Treatment of Coccidioidomycosis

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Disclosures

• No conflict of interest to disclose

• Nearly all medications for coccidioidomycosis discussed will be FDA “off-label”

• The only FDA approved medications with an indication for coccidioidomycosis
  • Ketoconazole
  • Amphotericin B deoxycholate
Objectives

• At the conclusion of this talk, the audience will be able to:
  • Describe the management of chronic pulmonary and disseminated coccidioidomycosis.
  • List the FDA approved antifungal therapies for the management of coccidioidomycosis.
  • Discuss alternative strategies in patients who are intolerant of or not improving with standard antifungal treatment.
Treatment of Coccidioidomycosis

• Begins with a careful history & exam

• Want to define the severity, location and chronicity of infection

• Define the presence of extrapulmonary infection
  • Skin and soft tissues
  • Bone and joints
  • Meningeal infection
No Antifungal Treatment

- Mild-moderate primary pulmonary coccidioidomycosis (healthy host)

- No treatment is common early in 1° infection
  - ie, levofloxacin for presumed bacterial CAP

- Most resolve without sequelae

- VA study
  - Approx 50% pts with 1° pulm cocci given tx on basis of clinical severity
  - Complications only seen in tx group after tx stopped

Therapeutic Agents

- Amphotericin preparations
  - Amphotericin deoxycholate
  - Lipid associated amphotericin

- Azoles
  - Ketoconazole
  - Fluconazole
  - Itraconazole
  - Voriconazole
  - Posaconazole

- Future: Nikkomyacin Z, others
Amphotericin B

• First effective med vs. coccidioidomycosis
• IV, IT, intraleisonally, intraarticular, not oral
• IV not effective for cocci meningitis
• Perceived to have more rapid onset of action
• Some experts prefer for rapidly progressing infection

• Amphotericin B deoxycholate
  • 0.5 – 1.5 mg/kg IV daily or every other day
  • Infusional toxicity: fever, rigors, hypotension, etc
  • Cumulative toxicity: creatinine ↑, K ↓, Mg ↓
Lipid associated Amphotericin B

- Developed as a safer alternative to AMB
- 3 formulations available in US
  - ABCD: Ampho B Cholestyrl Sulfate Complex
  - ABLC: Ampho B Lipid Complex
  - Liposomal Ampho B
- Acute febrile reactions less frequent, still occur
- All have lower renal toxicity
- Expensive ≈$400 per day
- ≥ 2-5 mg/kg IV daily
- No data demonstrates improved efficacy vs. coccidioidomycosis
Azoles

• Relative lack of toxicity
• Oral bioavailability
• Tolerable for short or long treatment courses
• Formal studies show azoles are efficacious
• No studies show clear superiority among azoles
Fluconazole

• Good oral bioavailability
• 400-800 mg daily
• Useful to treat many/most coccidioidal infections
• Well tolerated
• Relatively inexpensive
  • Previously ¢, now $ 
• Infrequent hepatitis
• Monitor liver enzymes periodically
Itraconazole

- Oral availability
- Requires gastric acid for absorption
- Requires measurement of serum levels
- Black Box warning
  - CHF, Drug interactions
- 200 mg twice or thrice daily
- ≈$15-20 per day
- Well tolerated
- Has shown superiority vs. flu in skeletal cocci
Voriconazole

- In vitro susceptibility better than itraconazole
- Good tissue & CNS penetration
- Has been used in salvage cases, often, but not invariably, successfully
  - In salvage, 67% improved after 6 months
- 200-300 mg po or IV BID
- ≈$40-250 per day (vs $4 flu)
- Phototoxicity
- Transient visual changes

Kim Clin Infect Dis 2011;53:1060-6
Voriconazole

- Therapeutic drug levels should be performed.
  - Oral bioavailability excellent independent of gastric acid
  - High fat meal ↓ levels
  - Metabolism by CYP219 variable
  - Inhibits CYP 219, 2C8/9, 3A4
    (Multiple drug interactions)
  - Inter- intra subject variation
  - Levels may ↓ with time
  - Levels correlate w efficacy in other fungal infections
Posaconazole

