Systemic Candidiasis for the clinicians: between guidelines and daily clinical practice

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Conflicts of interest

✓ Advisory boards
  GILEAD, PFIZER, MSD

✓ Honorarium for lectures
  GILEAD, ViiV, BMS, MSD, ASTELLAS

✓ Funding during the last 5 years
  GILEAD
  NIH/INSIGHT

✓ Support for participation in congresses
  GILEAD, BMS, ASTELLAS, PFIZER
Invasive/Systemic Candidiasis
Definition

a. Candidemia: at least one blood culture positive for Candida sp

Proved systemic candidiasis if with symptoms
Probable systemic candidiasis if without symptoms

b. Focal systemic candidiasis: isolated organ or system disease with or without candidemia

S. Ascioglu, et al. CID 2002; 34:7–14
Candidemia is the most “obvious” presentation invasive candidiasis (corresponding to 10-20% of cases of invasive disease)

www.doctorfungus.org
Invasive/Systemic Candidiasis

Pathogen: *Candida spp*

- > 200 Candida species
- only 10% of them pathogenic to humans

96%

- *C. albicans*
- *C. glabrata*
- *C. tropicalis*
- *C. parapsilosis*
- *C. krusei*

- *C. kefyr*
- *C. lusitaniae*
- *C. dubliniensis*
- *C. guilliermondii*
- *C. lipolytica*

- *C. rugosa*
- *C. pelliculosa*
- *C. inconspicua*
- *C. norvengensis*
- *C. zeylanoides*
- *C. lambica*
Candidemia

- 3rd most common cause of bacteremia in the ICU and 4th in the hospital
- 2-16% of patients admitted to the ICU
- 77% surgical ICU patients
- the majority in the presence of a CVC

Leon c et al, ICM 2014
Tortorano, Mycoses 2012
Fagan R, iche 2013
Schelenz S. J Antimicrob Chemother. 2008 Jan;61
Consistently high crude mortality rates 30-60% (10-20% attributed)
[despite a reduction in CLABSI and in some centres a reduction in mortality after the introduction of echinocandins in clinical practice – but not <30%]

50% of systemic candidiasis is without positive blood cultures. Early and precise diagnosis remains a challenge

15-40% premortal diagnosis

Leon c et al, ICM 2014
Tortorano, Mycoses 2012
Fagan R, Iche 2013

Schelenz S. J Antimicrob Chemother. 2008 Jan;61

- 24 tertiary hospitals in Paris
- 1,206 ICU candidemias (48.5%)

- Mortality 40->50%
- 50% use of echinocandins
- Previous echinocandin use related to C. parapsilosis isolation
- Mortality related to delayed treatment, age, Candida species, CVC and previous use of an echinocandin
Emerging resistance of C. glabrata to echinocandins

- Resistance of C. glabrata to fluconazole is well known (2-20%)
- In epidemiological studies of the last 5 years an emerging resistance of C. glabrata to echinocandins is noted (from zero before 2004 to 3.5-8% after 2008)
- Related to FKS1,2 gene mutations
- Cross resistance to all echinocandins
- 36% of resistant C. glabrata to echinocandins also resistant to fluconazole.
- Related to increased echinocandin exposure
Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America


ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients

Guidelines do not intent to replace clinical judgment..

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.

_IDSA GUIDELINES, CID, December 2015_
The echinocandins are the first line empiric treatment recommended by the new IDSA guidelines except for UTI, CNS and eye infections.

Caspofungin and micafungin are approved by the US Food and Drug Administration (FDA) for use in children.

No use in pregnancy due to lack of data.

No TDM needed.

They are all used in neutropenic patients.

All echinocandins have a strong safety profile with minimal side effects.

They exert fungicidal activity.

