

Challenging Case Scenario in Candidiasis

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A 81-year old man

- Underlying HT, COPD, chronic aortic dissection, gout
- History of frequent aspirations
- Flu-like symptoms for 2 days progressive to dyspnea, productive cough and fever
- Admitted at a private hospital for 3 days
- Desaturation and hypotension
- CXR: infiltrates at RML and LUL
- Sputum: numerous gram-negative bacilli



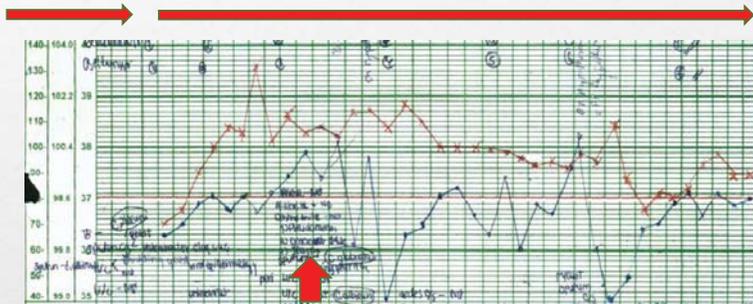
A 81-year old man (progress)

- Diagnosis: multi-lobar pneumonia with ARDS and septic shock
- Antimicrobials: sulbactam/cefoperazone + moxifloxacin
- Referred to RCU at Siriraj Hospital: changed to doripenem + levofloxacin + oseltamivir
- Supportive treatment: ET intubation with ventilator, central venous catheter and TPN, urinary catheter, hemodialysis
- Hydrocortisone, norepinephrine, dopamine
- Fever subsided
- 5 days later: breakthrough fever



A 81-year old man (progress)

Cpz/sul + Moxi Dori+Levo+Osel + Vancomycin



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A 81-year old man (progress)

- Sputum exam: mixed gram-positive and gram-negative bacteria and rare budding yeasts
- Sputum culture: *Candida albicans*
- Urinalysis: WBC 5-10, RBC 0-1, budding yeast 1+
- Urine culture: *Candida albicans*



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Predisposing factors for candidemia in this patient

- Broad spectrum antibiotics
- Central venous catheter with TPN
- Multi-site *Candida* colonization
- Urinary catheter
- ET intubation with mechanical ventilation
- Hemodialysis
- Severe sepsis



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Candida Scores

Leon score¹

For non-neutropenic patients

Criteria

- Multifocal *Candida* colonization
- Surgery
- TPN
- Severe sepsis (X 2)

- Positive: Total score ≥ 3
- Sensitivity 81%
- Specificity 74%

Ostrosky-Zeichner score²

Major criteria

- ICU stay ≥ 4 days and
- Systemic ATB therapy or central venous catheter

Minor criteria

- TPN
- Any dialysis
- Any major surgery
- Pancreatitis
- Steroid use
- Immunosuppressive drug use

- Positive: 2 major + 2 minor criteria
- Sensitivity 34%
- Specificity 90%



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1 Cristóbal León, Sergio Ruiz-Santana, Pedro Saavedra, et al; Crit Care Med 2009 Vol. 37, No. 5
2 L. Ostrosky-Zeichner, C. Sable, J. Sobel, et al; Eur J Clin Microbiol Infect Dis (2007) 26:271-276

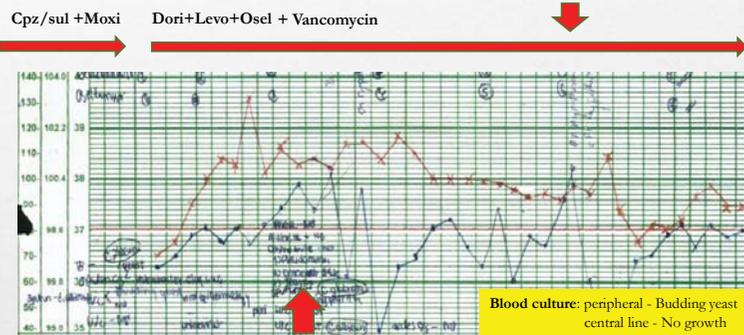
Would you prescribe antifungal agent in this case?