Animal studies: fungicidal activity
- 400 mg BID liquid or 300 QD pill
- Requires fatty meal for absorption
- Saturable absorption
  - In order to ↑ dose delivered, need to ↑ frequency of doses
- Highly protein bound
- Penetration into CNS variable
- ≈$120 per day (vs fluconazole $4)
Posaconazole

- 17/20 (85%) satisfactory response in open label, 1st tx of chronic pulm & nonmeningeal 400/d
  Catanzaro 2007 CID

- 11/15 (73%) success in chronic pulm or disseminated patients failing other standard antifungal regimens. Posa 800 mg/day
  Stevens 2007 Chest

- 12/16 (75%) pts improved w posaconazole in salvage therapy
  Kim CID 2011

- 5/6 improved with disseminated cocci failing other therapy
  Anstead 2005 CID

- Other single cases reported with success
Ketoconazole

- Inexpensive azole option where resources limited.
- 400 mg daily
- Interferes with testosterone production and cortisol responses
  - Male oligospermia, gynecomastia
  - Female menstrual irregularities
- FDA: when other effective antifungal therapy is not available or tolerated and potential benefits are considered to outweigh the potential risks
Nikkomycin Z

• Currently under development
• Inhibitor of chitin synthase, a major component of fungal cell wall
• In vitro studies show potential for cure
• Phase I: No safety concerns
• Phase II: 2015 early pulm cocci
• www.vfce.arizona.edu
Nikkomycin Z

- In vivo studies show promise
  - 7 dogs improved
  - 3 dogs resolved cocci pneumonia

Shubitz et al 2013 Medical Mycology

- www.vfce.arizona.edu
....But what about…?

Newer Azoles
  • Ravuconazole
  • Isavuconazole

Ecchinocandins
Echinocandins

• No good in vivo studies to suggests efficacy in coccidioidomycosis as a sole agent.

• One animal study suggests efficacy when combined with amphotericin
  Gonzalez 2007 J Antimicrob Chemother

• Limited case reports using combination therapy show mixed results
  Park 2006 BMC Inf Dis
  Antony 2004 CIM
  Hsue 2004 J Antimicrob Chemother

• No recommendation for use at present.
Combination Therapy?

• Not uncommonly observed azole + AMB in rapidly progressing illness

• No formal studies addressing the role of combination antifungal therapy for synergy

• Hypothetical risk of antagonism raised concern in other fungal organisms, but antagonism has not been clinically demonstrated.

• Further study is needed
Surgical Debridement

- Occasionally surgery plays important role in control of infection

- Situations where surgery could be considered:
  - Large abscess
  - Progressively enlarging lesions despite medical treatment
  - Destructive lesions
  - Presence of boney sequestration
  - Unstable spine
  - Impingement on critical structure or tissue
  - Recurrent lesion after successful treatment
Treatment Guidelines for Coccidioidomycosis

- Infectious Diseases Society of America
- Revised November 2005
- Revision anticipated 2015
- [http://www.journals.uchicago.edu/doi/pdf/10.1086/496991](http://www.journals.uchicago.edu/doi/pdf/10.1086/496991)
- Cases to illustrate these guidelines
Case 1: Treatment Acute Pulmonary Coccidioidomycosis

- 74 year old woman
- HTN, hyperlipidemia
- Subacute onset of:
  - HA
  - Cough, green sputum
  - Dyspnea, pleuritic and non pleuritic chest pain
  - Malaise and fatigue
  - Chills and night sweats, no fever
Case 1: Acute Pulmonary Coccidioidomycosis

- WBC 10.2
  - 67% PMNs, 18% Lymphocytes, 8% eosinophils
- ESR 68
- Cocci (EIA) IgG and IgM negative
- CXR performed
Acute Pulmonary Coccidioidomycosis

Baseline CXR 1 month previous to symptoms

With cough, dyspnea, chest pain
Case 1: Acute Pulmonary Coccidioidomycosis

- Clinically improves
- Follow up serology
  - EIA IgG+, IgM+
  - CF 1:8
  - ID IgG+
- Diagnosed with acute pulmonary coccidioidomycosis
- Not treated, symptoms slowly resolved
- CT scan nodule followed, stable
Treatment of Acute Pulmonary Coccidioidomycosis

- Mild, absent or resolved symptoms
  - No antifungal therapy
  - Periodic reassessment
- For immunosuppressed patients
  - Treatment may be considered
  - Follow closely
Case 2: Acute Pulmonary Coccidioidomycosis

