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SAPIENZA
UNIVERSITÀ DI ROMA

Candida bloodstream infections: species distribution and antifungal resistance in General Medicine wards and in Intensive Care Units (ICUs)

Maria Teresa Mascellino

Las Vegas, August 5th-7th 2013

Clinical presentations of fungal infections

Life-threatening

- Superficial infections (skin, nails, hairs) -
  - Dermatophytes
- Mucosal infections (oro-pharynx, vagina) -
  - *Candida* spp.
- Invasive infections (blood, organs, brain) +
  - *Candida* spp.
  - *Aspergillus* spp.
  - *Cryptococcus* spp.
  - Other Fungi (*Fusarium* spp., *Mucor* spp., *Scedosporium*)

Critical Reviews in Microbiology, 2010; 36(1): 1–53

informa
healthcare

REVIEW ARTICLE

Epidemiology of Invasive Mycoses in North America

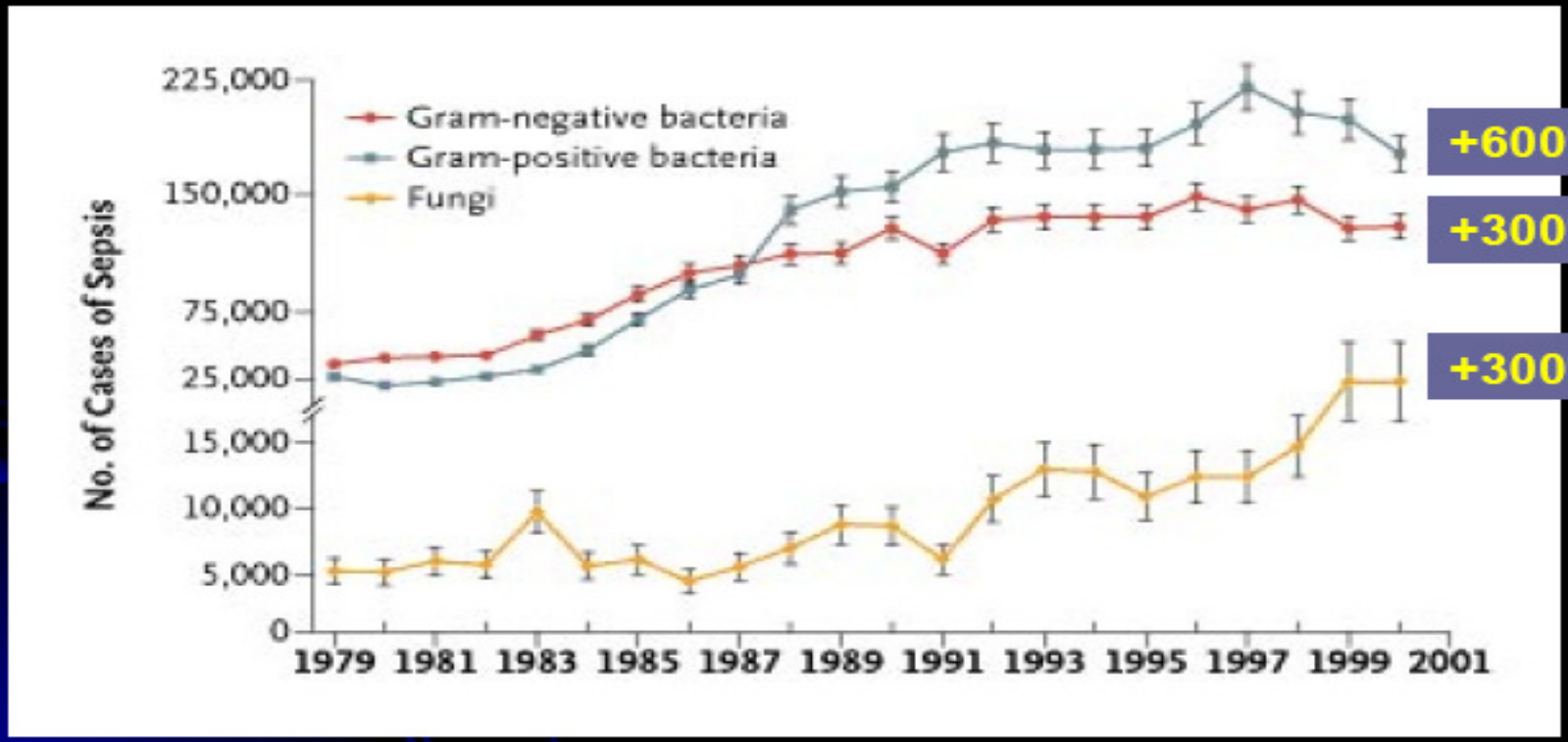
Michael A. Pfaller, and Daniel J. Diekema

Table 3. Cumulative incidences of selected invasive mycoses.

	Incidence per million per year (period)				
	CPHA[a]	CDC[b]	NHDS[c]	CDC[d]	NHDS[e]
Mycosis	(1980–1982)	(1992–1993)	(1996)	(2000)	(2003)
Candidiasis	2.6	72.8	228.2	100.0	290.0
Histoplasmosis	13.9	7.1	13.6	NA[f]	NA
Aspergillosis	8.4	12.4	34.3	NA	22.0
Cryptococcosis	4.0	65.5	29.6	13.0	NA

[a]CPHA, Commission on Hospital and Professional Activities (Reingold et al. 1986).
[b]CDC, Centers for Disease Control and Prevention (Rees et al. 1998).
[c]NHDS, National Hospital Discharge Survey (Wilson et al. 2002).
[d]CDC (Hajjeh et al. 2004; Mirza et al. 2003)
[e]NHDS (Pfaller et al. 2007a).
[f]NA, data not available.

Increasing rate of candidiasis in the US



Mortality:

Bacterial bloodstream infections: 30-50%

Fungal bloodstream infections: 60%

Bacterial Infection vs Fungal Infections

Gram +ve Gram -ve Fungal

Identical clinical syndrome in severe infection/septic shock

Mortality	
Bacterial severe sepsis/septic shock	30-50%
Fungal severe sepsis/septic shock	60%+

Definitions

- **Candidaemia: at least one positive blood culture yielding *Candida spp* in patients with fever or other clinical signs of infection**
- **Nosocomial candidaemia: a candidaemia occurring ≥48h after hospitalisation**
- **Indwelling catheter candidaemia: a semiquantitative culture of the catheter tip yielding >15 colony-forming units (CFU/ml) of *Candida spp***
- **Candidaemia attributable mortality: a candidaemia regarded as the primary cause of death in patients died with microbiological, histological and/or clinical evidence of fungal infection without no other cause of death**

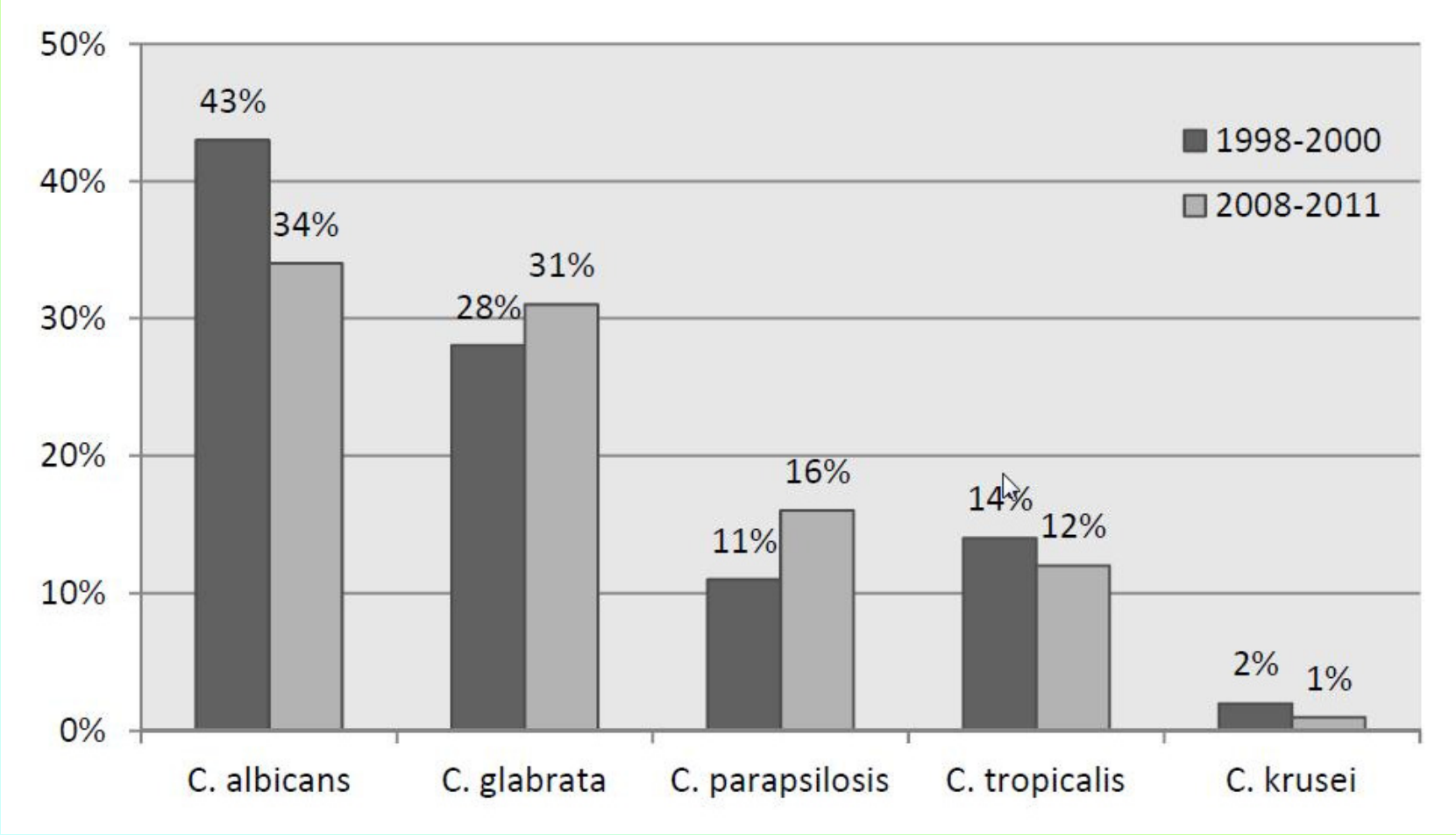
Candidaemia: the problem (1)