- Yes
- No

What antifungal agent to be used?

- Fluconazole
- Voriconazole
- Amphotericin B deoxycholate
- An echinocandin
- Liposomal amphotericin B

A 81-year old man (progress)



Guidelines for Invasive Candidiasis

IDSA 2009

- ☐ Moderate to severe illness, recent azole exposure
 - Echinocandins - AI
- ☐ Mild to moderate illness, hemodynamically stable, no recent azole exposure
 - Fluconazole - AI

ESCMID 2012

- Echinocandins – AI
- Liposomal AMB – BI
- Voriconazole – BI
- Fluconazole – CI

C. parapsilosis

– Preferred fluconazole or amphotericin B (will be changed in 2015 guidelines)

Echinocandins as a first line therapy of candidemia

- Broad spectrum and fungicidal
- Unmask *Candida* cell wall targets for the immune response
- Activity against biofilm
- Limited or no drug to drug interactions
- Better clinical performance than Fluconazole and Isavuconazole in clinical trials
- Safer than AMB formulations

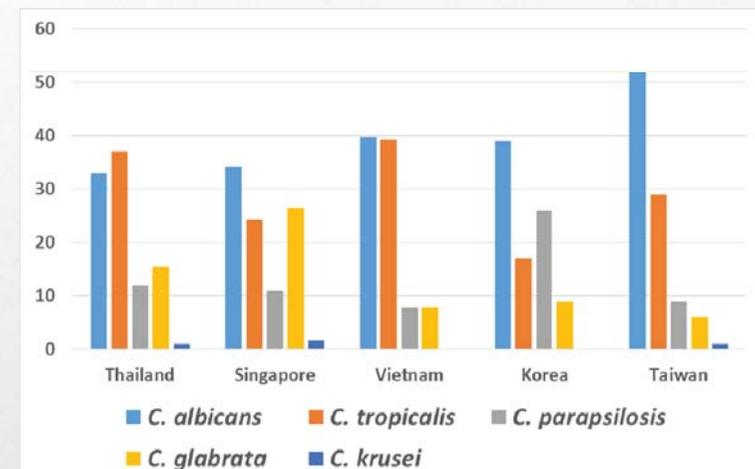
A patient-level quantitative review of 7 clinical trials: 1,895 patients with invasive candidiasis

Organisms ^a	Factor	Mortality			Factor	Success		
		P	OR	95% CI		P	OR	95% CI
All organisms (n = 978)	Age	.02	1.01	1.00-1.02	APACHE II	.0001	0.94	.93-.96
	APACHE II score	.0001	1.11	1.08-1.14	Echinocandin	.01	2.33	1.27-4.35
	Immunosuppressive therapy	.001	1.69	1.18-2.44	CVC removed	.001	1.69	1.23-2.33
	<i>Candida tropicalis</i>	.01	1.64	1.11-2.39	Study	NS		
	Echinocandin	.02	0.65	.45-.94				
	CVC removed	.0001	0.50	.35-.72				
	Study	NS						
<i>Candida albicans</i> (n = 408)	APACHE II score	.0001	1.09	1.05-1.13	APACHE II score	.005	0.92	.92-.99
	Immunosuppressive therapy	.002	2.22	1.30-3.70	Echinocandin	.005	3.70	1.49-9.09
	Surgery	.05	0.58	.34-.98	Study	NS		
	Malignancy	.03	1.89	1.05-3.45				
	Echinocandin	.03	0.55	.32-.95				
	CVC removed	.01	0.52	.31-.90				
	Study	NS						

Factors associated with 30-day mortality in 640 ICU adult patients (22 medical centers)

Variables	OR	P value
Receipt of corticosteroids	4	<0.0001
Admission at Period 1 vs 2	2.49	0.01
APACHE II Score	1.05	0.03
Age	1.03	0.003
Therapy with Echinocandin	0.20	0.003

