



# Geographic variability in the epidemiology of candidemia

**Arnaldo Lopes Colombo**  
Professor of Medicine  
Division of Infectious Diseases  
Federal University of São Paulo, Brazil

# Agenda

- ❖ Global burden of candidemia
- ❖ Status of species distribution
- ❖ Status of Antifungal resistance
  - ❖ Azoles
  - ❖ Echinicandins

# Burden of invasive candidiasis: Is candidemia still a relevant problem Worldwide?

- ✓ The incidence rates of *Candida* BSI assessed by papers published during 1995-2005 was found to be stable, for most centers

*Morgan J. Curr Infect Dis Reports 2005,7:429-39*

- ✓ Specific-patient populations may exhibiting decreasing trends (Ex: ICU patients)

*Trick WE et al Clin Infect Dis 2002, 35:627-630*

- ✓ Differences do exist in the epidemiology of candidemia among different countries

*Colombo AL et al J. Clin. Microbiol. 2006 44(8): 2816-23*

# Incidence rates of Candidemia Worldwide

## Population-based studies

Region Number of studies	Period	No of cases per 100,000 pers. Range (mean)
Europe (6)	1995-2004	1.9 – 11 (4,8)
United States (5)	1992-2000	6.0 – 24 (10,58)
Canada (1)	1999-2004	2.8
Australia (1)	2001-2004	1.81

*Pfaller MA and Diekma DJ Clin Microb Rev 2007; 20(1):133-163*  
*Chen S et al Emerging Infect Dis 2006; 12(10):1508-1516*

# Laboratory-based surveillance of candidemia

# Rates of BSI in the USA and Brazil (per 1,000 admissions)

Pathogen	Brazil	EUA
Coagulase negative staph	11.97	1.58
<i>S. aureus</i>	7.31	1.03
<i>P. aeruginosa</i>	3.68	0.43
<i>Klebsiella</i> sp	2.92	0.48
<i>Candida</i> spp.	2.49	0.46

Colombo et al. *J Clin Microbiol* 2006 (in press)  
Wisplinghoff et al. *Clin Infect Dis* 2004;39:309-17

# Incidence of Candidemia in European Hospitals

Author, year	Study period	Rate / 1,000 admissions	Country
Richet, 1998	1995	0.17	France
Arendrup, 2005	2003-2004	0.49	Denmark
Doczi, 2002	1996-2000	0.2 – 0.4	Hungary
Marchetti, 2003	1991-2000	0.27	Switzerland
Tortorano, 2002	1997-1999	0.38	Italy
Garbino, 2000	1990-1999	0.62	Switzerland
Viudes, 2002	1995-1997	0.76	Spain
Almirante, 2005	2002-2003	0.53	Spain
Colombo, 2007 (SP)	2002-2003	1.66	Brazil
Colombo, 2006 (Br)	2003-2004	2.49	Brazil

# Incidence rates of Candidemia in different countries: Latina America vs USA/Europe

Author, year, country	Rate per 1,000 Admissions
Richet, 1998, France	0.17
Viudes, 2002, Spain	0.76
Marchetti, 2003, Switzerland	0.27
Banerjee, 1991, USA	0.28 – 0.61
Pittet, 1995, USA	0.96
Wisplinghoff, 2002, USA	0.46
Paganini, 2002, Argentina*	1.09
Colombo, 2006, Brazil	2.49
Pacheco-Rios, Mexico*	4.70

# Geographic trends on *Candida* species distribution

# Temporal trends in terms of Candida BSI species distribution

- ✓ Decreasing incidence of isolation of *C albicans*

*Ruhnke et al, Current Drugs Target 2006*  
*Pfaller & Diekma Clin Microbiol Reviews, 2007*

- ✓ Increasing incidence of *C tropicalis*: mostly Latin America, Asia, Middle- east