- Epidemiology of candidaemia has been the subject of numerous studies and rates as different as 1.2–25 cases per 100000 population or 0.19–2.5 per 1000 admissions have been reported, illustrating the complexity of this topic
- Among the Nordic countries, Norway, Finland and Sweden report incidences of candidaemia around 3/100000 population whereas Denmark reports 11/100000 population in a seminational survey

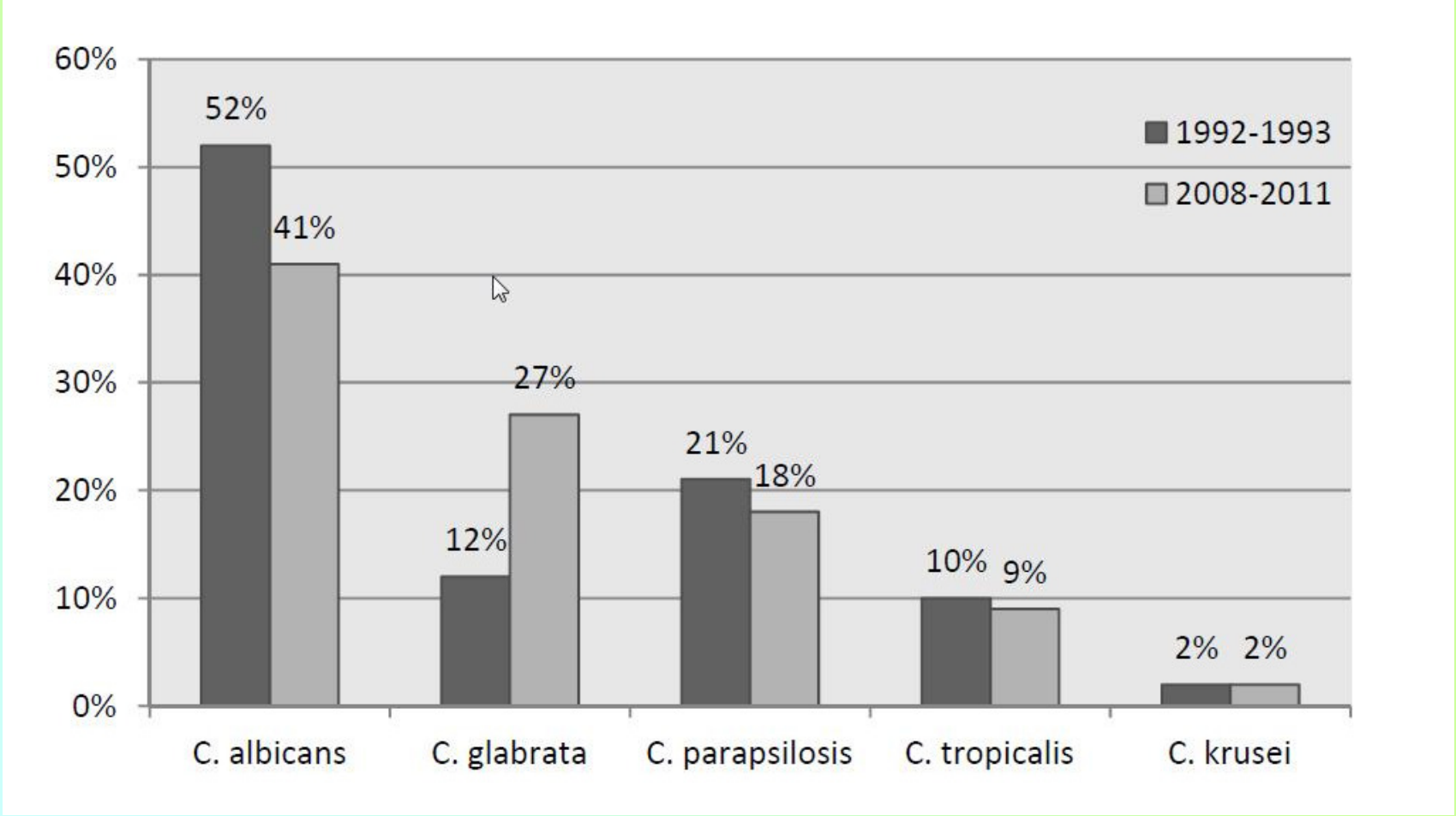
Candidaemia: the problem (2)

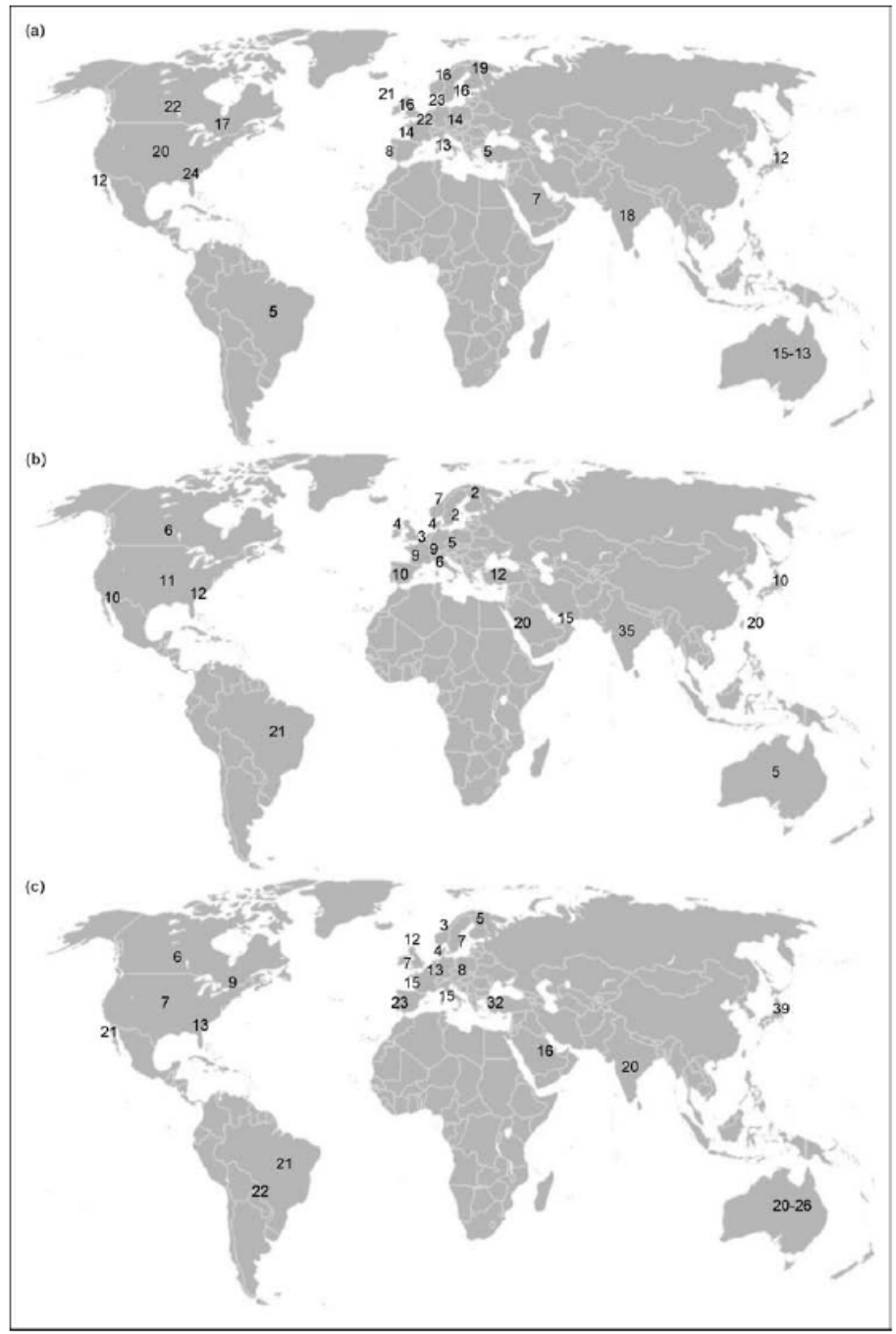
- In the middle and southern parts of Europe population-based surveys in Switzerland, UK, Scotland, Spain and Italy have reported 1.2–6.4 per 100000 population
- Finally, in the US surveys conducted in Iowa, San Francisco, Atlanta and Connecticut rates of 6–14 have been reported with the exception of the Baltimore area reporting 25/100000