_Pappas et al, Clin Infect Dis 2015_
Echinocandins: Advantageous in our daily clinical practice

- A survival advantage associated with the use of an echinocandin as initial treatment in patients with invasive candidiasis was suggested in pooled analysis of RCTs of treatment of invasive candidiasis in nonneutropenic patients (Andes CID 2012)

- Echinocandins achieve therapeutic concentrations in all sites except the eye, CNS and urine

- None of the echinocandins require dose adjustment for renal insufficiency or dialysis

- A dose reduction in patients with moderate to severe hepatic dysfunction is recommended only for caspofungin

_Pappas et al, Clin Infect Dis 2015_
Recent case series have been presented with emerging C. glabrata resistance to echinocandins leading to clinical failure. Susceptibility testing of C. glabrata and C. parapsilosis (higher MICs) is always recommended.

The echinocandins have all similar pharmacologic properties. The new guidelines still comment on inter changable use between echinocandins.

Micafungin does not need a loading dose.

Echinocandins have potent activity against biofilm infections.

In Endocarditis higher doses are recommended.

Pappas et al, Clin Infect Dis 2015
Female, 48 years old, with a diagnosis of antiphospholipid syndrome and SLE since 2014, plus an homozygotic condition for V Leiden factor. On high dose steroids plus hydroxychloroquine. Multiple episodes of DVT and pulmonary embolism, despite anticoagulation. She has a filter in lower vena cava. History of multiple hospitalizations and relapsing fever episodes some of them with polymicrobial bacteremias. Heavy consumption of antibiotics. History of allergy reactions to many drugs.
Admitted nearly a month ago because of fever, 2 days after discharge from another hospital
A CVC was inserted because of no peripheral vein access
In DD, the underlying disease and lymphoma is also considered as a possible cause of her unresponsive fever (splenomegaly is the only remarkable clinical sign)
She is on wide spectrum antibiotics (after consultation from the allergy department)
On day 19, we are informed that a blood culture drawn 2 days ago is positive for yeast.

What will your empiric treatment be?
To decide about initial empiric antifungal treatment we need INFORMATION about:

- the history of any previous antifungal treatment
- the epidemiology of Candida strains in our hospital
- the epidemiology of resistance of candida strains isolated in candidemias in our hospital
- Underlying diseases and severity of illness of our patient
- Probable site of infection (CNS, heart, deep space organs)
- the necessity of foreign bodies present (e.g. CVC)
Candidemia treatment basic principles

- A blood culture positive for Candida spp is always evaluated irrespective of the site drawn and always treated, even if the patient is without symptoms.

- Initiation of treatment should be done as soon as possible.

- Candida is always identified to species level and tested for sensitivity to antifungals.

Epidemiology of Candida spp

USA and N. Europe

- C. albicans: 42%
- C. glabrata: 27%
- C. parapsilosis: 16%
- C. tropicalis: 9%
- C. krusei: 3%

South Europe

- C. albicans: 50.50%
- C. glabrata: 9.50%
- C. parapsilosis: 28.40%
- C. tropicalis: 6.60%
- C. krusei: 2.60%

Leon ICM 2014
Basseti Plos one 2011
Delayed treatment related to increased mortality


Morrell M, et al. AAC 2005 Sep;49(9):3640
What do the 2015 guidelines recommend?

- An echinocandin is recommended as initial therapy (strong recommendation, high quality of evidence)

- Fluconazole is an acceptable alternative 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)

- At high risk for fluconazole resistant species are those previously exposed to azoles, the elderly, diabetics and those with underlying malignancy
Micafungin is administered to the patient as initial antifungal regimen (pending the results)

The Candida is identified as *parapsilosis* and the result of the sensitivity testing is pending

The patient is stable with low grade fever and a new blood culture is drawn

Would you change treatment replacing the echinocandin?
What do the 2015 guidelines recommend?