*Nucci & Colombo Diagn Microbiol Infect Dis, 2007*

- ✓ Increasing incidence of *C parapsilosis*: mostly in LATIN AMERICA and some European centers

*San Miguel et al Infect Control Hosp Epidemiol 2005*  
*Colombo et al Drugs Today, 2008*

- ✓ *C glabrata* became a major agent of candidemia in USA

*Warnock D Jpn J Med Mycol, 2007*

# *C glabrata*: the first most common non-*albicans* species in 8/9 USA regions

Species distribution of 3,863 *Candida* BSI collected during 1992-2001 in 9 different geographic areas within USA

% of isolates by US census region

Species	1	2	3	4	5	6	7	8	9	All
No. tested	439	261	302	162	376	94	83	736	1230	3863
<i>C. albicans</i>	48.7	64.5	60.6	56.8	47.6	61.7	47.0	51.1	56.4	54.4
<i>C. glabrata</i>	18.5	15.3	18.9	11.7	26.3	18.0	37.3	18.8	15.5	18.3
<i>C. parapsilosis</i>	18.5	4.6	7.6	13.6	10.7	4.3	9.7	17.1	13.9	13.2
<i>C. tropicalis</i>	9.6	8.8	10.6	9.9	9.3	11.7	4.8	8.7	10.3	9.6
<i>C. krusei</i>	2.5	1.1	0.7	5.6	3.7	4.3	1.2	1.9	1.6	2.1
<i>C. lusitanae</i>	1.6	2.7	0.9	1.2	2.4	0.0	0.0	1.2	0.9	1.3
<i>C. guilliermondii</i>	0.6	1.5	0.0	0.0	0.0	0.0	0.0	0.5	0.5	0.5
Other species <sup>a</sup>	0.0	1.5	0.7	0.6	0.0	0.0	0.0	0.7	0.9	0.6

# Species distribution of *Candida* BSI in Europe

## Relevance of *C parapsilosis* and *C glabrata*

	Italy <sup>1</sup> (136)	France <sup>2</sup> (156)	Switzerland <sup>3</sup> (1,137)	Spain <sup>4</sup> (351)	Europe <sup>5</sup> (2,089)
<i>C. albicans</i>	61	53	64-66	51	56
<i>C. parapsilosis</i>	16	16	6-1	23	13
<i>C. tropicalis</i>	5	10	2-9	10	6
<i>C. glabrata</i>	9.5	11	14-15	9	13
Others	8,5	10	14-9	7	8

<sup>1</sup>Bassetti et al Diagn Microbiol Infect Dis 2007; 58:325-331

<sup>2</sup>Richetat al., Clin. Microbiol. Infect. 8:450-412, 2002

<sup>3</sup>Marchetti et al., Clin. Infect. Dis. 38:311-320, 2004

<sup>4</sup>Almirante et al., J. Clin. Microbiol. 43(4):1829- 1835, 2005

<sup>5</sup>Tortorano et al., Eur. J .Clin. Microbiol. Infect. Dis. 23:317-322, 2004

# Species distribution of *Candida* BSI in ASIA

## Relevance of *C tropicalis* and *C glabrata*

	Singapore <sup>1</sup> (52)	India <sup>2</sup> (275)	India <sup>3</sup> (579)	Taiwan <sup>4</sup> (179)	Taiwan <sup>5</sup> (383)
<i>C. albicans</i>	29↓	21.5↓	25↓	63	55,6
<i>C. parapsilosis</i>	10	20	6	10	17,5
<i>C. tropicalis</i>	36	35,3	42	12	16,5
<i>C. glabrata</i>	21	17,5	2	11	5,2
Others	4	5,7	25	4	5,2

