I biofilms come organizzazione "sociale" dei microrganismi: impatto del "biofilm lifestyle" nelle infezioni in ambito umano

Sessione: BIOFILM MICROBICI

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Curr Genet
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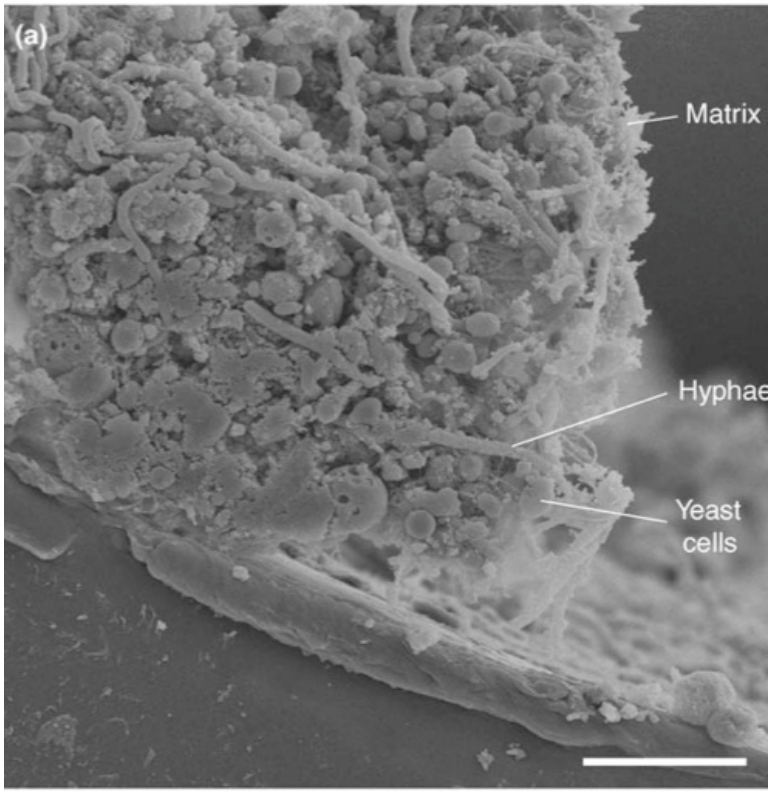
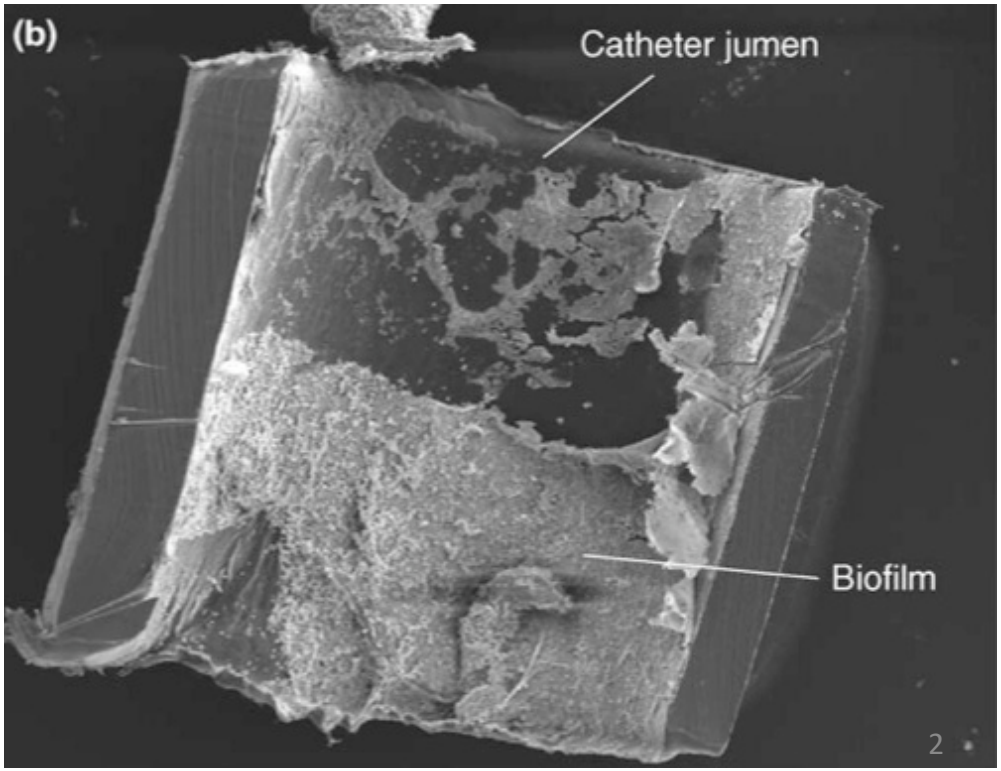
2013