- In spite of laboratory observations with higher MICs against C. parapsilosis and probable poorer activity, there have been no clinical studies that have demonstrated superiority of fluconazole over the echinocandins for the treatment of C. parapsilosis infections.
- Moreover, recent observational data from Spain among almost 200 patients with candidemia due to C. parapsilosis suggested no difference in outcome among patients who received initial treatment with an echinocandin compared with those who received other regimens.
- Any recommendation supporting fluconazole over an echinocandin is generally based on theoretical concerns rather than on observed therapeutic failure of the echinocandins in these patients.
200 candidemias due to C. Parapsilosis. Initial echinocandin treatment was not a risk factor for failure (in uni-multivariatate and propensity score analysis)
Case #1

- The patient is stable
- No sensitivity is known yet
- No evidence that outcome will be compromised if C. parapsilosis is treated with an echinocandin

We decide to wait for the sensitivity results, leaving the patient on echinocandin

Sensitivity testing of *C. parapsilosis*:
- AMB=0.064mg/l,
- Fluconazole =32mg/L, Vori=0.5mg/l,
- Caspofungin=0.75mg/L, Micafungin=0.5mg/L
<table>
<thead>
<tr>
<th>Candida Organism</th>
<th>Antifungal Agent</th>
<th>S</th>
<th>SDD</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>Fluconazole</td>
<td>≤2</td>
<td>4</td>
<td>≥8</td>
<td></td>
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<tr>
<td></td>
<td>Itraconazole</td>
<td>≤0.12</td>
<td>0.25–0.5</td>
<td>≥1</td>
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<tr>
<td></td>
<td>Voriconazole</td>
<td>≤0.12</td>
<td>0.25–0.5</td>
<td>≥1</td>
<td></td>
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<tr>
<td></td>
<td>Posaconazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anidulafungin</td>
<td>≤0.25</td>
<td>0.5</td>
<td>≥1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caspofungin</td>
<td>≤0.25</td>
<td>0.5</td>
<td>≥1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Micafungin</td>
<td>≤0.25</td>
<td>0.5</td>
<td>≥1</td>
<td></td>
</tr>
<tr>
<td>C. glabrata</td>
<td>Fluconazole</td>
<td>32</td>
<td>≥64</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Itraconazole</td>
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<tr>
<td></td>
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<td>0.25</td>
<td>≥0.5</td>
<td></td>
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<tr>
<td></td>
<td>Micafungin</td>
<td>≤0.06</td>
<td>0.12</td>
<td>≥0.25</td>
<td></td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>Fluconazole</td>
<td>≤2</td>
<td>4</td>
<td>≥8</td>
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<td></td>
<td>Itraconazole</td>
<td></td>
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<td>≤0.12</td>
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<tr>
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<td>≤2</td>
<td>4</td>
<td>≥8</td>
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</table>
The patient continues on micafungin. Blood cultures are negative and the patient continues with low grade fever. A fundoscopy is negative.

Would you change the CVC?

Would you give higher doses of micafungin (e.g. treating possible intravascular infection)?

Duration of treatment?
What do the 2015 guidelines recommend?

For all patients with candidemia, the Expert Panel strongly advises a dilated funduscopic examination, preferably performed by an ophthalmologist, within the first week after initiation of specific antifungal therapy.

..as many as 16% of patients with candidemia have some manifestation of ocular involvement, and some of these patients will develop severe, sight-threatening endophthalmitis.

Pappas et al, Clin Infect Dis 2015
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).

Pappas et al, Clin Infect Dis 2015
Follow-up blood cultures every day or every other day until demonstration of clearance of Candida from the bloodstream are helpful to establish the appropriate duration of antifungal therapy.

If there are no metastatic complications of candidemia, the duration of therapy with systemic antifungal agents should be 14 days following documented clearance of Candida species from the bloodstream and resolution of signs and symptoms attributable to infection.

Pappas et al, Clin Infect Dis 2015
Case #1

- The patient continues on micafungin.
- Blood cultures are negative and the patient is afebrile.
- A fundoscopy is negative.
- A high dose of micafungin (150 mg) is administered as in endocarditis, or intravascular infection.

