

CANDIDEMIA: TREATMENT STRATEGIES



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Disclosure

Speaker Bureau and Travel Grant

- Astellas®
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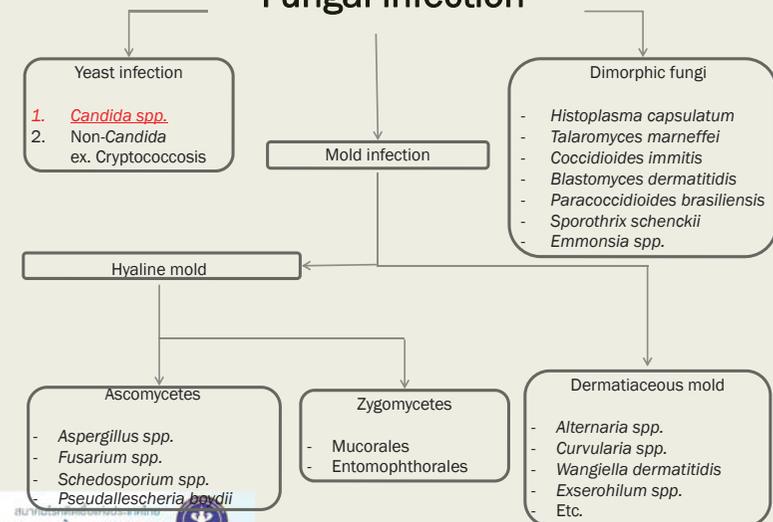
Outlines

- Risk factors and epidemiology of candidemia
- Diagnostic tool
- Prophylactic and preemptive strategies
- Treatment in general and specific situations
- Future directions

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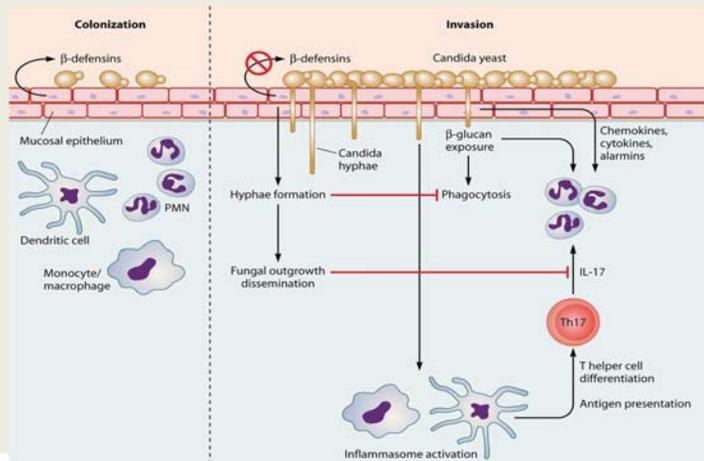
Fungal infection



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Defense mechanisms for *Candida*



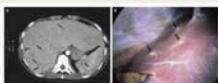
Risk factors for invasive candidiasis

Immunocompromised	Invasive Procedure	General
<ul style="list-style-type: none"> - Hematologic malignancies - HSCT - Neutropenia - Chemotherapy - Steroid > 50 mg prednisone - Other immunosuppressant usage - Liver diseases - DM - Renal failure and HD 	<ul style="list-style-type: none"> - CVC - Urinary catheter - GI/hepatobiliary surgical procedure 	<ul style="list-style-type: none"> - Parenteral nutrition - Broad spectrum antibiotic - Colonization - Necrotizing pancreatitis - Mucositis - Blood transfusion

Clinical presentations

Neutropenia

- Neutropenic fever/sepsis
- Acute disseminated candidiasis
- Chronic disseminated candidiasis



Non-neutropenia

- CLABSI
- Endovascular infection
- Intra-abdominal infection
- UTI

**ALL CAUSE MORTALITY
40 - 60%**

Species Distribution



General patterns of susceptibility of *Candida* species

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Flucytosines	Amphotericin B	Candins
<i>C. albicans</i>	S	S	S	S	S	S	S
<i>C. tropicalis</i>	S	S	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	S	S	S to R ^a
<i>C. glabrata</i>	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S
<i>C. krusei</i>	R	S-DD to R	S	S	I to R	S to I	S
<i>C. lusitanae</i>	S	S	S	S	S	S to R	S

NOTE. I, intermediately susceptible; R, resistant; S, susceptible; S-DD: susceptible dose-dependent. a Echinocandin resistance among *C. parapsilosis* isolates is uncommon.

