

FAUT-IL S'INQUIETER DES RESISTANCES CHEZ CANDIDA sp. ?

Le point de vue de l'infectiologue

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CANDIDA

FAIT'IDE LA

RESISTANCE

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Candidemia represents 45% of IFI in France

French Hospital Database (2001-2010)

35,876 incident IFI episodes

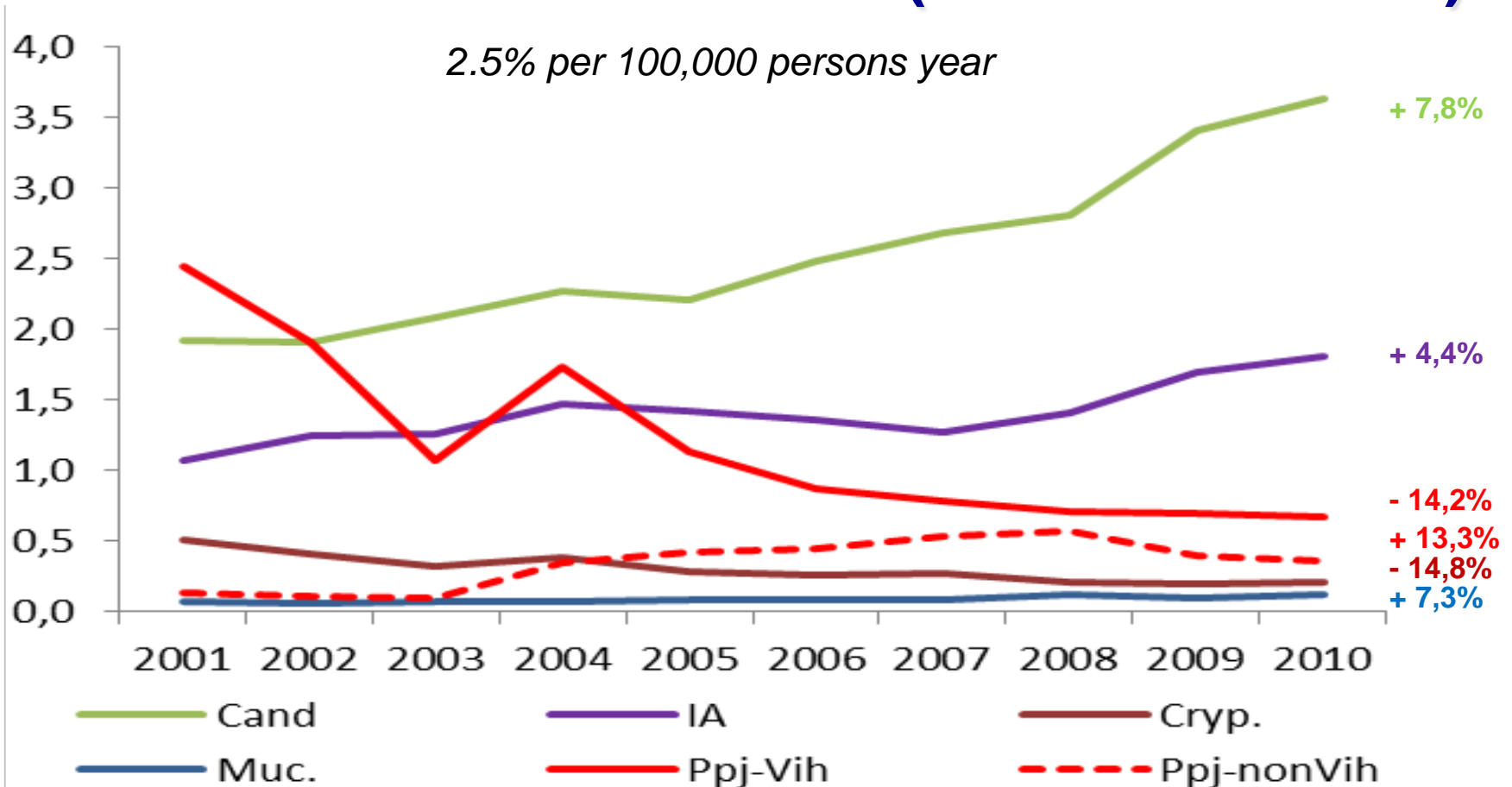
- ✓ **N° 1: Candidemia (43.4%)**
- ✓ **N° 2: *P. jirovecii* pneumonia (26.1%)**
- ✓ **N° 3: Invasive aspergillosis (23.9%)**

Prospective lab-based surveillance « RESSIF » (2012-2014)