An FDG-PET is performed and is negative for endocarditis, intravascular or vena-cava filter infection.

Treatment is discontinued 14 days after the documentation of sterile blood cultures.
Male 70 years old.

History of cystectomy because of bladder cancer and ureterostomy with a pig tail catheter placed through the ureterostomy.

Admitted because of fever, worsened renal insufficiency (creat=4) and obstruction of the ureterostomies.

He undergoes immediate change of the nephrostomy tubes and the pig tail catheter and a urine sample is sent for culture. He is placed on empiric antimicrobial treatment.

The urine culture is positive for *Candida albicans*. Sensitivity testing is pending and the patient is still febrile and stable. The blood culture is negative.
Fluconazole in a modified dose is started pending the culture sensitivity testing.

Candida albicans sensitivity testing:
- Amphotericin B = 1 mg/L, Fluucytosine = 0.05 mg/L
- Fluconazole = 256 mg/L, Voriconazole = 1 mg/L
- Caspofungin = 0.25 mg/L, Micafungin = 0.25 mg/L

A CT urography is suggestive of infection of the renal parenchyma.

What do you do?
Case #2

- An echinocandin is started, since no amphotericin B deoxycholate, nor flucytosine is available from the hospital’s pharmacy.

- The patient becomes afebrile and surprisingly, the urine culture 5 days later is sterile!

Treatment of candiduria with micafungin: A case series

Danny Lagrotteria MD FRCPC¹, Coleman Rotstein MD FRCPC¹, Christine H Lee MD FRCPC¹,²,³

Case #3

- Male 50 years old, admitted to the ICU after a few days of hospitalization in a medical ward, with the diagnosis of acute pancreatitis with necrosis (50%).
- He has MOF, he is on MV and CVVH because of deteriorating kidney failure.
- He has 2 CVCs, an arterial catheter, a urinary catheter and he is on parenteral nutrition.
- He is stable, afebrile and on antibiotic treatment because of the pancreatic necrosis.

Would you add antifungal prophylaxis?
Risk factors for candidemia:
- Fever, septic syndrome, MOF
- Multifocal Candida colonization
- BG Mannan/ Antimannan PCR

Positive blood culture

An adult patient in the ICU

PROPHYLAXIS

EMPIRIC/PREEMPTIVE THERAPY

TARGETED THERAPY
What do the 2015 guidelines recommend?
Antifungal prophylaxis in critically ill patients with high risk of candidiasis

- Fluconazole, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily, could be used in high-risk patients in adult ICUs with a high rate (>5%) of invasive candidiasis (weak recommendation; moderate-quality evidence).
- An alternative is to give an echinocandin (caspofungin: 70-mg loading dose, then 50 mg daily; anidulafungin: 200-mg loading dose, then 100 mg daily; or micafungin: 100 mg daily) (weak recommendation; low-quality evidence).
- Daily bathing of ICU patients with chlorhexidine, which has been shown to decrease the incidence of bloodstream infections including candidemia, could be considered (weak recommendation; moderate-quality evidence).

Pappas et al, Clin Infect Dis 2015
Prophylaxis of *Candida* infections in adult trauma and surgical intensive care patients: a systematic review and meta-analysis
Double blind, placebo controlled study n 222 high risk patients. Caspofungin vs placebo

≥3 days in ICU
MV
Antibiotics
CVC

PLUS ONE FROM: parenteral nutrition, hemodialysis, pancreatitis, surgery, steroids or other immunosuppressives

Trend towards reduced candidiasis in the caspofungin arm without statistical significance. Small sample size

Clin Infect Dis 2014
Double blind placebo controlled study in patients following surgery for intrabdominal infections hospitalized in the ICU for more than >48 ωρες

124 placebo treated, 117 micafungin treated

No difference between arms in the incidence of systemic candidiasis (8.9% in placebo and 11.1% in the micafungin arm)

This may have been because the drug was administered too late to prevent IC, coupled with an overall low number of IC events