Distribution of Candidiasis in Atlanta



Distribution of Candidiasis in Baltimora

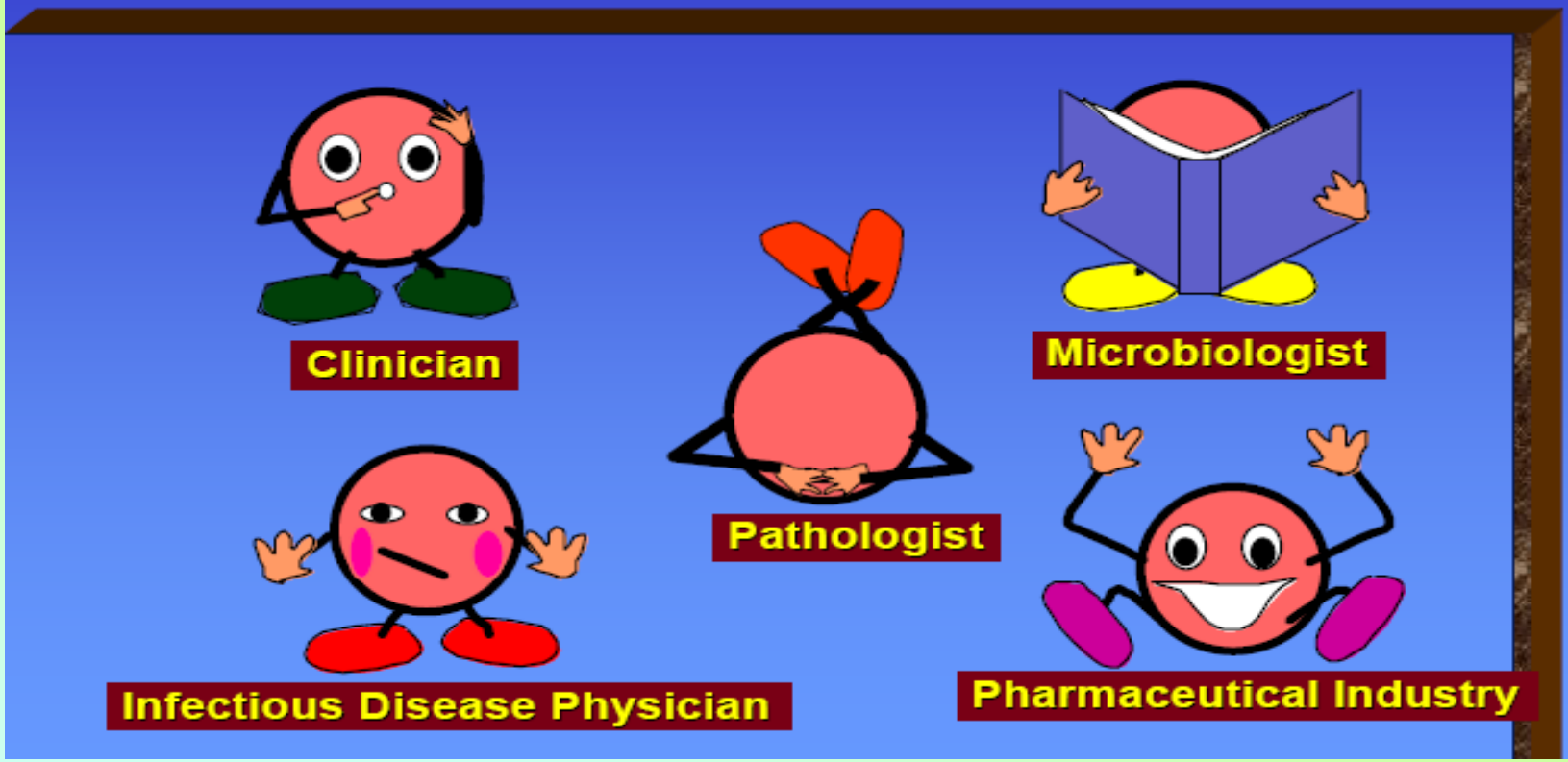




Geographical differences in proportion of candidaemia cases involving *Candida glabrata* (a), *C. tropicalis* (b) and *C. parapsilosis* (c), respectively

From: Arendrup *et al.*, Curr Opin Crit Care, 2010

Diagnosis of invasive candidiasis is often a challenge…..



…clinical manifestation are non specific

….blood cultures are usually positive late in the course of infection

…the usefulness of serological test (β-D-glucan, mannans..) is cotroversial

Table 3
Diagnostic tests used for different types of invasive fungal infections.[a]

Diagnostic test	*Candida* spp.	*Aspergillus* spp.	Endemic fungi	Other yeast	Mucormycetes	Other moulds	Unidentified moulds	Unidentified yeasts
	n = 5036 (%)	*n* = 962 (%)	*n* = 131 (%)	*n* = 462 (%)	*n* = 121 (%)	*n* = 182 (%)	*n* = 53 (%)	*n* = 32 (%)
Culture	5021 (99.7)	687 (71.4)	101 (77.1)	337 (72.9)	100 (82.6)	176 (96.7)	4 (7.5)	21 (65.6)
Histopathology	179 (3.5)	237 (24.6)	60 (45.8)	96 (20.7)	81 (66.9)	76 (41.7)	17 (32.0)	11 (34.3)
Imaging	384 (7.6)	592 (61.5)	41 (31.3)	117 (25.3)	60 (49.5)	70 (38.4)	43 (81.1)	6 (18.7)
Chest radiograph	50 (13.0)	161 (27.2)	16 (39.0)	40 (34.1)	12 (20.0)	10 (14.2)	18 (41.8)	
Computed tomography scan	340 (88.5)	515 (86.9)	35 (85.3)	84 (71.7)	50 (83.3)	57 (81.4)	30 (69.7)	6 (100.0)
Magnetic resonance imaging	25 (6.5)	23 (3.8)	4 (9.76)	11 (9.4)	11 (18.3)	8 (11.4)	1 (2.3)	
Nonculture	136 (2.7)	419 (43.5)	51 (38.9)	215 (46.5)	2 (1.6)	12 (6.5)	37 (69.8)	
Antigen test			41 (80.3)	188 (87.4)				
Galactomannan enzyme immunoassay		399 (95.2)		2 (0.9)	2 (100.0)	7 (58.3)	35 (94.5)	
β-D-Glucan test	24 (17.6)	5 (1.1)		3 (1.4)		1 (8.3)		
Polymerase chain reaction	1 (0.7)	63 (15.0)	2 (3.9)	1 (0.4)		2 (16.6)	1 (2.7)	
Other	115 (84.5)	9 (2.1)	12 (23.5)	35 (16.2)		3 (25.0)	1 (2.7)	

[a] Diagnostic tests were not mutually exclusive: >1 test might have been used for the diagnosis of 1 invasive fungal infection. Patients with >1 pathogen were not included in this table.

