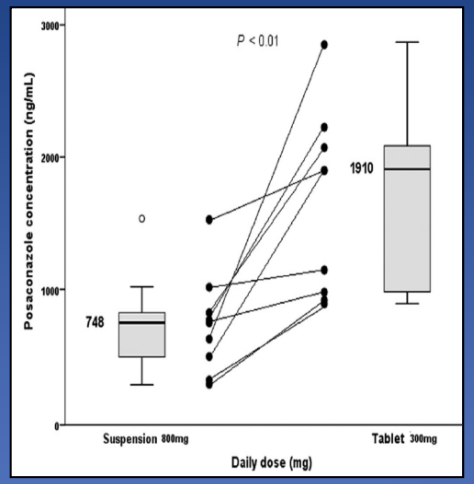


P=0.007 P<0.001

Thompson GR 3rd, et al. ***Antimicrob Agents Chemother***. 2018
Davis M, Nguyen V…Thompson GR, et al. ***Journ Antimicrob Chemo 2020***

Treatment: Toxicity (Posaconazole and Itraconazole)

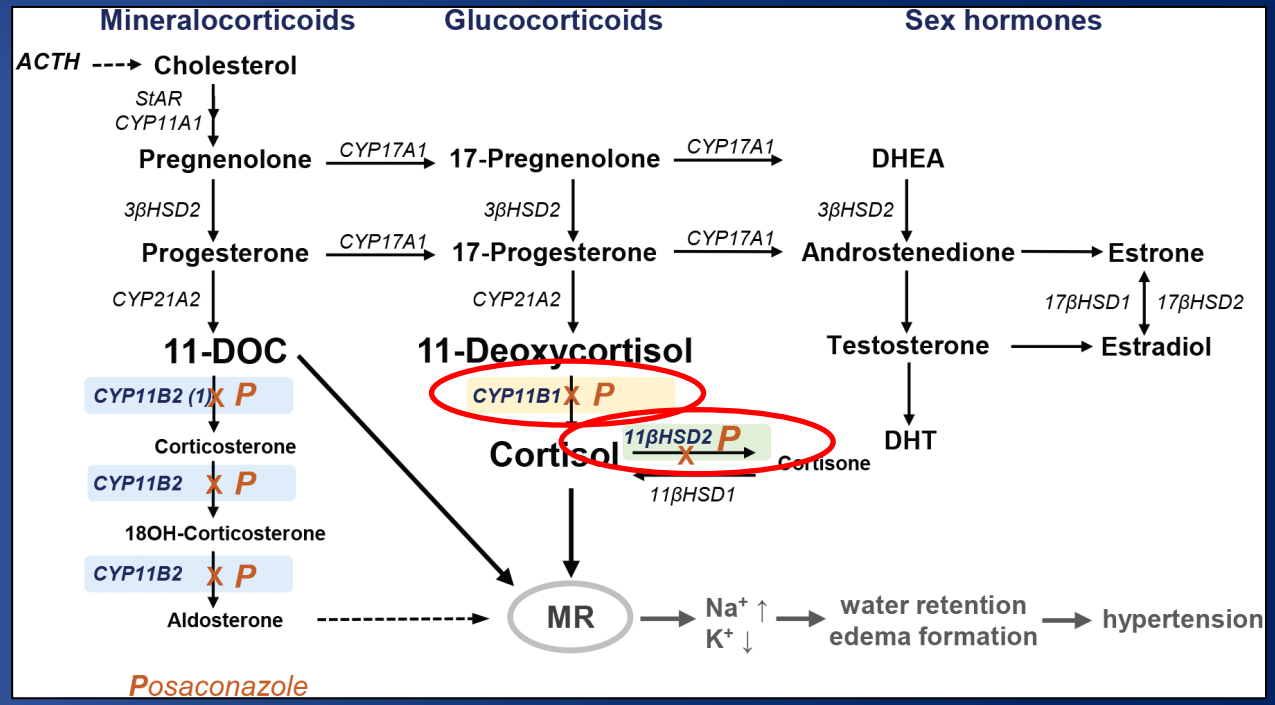
- Tablet formulation has improved serum [conc] (median of 0.74 → 1.92 µg/mL)



- 10% with levels > 3.5 µg/mL
- Ceiling for toxicity?