Significant correlation of BG with systemic candidiasis (OR=3.66)

Clin Infect Dis 2015 (1/12/2015)
Antifungal prophylaxis in critically ill patients with high risk of candidiasis

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent abdominal surgery AND recurrent gastrointestinal perforations or anastomotic leakages</td>
<td>To prevent intraabdominal Candida infection</td>
<td>Fluconazole 400 mg/day</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caspofungin 70/50 mg/day</td>
<td>C</td>
<td>IIa</td>
</tr>
<tr>
<td>Critically ill surgical patients with an expected length of ICU stay ≥3 day</td>
<td>To delay the time to fungal infection</td>
<td>Fluconazole 400 mg/day</td>
<td>C</td>
<td>I</td>
</tr>
<tr>
<td>Ventilated for 48 h and expected to be ventilated for another ≥72 h</td>
<td>To prevent invasive candidiasis/candidaemia</td>
<td>Fluconazole 100 mg/day</td>
<td>C</td>
<td>I</td>
</tr>
<tr>
<td>Ventilated, hospitalized for ≥3 day, received antibiotics, CVC, and ≥1 of parenteral nutrition, dialysis, major surgery, pancreatitis, systemic steroids, immunosuppression</td>
<td>To prevent invasive candidiasis/candidaemia</td>
<td>Caspofungin 50 mg/day</td>
<td>C</td>
<td>IIa</td>
</tr>
<tr>
<td>Surgical ICU patients</td>
<td>To prevent invasive candidiasis/candidaemia</td>
<td>Ketoconazole 200 mg/day</td>
<td>D</td>
<td>I</td>
</tr>
<tr>
<td>Critically ill patients with risk factors for invasive candidiasis/candidaemia</td>
<td>To prevent invasive candidiasis/candidaemia</td>
<td>Itraconazole 400 mg/day</td>
<td>D</td>
<td>I</td>
</tr>
<tr>
<td>Surgical ICU with catabolism</td>
<td>To prevent invasive candidiasis/candidaemia</td>
<td>Nystatin 4 Mio IU/day</td>
<td>D</td>
<td>I</td>
</tr>
</tbody>
</table>
While discussing benefits and arguments for adding antifungal prophylaxis, the patient spikes 39°C. CVCs are changed and antimicrobial treatment is modified. The patient is stable, without signs of VAP. A CT scan of the abdomen is planned.

Would you consider adding empiric antifungal treatment?

What if the patient presents with hemodynamic instability?
Empiric antifungal treatment in the critically ill: What do the guidelines recommend?

Empiric antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors, surrogate markers for invasive candidiasis, and/or culture data from nonsterile sites (strong recommendation; moderate-quality evidence).

Empiric antifungal therapy should be started as soon as possible in patients who have the above risk factors and who have clinical signs of septic shock (strong recommendation; moderate-quality evidence).

Pappas et al, Clin Infect Dis 2015
# Empiric Treatment and Clinical Prediction Rules