Diagnosis

- Culture evidence is the mainstay
- Culture of sterile sites is definitive
- Culture of nonsterile sites only defines colonization
- Mean time to (+) blood culture 2-3 days
- Low sensitivity, even with disseminated infection

The MALDI-TOF MS: a revolution in clinical microbial identification

Direct depcsition of samples on target plates at the bench

Processing by MALDI-TOF MS

Valid and accurate result

Interpretation ard validation o² identification

Clinical result

Non-reliable or doubtful result

Protein extraction under chemical hood

MALDI-TOF MS improves clinical laboratory identification of human pathogenic yeasts

Study	No. of isolates/species	% of isolates identified
Marklein et al. 2009	267 isolates 25 species	92.5
Van Veen et al. 2010	61 isolates 12 species	85.2
Bizzini et al. 2010	24 isolates 4 species	100
Stevenson et al. 2010	194 isolates 23 species	87.1 (99)[a]
Bader et al. 2010	1192 isolates 36 species	97.6
Dhiman et al. 2011	138 isolates 14 species	92 .0 (96.3)[a]

- **Several closely related species (e.g., *Candida* 'psilosis' or *Candida glabrata*/*bracarensis*) could be resolved by MALDI-TOF MS, but not by a biochemical approach**
- **Reproducible and accurate**
- **Requires minimal sample preparation efforts and costs**

- Beta-glucan is a screening test that may identify patients with invasive fungal infections, such as invasive aspergillosis and invasive candidiasis.
- Available data suggest that beta-glucan is a reliable test to estimate the diagnostic accuracy for these invasive fungal infections in adults only.
- A frequency of 2 tests per week which was performed in most studies seems an appropriate screening strategy.
- Results of the beta-glucan assay may complement clinical, radiological and laboratory criteria for the diagnosis of IFI.
- The threshold for positive results depends on the test which is used. Evidence from the available data suggest the following cut-off:
  - Fungitell: between 60 and 80 pg/ml.
  - Wako / Maruha: between 7 and 11 pg/ml
  - Fungitec-G: 20 pg/ml.
- The criteria of two consecutive specimens to define the test as positive increases the specificity but decreases the sensitivity

Posteraro et al. Critical Care 2011, 15:R249
http://ccforum.com/content/15/5/R249

CRITICAL CARE

RESEARCH Open Access

Early diagnosis of candidemia in intensive care unit patients with sepsis: a prospective comparison of (1→3)-β-D-glucan assay, *Candida* score, and colonization index

Brunella Posteraro[1], Gennaro De Pascale[2], Mario Tumbarello[3*], Riccardo Torelli[1], Mariano Alberto Pennisi[2], Giuseppe Bello[2], Riccardo Maviglia[2], Giovanni Fadda[1], Maurizio Sanguinetti[1] and Massimo Antonelli[2]

Table 3 Performances of (1→3)-β-D-glucan assay (BG), *Candida* score (CS), and colonization index for detection of invasive candidiasis in 95 patients

	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	PLR (%) (95% CI)	NLR (%) (95% CI)
BG cut-off value, 80 pg/mL	92.9 (66.1 to 99.8)	93.7 (85.8 to 97.9)	72.2 (46.5 to 90.3)	98.7 (92.8 to 99.9)	14.74 (4.65 to 47.52)	0.07 (0.02 to 0.39)
CS ≥3	85.7 (57.2 to 98.2)	88.6 (79.5 to 94.7)	57.1 (34.0 to 78.2)	97.2 (90.3 to 99.7)	7.51 (2.79 to 18.29)	0.16 (0.02 to 0.54)
Colonization index ≥0.5	64.3 (35.1 to 87.2)	69.6 (58.2 to 79.5)	27.3 (13.3 to 45.5)	91.7 (81.6 to 97.2)	2.12 (0.84 to 4.25)	0.51 (0.16 to 1.11)

Clinical Infectious Diseases Advance Access published May 9, 2012

(1,3)-ß-D-Glucan (BG) as a Prognostic Marker of Treatment Response in Invasive Candidiasis

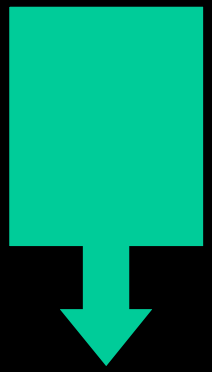
Siraya Jaijakul,[1] Jose A. Vazquez,[2] Robert N. Swanson,[3] Luis Ostrosky-Zeichner[1]

Conclusions. A decrease in BG levels during therapy is associated with treatment success. An initial BG of < 416 pg/ml has potential to predict successful treatment outcomes. Baseline and consecutive serum BG measurements may be useful as prognostic markers of treatment outcome in patients with IC receiving primarily echinocandin therapy.

Objective and study design

- **Aim of our study was to analyze the different *Candida* species isolated from bloodstream infections and the related antifungal susceptibility pattern over a four year period at Policlinico Umberto I of Rome**
- **542 isolates during 2009-2012 coming from ICUs and non-ICUs settings were examined**
- **Only a single strain of *Candida spp* was found in each patient with the exception of five patients**
- **The mean number of positive blood cultures per patient was 2 (range 1-10)**

542 isolates of *Candida spp* between 2009-2012



241 in ICU (44,5%)

301 in General Medicine and Surgery non-ICU (55,5%)

Microbiological methods

- **CVC, peripheral veins, arterial blood**

↓

- **BACTEC Mycosis IC/F or BACTEC Plus Aerobic/F medium in Bactec 9240 (automated culture system, BD)**

↓ *If positive*

- **Passages to blood agar and Sabouraud dextrose agar**

↓ *If positive for Candida spp*

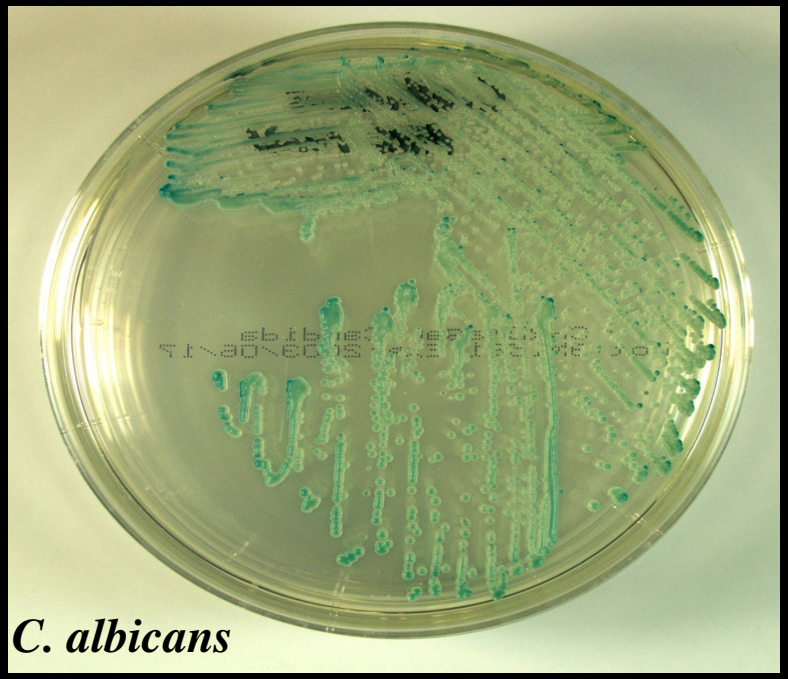
- **Inoculation in chromogenic Candida plates (Chromagar BD)**
- **(presumptive species identification)**