Study of 69 patients on posaconazole:
Most with: Undetectable renin and aldo
Elevated 11-deoxycortisol, and cortisol/cortisone ratio

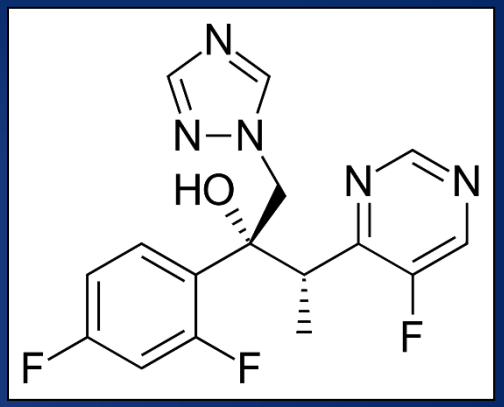
Median posa (3.0 vs 1.2 µg/mL, *P* ≤ .0001).



Jung DS, et al. ***Antimicrob Agents Chemother***. 2014 58(11): 6993–6995. Nguyen et al. ***Clin Infect Dis***. 2020;70:2593-98

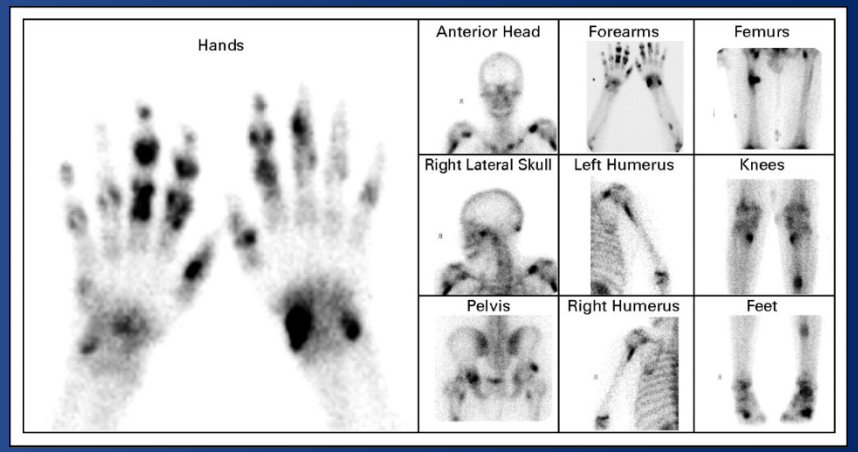
Treatment: Toxicity (Voriconazole)

- CNS and peripheral neuropathy
- Hepatotoxicity
- Photopsia
  - Bipolar On-Cells
- Photosensitivity
  - N-oxide metabolite



Long term use:

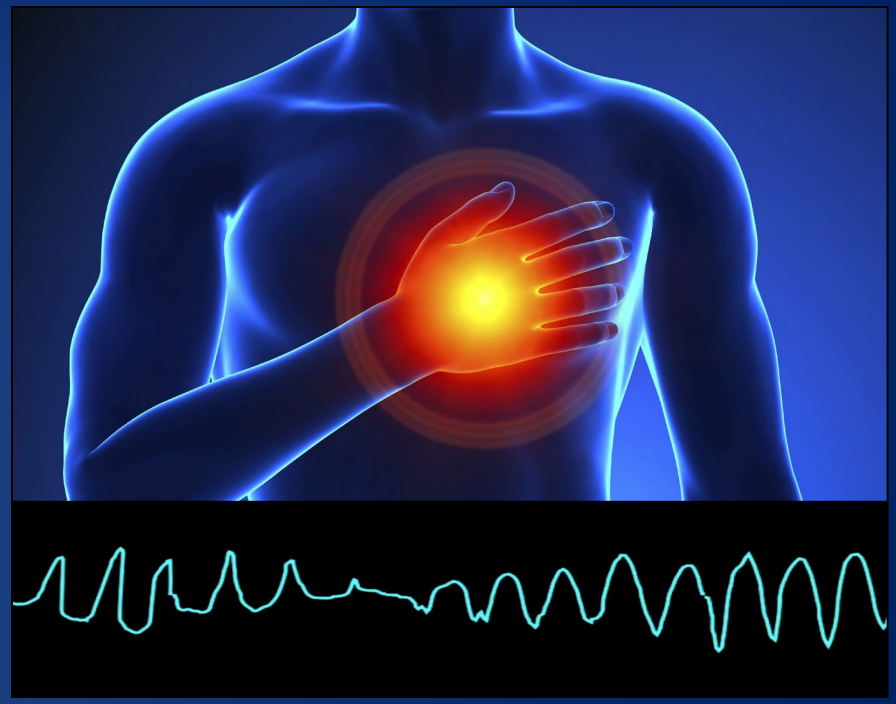
- Cutaneous malignancy
- Fluoride toxicity



Lat A, Thompson GR 3rd. ***Infect Drug Resist***. 2011;4:43-53.
Thompson GR 3rd, et al. ***Antimicrob Agents Chemother***. 2012 Jan;56(1):563-4.