<sup>1</sup> Chai et al *Medical Mycology* ; 45:435-439, 2007

<sup>2</sup> Xess., *Infection*. 35:256-259, 2007

<sup>3</sup> Chakrabati et al., *Indian J Med Research*. 104:171-76, 1996

<sup>4</sup> Tsai et al., *J Microbiol Immunol Infect*. 41:414-421, 2008

<sup>5</sup> Chen et al., *Diagn Microbiol Infect Dis*. 48:33-37, 2004

# Geographic distribution of *Candida* BSI Brazil vs Europe

	Brazil (712)	France <sup>1</sup> (156)	Switzerland <sup>2</sup> (1,137)	Spain <sup>3</sup> (351)	Europe <sup>4</sup> (2,089)
<i>C. albicans</i>	41	53	64-66	51	56
<i>C. parapsilosis</i>	20* ↑	16	6-1	23	13
<i>C. tropicalis</i>	21* ↑	10	2-9	10	6
<i>C. glabrata</i>	5* ↓	11	14-15	9	13
Others	13	10	14-9	7	8

P value < 0,05

<sup>1</sup> Richetat al., *Clin. Microbiol. Infect.* 8:450-412, 2002

<sup>2</sup> Marchetti et al., *Clin. Infect. Dis.* 38:311-320, 2004

<sup>3</sup> Almirante et al., *J. Clin. Microbiol.* 43(4):1829- 1835, 2005

<sup>4</sup> Tortorano et al., *Eur. J .Clin. Microbiol. Infect. Dis.* 23:317-322, 2004

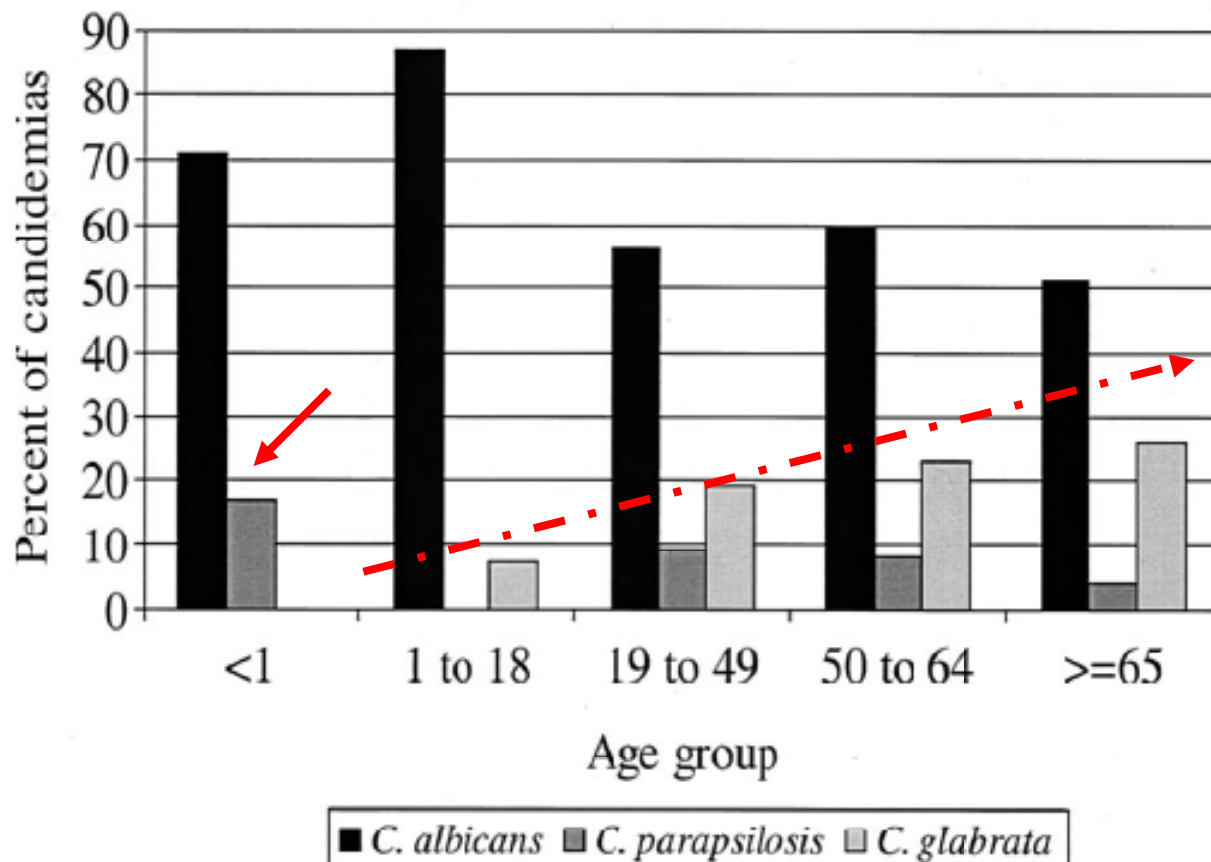
# Regional Distribution of *C parapsilosis*, *C orthopsilosis* and *C metapsilosis* (ARTEMIS: 89 medical centers-29 countries)