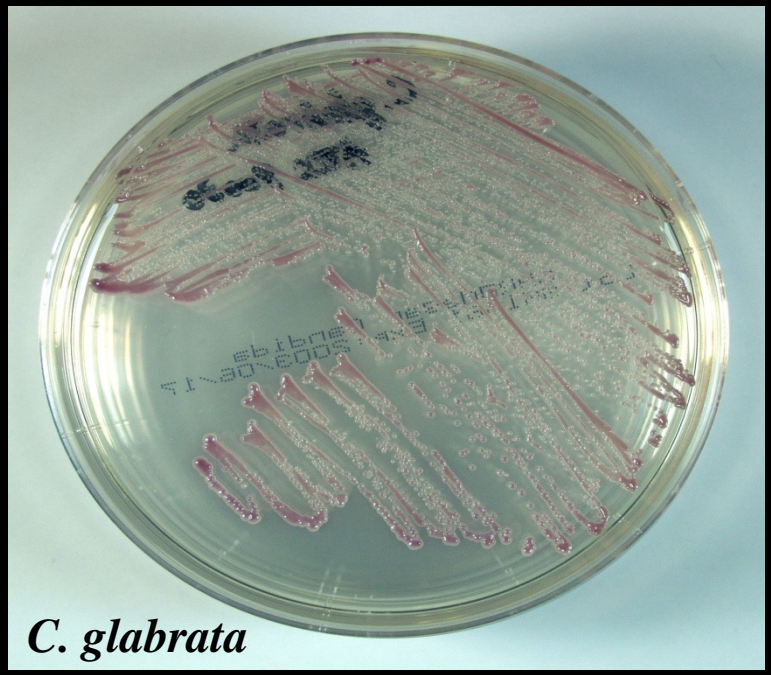
↓

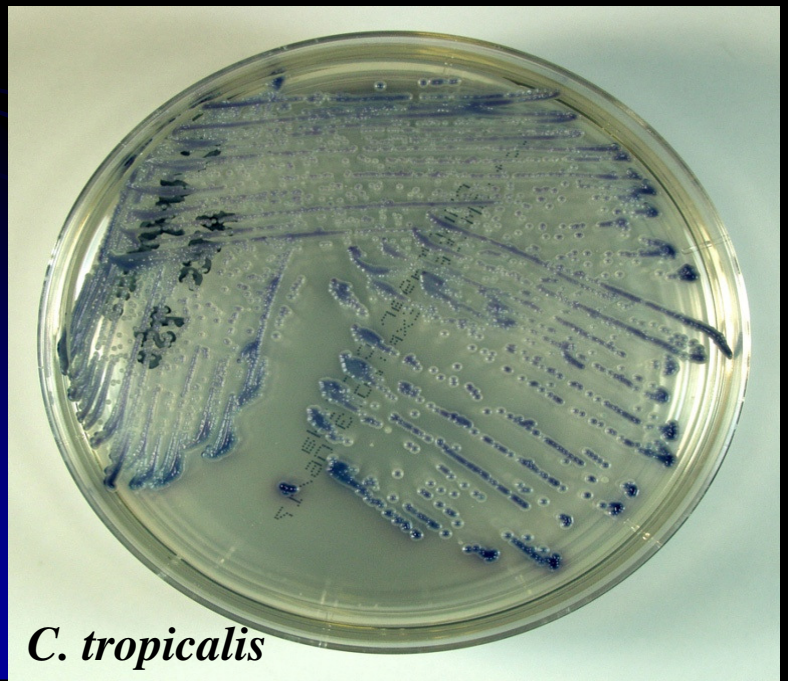
- **API ID 32C System (Bio-Merieux)**
- **(definitive species identification)**

↓

- **Susceptibility to antimicrobial agents**
- **(Sensititre Yeast One 10 following EUCAST breakpoints)**


C. albicans


C. glabrata


C. tropicalis


C. krusei
www.medmicro.info

ANTIFUNGAL AGENTS TESTED

POS=Growth Control

MF=MICAFUNGIN

CAS=CASPOFUNGIN

FC=5-FLUOROCYTOSINE

IZ=ITRACONAZOLE

VOR=VORICONAZOLE *

AB=AMPHOTERiCIN B *

AND=ANIDULAFUNGIN *

PZ=POSACONAZOLE *

FZ=FLUCONAZOLE *

* For these antifungal agents, the EUCAST breakpoints interpretation is needed .

European Committee on Antimicrobial Susceptibility Testing

Antifungal Agents

Breakpoint tables for interpretation of MICs

Version 6.1, valid from 2013-03-11

Table	Changes from version 6.0 (Changes are marked with blue highlights)
Candida spp.	Typos corrected on fluconazole BPs for *C. glabrata* and *C. krusei*.

Table	Changes from version 5.0 (Changes are marked with yellow highlights)
Candida spp.	Micafungin BPs have been added. Fluconazole BPs have been revised for *C. glabrata*. Anidulafungin BPs have been revised for *C. parapsilosis*.

Candida spp.

EUCAST Antifungal Clinical Breakpoint Table v. 6.1, valid from 2013-03-11

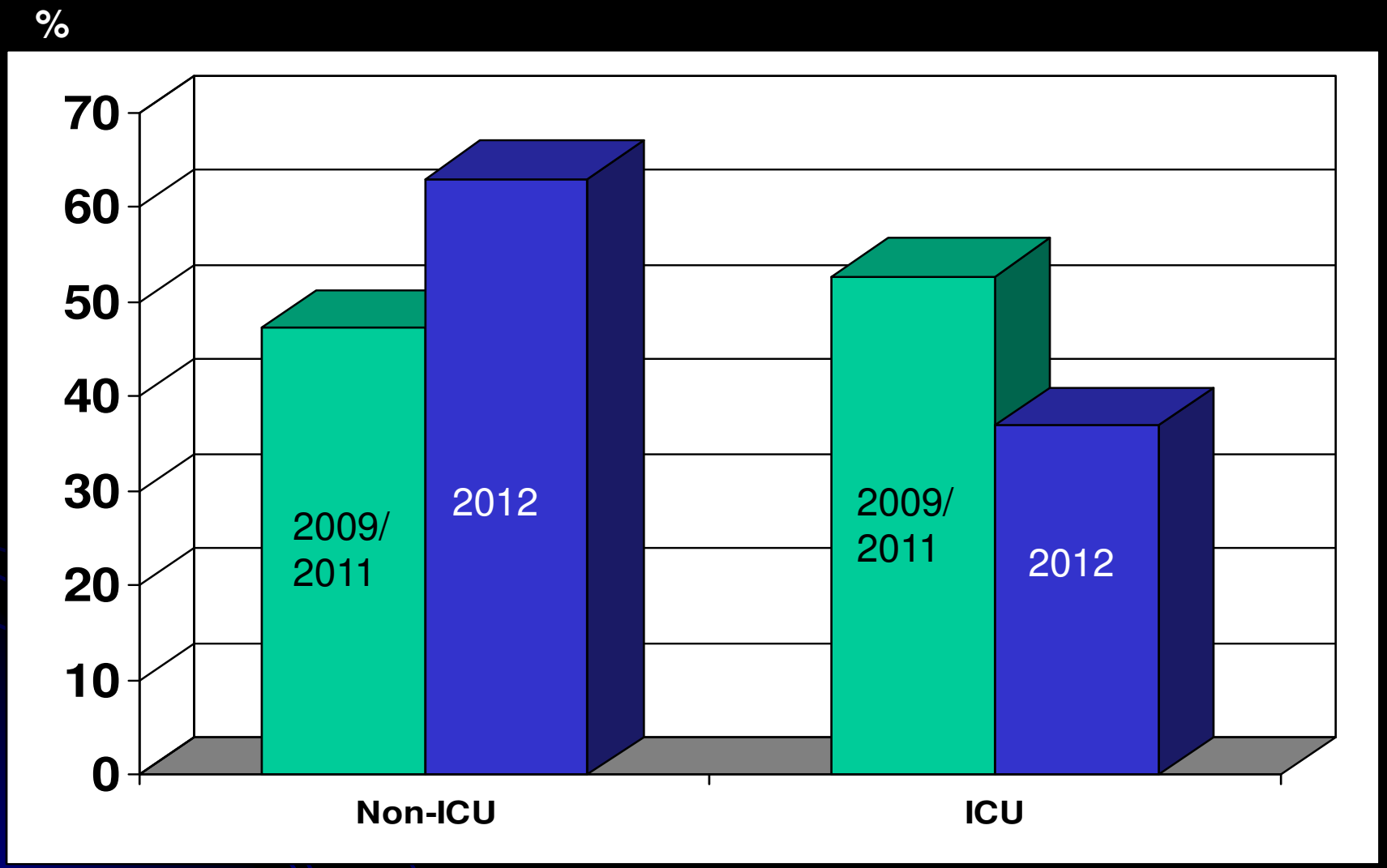
MIC method (EUCAST standardised broth microdilution method)
Medium: RPMI1640-2% glucose, MOPS buffer
Inoculum: Final $0.5x10^5$ – $2.5x10^5$ cfu/mL
Incubation: 18-24h
Reading: Spectrophotometric, full inhibition for amphotericin B but 50% growth inhibition for other compounds
Quality control: *C. parapsilosis* ATCC 22019 or *C. krusei* ATCC 6258

Antifungal agent	MIC breakpoint (mg/L)														Notes
	C. albicans		*C. glabrata*		*C. krusei*		*C. parapsilosis*		*C. tropicalis*		*C. guilliermondii*		Non-species related breakpoints[1]		
	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	
															1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.
Amphotericin B	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	**2.** The ECOFFs for these species are in general higher than for *C. albicans*.
Caspofungin	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	-	-	Note[3]	Note[3]	IE[2]	IE[2]	IE	IE	**3.** Due to significant inter-laboratory variation in MIC ranges for caspofungin, EUCAST breakpoints have not yet been established.
Fluconazole	2	4	0.002	32	-	-	2	4	2	4	IE[2]	IE[2]	2	4	
Itraconazole	IP	IP	IP	IP	IP	IP	IP	IP	IP	IP	IP	IP	IP	IP	
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	**4.** MICs for *C. tropicalis* are 1-2 two-fold dilution steps higher than for *C. albicans* and *C. glabrata*. In the clinical study successful outcome was numerically slightly lower for *C. tropicalis* than for *C. albicans* at both dosages (100 and 150 mg daily). However, the difference was not significant and whether it translates into a relevant clinical difference is unknown. MICs for *C. krusei* are approximately three two-fold dilution steps higher than those for *C. albicans* and, similarly, those for *C. guilliermondii* are approximately eight two-fold dilutions higher. In addition, only a small number of cases involved these species in the clinical trials. This means there is insufficient evidence to indicate whether the wild-type population of these pathogens can be considered susceptible to micafungin.
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	**5.** Strains with MIC values above the S/I breakpoint are rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