25 laboratories / univ hosp;
3990 episodes

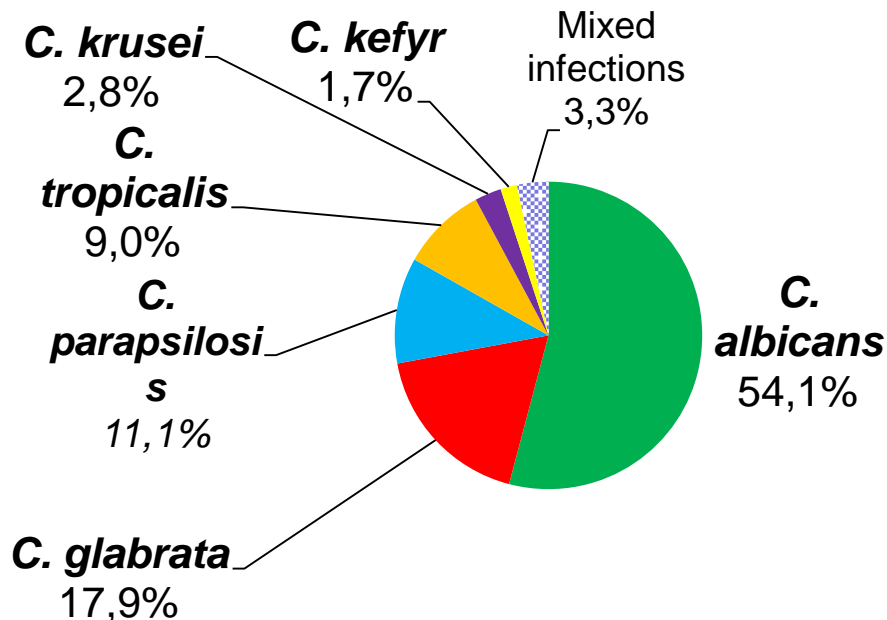
- ✓ **N° 1: Fungemia (48.7%)**
- ✓ **N° 2: *P. jirovecii* pneumonia (19.8%)**
- ✓ **N° 3: Invasive aspergillosis (16.4%)**

IFI Incidence Trends (PMSI 2001-2010)



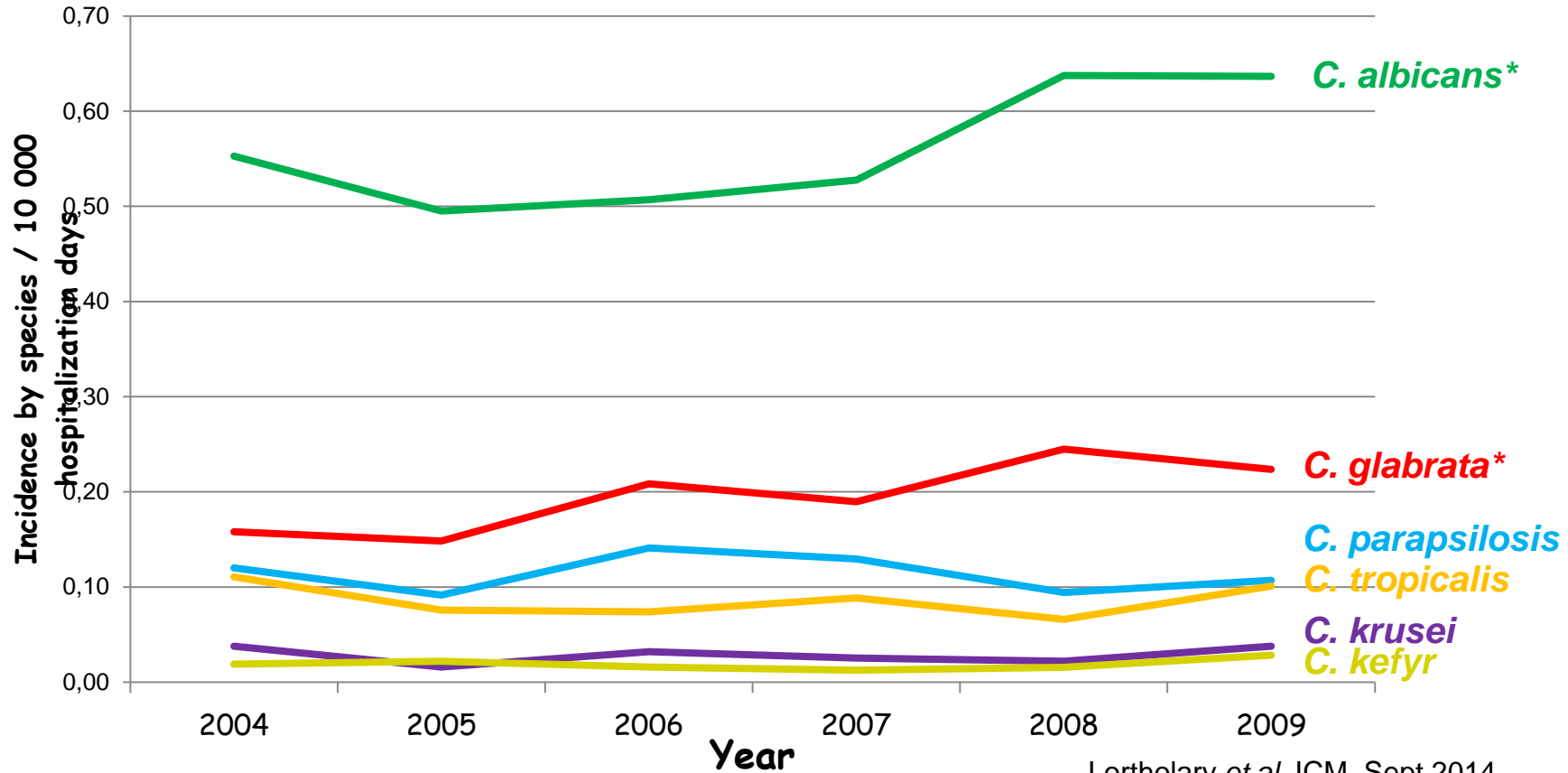
Characteristics of 2507 incident episodes of candidemia in Paris area

