Management of candidemia

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Case A

- 31 yr old IVDA
- Status post HCV, Child B liver cirrhosis, type 1 diabetes, glomerulonephritis (?HCV), renal failure, hemodialysis (cath)
- New fever → admission, empirical flucloxacillin
Case A

- IVDA
- Status post HCV, Child B liver cirrhosis, type 1 diabetes, glomerulonephritis (?HCV), renal failure, hemodialysis
- New fever $\rightarrow$ empirical flucloxa
  - d2: BCs (p+c) from d0 positive for S. aureus
  - defervescence
  - control BCs
Case A

- IVDA
- Status post HCV, Child B liver cirrhosis, type 1 diabetes, glomerulonephritis (?HCV), renal failure, hemodialysis
- S. aureus BSI, flucloxa therapy
Case A

- IVDA
- Status post HCV, Child B liver cirrhosis, type 1 diabetes, glomerulonephritis (?HCV), renal failure, hemodialysis
- *S. aureus* BSI, flucloxa therapy
  - d4: BCs (p+c) from d2 positive for *S. aureus* + *Lactobacillus rhamnosus*
Case A

- IVDA
- Status post HCV, Child B liver cirrhosis, type 1 diabetes, glomerulonephritis (?HCV), renal failure, hemodialysis
- *S. aureus* BSI, flucloxa therapy
  - d4: BCs (p+c) from d2 positive for *S. aureus* + *Lactobacillus rhamnosus*
  - d6: BCs (p+c) from d4 positive for *S. aureus* + *Lactobacillus rhamnosus* + *Candida dubliniensis*
## Case A

<table>
<thead>
<tr>
<th>Date</th>
<th>Temp</th>
<th>WBC</th>
<th>CRP</th>
<th>Abx</th>
<th>Microbiology</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Day 0</td>
<td>38.2</td>
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<td>104</td>
<td>Flucloxa</td>
<td>BC p+c S.aureus</td>
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<tr>
<td>Day 1</td>
<td>X</td>
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<tr>
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<td>iv cath tip: C.dubliniensis,</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C.glabrata, L.rhamnosus</td>
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<td>Fluco iv cath removed</td>
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<tr>
<td>Day 7</td>
<td>4.2</td>
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<td>X</td>
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<td>iv cath removed</td>
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<td>X</td>
<td></td>
<td>BC L.rhamnosus</td>
<td>Chorioretinitis</td>
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<tr>
<td>Day 9</td>
<td>X</td>
<td></td>
<td></td>
<td>Fluco +</td>
<td>BC L.rhamnosus</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Anidula</td>
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<td>Day 10</td>
<td>6.6</td>
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<td>Flucloxa + Moxifloxa</td>
<td>BC neg</td>
<td>Heart US: no vegs</td>
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<td>Day 12</td>
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<td>Fluco</td>
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<td>LFT ↑</td>
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<tr>
<td>Day 15</td>
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<td>Chorioretinitis improved</td>
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<tr>
<td>Day 16</td>
<td>X</td>
<td></td>
<td></td>
<td>Clinda po</td>
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<td>Day 21</td>
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</table>
Case A Summary

- IVDA
- Status post HCV, Child B liver cirrhosis, type 1 diabetes, glomerulonephritis (?HCV), renal failure, hemodialysis
- Polymicrobial BSI, injection-/iv catheter-related (S.aureus + L.rhamnosus + C.dubliniensis
  - no severe sepsis
  - with chorioretinitis (probably Candida-related, no surgery needed)
  - without evidence for endocarditis or other deep-seated foci
• Most common form of invasive *Candida* infection
• Defined by ≥1 positive blood culture
• ~50% are among intensive care patients
• Often iv catheter-related
• High case-fatality if not treated promptly
• 13 ICUs in Canada
• 1,097 cases with bacteremia and 93 with candidemia
• Initial = within one (calendar) day
Table 2. Multivariable model results, stratified by bacteremia versus candidemia, for the effect of inadequate initial empiric treatment on patient mortality.

<table>
<thead>
<tr>
<th>Model</th>
<th>Stratum</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>Bacteremia</td>
<td>1.16 (0.83–1.61)</td>
<td>0.379</td>
</tr>
<tr>
<td>N = 1,190</td>
<td>Candidemia</td>
<td>3.69 (1.46–9.31)</td>
<td>0.006</td>
</tr>
<tr>
<td>Adjusteda</td>
<td>Bacteremia</td>
<td>1.02 (0.70–1.48)</td>
<td>0.934</td>
</tr>
<tr>
<td>N = 1,161</td>
<td>Candidemia</td>
<td>2.89 (1.05–7.99)</td>
<td>0.040</td>
</tr>
</tbody>
</table>

OR–odds ratio. CI–confidence interval.