Variables	<i>C parapsilosis</i>	<i>C orthopsilosis</i>	<i>C metapsilosis</i>
North America	600	32 (5%)	4 (0,6)
South America*	337	42 (11%)*	5 (1,3)
Europe and Middle East	454	17 (3,5%)	14 (2,9)

\*p value < 0,05

Lockhart et al J Clin Microbiol 46(8): 2659:2664,2008

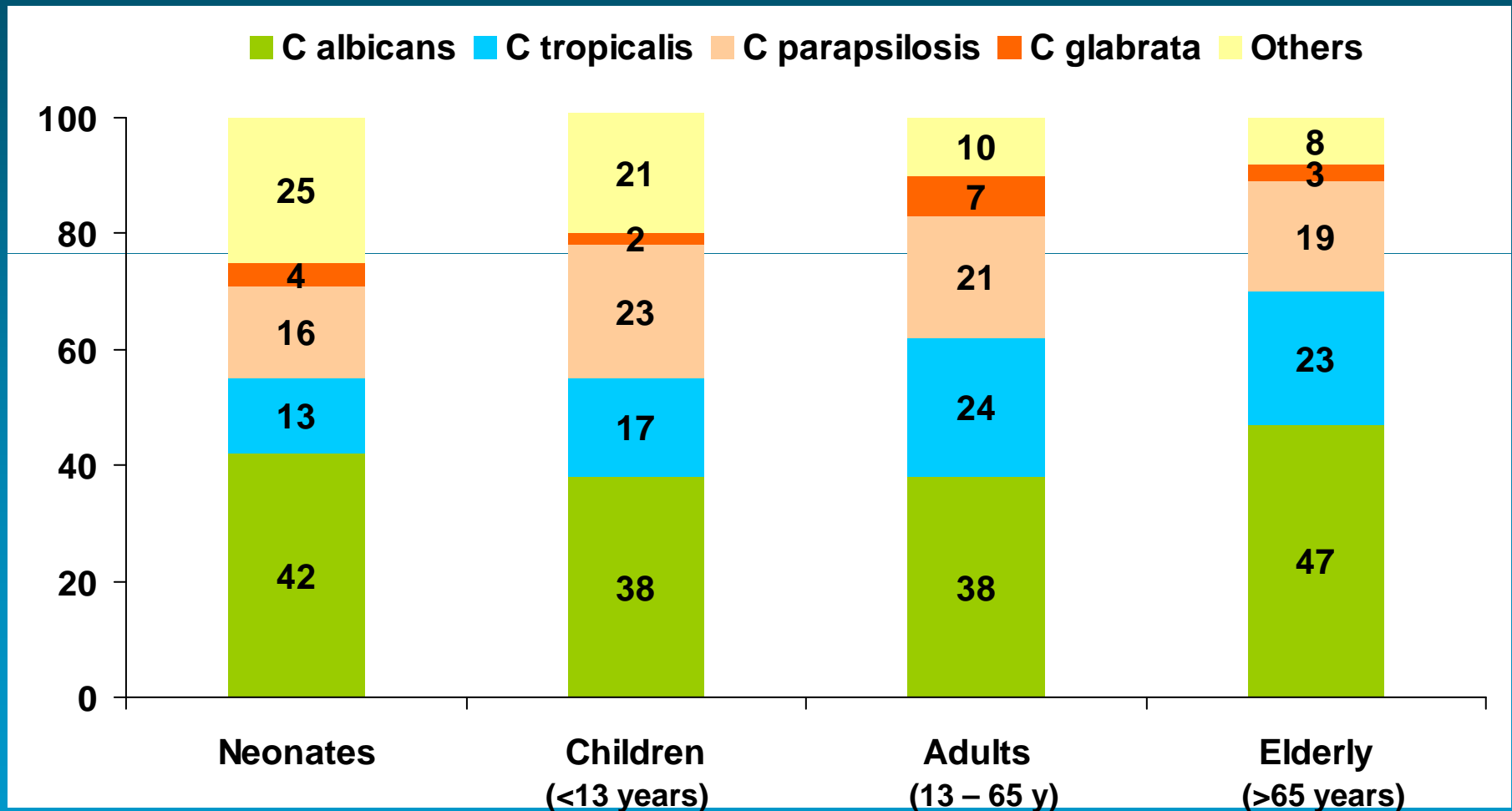
# Iowa Survey: IMPACT OF AGING in Species Distribution of Candidemia