Patients' characteristics (N=2507)	
Male gender	60,3%
Mean age (\pm sd) years	60 (\pm 17)
Intensive care unit	48.1%
Malignancy	50.3%
Prior surgery (30 days)	38.7%
Central venous catheter	74%



2571 isolates in 2507 incident episodes
(2424 single, 83 mixed infections)

Incidence by species



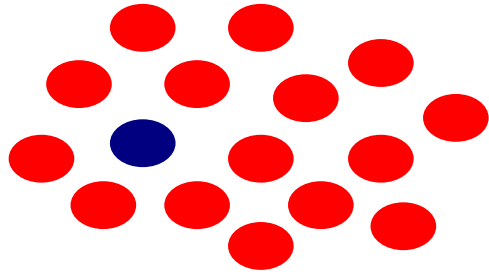
Definition : EUCAST clinical breakpoints

Antifungal agent	MIC breakpoint (mg/L)														
	<i>C. albicans</i>		<i>C. glabrata</i>		<i>C. krusei</i>		<i>C. parapsilosis</i>		<i>C. tropicalis</i>		<i>C. guilliermondii</i>		Non-species related breakpoints ¹		
	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	
Amphotericin B	1	1	1	1	1	1	1	1	1	1	1	IE	IE	IE	IE
Anidulafungin	0.03	0.03	0.06	0.06	0.06	0.06	0.002	4	0.06	0.06	IE ²	IE ²	IE	IE	
Caspofungin	Note ³	Note ³	Note ³	Note ³	Note ³	Note ³	Note ³	Note ³	Note ³	Note ³	Note ³	IE ²	IE ²	IE	IE
Fluconazole	2	4	0.002	32	-	-	2	4	2	4	IE ²	IE ²	2	4	
Itraconazole	0.06	0.06	IE ²	IE ²	IE ²	IE ²	0.12	0.12	0.12	0.12	IE ²	IE ²	IE	IE	
Micafungin	0.016	0.016	0.03	0.03	IE ⁴	IE ⁴	0.002	2	IE ⁴	IE ⁴	IE ⁴	IE ⁴	IE	IE	
Posaconazole	0.06	0.06	IE ²	IE ²	IE ²	IE ²	0.06	0.06	0.06	0.06	IE ²	IE ²	IE	IE	
Voriconazole	0.12 ⁵	0.12 ⁵	IE	IE	IE	IE	0.12 ⁵	0.12 ⁵	0.12 ⁵	0.12 ⁵	IE ²	IE ²	IE	IE	

Resistance in *Candida* spp.

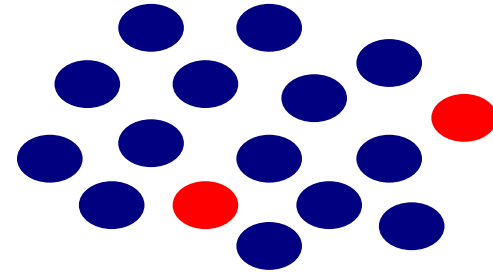
- Resistant isolate
- Susceptible isolate

Intrinsic resistance +++



Resistant species

Acquired resistance



« low process »
No horizontal transmission

Susceptible species

1. Appropriate identification at the species level
2. ATF: most often selection of species with higher MIC values

Fluconazole R *Candida albicans*






MAXIMUM 2%

- *C. albicans* : **2.1%** Fluco R (1992–2000) 1.6% (2005)
Houston *Lewis. Curr Med Res Opin 2009*
- *C. albicans* : **0%** Fluco R (SENTRY 2008–2009)
International *Pfaller et al. AAC 2011*
- *C. albicans* : **0–2%** Fluco R (6082 isolates 1992–2001)
International *Pfaller et al. AAC 2011*
- *C. albicans* : **0%** Fluco R (107 candidemia 33 months, 2005–2008)
UK *Das et al. Int J Infect Dis 2011*
- *C. albicans* : **2%** Fluco R (348 candidemia 2008–2010)
Italy *Bassetti et al. PLoS ONE 2011*



Echinocandin resistant *Candida* isolates

Historically rare in the absence of prior exposure !

