Newer Guidelines for the Treatment of Invasive Candidiasis in Non-neutropenic Patients

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Disclosures

• No conflicts of interest
Introduction

• There are at least 15 distinct Candida species that cause human disease
• >90% of invasive disease is caused by the 5 most common pathogens
  – C. albicans
  – C. non-albicans
  • C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei
• Each of these organisms has unique virulence potential, antifungal susceptibility, and epidemiology
Invasive Candidiasis

Risk factors

- Central venous catheters
- Parenteral nutrition
- Broad-spectrum antibiotics
- High APACHE scores
- Glucocorticoids
- Renal failure, particularly if requires hemodialysis
- Acute/chronic liver failure
- Recent major surgery, particularly abdominal
- Gastrointestinal tract perforations and anastomotic leaks
- Necrotizing pancreatitis
- Trauma-burns
- Candida colonization
Invasive Candidiasis
Clinical manifestations

- candidemia
- disseminated hepatosplenitis
- endophthalmitis
- esophagitis
Invasive Candidiasis

Clinical manifestations

- brain abscess
- renal fungus ball
- endocarditis
- osteomyelitis
Why should we care about candidemia?

Increasing incidence of candidemia worldwide

Early diagnosis of candidemia is challenging

- It is a late cause of sepsis with no specific signs and symptoms
- Culture-based methods are insensitive (<50%) and time consuming
- Increasing rates of non-albicans candidemia
- High Mortality

Bitar D, Lortholary O et al, Emerging Infectious Diseases Vol. 20, No. 7, July 2014

Mortality according to Candida species

% Crude mortality

Day 7, Day 14, Day 30
Mortality in Candidemia

Garey G, Clinical Infectious Diseases 2006; 43:25–31
Outline

• Patient work-up after candidemia diagnosis
• First line recommendation for antifungal therapy
• Time of treatment and step-down therapy to azoles
• The issue of C. parapsilosis and candins
• Relevance of source control
Patient work-up on diagnosis I

• Baseline
  – Identification of Candida at species level + susceptibility testing
  – Ocular examination is mandatory: at least one
  – Abdominal CT or US for surgical patients/pancreatitis with candidemia and suspicion of abdominal collections and abscess

Cornely AO et al Clin Microbiol Infect. 18 Suppl 7:19-37, 2012
Patient work-up on diagnosis II

• Plan to repeat blood cultures up to first negative
  – No need to collect daily 20 ml of blood from critically ill patients
    • It takes at least 2-3 days to clear blood cultures for most patients
  – We target day-3 and day-5 after starting ATF therapy
    • If blood cultures are still positive at day 5:
      ✓ Check all intravenous catheters, repeat ocular examination, images and plan new cultures

Cornely AO et al Clin Microbiol Infect. 18 Suppl 7:19-37, 2012
Patient work-up on diagnosis III

• Transesophageal Echocardiography
  – Only for HIGH RISK patients
    • Patients with persistent candidemia at day 5
    • Previous valvular heart diseases/prosthetic valves or clinical suspicion of endocarditis

Cornely AO et al, Clin Microbiol Infect. 18 Suppl 7:19-37, 2012
Antifungal Agents

Pharmacologic Considerations for Therapy for Candidiasis

Systemic antifungal agents effective for the treatment of invasive candidiasis

• **Polyenes** (amphotericin B [AmB] deoxycholate, liposomal AmB, AmB lipid complex [ABLC], and amphotericin B colloidal dispersion [ABCD])

• **Triazoles** (fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole)

• **Echinocandins** (caspofungin, anidulafungin, and micafungin)

• **Flucytosine**
First line recommendation for antifungal therapy

ECHINOCANDINS

- Broad spectrum and fungicidal activity
- Activity against biofilm
- Limited or no drug-drug interactions
- Better clinical performance than Fluconazole and Isavuconazole in clinical trials
- Safer than AMB formulations

EXCEPTION!!!
- CNS
- EYE
- URINARY TRACT

and Isavuconazole in clinical trials
First line recommendation for antifungal therapy

Candidemia

- An echinocandin is recommended as initial therapy (strong recommendation; high-quality evidence)
  - Caspofungin: loading dose 70 mg, then 50 mg daily
  - Micafungin: 100 mg daily
  - Anidulafungin: loading dose 200 mg, then 100 mg daily

Pappas G et al, Clin Infect Dis. 2015 Dec 16
First line recommendation for antifungal therapy