1. Predominance of *C. parapsilosis* among Non *albicans* strains in neonates

2. ↑ *C. glabrata* with increasing patient age

# Species Distribution of 712 episodes of Candidemia in Different Age Groups



**Geographic and temporal trends  
on *Candida* resistance to  
Fluconazole**

# Temporal trends in terms of Fluconazole resistance to *Candida* strains

The longitudinal nature of the ARTEMIS Disk surveillance program provides robust data to evaluate trends in terms of fluconazole resistance:

- 1) *C albicans*, *C parapsilosis* and *C tropicalis*: most isolates (> 95% remain susceptible to FLUCO)
- 2) Elevated rates of resistance were noted with
  - C glabrata* (from 14% to 23%)
  - C guilliermondii* (from 6% to 26%)
  - C rugosa* (from 14% to 66%)
  - C famata* (from 10% to 44%)

*Pfaller et al J Clin Microbiol., 2005 43(12):5848-5859*

*Pfaller et al., Clin. Microbiol. Rev., 2006, 19: 435-447*

*Pfaller MA and Diekma DJ Clin Microb Rev 2007; 20(1):133-163*

**Worldwide surveillance of fluconazole  
Resistance  
Network ARTEMIS-BIOMIC  
CLSI-agar-based method**

# Geographic variation in the susceptibility of 205,329 *Candida* spp to azoles (ARTEMIS-BIOMIC)

Region	Drugs	<i>C. albicans</i>		<i>C. glabrata</i>		<i>C tropicalis</i>	
		N	% R	N	%R	N	%R
EUROPE	Fluco	52,127	1.2	8,642	16	3,930	2.6
	Vori	50,926	1.1	8,492	9.9	3,817	3.5
Latin America	Fluco	10,288	2.4	1,472	14	2,525	3.0
	Vori	9,830	1.9	1,434	9.6	2,423	4.4
North America	Fluco	4,644	5.1	2,106	20.5	740	3.6
	Vori	4,608	3.7	2,098	15.3	729	4.7

*Pfaller, Diekma, Gibbs, Newell, Meis, Gould, Fu, Colombo AI, Rodriguez-Noriega  
J Clin Microbiol 45:1735-1745, 2007*

