Updated Guidelines for Management of Candidiasis

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Statement of Disclosure

I have no actual or potential conflict of interest in relation to this presentation
Outline

• Review mechanisms of antifungal drugs
• Present Infectious Disease Society of America Clinical Practice Guidelines for the Management of Candidiasis
• Emphasis on treatment for oropharyngeal candidiasis
• Development of resistance
Introduction

• Invasive fungal infections
  – 1.5 million deaths worldwide each year
  – 30-40% mortality for invasive candidiasis
  – 20-30% for cryptococcosis
  – 20-30% for aspergillosis

• Mucosal and skin
  – Candida
    • 4th nosocomial infections
    • C. glabrata
Antifungal Drugs

Taken and adapted from: Mechanisms in Medicine
Antifungal Drugs

Azoles

fungistatic
Antifungal Drugs

Azoles

Imidazoles: Clotrimizole, miconazole, ketoconazole
Triazoles: Fluconazole, itraconzole
  Voriconazole, posiconazole, isavuconazole
Antifungal Drugs

Polyenes

fungicidal
Antifungal Drugs

Echinocandins

Caspofungin
Mucofungin
Andulofungin

Fungistatic
Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,1 Carol A. Kauffman,2 David R. Andes,3 Cornelius J. Clancy,4 Kieren A. Marr,5 Luis Ostrosky-Zeichner,6 Annette C. Reboli,7 Mindy G. Schuster,8 Jose A. Vazquez,9 Thomas J. Walsh,10 Theoklis E. Zaoutis,11 and Jack D. Sobel12

1University of Alabama at Birmingham; 2Veterans Affairs Ann Arbor Healthcare System and University of Michigan Medical School, Ann Arbor; 3University of Wisconsin, Madison; 4University of Pittsburgh, Pennsylvania; 5Johns Hopkins University School of Medicine, Baltimore, Maryland; 6University of Texas Health Science Center, Houston; 7Cooper Medical School of Rowan University, Camden, New Jersey; 8University of Pennsylvania, Philadelphia; 9Georgia Regents University, Augusta; 10Weill Cornell Medical Center and Cornell University, New York, New York; 11Children’s Hospital of Pennsylvania, Philadelphia; and 12Harper University Hospital and Wayne State University, Detroit, Michigan

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient’s individual circumstances.

Keywords. candidemia; invasive candidiasis; fungal diagnostics; azoles; echinocandins.
Background

- HIV infection, diabetes, steroid, leukemia, RT and antimicrobial therapy
- Dramatic decline (antiretroviral therapy)
- Fluconazole or multiazole resistance or emergence of non-albicans species
  - Repeated
  - Long-term exposure
- Symptomatic relapse to topical therapy
  - Sooner
  - More frequently
# Candidemia

<table>
<thead>
<tr>
<th></th>
<th>2016</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial</strong></td>
<td>Echinocandin C 70 mg/50 mg M 100 mg A 200 mg/100 mg</td>
<td>Fluconazole 800/400 Echinocandins (neutropenic)</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>Fluconazole 800/400mg</td>
<td></td>
</tr>
<tr>
<td><strong>Transition</strong></td>
<td>Fluconazole (5-7 d)</td>
<td></td>
</tr>
<tr>
<td><strong>C. Glabrata</strong></td>
<td>AmB lipid formulation</td>
<td>Echinocandin</td>
</tr>
<tr>
<td><strong>Azole resistant</strong></td>
<td>Echinocandin resistant</td>
<td></td>
</tr>
<tr>
<td><strong>Transition</strong></td>
<td>Fluconazole 800 mg Voriconazole 2-300 BID</td>
<td></td>
</tr>
</tbody>
</table>
# Oropharyngeal Candidiasis

<table>
<thead>
<tr>
<th></th>
<th>1st Line</th>
<th>Alternative</th>
<th>2009</th>
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<tbody>
<tr>
<td>Mild</td>
<td>Clotrimazole 10mg 7-14d</td>
<td>Nystatin suspension</td>
<td>Clotrimazole</td>
</tr>
<tr>
<td></td>
<td>Miconazole 50 mg QD</td>
<td>Nystatin pastilles</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Fluconazole 100-200 7-14 d</td>
<td></td>
<td>Fluconazole</td>
</tr>
<tr>
<td>Refractory</td>
<td>Itraconazole soln 200mg QD</td>
<td>Voriconazole 200mg BID</td>
<td>Same initial therapy</td>
</tr>
<tr>
<td></td>
<td>Posiconazole sus 400mg BID</td>
<td>AmB oral 100mg/mL QID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3 d then QD up to 28 d)</td>
<td>IV echinocandin or AmB*</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>Fluconazole 100 mg 3x/week</td>
<td></td>
<td>Fluconazole 100 mg 3x/week</td>
</tr>
<tr>
<td>Suppressive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denture</td>
<td>Disinfection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Midatech Direct Rx Form**