- The susceptibility of *Candida* to the currently available antifungal agents is generally predictable if the species is known



Blood culture

- Yeasts except for *M. furfur* are usually detected in aerobic broth systems
- Automated system with special fungal media may enhance recovery (faster eg. *C. glabrata*)
- Adequate volume (40-60 mL) for adults, incubate at least 5 d
- The overall sensitivity is roughly 50% (21-71%); Limit of detection ≤ 1 CFU/mL
- Median time to positivity 2-3 d (1 to ≥ 7 d) > significant longer in *C. glabrata*



Species identification

Growth characteristics

Germ tube production

- incubate in serum 35-37°C, 2-3 h (false positive > 3 hrs)
- C. albicans*, *C. dublinensis*



- C. tropicalis* > hypha that is constricted at the site of germination



Identification

CHROMagar™ Candida
INTERPRETATION

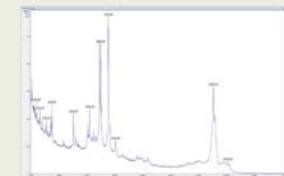
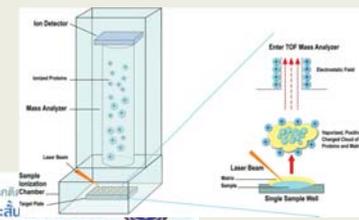
Microorganism	Typical colony appearance
<i>C. albicans</i>	→ green
<i>C. tropicalis</i>	→ metallic blue
<i>C. krusei</i>	→ pink, fuzzy
<i>C. kefyr</i> , <i>C. glabrata</i>	→ mauve-brown
Other species	→ white to mauve

Typical colony appearance

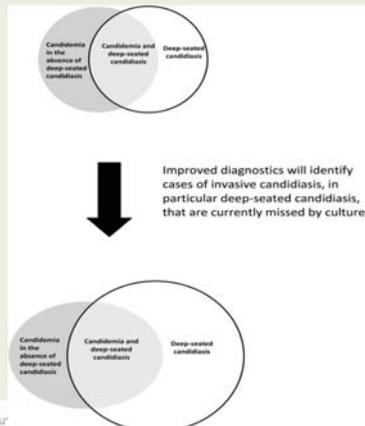
The pictures shown are not contractual.

MALDI-TOF MS

- Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
- 98 - 100% concordance with conventional identification
- From positive blood culture bottle: investigational concordance results: 95.9% for *C. albicans* and 86.5% for non-*albicans* (reliability in *C. glabrata* and *C. parapsilosis*)



Non-culture methods



Non-molecular

- Mannan Ag and antimannan-Ab
- BDG
- *C. albicans* germ tube antibody (CAGTA)

Molecular

- Biofire FilmArray BCID panel

Other

- T2 Candida

Clinical Infectious Diseases 2013;56(9):1284-92
J Clin Microbiol. 2018 Apr;56(5)

Prediction for invasive candidiasis in ICU

Score	Trial	Performance
Clinical prediction rule	Multicenter retrospective Incidence 3%; (n = 2890) "Rule 3"	RR 4.36 Sense 34%, Spec 90% NPV 97% Proven / probable IC
Clinical prediction rule	Multicenter retrospective Incidence 3.7%; (n = 597)	
Candida Score	Prospective, cohort, observational, multicenter surveillance study Incidence 5.7%; (n = 1669)	Candida score > 2.5 Sense 81%, Spec 74% Proven IC
UK FIRE study risk predictive model	Systematic review Incidence 0.6%; (n = 60,778)	At the end of calendar D3 Sense 24 - 54% Spec 73 - 93.6% NPV 99.7
Three-tiered risk predictive model, Australia	Prospective, cohort, multicenter surveillance study Incidence 1.4%; (n = 6685) Non-neutropenic patient	Risk stratification High risk score ≥ 6 Sense 40%, Spec 96% NPV 99.1%

Antimicrob Agents Chemother. 2018 Jul;27(8): pii: e00355-18.