- **5%** Caspofungin R (168 *Candida* sp 2001–2007)
Houston *Sipsas et al. Cancer 2009* 
- **0–1%** MIC >2 Caspofungin (13147 *Candida* sp 1992–2006)
International database *Lewis et al. Curr Med Res Opin 2009* 
- **0–2%** Caspofungin R (238 bloodstream isolates 2005–2006)
Sweden *Axner-Elings et al. JCM 2011* 
- **0.4%** (6/1643) Caspofungin R among *C. albicans*, *C. glabrata*
and *C. krusei* isolates (1643 isolates, 2002–2009) Paris
Dannaoui et al. Emerg Infect Dis 2012 
- **1%** Echinocandin R (2329 *Candida* spp. 65% *C. glabrata* 2008–2011)
Atlanta & Baltimore *Cleveland et al. CID 2012* 

→ Recent increase: 1.2 to 2.9% (+ 147%) and 2.0 to 3.5% (+ 77%) from 2008 to 2013 in Atlanta and Baltimore *Cleveland et al. PLoS ONE 2015*

Echinocandin resistant / MDR *Candida glabrata* isolates (2012-2014)

Does exist in the absence of prior exposure !



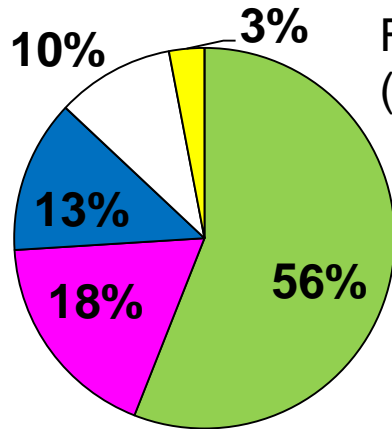
% Echinocandin R	% MDR (azoles & echinocandins)	Reference
	1	CDC Sentry, Pfaller JCM 2012
	1	Pham AAC 2014
11 (18% <i>FKS</i> mutants)	-	Beyda CID 2014
6.7 (increase 2001-2010)	3.5	Alexander CID 2013
10.3	6.8	Farmakiotis EID 2014
	2.6	Cleveland PLoS ONE 2015

First isolation of cholesterol dependent MDR *C. glabrata* (AmB & azoles)



Influence of recent* FCZ / CAS exposure on *Candida* spp. distribution during fungemia

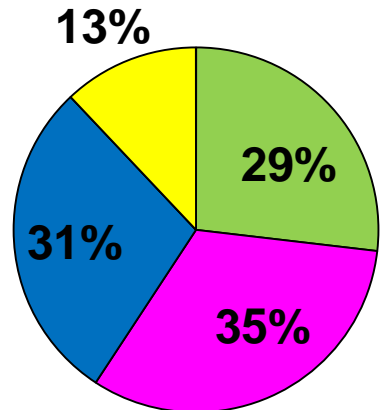
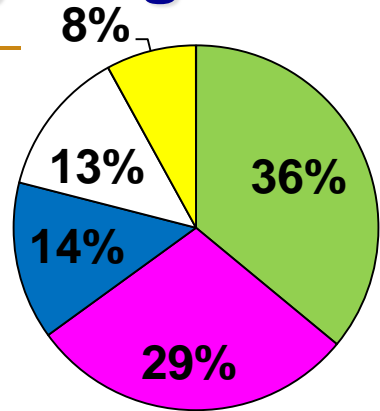
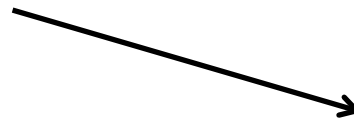
- *C.albicans*
- *C.glabrata*
- *C.parapsilosis*
- *C.tropicalis*
- *C.krusei*



Fluconazole (n=159)
(P<0.001)



Caspofungin (n=61)
(P<0.001)



*recent ≤ 30 d

Risk of candidemia due to fluconazole non-susceptible isolates

- ✓ **Candipop study, 29 hospitals, Spain 2010-2011:**

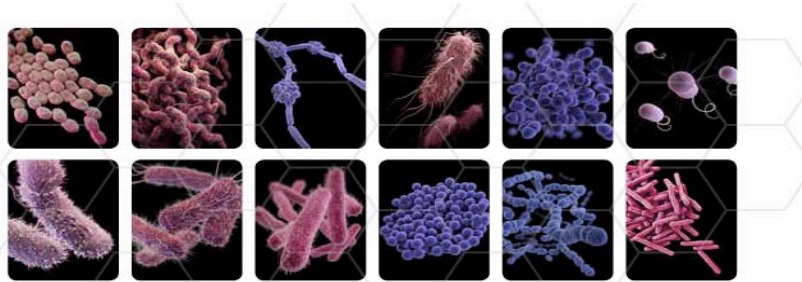
617 patients (21.7% FCZ non-susceptible)