*aAdjusted for admission category, vasopressor use, acquisition (community, hospital, ICU), unknown infection source, peripheral vascular disease, cirrhosis, highly resistant organism, sex and age. Age was included in the model as a continuous variable.
Candidemia epidemiology
(Australia, population-based surveillance 2001-2004)

- <1/1000 admissions
- 1-2 per 100,000 population and year
- <10% community-acquired
Candidemia epidemiology
(Barcelona, population-based surveillance 2001-2004)

- <1/1000 admissions
- ~4 per 100,000 population and year
- >50% iv catheter-related
Candidemia epidemiology
(Spain, multicenter study)

- ~1/1000 admissions
- Case fatality 20%
- *C. albicans* 50%, *C. parapsilosis* 20%
- FlucoR or Flucol <10%
Candidemia in intensive care (EPIC II)

- 7/1000 cases
- Clinical severity similar to other bloodstream infections
- ICU mortality 43%
Candidemia in intensive care (Italy)

- 18 ICUs
- Incidence 16.5/1000
- Species
  - 40% C. albicans
  - 37% C. parapsilosis
  - 16% C. glabrata

- 38 ICUs
- Incidence 10.1/1000
- Species
  - 60% C. albicans
  - 13% C. parapsilosis
  - 13% C. glabrata

Montagna et al *Infection* 2013
Tortorano et al *Mycoses* 2012
Species distribution

- 72 ICUs
- 14 European countries
- 2006-2008
- Species
  - 54% C. albicans
  - 19% C. parapsilosis
  - 14% C. glabrata
Species distribution

- 72 ICUs
- 14 European countries
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- Species
  - 54% C. albicans
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- 13 EORTC cancer centers in 7 countries
- Incidence (fungemia) ~2/1000
- Species (candidemia)
  1. C. albicans (48%)
  2. C. tropicalis
  3. C. glabrata & parapsilosis
The graph shows the percent survival over time to death (in weeks) for different Candida species. The species and their respective sample sizes are as follows:

- **C. albicans** (N=120)
- **C. glabrata** (N=29)
- **C. tropicalis** (N=39)
- **C. parapsilosis** (N=28)
- **C. krusei** (N=25)
Candidemia management

- Empiric therapy
- iv catheter (device) management
- Targeted therapy aspects
  - Species/susceptibility
  - Contraindications, drug-drug interaction, dosing
  - Special situations: eye involvement, endocarditis, CNS involvement, neonates, chronic hepatosplenic (disseminated) candidiasis
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 Kieron 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

Clinical Infectious Diseases 2016;62(4):e1–50
I. What Is the Treatment for Candidemia in Nonneutropenic Patients?

Recommendations

1. An echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily) is recommended as initial therapy (strong recommendation; high-quality evidence).

2. Fluconazole, intravenous or oral, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant Candida species (strong recommendation; high-quality evidence).
• Fluconazole-resistant
  \[\rightarrow C. \textit{krusei}\]
  \[\rightarrow C. \textit{glabrata}\]

• Echinocandin-“resistant” (less susceptible)
  \[\rightarrow C. \textit{parapsilosis}\]
C. albicans

C. krusei

C. glabrata
C. albicans

C. krusei

C. glabrata

Flucytosine

MIC Distribution - Reference Database 2016-06-28

Flucytosine 1x400 mg

C max by

C. albicans

by

ESCMID Online Lecture Library

© by author
**C. albicans**

Fluconazole / Candida albicans EUCAST

*MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance*

- **Fluconazole 1x400 mg**
  - $C_{\text{max}}$ ~ 20-30 mg/L
  - $C_{\text{min}}$ ~ 15-20 mg/L

**C. glabrata**

ESCMID Online Lecture Library © by author
C. albicans

C. parapsilosis
### Table 3. Microbiologic and Global Responses at the End of Intravenous Therapy in the Modified Intention-to-Treat Population.*