Candida Species Distribution in Asia Pacific

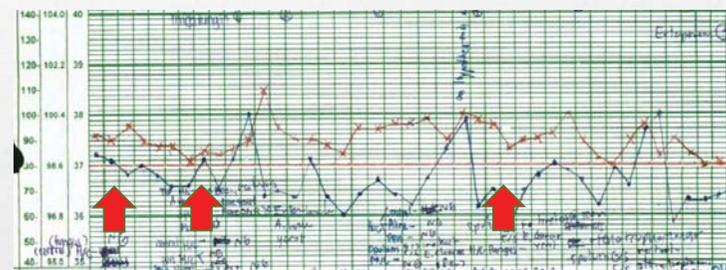


Organism	Reportable reading conditions	Breakpoints				ECV	
		Susceptible	S-DD	Intermediate	Resistant	WT	Non-WT
C. glabrata							
Caspofungin	24-h 50%	≤0.12	-	0.25	≥0.5	≤0.12	>0.12
Anidulafungin	24-h 50%	≤0.12	-	0.25	≥0.5	≤0.25	>0.25
Micafungin	24-h 50%	≤0.06	-	0.12	≥0.25	≤0.03	>0.03
Fluconazole	24-h 50%	-	≤32	-	≥64	≤32	>32
Voriconazole	24-h 50%	-	-	-	-	≤0.5	>0.5
Posaconazole	24-h 50%	-	-	-	-	≤2	>2
Itraconazole	48-h 50%	≤0.12	0.25-0.5	-	≥1	-	-

	MIC (µg/mL)	Interpretation	ECV (WT)
Amphotericin B	1	No BP	No ECV
Fluconazole	16	SDD	≤ 32
Itraconazole	1	R	No ECV
Voriconazole	0.5	No BP	≤ 0.5
Posaconazole	2	No BP	≤ 2
Caspofungin	0.25	I	≤ 0.12
Anidulafungin	0.12	S	≤ 0.25
Micafungin	≤ 0.008	S	≤ 0.03

A 81-year old man (progress)

Doripenem+ Levofloxacin+ Micafungin
(Oselt and Vanco-discontinued)



Day 2 H/C central line -NG
Day 3 catheter tip C/S -NG

Day 6 H/C -NG

A 81-year old man (progress)

- Repeat blood culture 3 and 6 days after initiation of antifungal agent
- Continue micafungin for 14 days after blood culture negative (total 21 days)
- Remove central catheter
- Normal eye exam
- Clinically improved

Question to be solved

- How often and when to repeat blood culture after antifungal therapy?
- When to de-escalate antifungal agent?
- Do we need to remove central catheter?
- When should we perform eye exam?
- Do we need to perform echocardiography? – ESCMID guidelines recommend !

IDSA Guidelines 2009

- Dilated ophthalmological examination –
 - Non-neutropenics- performed at a time when the candidemia appears to be controlled
 - Neutropenic patients - after recovery of the neutrophil count
- Blood cultures be performed daily or every other day
- Central venous catheter removal
 - Non-neutropenics- strongly recommended (A-II)
 - Neutropenics-should be considered (B-III)

ESCMID 2012 Guidelines on Treatment of Candidaemia and Invasive Candidiasis in Adult Patients

Population	Intention	Intervention	SoR	QoE
Candidemia with no organ involvement detected	To avoid organ involvement	Treat for 14 days after the end of candidaemia	B	II
		Take at least 1 blood culture per day until negative	B	III
	To detect organ involvement	Transesophageal echocardiography	B	II _a
		Fundoscopy	B	II
Any	To simplify treatment	If CVC, PICC, or intravascular devices, search for thrombus *Step down to fluconazole after 10 days of IV, if species is susceptible, patient tolerates PO, and patient is stable	B	II

Proposed work-up on diagnosis

- Baseline:
 - Identification of *Candida* at species level and susceptibility testing
 - Ocular examination: **at least one**
 - Abdominal CT or US for surgical patients - suspicion of abdominal collections
- Plan to repeat blood cultures up to first negative
 - It takes at least 2-3 days to clear blood cultures for most patients
 - Target day-3 and day-5 after starting ATF therapy
- 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