- ✓ **Independent factors with FCZ-NS:**

- Transplant recipient (AOR 2.13; 95% CI 1.01-4.55)
- Hospitalization in a unit with high prevalence ($\geq 15\%$) of FCZ-NS strains (7.53; 4.68-12.10)
- Previous azole therapy ($\geq 3d$, within 30 d) (2.04; 1.16-3.62)

- ✓ **Definition and validation of a predictive score**

Public health impact of fluconazole resistance in *Candida* ?



THREAT LEVEL
SERIOUS



These bacteria are a serious concern and require prompt and sustained action to ensure the problem does not grow.

MICROORGANISMS WITH A THREAT LEVEL OF SERIOUS

Multidrug-resistant *Acinetobacter*

Drug-resistant *Campylobacter*

Fluconazole-resistant *Candida* (a fungus)

Extended spectrum β -lactamase producing *Enterobacteriaceae* (ESBLs)

Vancomycin-resistant *Enterococcus* (VRE)

Multidrug-resistant *Pseudomonas aeruginosa*

Drug-resistant non-typhoidal *Salmonella*

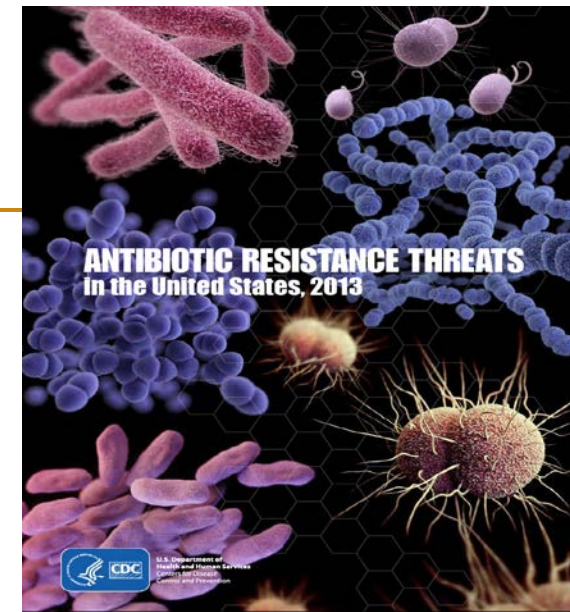
Drug-resistant *Salmonella* Typhi

Drug-resistant *Shigella*

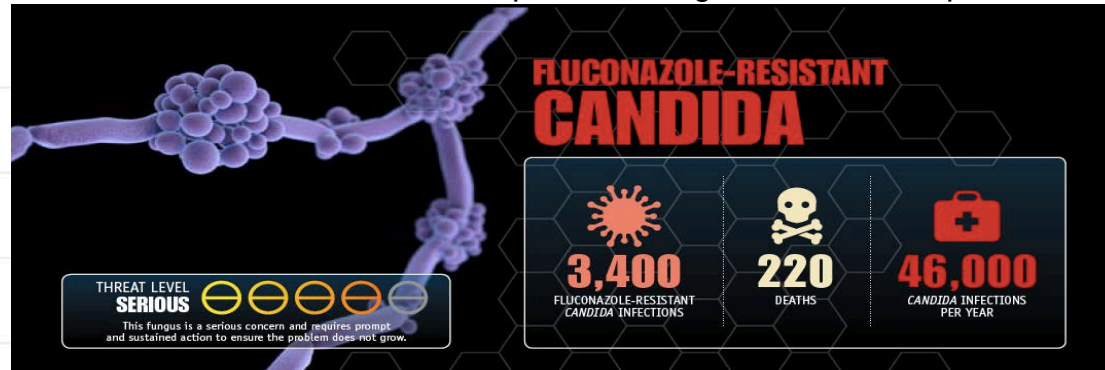
Methicillin-resistant *Staphylococcus aureus* (MRSA)

Drug-resistant *Streptococcus pneumoniae*

Drug-resistant tuberculosis



<http://www.cdc.gov> ; Threats Report 2013



Echinocandin exposure in hematology associated with echinocandin reduced activity during subsequent candidemia

- ✓ Matched case-control study (51/102 pts) in Paris
- ✓ October 2002–February 2010
- ✓ Matching for center and date; MIC ≥ 0.5 $\mu\text{g/ml}$

Blanchard, AAC 2011

Multivariate analysis	OR	CI 95%	<i>p</i>
Prior exposure to caspofungin (< 30 days)	5.25	[1.68-16.35]	0.004
Age at fungemia (≤ 65 yrs vs > 65 yrs)	3.27	[1.26-8.50]	0.015