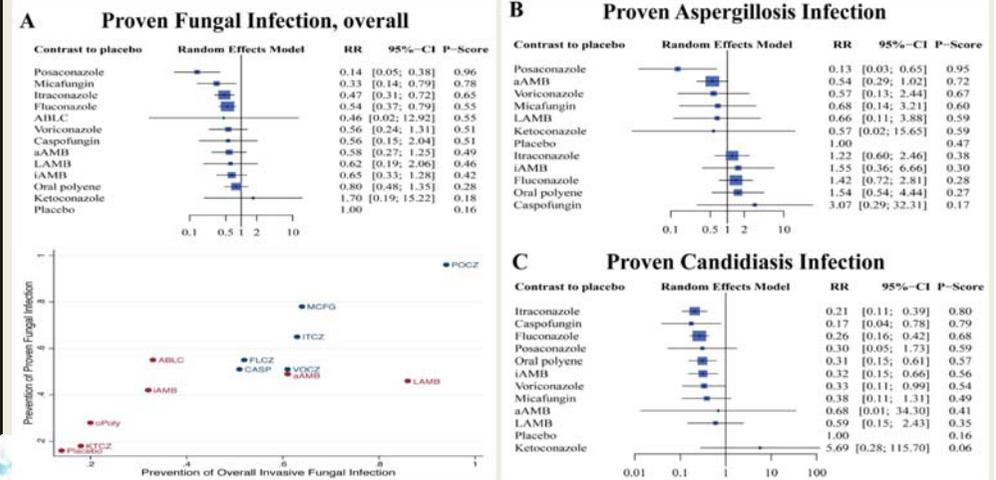
Prophylaxis candidiasis in ICU

- Fluconazole 400 mg/day to prevent intra-abdominal candidiasis in high risk population. (after abdominal surgery with recurrent gastrointestinal perforations or anastomotic leakages)
- Meta-analysis showed lower rate of candidemia and mortality rate in trauma and SICU patients.
- Prophylaxis may be considered in ICU with high incidence of invasive candidiasis > 5 - 10%
- Echinocandin is not better than fluconazole

Intensive Care Med (2005) 31:1479-1487
Clinical Infectious Diseases 2016;62(4):e1-50
Clin Microbiol Infect 2012; 18 (Suppl. 7): 19-37

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Prophylaxis in Hematologic Malignancies



Antimicrob Agents Chemother. 2018 Jul;27(8): pii: e00355-18.

Prophylaxis for *Candida* infection in HSCT

Study	Design	Agents	Outcomes
Gøtzsche PC, et al.	Cochrane meta-analysis	Nystatin vs Placebo Nystatin vs Fluconazole	= colonization > Colonization > Fungal invasion = Death
Goodman JL, et al.	Double-blind, randomized, multicenter trial	Fluconazole 400 mg/d Vs Placebo	< superficial infection < systemic infection < attributable mortality
Marr KA, et al.	Double-blind, randomized, controlled trial	Fluconazole 400 mg/d Vs Placebo 75 days	> Survival < incidence of ICI < early and late mortality from ICI.
Van Burik JH, et al.	Double-blind, randomized, multicenter trial	Fluconazole 400 mg/d Vs Micafungin 50 mg/d	< prophylactic efficacy.

Fluconazole < 200 mg/day may not be effective.

Risk factors in liver Tx

- *Candida* species account for 60-80% followed by *Aspergillus* 1-8%

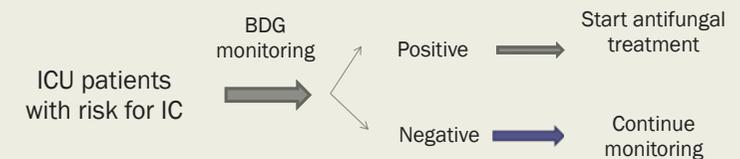
Risk

- Pre and post-operative renal failure
- Re-transplantation
- Substantial infusions of intraoperative cellular blood products
- Choledochojejunostomy anastomosis
- *Candida* colonization
- CMV viremia or disease
- Re-exploration after transplant
- Long operating time
- Fulminant hepatitis

Prophylaxis in liver Tx

- Selective digestive decontamination (non-absorbable agents) may decrease incidence of fungal infection.
- Patients with fluconazole 400 mg daily had significantly lower proven fungal infection compare with placebo.
- Fluconazole = echinocandin (micafungin / aniduladungin)
- Duration of prophylaxis 4 - 6 weeks.

Preemptive approach



- Decreased incidence of IC was shown in several studies, however mortality and length of stay were not different.
- No clear evidence demonstrated benefit of using echinocandins as preemptive antifungal agent in ICU patients.