Candidemia

• Fluconazole, intravenous or oral, 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) (strong recommendation; high-quality evidence)
  – In patients who are not critically ill and are considered unlikely to have a fluconazole-resistant Candida species

Pappas G et al, Clin Infect Dis. 2015 Dec 16
First line recommendation for antifungal therapy

Candidemia

• Lipid formulation amphotericin B (AmB) (3–5 mg/kg daily)
  (strong recommendation; high-quality evidence)
  – Among patients with suspected azole- and echinocandin resistant Candida infections
  – Reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents

Pappas G et al, Clin Infect Dis. 2015 Dec 16
First line recommendation for antifungal therapy

Candidemia

• Voriconazole 400 mg (6 mg/kg) twice daily for 2 doses, then 200 mg (3 mg/kg) twice daily is effective, but (strong recommendation; moderate-quality evidence)
  – offers little advantage over fluconazole as initial therapy
  – is recommended as step-down oral therapy for selected cases of candidemia due to C. krusei

Pappas G et al, Clin Infect Dis. 2015 Dec 16
First line recommendation for antifungal therapy

Candidemia

• Duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of Candida from the bloodstream and resolution of symptoms attributable to candidemia (strong recommendation; low quality evidence)

Pappas G et al, Clin Infect Dis. 2015 Dec 16
Time to step-down therapy to azoles
(Triazoles may be used to complete the total time of 14 days of treatment after first negative culture)

- As soon as you document that IV therapy with candins presented:
  - Clinical and microbiological success
  - No evidence of endocarditis
  - Candida was identified and susceptibility to azoles was confirmed
  - It usually takes 5-7 days of IV therapy with candins

Similar global success rate for patients with early switch to Fluco (N=102 vs 250)

<table>
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<th>Table 3 Responses at EOT and secondary timepoints in the MITT population and early switch subpopulation</th>
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<td>Missing/unknown</td>
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(Strong recommendation; moderate-quality evidence)


Vazquez et al. BMC Infectious Diseases 14:97, 2014
Source Control-Catheter management

Candidemia

- Central venous catheters should be removed as early as possible when the source is presumed to be the CVC and the catheter can be removed safely – especially if *C. parapsilosis* is identified (strong recommendation; moderate-quality evidence) – this decision should be individualized for each patient

*Pappas G et al, Clin Infect Dis. 2015 Dec 16*
First line recommendation for antifungal therapy
Chronic Disseminated (Hepatosplenic)/Intra-abdominal Candidiasis

- **Treatment** (strong recommendation; low-quality evidence)
  - Initial therapy for several weeks
    - Lipid formulation AmB
    - Echinocandin
  - Step-down to oral fluconazole if unlikely to have a fluconazole resistant isolate

- Therapy until lesions resolve on repeat imaging, which is usually after several months
- Treatment of intra-abdominal candidiasis should include source control, with appropriate drainage and/or debridement

*Pappas G et al, Clin Infect Dis. 2015 Dec 16*
First line recommendation for antifungal therapy
Endocarditis and Infections of Implantable Cardiac Devices

• Initial treatment (strong recommendation; low-quality evidence)
  – Lipid formulation AmB ± Flucytosine
  – High-dose Echinocandin

• Step-down therapy
  – Fluconazole
  – Voriconazole
  – Posaconazole

• Valve replacement is recommended and implantable cardiac device should be removed

• Treatment for at least 6 weeks after surgery and longer in perivalvular abscesses and other complications

• For patients who cannot undergo valve replacement, chronic suppression with fluconazole

Pappas G et al, Clin Infect Dis. 2015 Dec 16
First line recommendation for antifungal therapy

Osteoarticular Infections

• Treatment for 6–12 months
  (strong recommendation; low-quality evidence)
    – Fluconazole
    – Echinocandin for at least 2 weeks followed by fluconazole

• Surgical debridement is recommended in selected cases

Pappas G et al, Clin Infect Dis. 2015 Dec 16
First line recommendation for antifungal therapy

**Septic Arthritis**

- Treatment for 6 weeks
  (strong recommendation; low-quality evidence)
  - Fluconazole
  - Echinocandin for at least 2 weeks followed by fluconazole
- Surgical debridement is recommended in all cases
- Prosthetic devices should be removed
- If the prosthetic device cannot be removed, chronic suppression with fluconazole

*Pappas G et al, Clin Infect Dis. 2015 Dec 16*
First line recommendation for antifungal therapy

**Endophthalmitis**

- The extent of ocular infection (chorioretinitis with or without macular involvement and with or without vitritis) should be determined (strong recommendation; low-quality evidence)