→ Impact of echinocandin exposure confirmed in various studies:

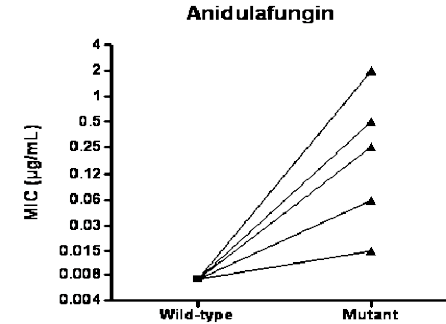
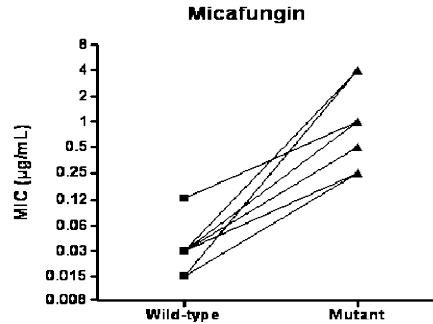
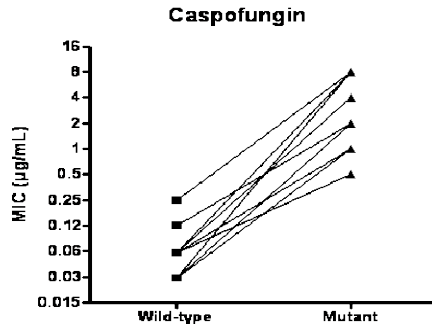
Shields AAC 2012, Alexander CID 2013, Beyda CID 2014, Farmakiotis EID 2014

→ Role of micafungin low dosage (50 mg/d) as prophylaxis : *Bizerra AAC 2014*

Emergence of *Candida* spp. infections with acquired echinocandin resistance in France

- ✓ **20 episodes in patients** (19 prior treatment by caspofungin including 13/19 currently receiving it [median 27 d (10–270 d)])
- ✓ **10 *C. glabrata*, 8 *C. albicans* and 2 *C. krusei***
- ✓ **14 episodes with initial and subsequent isolates : same genotype**
- ✓ **All mutated in Fksp sequence** (Hot Spot 1 FKS1 for *C. albicans* ; FKS1 or 2 for *C. glabrata*)

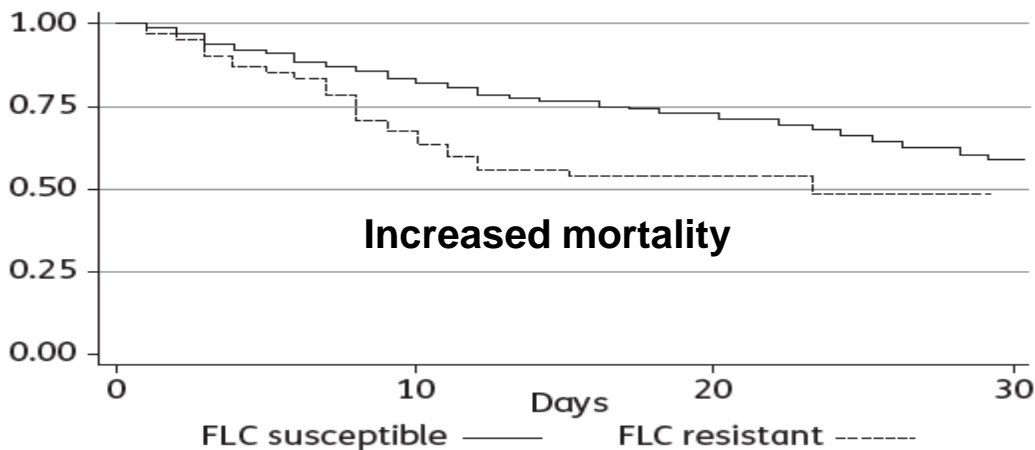
« Cross resistance »