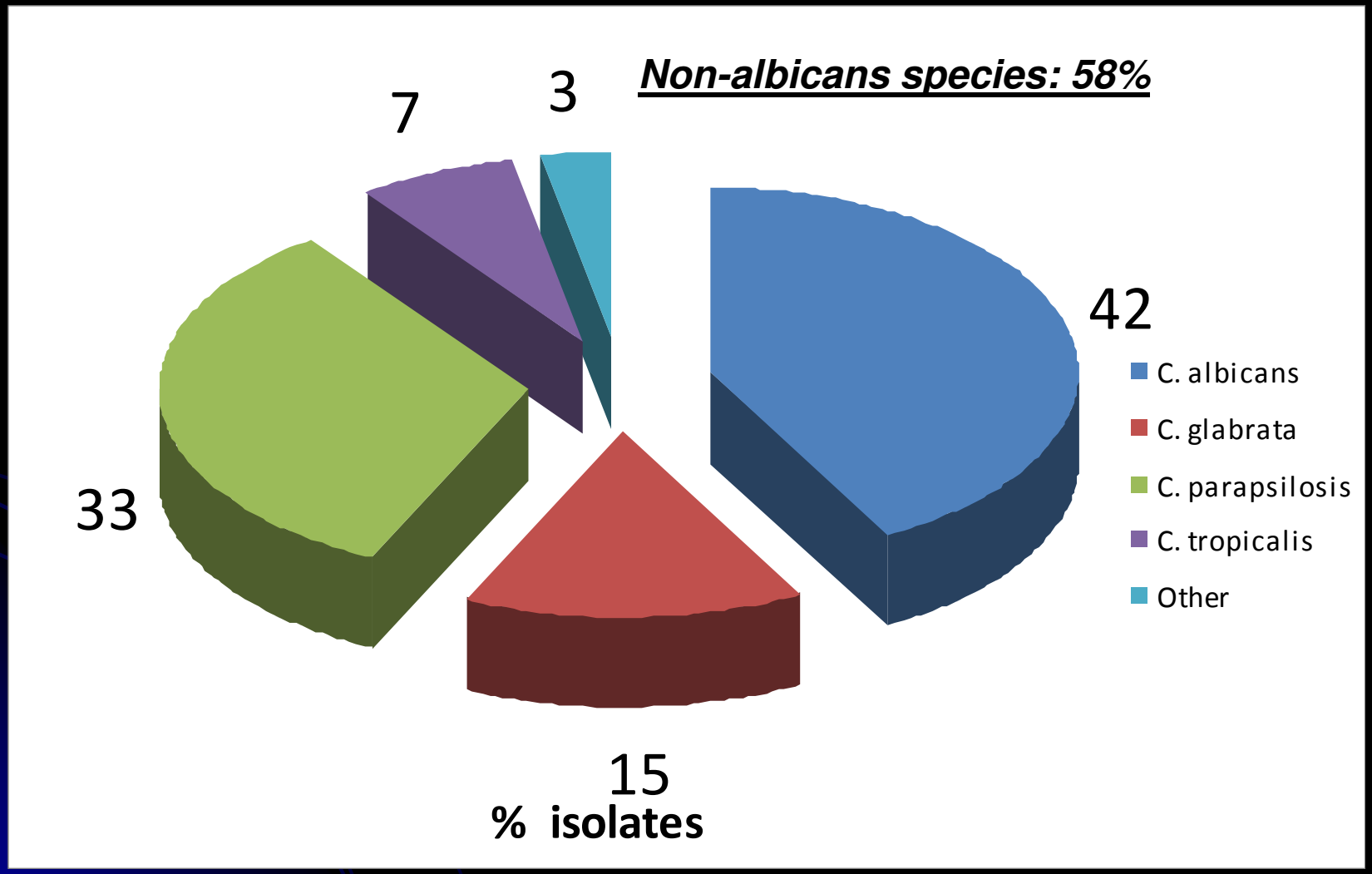
RESULTS

CANDIDA ISOLATION
IN INTENSIVE
CARE UNITS AND IN GENERAL
MEDICINE AT POLICLINICO UMBERTO I°
SAPIENZA UNIVERSITY OF ROME

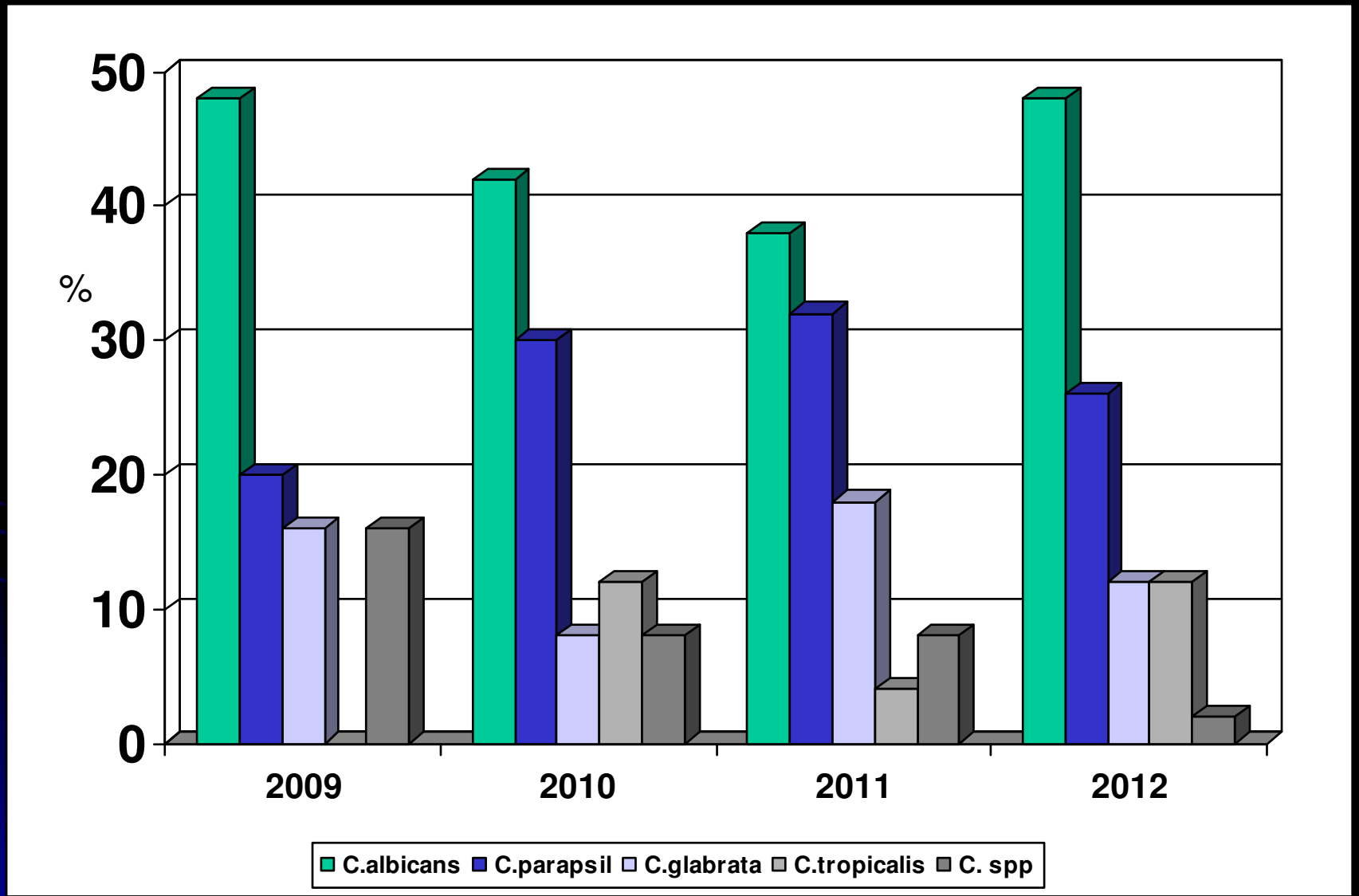
Invasive candidiasis and provenance



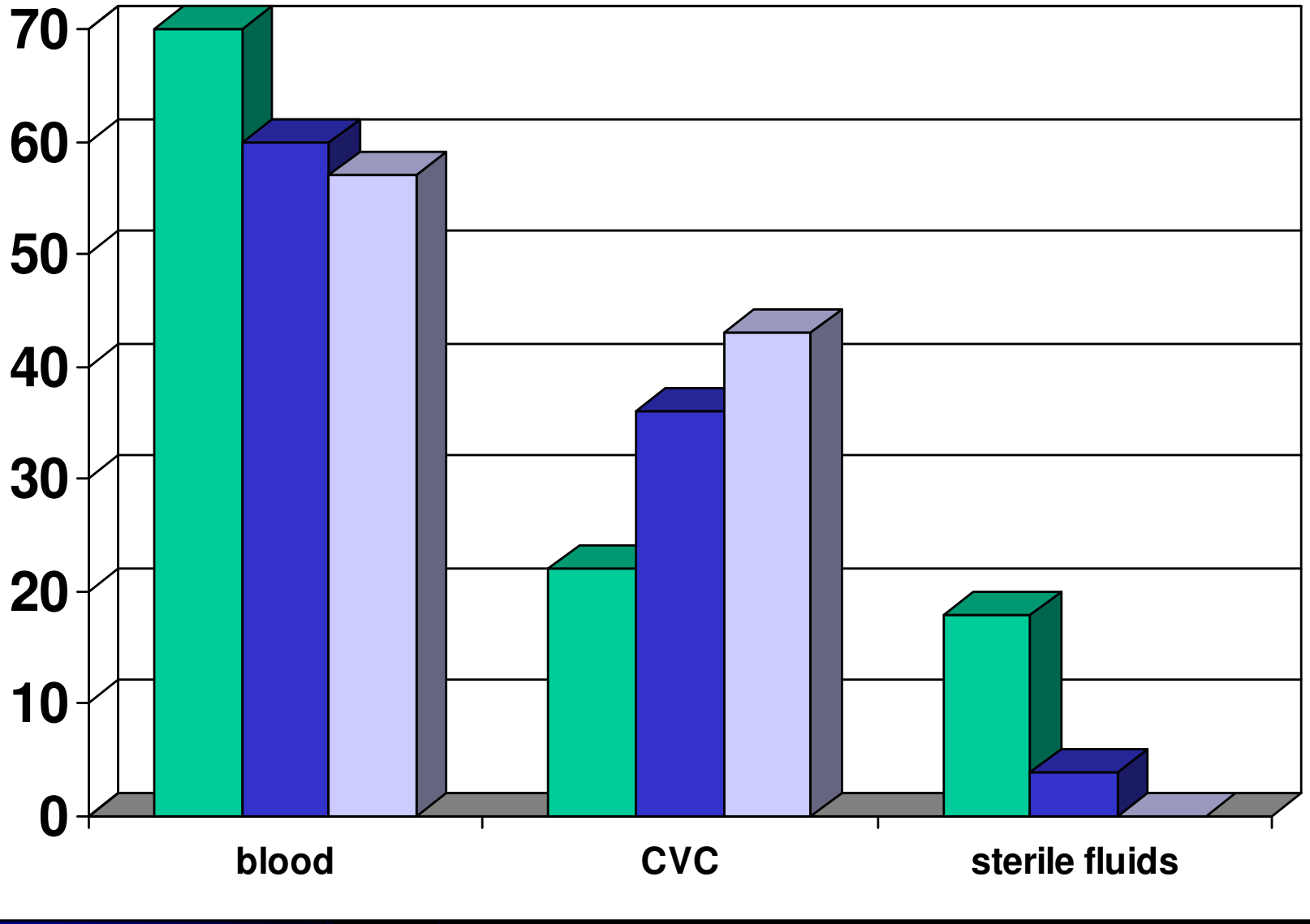
Overall distribution of Candida species (2009-2012)



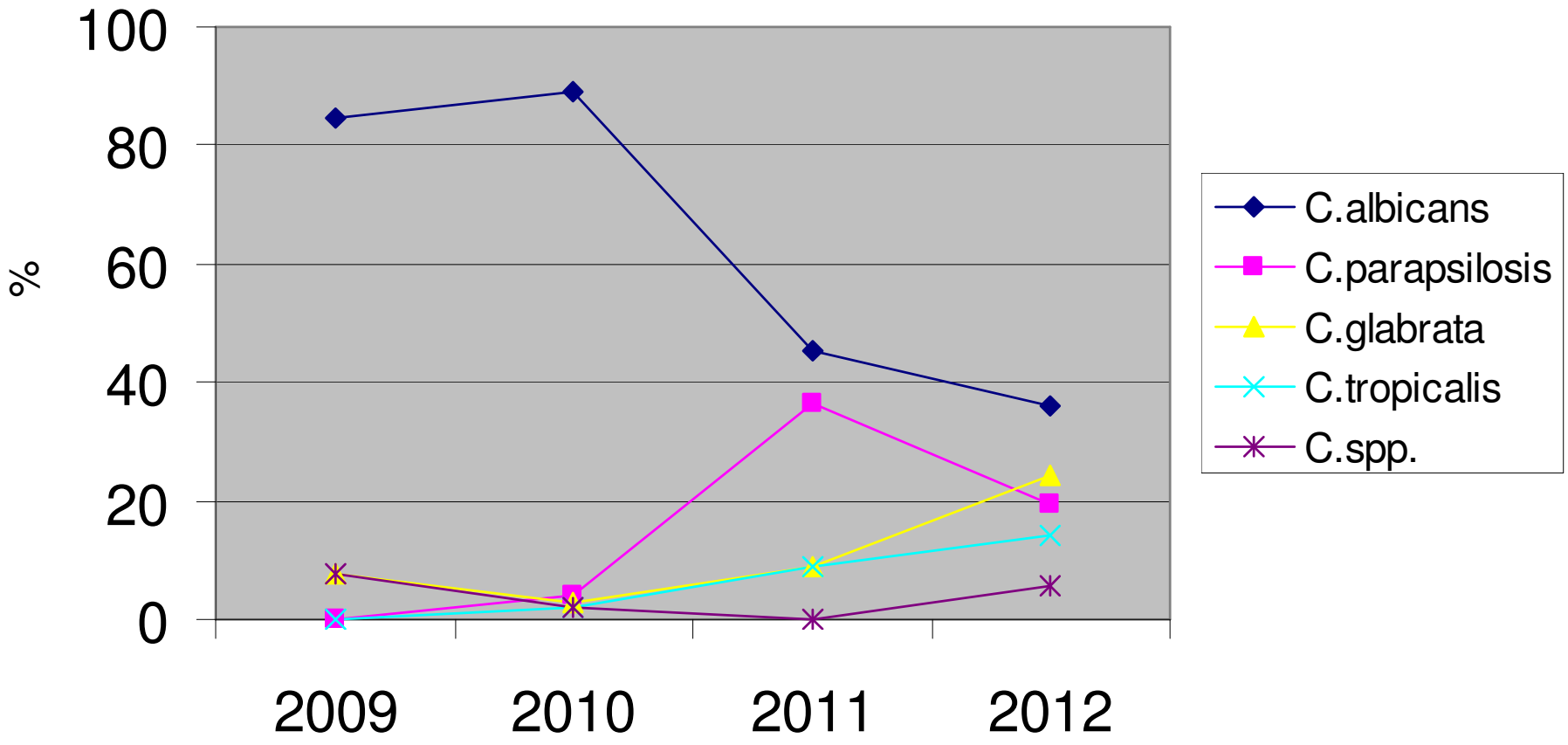
Isolates of candidaemia from 2009 to 2012



Candida isolates from different samples (%) in the years 2010, 2011 and 2012



Candidaemia in Medical Area 2009-2012



Reasons for the presence of different species of *Candida non-albicans* in invasive candidiasis

- Exposure to azoles
- Patient age
- Severity or underlying disease
- Geographic area
- Indiscriminate use of broad spectrum antibacterial agents

		Fluconazole		Voriconazole		Caspofungin		Anidulafungin	