- Treatment for 6 weeks
  - Fluconazole
  - Voriconazole
  - Lipid formulation AmB ± Flucytosine

- If macular involvement ➔ intravitreal injection of AmB deoxycholate or voriconazole

- If vitritis ➔ vitrectomy should be considered

*Pappas G et al, Clin Infect Dis. 2015 Dec 16*
First line recommendation for antifungal therapy
Central Nervous System Candidiasis

• **Initial treatment** (strong recommendation; low-quality evidence)
  – Lipid formulation AmB ± Flucytosine

• **Step-down treatment**
  – Fluconazole
  – Voriconazole for C. glabrata, C. Krusei

• Therapy should continue until all signs and symptoms and CSF and radiological abnormalities have resolved

• Infected CNS devices should be removed

_Pappas G et al, Clin Infect Dis. 2015 Dec 16_
First line recommendation for antifungal therapy

Urinary Tract Infections

Asymptomatic Candiduria

• Elimination of predisposing factors, such as indwelling bladder catheters
• Treatment with antifungal agents is NOT recommended unless (strong recommendation; low-quality evidence)
  – neutropenic patients
    • treat as candidemia
  – low-birth-weight infants (<1500 g)
    • treat as candidemia
  – patients who will undergo urologic manipulation
    • oral fluconazole OR AmB deoxycholate for several days before and after the procedure

Pappas G et al, Clin Infect Dis. 2015 Dec 16
First line recommendation for antifungal therapy

Urinary Tract Infections

Candida Cystitis

(strong recommendation; moderate-quality evidence)

• For fluconazole-susceptible organisms, oral fluconazole for 2 weeks
• For fluconazole-resistant C. glabrata or C. krusei, AmB deoxycholate for 1–7 days OR oral flucytosine for 7–10 days
• Removal of indwelling bladder catheter if feasible

Pappas G et al, Clin Infect Dis. 2015 Dec 16
First line recommendation for antifungal therapy

Urinary Tract Infections

Candida Pyelonephritis
(strong recommendation; moderate-quality evidence)

• For fluconazole-susceptible organisms, oral fluconazole for 2 weeks
• For fluconazole-resistant C. glabrata or C. krusei, AmB deoxycholate for 1–7 days with or without oral flucytosine
• Elimination of urinary tract obstruction is strongly recommended
• Nephrostomy tubes or stents in place should be removed or replaced

Pappas G et al, Clin Infect Dis. 2015 Dec 16
First line recommendation for antifungal therapy

Esophageal Candidiasis

• A diagnostic trial of antifungal therapy is appropriate before performing an endoscopic examination (strong recommendation; high-quality evidence)

• Initial treatment for 14-21 days
  – Oral or IV Fluconazole

• Fluconazole-refractory disease
  – Echinocandin
  – Oral or IV Voriconazole
  – Susp or tab Posaconazole
  – Sol Itraconazole
  – IV AmB

Pappas G et al, Clin Infect Dis. 2015 Dec 16
Does the Isolation of Candida Species From the Respiratory Tract Require Antifungal Therapy?

- Growth of Candida from respiratory secretions usually indicates colonization and rarely requires antifungal treatment

(strong recommendation; moderate-quality evidence)

Pappas G et al, Clin Infect Dis. 2015 Dec 16
The issue of candins versus C. parapsilosis
The issue of candins versus C. parapsilosis

- Candins present high MICs against C. parapsilosis but still within the therapeutic level
  

- General clinical response is not statistically inferior when compared to other antifungal drugs


- No difference in terms of clinical efficacy and mortality has been documented in meta-analysis

  Andes D Clin Infect Dis, 2012

- Good clinical response has been documented in recent series

The issue of candins versus C. parapsilosis

- Although echinocandins are usually effective for the treatment of C. parapsilosis fungemia, close monitoring for persistent fungemia is appropriate.

_Pappas G et al, Clin Infect Dis. 2015 Dec 16_
Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America


Clin Infect Dis. 2015 Dec 16
Question 1

Duration of therapy for candidemia is
1. 10 days
2. 2 weeks
3. 2 weeks after documented clearance of Candida from the bloodstream
4. 4-6 weeks
Question 2

Which sentence is WRONG about echinocandins?

1. Broad spectrum and fungicidal
2. Limited or no drug-drug interactions
3. Safer than AMB formulations
4. Good penetration in CNS and urinary tract
Question 3

The risk of mortality among patients with Candidemia is

1. 1%
2. <10%
3. 10-50%
4. >90%
Thank you