Impact of echinocandin exposure on *C. glabrata*

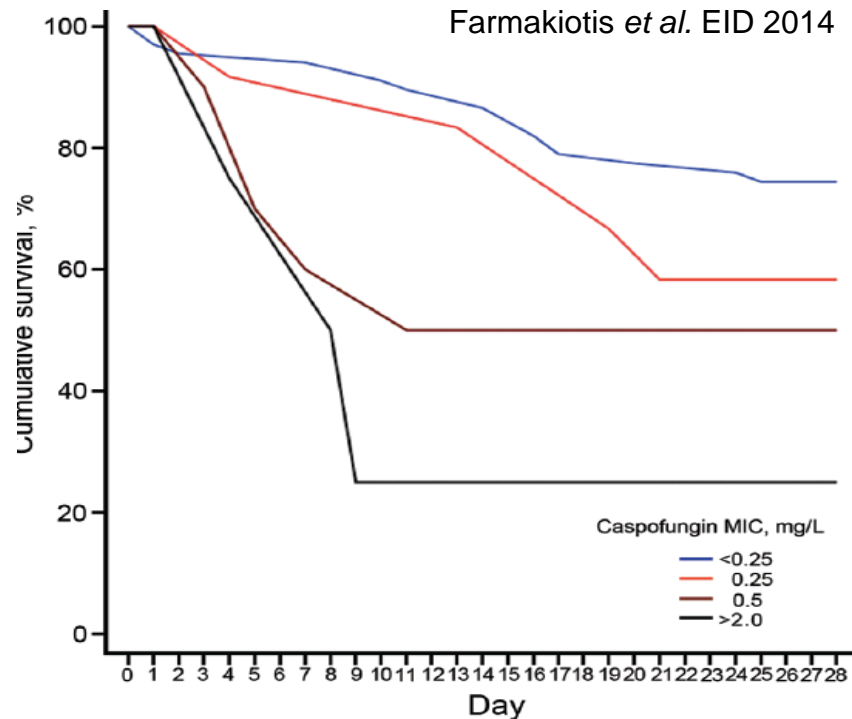
- ✓ **Multiply resistant *C. glabrata*:**
 - 78 FCZ R isolates => 14.1% with resistance to ≥ 1 echinocandin
- ✓ **Failure of echinocandin therapy during invasive candidiasis**
 - Relationship with prior echinocandin exposure
 - Impact of *FKS* mutations and elevated MICs
 - Failure rate : 60-91%

Impact of resistance during candidemia in onco-hematology patients



138 episodes; 39 FCZ resistant; CLSI; Australia
2001–2004

Slavin *et al.* JAC 2010



Farmakiotis *et al.* EID 2014

146 episodes *C. glabrata*; 30 FCZ/15 CAS resistant; CLSI; Houston 2005–2013

Why so few *Candida* spp. amphotericin B resistant ?

OPEN ACCESS Freely available online

 PLOS | BIOLOGY

Oct 2013

Fitness Trade-offs Restrict the Evolution of Resistance to Amphotericin B

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Amphotericin B resistant mutants :

- hypersensitive to oxidative stress, febrile temperatures, killing by neutrophils
- defects in filamentation and tissue invasion
- avirulent in a murine model

ESCMID 2012 Recommendations

✓ Candidemia in non neutropenic patients

Intervention	SoR	QoE	Comment
Anidulafungin 200/100 mg	A	I	Consider local epidemiology (<i>Candida parapsilosis</i> , <i>Candida krusei</i>), less drug–drug interactions than caspofungin
Caspofungin 70/50 mg	A	I	
Micafungin 100 mg	A	I	Consider local epidemiology (<i>C. parapsilosis</i>), less drug–drug interactions than caspofungin, consider EMA warning label
Amphotericin B liposomal 3 mg/kg	B	I	Similar efficacy as micafungin, higher renal toxicity than micafungin
Voriconazole 6/3 mg/kg/day ^{a,b}	B	I	Limited spectrum compared to echinocandins, drug–drug interactions, limitation of IV formulation in renal impairment, consider therapeutic drug monitoring
Fluconazole 400–800 mg ^a	C	I	Limited spectrum, inferiority to anidulafungin (especially in the subgroup with high APACHE scores), may be better than echinocandins against <i>C. parapsilosis</i>