<table>
<thead>
<tr>
<th>Clinical Prediction Rule</th>
<th>Description</th>
<th>Se / sp</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pittet (1994)</td>
<td><em>CCI</em> = <em>Candida Colonisation Index</em> Patients with <em>CCI</em> ≥ 0.5 at high risk</td>
<td>66%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Paphitou 2005</td>
<td>Presence of <em>new onset hemodialysis, TPN, diabetes mellitus</em> and <em>broad-spectrum antibiotics</em></td>
<td>83% / 50%</td>
<td>11%</td>
<td>98%</td>
</tr>
<tr>
<td>Leon 2006</td>
<td>“<em>Candida score</em>” <em>multifocal colonisation (1.1), surgery on ICU admission (1), severe Sepsis (2.03), TPN (1).</em> A “<em>Candida score</em>” &gt; 2.5 predicts IC A Candida score&lt;3 predicts the absence of IC</td>
<td>81% / 74%</td>
<td>16%</td>
<td>98%</td>
</tr>
<tr>
<td>CLINICAL PREDICTION RULE</td>
<td>DESCRIPTION</td>
<td>Se/sp</td>
<td>PPV</td>
<td>NPV</td>
</tr>
<tr>
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</table>
| **Ostrosky 2007** | Any systemic antibiotic (days 1–3) **OR** CVC (days 1–3) **AND** at least TWO of the following: 
TPN (days 1–3), any dialysis (days 1–3), any major surgery (days 7–0), pancreatitis (days 7–0), steroid use (days -7–3) other immunosuppressive drug (days 7–0) | 34% / 90% | 10% | 97% |
| **Hermsen 2011** | *Current systemic broad-spectrum antibiotic use, CVC, TPN, abdominal surgery within last 7 days, steroid use, hospital LOS* | 84% / 60% | 5% | 99% |
Antifungals are not added and after 4 days the patient continues to be stable but febrile. He has high intrabdominal pressure and he undergoes a minor surgery for drainage. Blood cultures and cultures of the intrabdominal fluid are pending. A urine culture is positive for Candida spp.

Would you now consider adding antifungal treatment empirically/preemptively?

Which antifungal?
Empiric antifungal treatment in the critically ill: What do the guidelines recommend?

- Preferred empiric therapy for suspected candidiasis in nonneutropenic patients in the ICU is an echinocandin (strong recommendation; moderate quality evidence)
- Fluconazole is an alternative

- Duration in the patient who responds is 2 weeks
- Duration in the patient who remains unresponsive is 4-5 days

Pappas et al, Clin Infect Dis 2015
Empiric antifungal treatment in the critically ill

- Level C, D ESCMID’ guidelines.

<table>
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<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult ICU patients with fever despite broad-spectrum antibiotics and APACHE II &gt;16</td>
<td>To resolve fever</td>
<td>Fluconazole 800 mg/day</td>
<td>D</td>
<td>I</td>
</tr>
<tr>
<td>ICU patients persistently febrile, but without microbiological evidence</td>
<td>To reduce overall mortality</td>
<td>Fluconazole or echinocandin</td>
<td>C</td>
<td>II_u</td>
</tr>
<tr>
<td>ICU patients with candida isolated from respiratory secretions</td>
<td>To cure invasive candidiasis or candidaemia early</td>
<td>Any antifungal</td>
<td>D</td>
<td>II_u</td>
</tr>
<tr>
<td>ICU patients with positive (1,3)-β-D-glucan test*</td>
<td>To cure invasive candidiasis or candidaemia early</td>
<td>Any antifungal</td>
<td>C</td>
<td>II_u</td>
</tr>
</tbody>
</table>
Empirical fluconazole versus placebo for intensive care unit patients: a randomized trial

- Double blind placebo controlled study (1995-2000, USA, 26 sites)
- 249 ICU patients with fever unresponsive to antibiotics
- CVC present and APACHE II > 16
- Fluconazole 800mg vs placebo for 2 weeks
- No difference in the incidence of candidemia (<10%)
- No difference in response of fever
Empiricus trial (23 French ICUs)

- Patients on MV for >4 days, sepsis syndrome MOF, and Candida colonization in ≥1 sites except the digestive tract, randomized to receive micafungin or placebo. Study outcome was survival on day 28 and without candidemia.
- The study has been concluded and results are pending.

*Timsit 2013*
The new guidelines confirm what clinical practice has been applying for the last 5 years. Echinocandins are currently the drug of choice for treating invasive candidiasis as targeted, prophylactic or empiric/preemptive treatment, with the exception of eye, CNS and urinary tract infections. Emerging cross resistance of C. glabrata to echinocandins is of concern. More effort is needed for establishing early diagnosis of invasive candidiasis and accurately defining patient populations at highest risk who are candidates for prophylaxis or preemptive treatment with antifungals.
If you want to go fast, go alone
If you want to go far, go together

African proverb