	Anno	**MIC50**	**MIC90**	**MIC 50**	**MIC 90**	**MIC 50**	**MIC 90**	**MIC 50**	**MIC 90**
C. albicans	2010	0.25	0.5	0.008	0.015	0.06	0.12	0.03	0.12
	2011	0.12	0.5	0.008	0.015	0.03	0.12	0.03	0.12
	2012	0.25	1 [a]	0.008	0.06 [b]	0.03	0.12	0.03	0.12
C. parapsilosis	2010	1	4 [a]	0.008	0.008	0.25	0.5	0.5	1
	2011	0.5	4 [a]	0.015	0.06 [b]	0.25	0.5	0.5	1
	2012	0.5	4 [a]	0.008	0.06 [b]	0.25	0.5	0.5	2[d]
C. glabrata	2010	2	4	0.06	0.12	0.06	0.12	0.03	0.06 [c]
	2011	4	16	0.06	0.12	0.12	0.25	0.03	0.06 [c]
	2012	8	16	0.25	0.5	0.12	0.25	0.03	0.06 [c]

breakpoint EUCAST: (R)

a > 4 µg/mL
b > 0.125 µg/mL
c > 0.06 µg/mL
d > 2 µg/mL

J Antimicrob Chemother 2010; **65**: 1460–1465
doi:10.1093/jac/dkq136 Advance Access publication 29 April 2010

Journal of Antimicrobial Chemotherapy

Candidaemia associated with decreased *in vitro* fluconazole susceptibility: is *Candida* speciation predictive of the susceptibility pattern?