Treatment for invasive candidiasis

Antifungal	Non-neutropenic	Neutropenic
Micafungin	100 mg daily (strong, high)	100 mg daily (strong, mod / All)
Anidulafungin	200 mg then 100 mg daily (strong, high)	200 mg then 100 mg daily (strong, mod / All)
Caspofungin	70 mg then 50 mg daily (strong, high)	70 mg then 50 mg daily (strong, mod / All)
Liposomal AMB (alternative) Resistance to other classes	3 - 5 mg/kg daily (strong, high)	3 - 5 mg/kg daily (strong, mod / All)
Fluconazole Stable pt. / low risk for azole R	800 mg then 400 mg daily (strong, high) (strong, mod) (weak, low / -)	800 mg then 400 mg daily (weak, low / -)
Step down in susceptible Candida C. glabrata	800 mg daily (strong, low)	-
Voriconazole	3 - 4 mg/kg bid (strong, low) Transit in C. glabrata	6 mg/kg bid x 2 doses then 3 - 4 mg/kg bid (weak, low / BII)

Echinocandins vs. Fluconazole

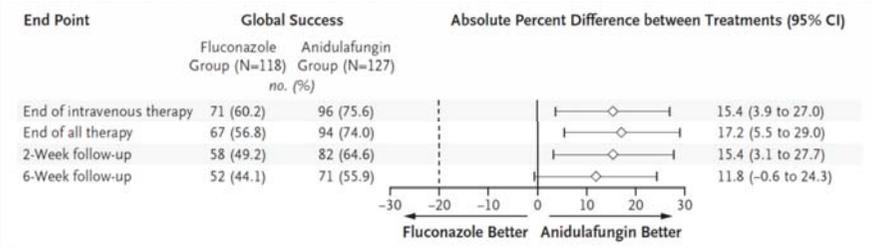
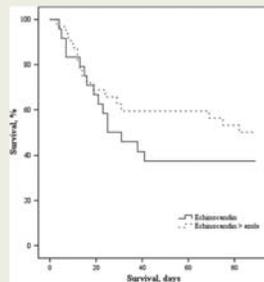
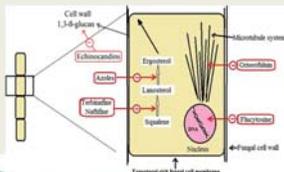


Table 3. Microbiologic and Global Responses at the End of Intravenous Therapy in the Modified Intention-to-Treat Population.²

Candida Pathogen	Successful Microbiologic Response			Successful Global Response†		
	Anidulafungin Group	Fluconazole Group	P Value	Anidulafungin Group	Fluconazole Group	P Value
	no. of isolates/total no. (%)			no. of patients/total no. (%)		
<i>Candida albicans</i>	77/81 (95)	57/70 (81)	0.01	60/74 (81)	38/61 (62)	0.02
<i>C. glabrata</i>	15/20 (75)	18/30 (60)	0.37	9/16 (56)	11/22 (50)	0.75
<i>C. parapsilosis</i>	9/13 (69)	14/16 (88)	0.36	7/11 (64)	10/12 (83)	0.37
<i>C. tropicalis</i>	13/15 (87)	7/11 (64)	0.35	13/14 (93)	4/8 (50)	0.04
Other candida species	5/6 (83)	3/3 (100)	1.00	3/4 (75)	2/3 (67)	1.00
All candida species	119/135 (88)	99/130 (76)	0.02	92/119 (77)	65/106 (61)	0.01

Echinocandins vs. Fluconazole

- Rapid clearance of positive blood culture
- Persistent candidemia
- Cost-effectiveness
- Sequential step-down therapy in critically ill patients

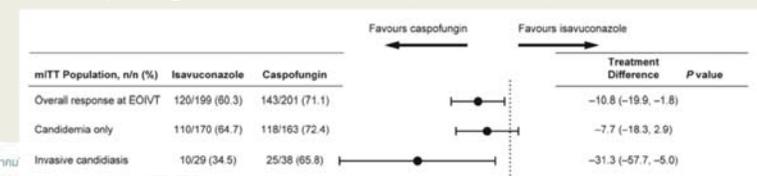


Echinocandins vs. New-azole

- MIC₉₀ (µg/ml) of azole anti-fungal agents against *Candida* spp.