**Prescriber**
- Prescriber Name
- Designation
- NPI

<table>
<thead>
<tr>
<th>Prescriber Name</th>
<th>Designation</th>
<th>NPI</th>
</tr>
</thead>
</table>

**Office Address**
- Street
- City
- State
- ZIP
- Office Contact Name
- Phone #

**Patient**
- Last Name
- First Name
- M.I.
- Date of Birth (MM/DD/YYYY)

<table>
<thead>
<tr>
<th>Last Name</th>
<th>First Name</th>
<th>M.I.</th>
<th>Date of Birth (MM/DD/YYYY)</th>
</tr>
</thead>
</table>

**Address**
- City
- State
- ZIP Code

**Home Phone**

**Cell Phone**

**Email Address**

**Deliver to (select one):**
- Patient
- Office

**Insurance**
- Primary Insurance
- Policy Holder
- Policy #
- Group #
- Insurance Co. Phone #

**Check if Medicare or Medicaid**
- Yes
- No

**Check if No Insurance**
- Yes
- No

**Attach Copy of Insurance Card (Front and Back)**

**Co-Pay Assistance:** $0 co-pay will automatically be applied for commercially insured patients.

**Patient Diagnosis**
- Primary Diagnosis (Required)
- ICD-10
- Allergies
- Stage
- Other meds prescribed for same diagnosis

**Oravig® - Dispense:** Oravig bottle (14-day supply). **Dose:** Apply 1 tablet QD.

**Oral thrush/Dyshidryseal Candidiasis Diagnosis:**
- Code
- Description (click all that apply)
  - ICD-10 B37.0
  - Candidal Stomatitis
  - ICD-10 B37.9
  - Candidiasis, unspecified

**Refills (Select One):**
- 01
- 02
- 03
- 04

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*Co-pay assistance not valid for prescription reimbursement in whole or in part under Medicaid, Medicare, including Medicare Advantage and Part D Rx drug plans or any other federal or state programs (including state pharmaceutical assistance programs) or where prohibited, taxed or otherwise restricted.

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## Esophageal

<table>
<thead>
<tr>
<th></th>
<th>2016</th>
<th>2009</th>
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<tbody>
<tr>
<td>Initial</td>
<td>Fluconazole 200-400 mg 14-21 d</td>
<td></td>
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<tr>
<td>Alternative</td>
<td>IV Fluconazole Echinocandin AmB Itraconazole</td>
<td>Also: Posaconazole</td>
</tr>
<tr>
<td>Refractory</td>
<td>Itraconazole Voriconazole Echinocandins</td>
<td></td>
</tr>
<tr>
<td>Suppressive</td>
<td>Fluconazole 100-200 mg 3x/week</td>
<td></td>
</tr>
</tbody>
</table>
Drug Resistance

• Efflux pumps
  – ATP-binding cassette proteins
  – Major facilitator superfamily
• ERG11 overexpression
• Erg3 Mutations
• FKS1 gene mutation
• Biofilms
Drug Resistance

• Efflux pumps
  – Major facilitator superfamily
  – ATP-binding cassette proteins
• ERG11
  – Overexpression
  – Change in drug target
• Erg3 Mutations
• FKS1 gene mutation
• Biofilms
Drug Resistance

- **Efflux pumps**
  - Major facilitator superfamily
  - ATP-binding cassette proteins
- **ERG11**
  - Overexpression
  - Change in drug target
- **Erg3 Mutations**
- **FKS1 gene mutation**
- **Biofilms**

Whaley SG et al. Front Microbiol 2017
Campoy S et al. Biochem Pharm 2016
Drug Resistance

- Efflux pumps
  - ATP-binding cassette proteins
  - Major facilitator superfamily
- ERG11
  - Overexpression
  - Change
- Erg3 Mutations
- FKS1 gene mutation
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Whaley SG et al. Front Microbiol 2017
Drug Resistance

- Efflux pumps
  - ATP-binding cassette proteins
  - Major facilitator superfamily
- ERG11 overexpression
- Erg3 Mutations
- FKS1 gene mutation
- Biofilms

Campoy S, Adrio JL Biochem Pharm 2016
Drug Resistance

• Efflux pumps
  – ATP-binding cassette proteins
  – Major facilitator superfamily
• ERG11 overexpression
• Erg3 Mutations
• FKS1 gene mutation
• Biofilms
  – Hydrolytic enzymes
  – Surfactants
  – Chelating agents
  – Biocides

Baker JL et al. Trends Microbiol 2017
# In the Pipeline

<table>
<thead>
<tr>
<th><strong>Candida Infections</strong></th>
<th><strong>Infections</strong></th>
<th><strong>Stage</strong></th>
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</thead>
<tbody>
<tr>
<td>B-glucan synthesis</td>
<td>SCY-078</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Biafungin</td>
<td>Phase 2</td>
<td>*longer t1/2</td>
</tr>
<tr>
<td>Mitochondrial function</td>
<td>T 2307</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Carbon metabolism</td>
<td>AR-12</td>
<td>Orphan drug</td>
</tr>
<tr>
<td>biofilm synthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azole</td>
<td>Isavuconazole</td>
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</table>
## Esophageal Candidiasis