<table>
<thead>
<tr>
<th>Candida Pathogen</th>
<th>Successful Microbiologic Response</th>
<th>Successful Global Response†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anidulafungin Group</td>
<td>Fluconazole Group</td>
</tr>
<tr>
<td></td>
<td>no. of isolates/total no. (%)</td>
<td>no. of patients/total no. (%)</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>77/81 (95)</td>
<td>57/70 (81)</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>15/20 (75)</td>
<td>18/30 (60)</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>9/13 (69)</td>
<td>14/16 (88)</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>13/15 (87)</td>
<td>7/11 (64)</td>
</tr>
<tr>
<td>Other candida species</td>
<td>5/6 (83)</td>
<td>3/3 (100)</td>
</tr>
<tr>
<td>All candida species</td>
<td>119/135 (88)</td>
<td>99/130 (76)</td>
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* Patients may have had more than one pathogen at baseline, but the majority had a single pathogen (94% in the anidulafungin group and 90% in the fluconazole group). Of 227 patients with candidemia, 138 had multiple positive blood cultures at baseline. However, because the protocol did not require blood to be drawn for culture on the first day of administration of the study drug, the number of patients with multiple positive blood cultures is likely to be underestimated.

† Patients included in this analysis had a single pathogen at baseline.
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† Patients included in this analysis had a single pathogen at baseline.
Review of this and other trials ...

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<th>Factor</th>
<th>Mortality</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
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<td>All organisms (n = 978)</td>
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<tr>
<td>Age</td>
<td>.02</td>
<td>1.01</td>
<td>1.00–1.02</td>
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<td>APACHE II score</td>
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<td>1.11</td>
<td>1.08–1.14</td>
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<td>Immunosuppressive therapy</td>
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<td>1.69</td>
<td>1.18–2.44</td>
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<tr>
<td>Candida tropicalis</td>
<td>.01</td>
<td>1.64</td>
<td>1.11–2.39</td>
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<td>Echinocandin</td>
<td>.02</td>
<td>0.65</td>
<td>.45–.94</td>
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<tr>
<td>CVC removed</td>
<td>.0001</td>
<td>0.50</td>
<td>.35–.72</td>
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Andes et al CID 2009
Yes, but ....

- Initial empiric therapy of *C. glabrata* BSI (n=94) with fluconazole not associated with more failures,

- and initial therapy of *C. parapsilosis* BSI (n=194) with echinocandin not associated with more failures.

- No significant difference between empiric fluconazole versus echinocandins even in pts with severe sepsis/septic shock.
Candidemia management

- Empiric therapy
- iv catheter (device) management
- Targeted therapy aspects
II. Should Central Venous Catheters Be Removed in Nonneutropenic Patients With Candidemia?

Recommendation

13. Central venous catheters (CVCs) should be removed as early as possible in the course of candidemia when the source is presumed to be the CVC and the catheter can be removed safely; this decision should be individualized for each patient (strong recommendation; moderate-quality evidence).
II. Should Central Venous Catheters Be Removed in Nonneutropenic Patients With Candidemia?

Best available evidence


OR 0.50; 95%CI 0.35-0.72; p=0.0001
Candidemia management

- Empiric therapy
- Iv catheter (device) management
- Targeted therapy aspects
  - Species/susceptibility
  - Contraindications, drug-drug interaction, dosing
  - Special situations: eye involvement, endocarditis, CNS involvement, neonates, chronic hepatosplenic (disseminated) candidiasis
Candidemia + eye involvement

- Fundusccopy recommended (but often not done)
- Prevalence 3 to >10%, different forms
- Difficult to predict clinically, initially usually asymptomatic
Candidemia + eye involvement

- Chorioretinitis
  → **azole therapy** (rather than echinocandin or AmB)

- dto + vitritis/endophthalmitis:
  → **azole therapy**
  + voriconazole or AmB intravitreal
  ± vitrectomy
Candidemia + eye involvement

Outcomes of ocular manifestations by fundoscopy results.

60 patients with ocular Candida manifestations

probable endophthalmitis (6)
- 5 diagnosed at baseline
  - 3 evaluable
    - 3 resolved
    - 2 not evaluable
    - 2 died
  - 1 developed during treatment
    - 1 evaluable
      - 1 failed
- 1 developed during treatment
  - 1 evaluable
    - 1 failed

probable chorioretinitis (24)
- 28 diagnosed at baseline
  - 22 evaluable
    - 21 resolved
    - 1 relapse
    - 6 not evaluable
    - 2 died
    - 1 no consent
    - 3 no follow-up
  - 6 developed during treatment
    - 3 evaluable
      - 3 resolved
    - 3 not evaluable
      - 3 no follow-up

possible chorioretinitis (20)
- 16 diagnosed at baseline
  - 8 evaluable
    - 6 resolved
    - 2 stable
  - 8 not evaluable
    - 4 died
    - 4 no follow-up
- 4 developed during treatment
  - 4 evaluable
    - 3 resolved
    - 1 stable
Candida and other sources/foci