# Candida spp resistance to Fluconazole and Voriconazole by using the CLSI Agar-based method (ARTEMIS-BIOMIC)

Region	Antifungal agent	No. of isolates tested	% Resistant
Asia-Pacific	Fluconazole	1,859	10.6
	Voriconazole	1,727	4.1
Europe	Fluconazole	4,962	16.5
	Voriconazole	4,801	5.6
Latin America	Fluconazole	940	13.2
	Voriconazole	910	5.4
North America	Fluconazole	1,276	18.0
	Voriconazole	1,278	9.0

Candida Resistance to FLUCO : Europe  $\cong$  USA and  $\gg$  Latin America and Asia

# Burden of FLUCO-R among BSI Candida strains: Brazil vs. USA (CLSI-microbroth)

Author	Medical centers	BSI Time	% <i>C alb</i>	% <i>C trop</i>	% <i>C glab</i>
Pfaller, 2002	SENTRY	2,047 97-00	1	0	7
Diekema, 2002	17	254 98-01	0	0	10
L Ostrosky, 2003	34	2,000 95-99	5	8	8
Hajjeh, 2004	47	935 98-00	1.2	6	7
Colombo, 2006	11	712 03-04	0.3	0	6
Colombo, 2007	5	1,000 95-03	0	0	4.5

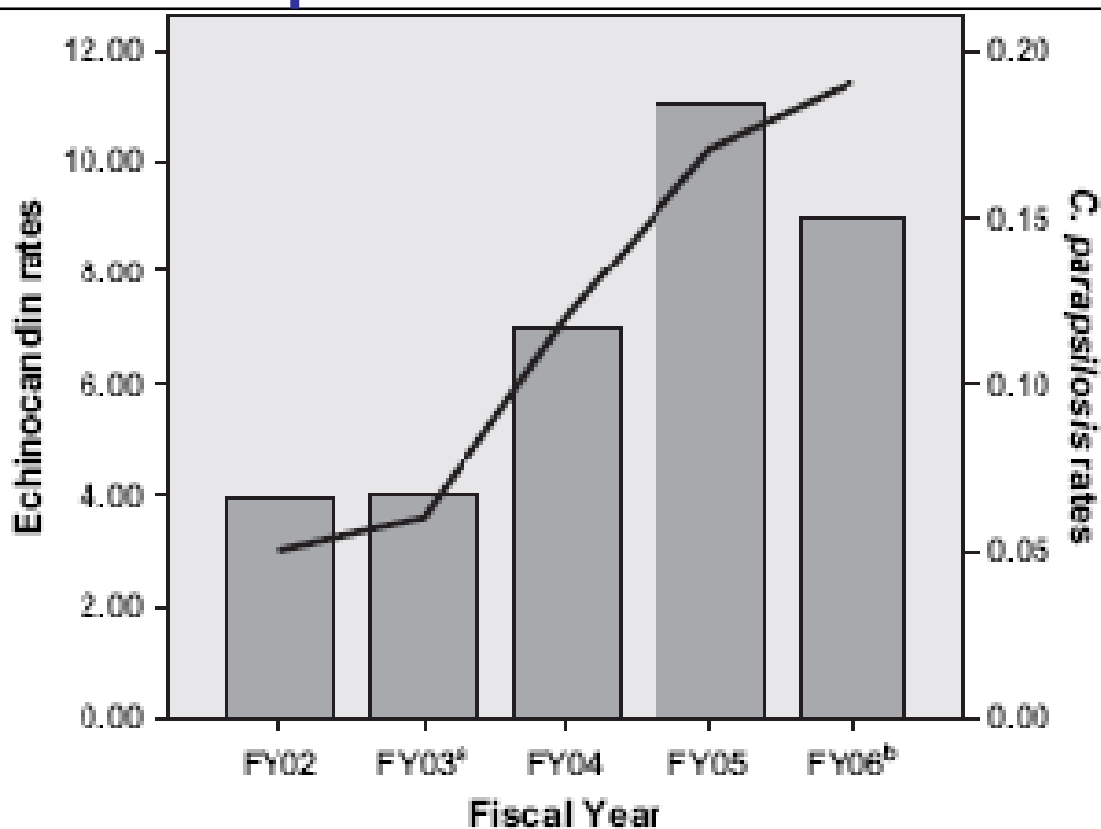
**Controversial issue:  
Clinical relevance  
Echinocandin MICs against  
*C parapsilosis***