	voriconazole	posaconazole	isavuconazole
<i>C. albicans</i>	0.015	0.03	0.03
<i>C. tropicalis</i>	0.12	0.25	0.12
<i>C. parapsilosis</i>	0.12	0.25	0.12
<i>C. krusei</i>	0.5	1	1
<i>C. glabrata</i>	1	2	2

- Caspofungin vs. Isavuconazole (ACTIVE Trial)



Limitation of echinocandins

Using against *C. parapsilosis*

- Prospective multicenter, population-based surveillance program on *Candida* BSI
- Propensity score analysis
- Clinical failure occurred in 32.8%

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P Value	Adjusted OR	95% CI	P Value
Oropharyngeal colonization at diagnosis	4.67	2.32-9.38	.000	2.81	1.19-6.65	.018
Septic shock	7.17	2.63-19.96	.000	2.91	89-9.64	.081
Hematogenous dissemination	6.75	1.32-34.56	.018	7.42	67-82.44	.103
Early CVC removal (L48 h)	0.41	20-.86	.016	0.43	19-.96	.040
Initial antifungal therapy						
Acute-based regimen	1			1		
Echinocandin-based regimen	1.34	60-2.97	.479	1.73	86-4.54	.265
Amphotericin B-based regimen	0.99	40-2.45	.969	0.99	34-2.89	.906
Combination regimen	0.86	31-2.36	.769	1.06	33-3.43	.922

Using in candidemia with UTI

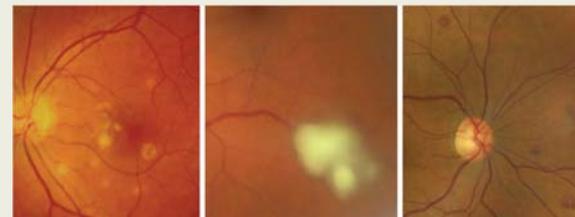
- Multicenter cohort of patients with candidemia
- Propensity score analysis
- Candidemia with concomitant candiduria by the same organism associated with significant urological comorbidity

Risk Factor	Adjusted OR (95% CI)	P Value
Severe sepsis/septic shock	1.66 (1.55-5.04)	.369
Acute renal failure	3.01 (1.01-8.91)	.047
Early urologic procedure	0.08 (0.02-.31)	<.001
Initial echinocandin therapy	0.32 (0.09-1.19)	.089
Propensity score of receiving echinocandins	14.69 (1.85-255.42)	.065

Abbreviations: CI, confidence interval; OR, odds ratio.

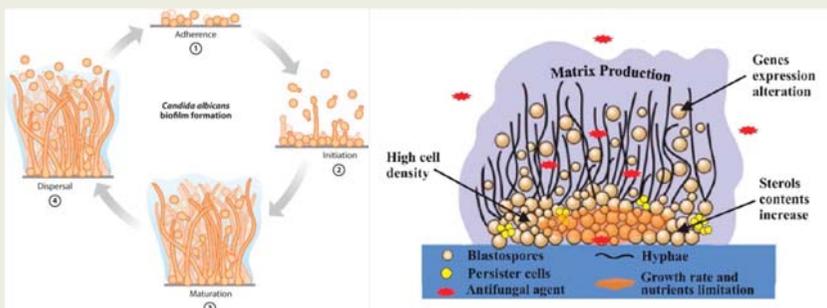
Ophthalmic examination

- Spectrum from chorioretinitis to endophthalmitis



- Eye involvement 10 - 16% of patients with candidemia >> endophthalmitis (1.6%)
- Duration of candidemia (time to negative culture)
- Diagnosis may lead to optimal anti-fungal option

Biofilm Formation & Endovascular Infection



- Antifungal penetration: echinocandin, voriconazole, fluconazole > posaconazole, amphotericin B
- Biofilms of *C. krusei* were the most resilient to antifungal permeation

Treatment for invasive candidiasis

Treatment	Non-neutropenic	Neutropenic
Remove CVC	(strong, mod)	(strong, low)
Dilated ophthalmological examination by ophthalmologist	Within 1 week (strong, low)	First week after recover from neutropenia (strong, low)
Daily blood culture until clear candidemia	(strong, low)	-
Duration treatment at least 2 wks after clearance of <i>Candida</i>	(strong, mod)	(strong, weak) Recover from neutropenia