David A. Oxman[1,2*], Jennifer K. Chow[1], Gyorgy Frendl[2], Susan Hadley[1], Shay Hershkovitz[2], Peter Ireland[2], Laura A. McDermott[1], Katy Tsai[1], Francisco M. Marty[2], Dimitrios P. Kontoyiannis[3] and Yoav Golan[1]

[1]*Tufts Medical Center, 800 Washington Street, Boston, MA 02111, USA;* [2]*Brigham & Women's Hospital, 75 Francis Street, Boston, MA, USA;* [3]*MD Anderson Cancer Center, 1400 Holcombe Blvd, Houston, TX, USA*

*Corresponding author. Division of Infectious Diseases, Brigham & Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. Tel: +1-617-525-6782; E-mail: doxman@partners.org

Received 1 February 2010; returned 4 March 2010; revised 12 March 2010; accepted 26 March 2010

Background: Candidaemia is often treated with fluconazole in the absence of susceptibility testing. We examined factors associated with candidaemia caused by *Candida* isolates with reduced susceptibility to fluconazole.

Methods: We identified consecutive episodes of candidaemia at two hospitals from 2001 to 2007. Species identification followed CLSI methodology and fluconazole susceptibility was determined by Etest or broth microdilution. Susceptibility to fluconazole was defined as: full susceptibility (MIC $\leq$8 mg/L); and reduced susceptibility (MIC $\geq$32 mg/L). Complete resistance was defined as an MIC $>$32 mg/L.

Results: Of 243 episodes of candidaemia, 190 (78%) were fully susceptible to fluconazole and 45 (19%) had reduced susceptibility (of which 27 were fully resistant). Of *Candida krusei* and *Candida glabrata* isolates, 100% and 51%, respectively, had reduced susceptibility. Despite the small proportion of *Candida albicans* (8%), *Candida tropicalis* (4%) and *Candida parapsilosis* (4%) with reduced fluconazole susceptibility, these species composed 36% of the reduced-susceptibility group and 48% of the fully resistant group. In multivariate analysis, independent factors associated with reduced fluconazole susceptibility included male sex [odds ratio (OR) 3.2, $P<0.01$], chronic lung disease (OR 2.7, $P=0.01$), the presence of a central vascular catheter (OR 4.0, $P<0.01$) and prior exposure to antifungal agents (OR 2.2, $P=0.04$).

Conclusions: A significant proportion of candidaemia with reduced fluconazole susceptibility may be caused by *C. albicans*, *C. tropicalis* and *C. parapsilosis*, species usually considered fully susceptible to fluconazole. Thus, identification of these species may not be predictive of fluconazole susceptibility. Other factors that are associated with reduced fluconazole susceptibility may help clinicians choose adequate empirical anti-*Candida* therapy.

Journal of Medical Microbiology (2012), **61**, 389–393 DOI 10.1099/jmm.0.037895-0

Antifungal susceptibility profiles of *Candida* isolates from a prospective survey of invasive fungal infections in Italian intensive care units

Anna Maria Tortorano,[1] Anna Prigitano,[1] Giovanna Dho,[1] Anna Grancini,[2] Marco Passera[3] for the ECMM-FIMUA Study Group†

Table 1. *In vitro* susceptibilities of 302 *Candida* isolates from blood or other normally sterile body sites

–, Concentrations not investigated; NA, no breakpoints available.

Species (no. isolates tested)	Antifungal agent	No. of isolates with MIC (mg l^{-1}) of:														%
		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	R
C. albicans (169)	Anidulafungin	169										–	–	–	–	0
	Caspofungin		119	24	16	10						–	–	–	–	0
	Micafungin	169										–	–	–	–	0
	Fluconazole	–	–	–	–	145	7	6	2			1	1		7	5.3
	Posaconazole	–	156	6	1							6	–	–	–	3.6
	Voriconazole	–	163									6	–	–	–	3.6
C. parapsilosis (58)	Anidulafungin	1					4	23	29	1		–	–	–	–	0
	Caspofungin		4				3	20	31			–	–	–	–	0
	Micafungin		4			4	31	16	3			–	–	–	–	0
	Fluconazole	–	–	–	–	7	16	9	10	3	5	8				25.8
	Posaconazole	–	39	15	4								–	–	–	0
	Voriconazole	–	30	12	4	8	1	3					–	–	–	5.2
C. glabrata (31)	Anidulafungin	26	5									–	–	–	–	0
	Caspofungin			1		1	29					–	–	–	–	0
	Micafungin	31										–	–	–	–	0
	Fluconazole	–	–	–	–			2	1	13	4	5	3		3	9.7
	Posaconazole	–	1	5	4	5	8	4	4				–	–	–	25.8
	Voriconazole	–	2	6	6	9	2	2	1	3			–	–	–	19.3
C. tropicalis (27)	Anidulafungin	24	3									–	–	–	–	0
	Caspofungin	1		4	2	12	8					–	–	–	–	0
	Micafungin	27										–	–	–	–	0
	Fluconazole	–	–	–	–	6	6	7	2				1	1	4	22.2
	Posaconazole	–	14	6	3				1			3	–	–	–	14.8
	Voriconazole	–	17	1	3	1						5	–	–	–	18.5
C. krusei (6)	Anidulafungin	1	1	4								–	–	–	–	0
	Caspofungin						2	4				–	–	–	–	0
	Micafungin	1	4	1								–	–	–	–	0
	Fluconazole	–	–	–	–						1	1	4			100
	Posaconazole	–	1			4	1						–	–	–	0
	Voriconazole	–			1		3	1				1	–	–	–	16.7
Other spp.* (8)	Anidulafungin	4	2			1	1					–	–	–	–	NA
	Caspofungin				1	2	1	3	1			–	–	–	–	NA
	Micafungin	4	2			1	1					–	–	–	–	NA
	Fluconazole	–	–	–	–	3	2	1		2						NA
	Posaconazole	–	3	4	1								–	–	–	NA
	Voriconazole	–	6	1	1								–	–	–	NA

*Other species include *C. lusitaniae* (4 isolates), *C. guilliermondii* (2), *C. kefyr* (1) and *C. dubliniensis* (1).

Diagnostic Microbiology and Infectious Disease 73 (2012) 45–48

Contents lists available at SciVerse ScienceDirect

Diagnostic Microbiology and Infectious Disease

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Mycology

The changing epidemiology of healthcare-associated candidemia over three decades☆

Daniel Diekema[a,b,*], Sophie Arbefeville[c], Linda Boyken[b], Jennifer Kroeger[b,d], Michael Pfaller[b,d,e]

Table 2
Antifungal susceptibility of *Candida* bloodstream isolates, 2004–2007.

Species (*n*)	Agent	MIC 50/90	MIC range	% Susceptible	% Resistant
C. albicans	Fluconazole	0.25/0.5	0.12–2.0	100	0
(51)	Caspofungin	0.015/0.03	0.007–0.12	100	0
C. glabrata	Fluconazole	8.0/128	2.0–128	84[a]	16
(31)	Caspofungin	0.03/0.12	0.015–0.25	97[b]	0
C. parapsilosis	Fluconazole	0.5/1.0	0.25–1.0	100	0
(13)	Caspofungin	0.25/0.5	0.12–0.5	100	0
C. tropicalis	Fluconazole	0.5/1.0	0.25–1.0	100	0
(6)	Caspofungin	0.015/0.06	0.007–0.06	100	0

[a] With the new CLSI breakpoints, all *C. glabrata* strains with MIC ≤32 μg/mL are designated as susceptible dose-dependent.

Factors Associated With Mortality

Overall Rate of Mortality= 40-55%

- **Omitted, delayed or indequate antifungal therapy**
- **Treatment with an agent to which the organism is resistant**
- **Infection with biofilm forming *Candida* species**
- **Apache II score at the admission (severity of illness)**

CONCLUSIONS I

- **Invasive candidiasis can no longer be considered to be just an ICU-related infections**
- **Preventive and diagnostic strategies must be expanded to include other at-risk population and hospital environments**
- **Overall fluconazole resistance was higher in ICUs strains than in non-ICUs strains**
- ***C. albicans* is the most frequently isolated fungal species followed by *C. parapsilosis and C. glabrata***
- ***C.glabrata* shows a marked and increasing resistance to azoles**

CONCLUSIONS II

- **Prophylaxis with fluconazole has been identified as a risk factor for *non-albicans Candida* species**

- **No class of antifungal agent is immune to the development of resistance**

- **Echinocandins could be a valid choice for *Candida* treatment**

- **Mortality attributable to invasive candidiasis remains high**

Shift in non-albicans species isolation in the latest period.


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