- 48 year old woman
- Healthy
- Landscaping her AZ winter home
- 1 week later, fever, chills, night sweats, cough, dypsnea, severe headache, fatigue, myalgia
- Hypoxic, septic
- Admitted to the hospital
Case 2: Acute Pulmonary Coccidioidomycosis
Case 2: Acute Pulmonary Coccidioidomycosis

- Required intubation, mechanical ventilation
- Received broad antibiotics
- Sputum culture *Coccidioides*
- Serology (EIA) IgM and IgG positive
- Ambisome 5mg/kg given
- Later changed to fluconazole 400 mg daily
Case 2: Acute Pulmonary Coccidioidomycosis

• Discharged on fluconazole and O$_2$

• 1 month later, she was recovering, beginning her exercise program, improving daily.

• 3 months later, complete resolution of symptoms
Treatment Guidelines
1° Pulmonary Coccidioidomycosis

• Mild, absent or resolved symptoms
  • No antifungal therapy
  • Periodic reassessment
  • Immunosuppressed: consider treatment, follow closely

• Moderate or severe infection
  • Fluconazole 400 mg/d x 3-6 mo
  • Itraconazole 200 mg BID
  • Liposomal AMB if rapidly progressing
Treatment Guidelines
1º Pulmonary Coccidioidomycosis

• BUT: what constitutes moderate or severe infection?
  • Symptoms > 2 months
  • Weight loss > 10%
  • Night sweats > 3 weeks
  • Pulm infiltrate >50% of lung
  • Inability to work
  • Age > 55
  • CF titer > 1:16
  • Sick enough to hospitalize
Treatment of 1° Pulmonary Coccidioidomycosis Summary

- Many healthy people do well without treatment.
  - Monitor and follow up
- Treatment of persons with immunosuppression should be considered for treatment
- Moderate-Severe infection
  - Treat with amphotericin if rapid progression, then deescalate to oral azole
  - Treat entire episode oral azole
  - Duration 3-6 months
Case 3 Diffuse Coccidioidal Pneumonia

- 84 year old male
- Hx myesthenia gravis on prednisone and mycophenolate moffetil
- Lives in Hawaii but gets neurological care at Mayo Clinic Arizona
- 2 weeks fever, cough, dyspnea, confusion
- Flew to AZ for evaluation
Case 3 Diffuse Coccidioidal Pneumonia

- Miliary pattern on chest radiograph
- Placed empirically on IV azole, 4-TB medications (Family refused amphotericin)
- Respiratory failure
  - Bipap (intubation refused)
- Cocci serology
  - EIA igG+, IgM-
  - CF 1:32, ID IgG+, IgM-
  - Cultures of sputum, urine all positive for *Coccidioides*
Case 3 Diffuse Coccidioidal Pneumonia

- After cocci diagnosis was established
- Fluconazole 800-600 mg daily
- Markedly improved after a 3 week hospitalization
- Continued fluconazole
Diffuse Coccidioidal Pneumonia

• Treat at least 12 months
• May treat longer if immunosuppressed
• Mild symptoms
  • Fluconazole 400 mg/d
  • Itraconazole 200 mg twice/d
• Moderate-severe symptoms
  • Consider initiating therapy with AMB or LAMB until clinically stable, then azole
Case 4: Chronic Coccidioidomycosis

- 26 year old healthy Caucasian woman
- 1972 fever, cough, pain in shoulder
  - Dx coccidioidomycosis, no treatment, sx improved
- Felt ok, progressively abnormal CXR
- 1994
  - Cough recurred
  - Sputum culture +, serology +
  - AMB 5.5 months, felt better
Case 4: Chronic Coccidioidomycosis

- 1995-2000 Cough recurred
- Various trials of fluconazole, no improvement

2000
- Posaconazole trial
- Symptoms improved
- Adverse effects of medication, discontinued after 3 years

- 2004 Cough recurred
  - CF 1:128
  - Chronic itraconazole, symptom control is acceptable, but not optimal.
Case 4: Chronic Coccidioidomycosis
Chronic Fibrocavitary Coccidioidal Pneumonia
Chronic, Progressive Fibrocavitary Coccidioidomycosis