- Endophthalmitis > fluconazole, voriconazole, LAMB
- Endovascular infection > LAMB +/- 5-FC, high dose echinocandins followed by azole
- Osteoarticular infection > fluconazole, echinocandins, LAMB
- CNS infection > LAMB +/- 5-FC followed by fluconazole
- UTI > fluconazole, AMB deoxycholate



Resistance mechanisms

Mechanisms	Drug class			
	Amphotericin B	Echinocandins	Azoles	Flucytosine
Drug target	Ergosterol	Glucan synthase	P450 demethylase	DNA and RNA synthesis
Target gene mutation	<i>ERG2, 3, 5, 6 and 11</i> → less ergosterol	<i>FKS1 and FKS2</i> → less binding	<i>ERG11</i> → less binding	
Target up-regulation			<i>UPC2</i> , Duplication of chromosome 5 Isochromosomes	
Efflux pumps			<i>CDR, MFS</i> <i>CgSNQ2, PDH1</i> (<i>C. glabrata</i>)	
Reduced drug uptake				Loss of permease
Reduced intracellular activation				<i>FCA1</i> (<i>C. albicans</i>), <i>FCY1b</i> (<i>C. glabrata</i>) <i>FUR1c</i>

Novel agents for IC

Rezafungin (CD101)



- Cyclic hexapeptide with a lipophilic tail derived from anidulafungin with acholine moiety at the C5 ornithine position
- Increase *in vitro* and *in vivo* stability compared to other echinocandins
- Half-life 40 hrs >> dose 400 mg IV once weekly
- Contains activity against *Candida* spp. including some strains with *FKS* mutation and *Aspergillus*
- Currently is in phase 2 study

Novel agents for IC

Ibrexafungerb (SCY-078)

- Orally bioavailable β -1,3-glucan synthesis inhibitor which is semisynthetic derivative of enfumafungin
- Represents the first compound of the triterpene class of antifungals
- Fungicidal, C_{max}/MIC or AUC₂₄/MIC

Species (no. of strains tested)	Antifungal agent	CLSI MIC (mg/L)			CLSI % by category			EUCAST MIC (mg/L)		
		range	50%	90%	S	SDDIT	R	range	50%	90%
<i>C. albicans</i> (29)	Mk-3118	0.06-2	0.12	1	NA	NA	NA	0.03-2	0.06	1
	compofungin	0.015-8	0.12	2	55.2	10.3	34.5	0.06-4	0.12	2
	fluconazole	0.06 - \geq 128	0.25	\geq 128	55.2	0.0	44.8	0.12 - \geq 128	0.25	\geq 128
<i>C. glabrata</i> (29)	Mk-3118	0.5-2	0.5	2	NA	NA	NA	0.5-2	0.25	1
	compofungin	0.03-16	0.12	16	58.6	6.9	34.5	0.03 - \geq 16	0.25	4
	fluconazole	2 - \geq 128	32	\geq 128	NA	58.6	41.4	2 - \geq 128	8	64
<i>C. parapsilosis</i> (15)	Mk-3118	0.25-1	0.25	0.5	NA	NA	NA	0.12-0.5	0.25	0.5
	compofungin	0.25-0.5	0.5	0.5	100.0	0.0	0.0	0.5-1	1	1
	fluconazole	0.25-64	1	64	60.0	6.7	33.3	0.5-32	1	32
<i>C. tropicalis</i> (21)	Mk-3118	0.06-2	0.25	1	NA	NA	NA	0.03-2	0.25	1
	compofungin	0.03-1	0.06	1	80.9	0.0	19.1	0.12-2	0.25	2
	fluconazole	0.12 - \geq 128	0.5	\geq 128	80.9	0.0	19.1	0.25 - \geq 128	1	\geq 128
<i>C. lusitana</i> (19)	Mk-3118	0.5-2	0.5	2	NA	NA	NA	0.25-1	0.5	1
	compofungin	0.12-8	0.12	1	79.0	16.5	10.5	0.25-4	0.5	1
	fluconazole	16 - \geq 128	32	\geq 128	NA	NA	NA	16 - \geq 128	32	\geq 128

Conclusions

- Prompt diagnosis and early treatment are important in candidemia
- Non-culture methods are helpful, if available
- Prophylaxis and preemptive approach should be considered in high risk population
- Echinocandins remain the first option for candidemia
- Ophthalmic evaluation and removal of FB should be considered in patients with candidemia