Time to step-down therapy to azoles

Similar global success rate for patients with early switch from anidulafungin to fluconazole/voriconazole

- Open-labelled, non-comparative
- 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

Response	MITT (N = 250)	Early switch (N = 102)
Global success	170/203 (83.7%)	81/90 (90.0%)
Global response at EOT		
Success	170/203 (83.7%)	81/90 (90.0%)
Failure	33	9
Missing/unknown	47	12
Clinical response at EOT		
Success	170/187 (90.9) [89.4-90.7]	88/89 (98.9) [88.0-98.5]
Sensitivity analysis*	174/250 (69.6) [63.9-75.3]	88/102 (86.1) [79.8-88.9]
Failure	13	6
Missing/unknown	68	13
Microbiological response at EOT		
Success	183/192 (95.3) [92.3-98.3]	87/90 (96.7) [93.0-100.0]
Sensitivity analysis*	183/250 (73.2) [67.7-78.7]	87/102 (85.3) [78.4-92.2]
Failure	9	3
Missing/unknown	58	12

Proposed care pathway for catheter management

- Non-neutropenic patients
 - Remove mainly if septic shock or blood culture still positive at 3rd day
- Surgical implanted CVC in neutropenic patients
 - Try to be more conservative once translocation is expected to be responsible for most cases
 - Remove CVC if the patient presents:
 - Severe sepsis
 - Fever during any infusion throughout the CVC
 - Signs of CVC infection
 - Breakthrough candidemia or persistent candidemia
 - Infections due to *C. parapsilosis*/*C. guilliermondii*



A 34-year-old man

- Tear anterior cruciate ligament of right knee
- ACL reconstruction with bone-patellar tendon-bone (BPTB) autograph
- Developed inflammation of his right knee and synovial fluid was culture-negative
- Ceftriaxone was prescribed with partial improvement
- Arthroscopy was performed with screw removal



Arthroscopy of right knee



Tissue from tibio-femoral compartment grew *Candida krusei*



Organism	Reportable reading conditions	Breakpoints				ECV	
		Susceptible	S-DD	Intermediate	Resistant	WT	Non-WT
<i>C. krusei</i>							
Caspofungin	24-h 50%	≤0.25	-	0.5	≥1	≤0.25	>0.25
Anidulafungin	24-h 50%	≤0.25	-	0.5	≥1	≤0.12	>0.12
Micafungin	24-h 50%	≤0.25	-	0.5	≥1	≤0.12	>0.12
Fluconazole*	24-h 50%	-	-	-	-	≤64	>64
Voriconazole	24-h 50%	≤0.5	-	1	≥2	≤0.5	>0.5
Posaconazole	24-h 50%	-	-	-	-	≤0.5	>0.5
Itraconazole	48-h 50%	≤0.12	0.25-0.5	-	≥1	-	-

	MIC (µg/mL)	Interpretation	ECV (WT)
Amphotericin B	≤ 0.12	No BP	No ECV
Fluconazole	64	N/A*	≤ 64
Itraconazole	0.5	SDD	No ECV
Voriconazole	2	R	≤ 0.5
Posaconazole	0.5	No BP	≤ 0.5
Caspofungin	0.5	I	≤ 0.25
Anidulafungin	0.06	S	≤ 0.12
Micafungin	0.12	S	≤ 0.12



Management of Osteoarticular Candidiasis

- IDSA Guideline: septic arthritis
 - Fluconazole for 6 weeks (BIII)
 - Liposomal AMB x 2 weeks, then fluconazole (BIII)
 - Alternative: AMB-d x 2 weeks, then fluconazole (BIII)
Echinocandin x 2 week, then fluconazole (BIII)
- All 3 echinocandins have not been approved for *Candida* osteoarticular infection, CNS infection and endocarditis
- The patient received micafungin for 6 weeks with complete recovery



Thank you

Q & A