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Fluconazole tablets</td>
<td>200 – 400 mg</td>
<td>14-21 d</td>
</tr>
<tr>
<td>IV fluconazole</td>
<td>400 mg</td>
<td></td>
</tr>
<tr>
<td>Echinocandin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micofungin</td>
<td></td>
<td></td>
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<tr>
<td>Caspofungin</td>
<td></td>
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<tr>
<td>Anidulafungin</td>
<td></td>
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<tr>
<td>AmB deoxycholate</td>
<td></td>
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<tr>
<td>Itraconazole solution</td>
<td>200 mg daily</td>
<td>14–21</td>
</tr>
<tr>
<td>Voriconazole (IV or oral)</td>
<td>200 mg twice daily</td>
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<tr>
<td>Recurrent Infection: Fluconazole</td>
<td>100-200 mg tablets 3 X week</td>
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Antifungal Drugs
## Coverage

<table>
<thead>
<tr>
<th></th>
<th>C. Albicans</th>
<th>C. glabrata</th>
<th>C. krusei</th>
<th>C. tropicalis</th>
<th>C. parapsilosis</th>
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<tr>
<td>Itraconazole</td>
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<td>+</td>
<td>+</td>
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<tr>
<td>Voriconazole</td>
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<td>-</td>
<td>+</td>
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<tr>
<td>Posiconazole</td>
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<tr>
<td>Ketoconazole</td>
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<tr>
<td>Miconazole</td>
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<tr>
<td>Caspofungin</td>
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<tr>
<td>Micafungin</td>
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<tr>
<td>Anidulafungin</td>
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<tr>
<td>AmB</td>
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<td>++</td>
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<td>Nystatin</td>
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<tr>
<td>Status</td>
<td>Taken By</td>
<td>Msg Date</td>
<td>Msg Time</td>
<td>Patient</td>
<td></td>
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<tr>
<td>New</td>
<td>Nathaniel Simon Tr...</td>
<td>03/20/2017</td>
<td>2:50 PM</td>
<td>Padwa, Thomas [16448587]</td>
<td></td>
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<tr>
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<td></td>
<td>Phone: 401-247-3004 Pool: NO</td>
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</tbody>
</table>

Sullivan, Cynthia E
- Female, 55 y.o., 07/05/1951
- MRN: 11549300
- Phone: 774-888-8820
- PCP: Rania Hussein, MD
- Allergies: AMOXICILLIN OXYCO...
- Last Weight: 43.4 kg (95 lb 10.9 oz)
- Language: English
- Need Interp: No
- Patient Gateway: Active
Mannoproteins

- β-1,3-glucans
- Glucose monomers
- β-1,6-glucans
- Chitin
  - Phospholipid bilayer of cell membrane
- Ergosterol
  - Ergosterol
  - 14-α demethylase

β-1,3-glucans synthesis: echinocandins

Inhibition of chitin synthase: nikkomycin and polyoxyxins

Bind to ergosterol: polyenes, naphthoquinones, eugenol analogues, isoquercetin.

Inhibition of 14-α demethylase: azoles

Inhibition of protein synthesis: sordarins

Microtubules assembly: griseofulvin

Inhibition of Calcineurin signaling: triphenylethylenes

This complex activates genes related to growth, cell wall integrity, stress responses, drug resistance, among others (Juvvadi et al, 2016).
Comparison of documented fluconazole resistance mechanisms in Candida species. (A) Erg3 inactivation results in utilization of alternative sterols in the yeast membrane. (B) Uptake of exogenous sterols helps circumvent endogenous sterol production inhibition by fluconazole. Increased production of both (C) ATP-binding cassette efflux pumps and (D) major facilitator superfamily transporters reduces intracellular accumulation of azoles. (E) Inherently low affinity of fluconazole binding to species-specific Erg11 may decrease fluconazole's potential to inhibit the protein. (F) Increased expression of Erg11 protein can help overcomeazole activity and (G) aneuploidy may promote genetic adaptation to azole exposure. (H) Mutations in ERG11 can also result in proteins with reduced affinity for fluconazole binding.
**Mannoproteins**
- β-1,3-glucans
- Glucose monomers
- β-1,6-glucans
- Chitin
- Phospholipid bilayer of cell membrane
- Ergosterol

**Inhibition of β-glucans synthesis: echinocandins**

**Inhibition of chitin synthase: nikkomycin and polyoxins**

**Bind to ergosterol: polyenes, naphthoquinones, eugenol analogues, isoquercitrin.**

**Inhibition of 14-α demethylase: azoles**

**Inhibition of DNA synthesis: 5-flucytosine**

**Inhibition of Hsp90**

**Production of ROS, RNS, leading to cell death: amphotericin B, miconazole, ciclopirox**

**Inhibition of protein synthesis: sordarins**

**Microtubules assembly: griseofulvin**

**Membrane**
- Activated calmodulin
- Calmodulin/calcineurin binding
- This complex activates genes related to growth