EKG: QTc changes

- Fluconazole: prolongs QTc
- Itraconazole: prolongs QTc
- Voriconazole: increase from 10-<60msec
- Posaconazole: healthy volunteers = no change, Package insert “warning”
- Isavuconazole: shortening by -13msec



QTc concerns most common in those who most often need treatment

P450 Potential Interactions

Azole	CYP2C8	CYP2C9	CYP2C19	CYP3A4
Fluconazole	++	++	+	++
Itraconazole	+	+	–	+++
Voriconazole	++	++	+++	++
Posaconazole	–	–	–	+++
Isavuconazole	–	–	–	+/++

Notes: –, no inhibition; +, mild inhibition; ++, moderate inhibition; +++, strong inhibition.

Consideration of drug interactions with any change in azole therapy

Venetoclax, glasdegib, midostaurin, quizartinib, gilteritinib, enasidenib, ivoseidenib, etc

Megias-Vericat et al. ***Ann Hematol***. 2020 99(9): 1989-2007

Necessity of TDM:

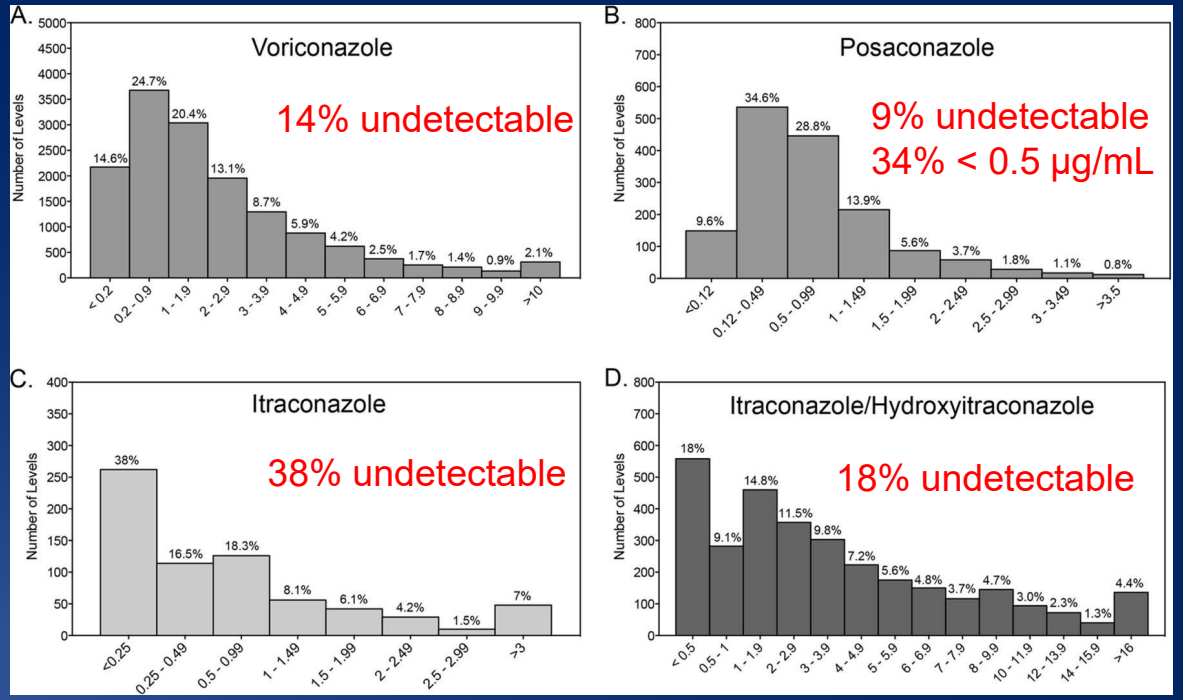
- **Accurate and cost effective; available**
- **Therapeutic range**
- **Intra/inter - patient variability**