# MIC-90 values of all 3 echinocandins against *Candida* spp

<i>Candida</i> Species	MIC <sub>90</sub> (µg/mL)		
	Caspofungin	Micafungin	Anidulafungin
<i>Albicans</i>	0.12–1	0.01–0.25	0.01–0.5
<i>Glabrata</i>	0.25–1	0.01–0.5	0.03–8
<i>Parapsilosis</i>	1–4	1.0–>8	2.0–>8
<i>Tropicalis</i>	0.12–1	0.03–2	0.06–2
<i>Krusei</i>	0.5–2	0.12–0.25	0.03–1
<i>Lusitanae</i>	0.5–2	2 <sup>b</sup>	0.12–>8
<i>Guilliermondii</i>	1–>8	2	1–4 <sup>c</sup>

# Increasing incidence of *C parapsilosis* candidemia after echinocandin use??

University of Maryland-USA:  
469 episodes of candidemia



## Limitations of the study

1. Retrospective and incomplete analysis of data
2. Problems with infection control strategies in the hospital ??
3. Outbreaks ??  
No strain typing was performed
4. Any change in risk population??
- 4 Increase of casuistic of community acquired candidemia??

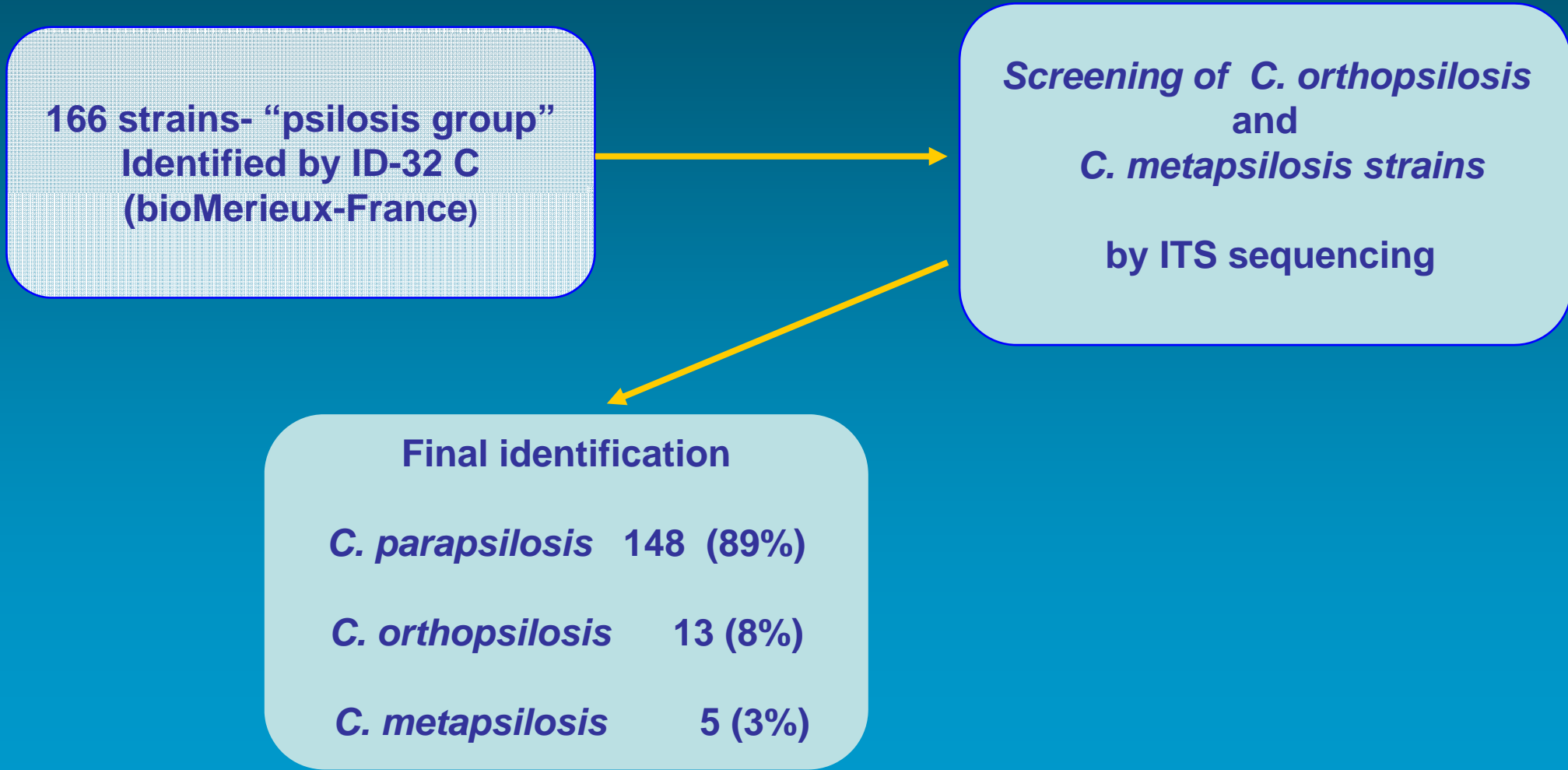
# In vitro susceptibility of 5,346 *Candida* spp against 3 echinocandins