- Treat at least 1 year or longer

- Options
  - Fluconazole 400 mg/d
  - Itraconazole 200 mg twice/d
  - Or AMB or LAMB
  - Or, trial of newer azole or study enrollment
Case 5: Asymptomatic Lung Nodule

- 67 yr woman
- 10 year AZ visitor
- Cardiac chest pain
- Incidental Rt. nodule
- Biopsy +
- Serology negative
- No treatment offered
Case 6: Asymptomatic Cavity

- 35 yr man
- Transient respiratory illness, resolved
- Routine physical
- Cavity noted
- Biopsy +
- CF 1:8
- Not treated
- Followed closely
Asymptomatic lung nodule or cavity

• No treatment needed
• Observe for stability
Case 7: Symptomatic Lung Cavity

- 34 year old healthy Chinese woman
- AZ resident x 6 years
- 4 months pregnant
- Hemoptysis
- Hospitalized elsewhere
Case 7: Symptomatic Lung Cavity

- Cocci serology positive
- Imaging showed a cavity
- Uncertain other diagnostic workup
- Amphotericin B until shortly prior to delivery.
- Hemoptysis resolved
- Following delivery, she opted for no treatment
Case 7: Symptomatic Lung Cavity
Case 7: Symptomatic Lung Cavity
Case 7: Symptomatic Lung Cavity

- 2 months later, hemoptysis
- Fluconazole various doses (400-800 mg daily)
- Hemoptysis continued
- Later voriconazole begun
- Episodic hemoptysis continued
- Left upper lobe and left middle lobe wedge resections.
- Voriconazole x a few months, then stopped.
- Hemoptysis resolved & never recurred.
Case 7: Symptomatic Lung Cavity, resected
Symptomatic cavity

- Optimal duration of treatment not established
- Options
  - Fluconazole 400 mg/d
  - Itraconazole 200 mg BID
  - Escalateazole, if needed
  - Consider surgical resection
Special Populations

• Pregnancy
  • Avoid azoles; FDA category D
    • (1st trimester is time of highest risk)
  • AMB

• Immunosuppression
  • May need longer treatment
  • May need to decrease or stop immunosuppressant
  • May relapse

• Transplant
  • Lifelong secondary prophylaxis
Skin and Soft tissue infections

Examples........
Skin/Soft tissue Dissemination

- Duration of treatment: prolonged
  - To resolution of abnormality then longer, follow serology
- Prospective studies: 60-90% efficacy
- Relapses common 20-30%
- Options
  - Fluconazole 400-800 mg/d
  - Itraconazole 200 mg BID-TID
  - AMB or L-AMB
  - May require debridement or resection
Skeletal Infection

- Prospective trials 60-80% azole efficacy
- Itraconazole superior to fluconazole in one study
- Relapses common
- Debridement recommended for most
- Options
  - Itraconazole 200 mg BID-TID
  - Fluconazole 400-800 mg daily
  - AMB or lipid associated AMB
- Prolonged duration
  - Minimum of radiographic-serological resolution
Case 8: Coccidioidal Meningitis

- 34 year old health man
- Oct. 2007 intermittent cough
- Followed by intermitted sinus headaches
- Dec. 2007 progressive headache, N/V
  - CT and MRI head performed
  - CSF exam
    - TNC 670 4%PMN, 61%lymphs, 26%eos
    - TPro 126, Glu 26
    - Cocci serology + in CSF and in serum
- Fluconazole 800 then 1200 mg daily with slow improvement
Treatment Coccidioidal Meningitis

- Fluconazole $\geq 800$ mg daily
- May decrease to 400-600 mg daily after improvement
- Shunt for hydrocephalus
- Alternatives
  - Intrathecal AMB
  - Newer azole
- Lifelong treatment needed
Summary

• Guidelines for treatment of coccidioidomycosis have been written, to be periodically updated.

• http://www.journals.uchicago.edu/doi/pdf/10.1086/496991

• Many infections do not require treatment.

• Every infection needs to be assessed for location, extent and chronicity of symptoms

• Treat according to location and characteristics of infection.

• If treatment needed, most infections can be treated with azoles
Summary, cont.

• Fluconazole and itraconazole most often used
• Voriconazole, posaconazole reserved for salvage situations at this time.
• Nikkomycin Z under development
• Much more study is needed.
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