- 2019 patients with candidemia (database analysis 2004-2008)
- Other sites involved (cases)
  - Abdomen 95 (?)
  - Lungs 17 (?)
  - Skin and soft tissue 14
  - Eyes 9
  - Heart 7
  - …
  - Central nervous system 2
Case B

- 38 yr old female
- Acute myeloid leukemia (Jan 2016), during febrile neutropenia (Feb 2016) BC positive for C. dubliniensis → iv cath change + caspofungin 14 days
- Poor prognosis AML, planned early alloHSCT → 22. March 2016
- Put on L-AmB Px
- Fever 29. March 2016
Case B

- Fever 29. March 2016, better on Abx, BCs sterile
- Relapsing fever 10. April 2016, abdominal pain, biochemical signs of cholestatic hepatitis, BCs sterile
- Neutrophil recovery 13. April 2016, still fever, chills, general condition not improved
Case B
Case B

- Neutrophil recovery 13. April 2016, still fever, chills, general condition not improved

?
Case B

- Neutrophil recovery 13. April 2016, still fever, chills, general condition not improved

- Liver biopsy 16. April:
  - abscess type lesions, no microorganisms
  - cultures negative
  - PCR: *C. dubliniensis*
Case B

- (chronic) hepatic (hepatosplenic) candidiasis
- relatively typical (↑ symptomatic around the time of neutrophil recovery)
- therapy changed to posaconazole (+CsA)
Case B

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  - !!! CsA may be synergistic with azoles against *C. dubliniensis* (and others)
Case B

• (chronic) hepatic (hepatosplenic) candidiasis
• relatively typical (↑ symptomatic around the time of neutrophil recovery)
• therapy changed to posaconazole (+CsA)
  ▪ !!! CsA may be synergistic with azoles against *C. dubliniensis* (and others)
• lesions persistent on abdominal US early June
Candida and other sources/foci

- 2019 patients with candidemia (database analysis 2004-2008)
- Other sites involved (cases)

- Abdomen 95 (?)
- Lungs 17 (?)
- Skin and soft tissue 14
- Eyes 9
- Heart 7
- ... 
- Central nervous system 2
Candida endocarditis

- 263 cases of candidemia (adults)
- Plan: echocardiography in all except 76 (died, critically or terminally ill, refusal) → 187 evaluable
- 11 cases of endocarditis (4.2% of the whole candidemic population and 5.9% of the population with echocardiographic study)
- 3 of them clinically unsuspected
X. What Is the Treatment for *Candida* Intravascular Infections, Including Endocarditis and Infections of Implantable Cardiac Devices?

**What Is the Treatment for Candida Endocarditis?**

**Recommendations**

59. For native valve endocarditis, lipid formulation AmB, 3–5 mg/kg daily, with or without flucytosine, 25 mg/kg 4 times daily, OR high-dose echinocandin (caspofungin 150 mg daily, micafungin 150 mg daily, or anidulafungin 200 mg daily) is recommended for initial therapy (*strong recommendation; low-quality evidence*).
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What Is the Treatment for *Candida* Endocarditis?

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Candida endocarditis

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<tr>
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<td>24 (34)</td>
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<tr>
<td>Intracardiac abscess</td>
<td>17 (24)</td>
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<td>Persistently positive cultures</td>
<td>12 (17)</td>
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<td>Stroke</td>
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<td>59 (84)</td>
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Summary

- Initial and targeted drug therapy well described, but:
  - note drug-drug interactions and
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  - PK-PD aspects not very well understood
- Catheter/device removal important
- Check (actively) for eye and heart involvement
- Individualized approaches for organ involvement needed, no first-class evidence available, clinical trials very limited
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- 44 yr old male
- previous (?) IVDA, chronic HCV infection, current C$_2$H$_5$OH abuser, status post head&neck cancer (now in remission)
- complex recent medical history:
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Case C

- early Feb 2016 new (recurrent) fever
- admission
  - BCs sterile
  - residual brain abscess punctured: sterile (PCR: S. agalactiae)
  - (minor) sternal wound healing problems
  - empiric vancomycin, rapid defervescence, stopped after 10 days, discharged
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- 2nd emergency valve replacement surgery
- Excised valve culture: *C. parapsilosis* → ???