- ✓ Isolates collected worldwide and tested by the CLSI microbroth (RPMI, 24 h reading, MIC-2)
- ✓ 97 – 100% of all isolates tested exhibited susceptibility at the MIC  $\leq 2 \mu\text{g/ml}$  against ANIDULA, MICA and CASPO
- ✓ NO CHANGE OVER TIME in the *in vitro* susceptibility to echinocandins (6 years-period)

# ECHINOCANDIN RESISTANCE : “*clinically and microbiologically documented*”

Author	<i>Candida</i> spp	Infection
Hernandez et al	<i>C albicans</i>	Esofagites (HIV)
Laverdiere et al	<i>C albicans</i>	Esofagites (HIV)
Miller ey al	<i>C albicans</i>	Esofagites (HIV)
Park et al	<i>C albicans</i> (2)	Hematogenous candidiasis
Daneman et al	<i>C glabrata</i> (3)	Hematogenous candidiasis
Dogson et al	<i>C glabrata</i>	Hematogenous candidiasis
Krogh- Madsen et al	<i>C glabrata</i>	Hematogenous candidiasis
Villareal et al	<i>C glabrata</i>	Hematogenous candidiasis
Cleary et al	<i>C glabrata</i>	Hematogenous candidiasis
Hakki et al	<i>C krusei</i>	Hematogenous candidiasis
Park et al	<i>C krusei</i>	Hematogenous candidiasis
<b>Moudegal et al</b>	<b><i>C parapsilosis</i></b>	<b>Prosthetic valve endocardites</b>

# “Psilosis group in Brazil”: Prevalence of *C. orthopsilosis* and *C. metapsilosis* among 166 yeast blood stream isolates originally identified as *C. parapsilosis*



# Caspofungin MICs against 166 blood stream isolates of the “psilosis group”

Species	N isolates tested	MIC-50% μg/ml	MIC-90% μg/ml	MIC ≥ 4 μg/ml
<i>C parapsilosis</i>	148	1.0	1.0	ZERO
<i>C orthopsilosis</i>	13	1.0	1.0	ZERO
<i>C metapsilosis</i>	5	----	----	ZERO

Sarah, Amorim C, Melo A, Nucci M, Godoy P, Colombo AL (Submitted)