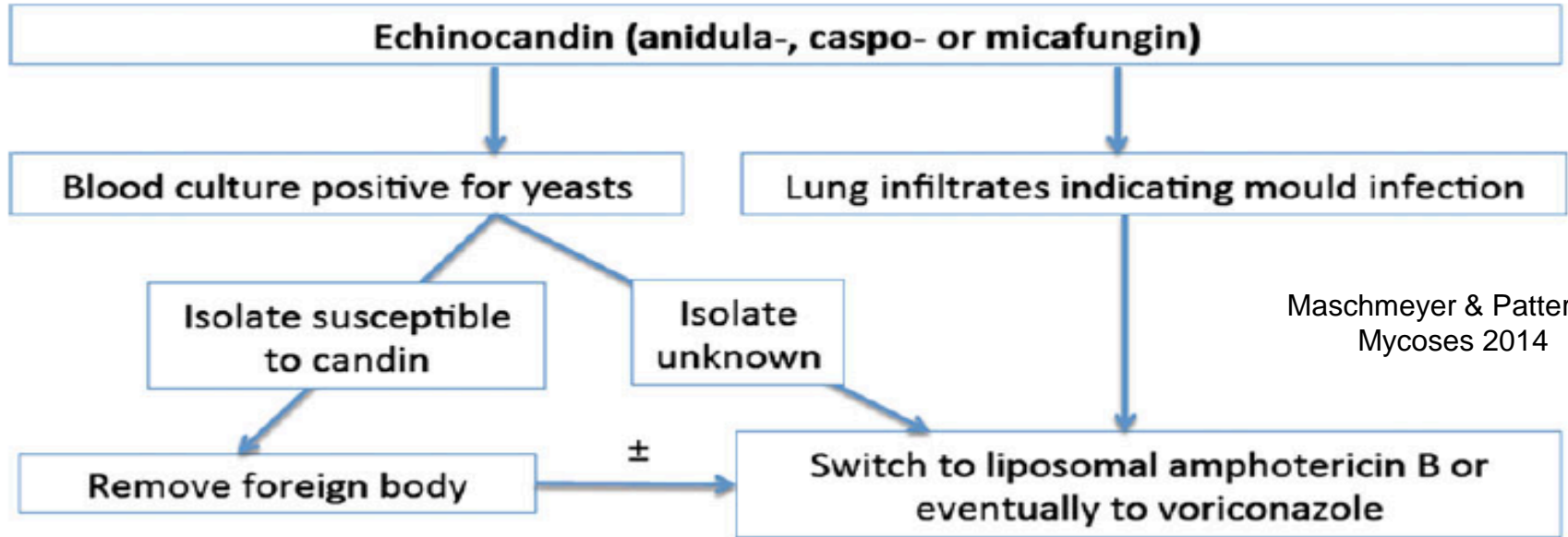
- **Duration of therapy 14d after the last positive culture** (daily BC until negativation)
- **Catheter withdrawal strongly recommended.** If not feasible, use an echinocandin or a lipid formulation of AmB

Exposure to ATF and/or resistance influences IDSA guidelines

Condition or treatment group	Therapy			
	Primary		Alternative	
	Recommendation	Rank	Recommendation	Rank
Non-neutropenic patients				
Candidaemia (targeted therapy)	Fluconazole or an echinocandin	A-I	Lipid formulation of AmB (LFAmB) or amphotericin B deoxycholate (AmB-d) or voriconazole	A-I (B-III for VRCZ)
Suspected candidiasis (empirical therapy)	As for candidaemia; echinocandin or fluconazole preferred	B-III	LFAmB or AmB-d	
Neutropenic patients				
Candidaemia (targeted therapy)	Echinocandin or LFAmB	A-II	Fluconazole or voriconazole	B-III
Suspected candidiasis (empirical therapy)	LFAmB or caspofungin or voriconazole	A-I (B-I for VRCZ)	Fluconazole or itraconazole	B-I

✓ **Echinocandins favoured in patients with recent azole exposure, and as initial therapy in patients at high risk of infection due to *C. glabrata* or *C. krusei* or those who are severely ill**

What to do in case of invasive candidiasis occurring during/shortly after echinocandin exposure?



Maschmeyer & Patterson
Mycoses 2014

What to do in case of invasive candidiasis caused by a MDR *Candida glabrata* isolate...???

Impact of early de escalation on survival during documented or suspected invasive candidiasis in ICU

AMARCAND 2 Study, French ICUs, 835 pts (647 alive at day 5; de escalation 22%)

- ✓ No significant effect of **de escalation** (ie. candins → fluco) at day 5 on 28d survival
- ✓ No significant effect of **stopping** antifungal therapy at day 5 on 28d survival of patients without documented invasive candidiasis

Optimal management of invasive candidiasis in 2015

- ✓ **First line echinocandin** (55% CAS ; [*Amarcand 2 Study, ICM revised*])
 - Spectrum + higher efficacy than fluconazole (*C. albicans*)
- ✓ **Local epidemiology/risk group to be considered**
- ✓ **Take into account prior exposure to echinocandin/azoles**
 - Azole => Candin ; Candin => L-AmB
- ✓ **Early adequate source control**
 - Catheter withdrawal (although persistent controversies)
 - Abdominal surgery ?
- ✓ **Early switching** (when infection controlled)
- ✓ **Urgent need for new antifungals** [*Denning & Bromley, Science 2015*]

Optimal prevention of infections due to *Candida* spp. resistant isolates in 2015

- ✓ « Fungal infections that are resistant to treatment are an emerging public health problem, but everyone has a role in preventing these infections and reducing antifungal resistance » *[CDC website, June 2015]*
- ✓ **Role of a National Reference Center**
 - Multicenter surveillance; ATF susceptibility; identify & understand resistance mechanisms, advice
- ✓ **Infection control staff: antifungal stewardship programs**
- ✓ **Doctors and nurses**
 - Prescribe antifungal medications appropriately
 - Increased awareness on antibacterial use
 - Document the dose, duration, and indication for every antifungal prescription.
 - Stay aware of local antifungal resistance patterns.
 - Follow hand hygiene and other infection control measures with every patient.