Voriconazole - ✓

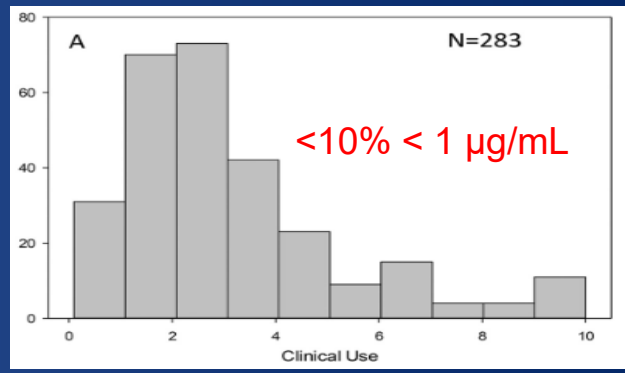
Posaconazole - ✓

Itraconazole - ✓

Isavuconazole – ? **Levels >4.6 ->AEs**



Bloodstream concentration for voriconazole, posaconazole, and itraconazole



Bloodstream concentrations for isavuconazole

Kosmidis C, et al. ***Antimicrob. Agents Chemother;65(1):e01511-20.***

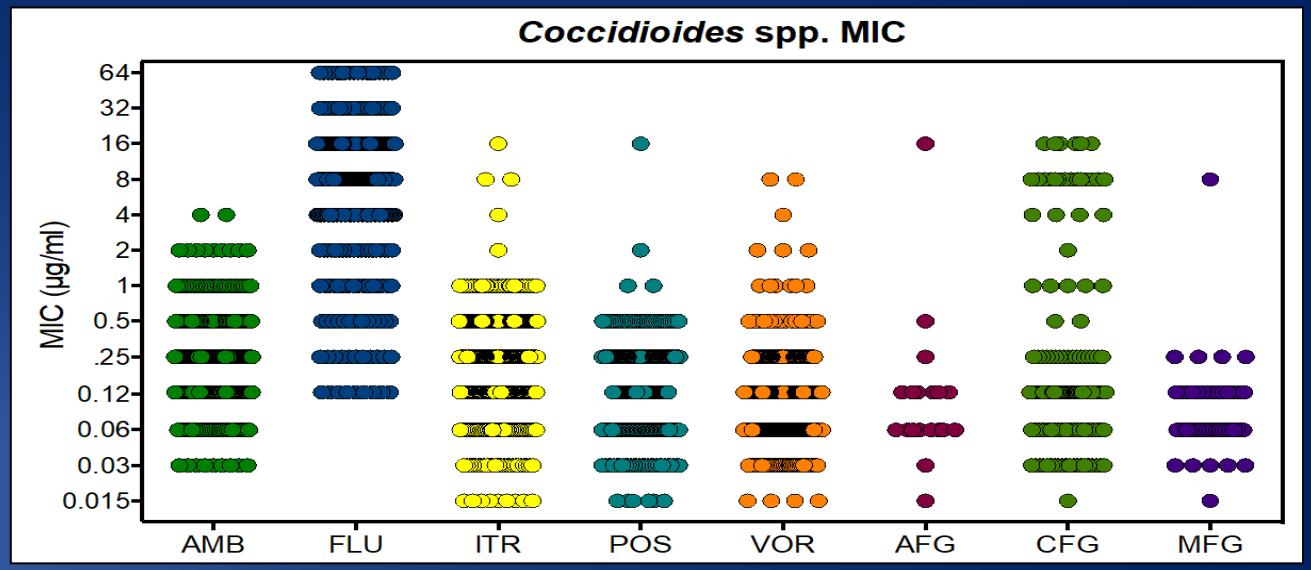
Wiederhold et al. ***Antimicrob. Agents Chemother***. 2014;58:424-431

Andes A et al. ***Antimicrob. Agents Chemother***. 2018;26;585-18

Culture/Susceptibility

Susceptibility

- Large scale testing
  - >400 isolates
- >1/3 of isolates with FLC MICs > 16 µg/mL
- 22 isolates with FLC MICs > 64
  - Variable MIC to ITC, POS, VOR – MICs > 2 rare



In vitro susceptibility of *Coccidioides* isolates to AMB, triazoles and echinocandins

ITC ≥ 2, 1.0% VOR ≥2, 1.2%;
POS ≥1, 1.1% AMB ≥ 2, 2.8%

Prior literature – animal models and one clinical trial suggest mould active azoles more favorable response – has this played a role in prior studies of 1º disease?

Thompson GR et al. ***Antimicrob Agents Chemother***. 2017

Key Questions

Treatment of Coccidioidomycosis:

- Does treatment of primary infection change outcomes?
- Complicated disease requires long courses of therapy
- Clear limitations of current agents
  - Sequestered sites, toxicity with long term therapy, lack of oral fungicidal agents
- Therapeutic Drug Monitoring (TDM)
- Resistance emerging

Thank You

UC-Davis:
Derek Bays
Stuart Cohen
Monica Donnelly
Vu Nguyen
Angie Gelli
Jane Sykes

NAU:
Bridget Barker

Bakersfield:
Royce Johnson
Arash Heidari

UCLA:
Manish Butte

UT-San Antonio:
Tom Patterson
Nathan Wiederhold
ChiungYu Hung
Fungus Testing Laboratory

NIH Grants:
U19AI166761
(Hung/López-Ribot)
U19AI166779
(Butte/Johnson)
U19AI166798
(Sil/Dandekar)

Research Support:
Astellas, CDC,
Cidara, F2G, Mayne,
Mundipharma,
Mycovia

Burden Family Gift Fund