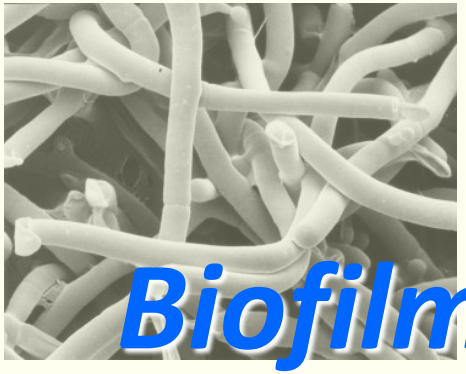
RESEARCH ARTICLE

Recent insights into *Candida albicans* biofilm resistance mechanisms

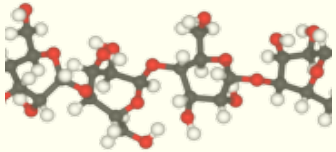
Lotte Mathé · Patrick Van Dijck

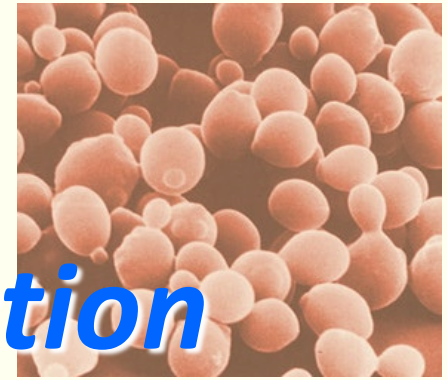




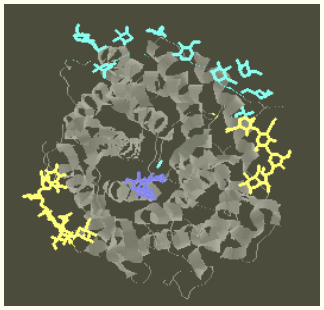


polysaccharides

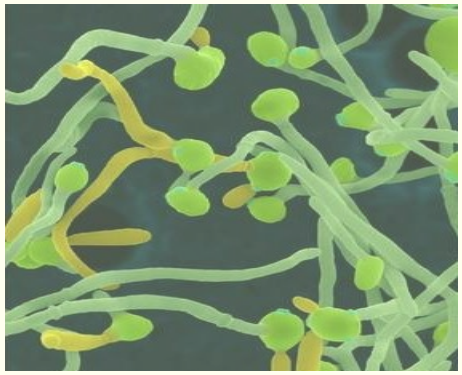


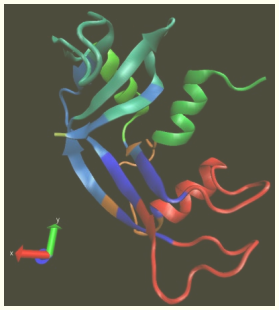


Biofilm production



carbohydrates





proteins

Attachment of microorganisms to the surfaces of medical devices triggers biofilm formation, by Candida bloodstream isolates and this has been associated with increased virulence

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ELSEVIER

Current Opinion in Microbiology

Bacterial biofilm development as a multicellular adaptation: antibiotic resistance and new therapeutic strategies

César de la Fuente-Núñez, Fany Reffuveille, Lucía Fernández and Robert EW Hancock

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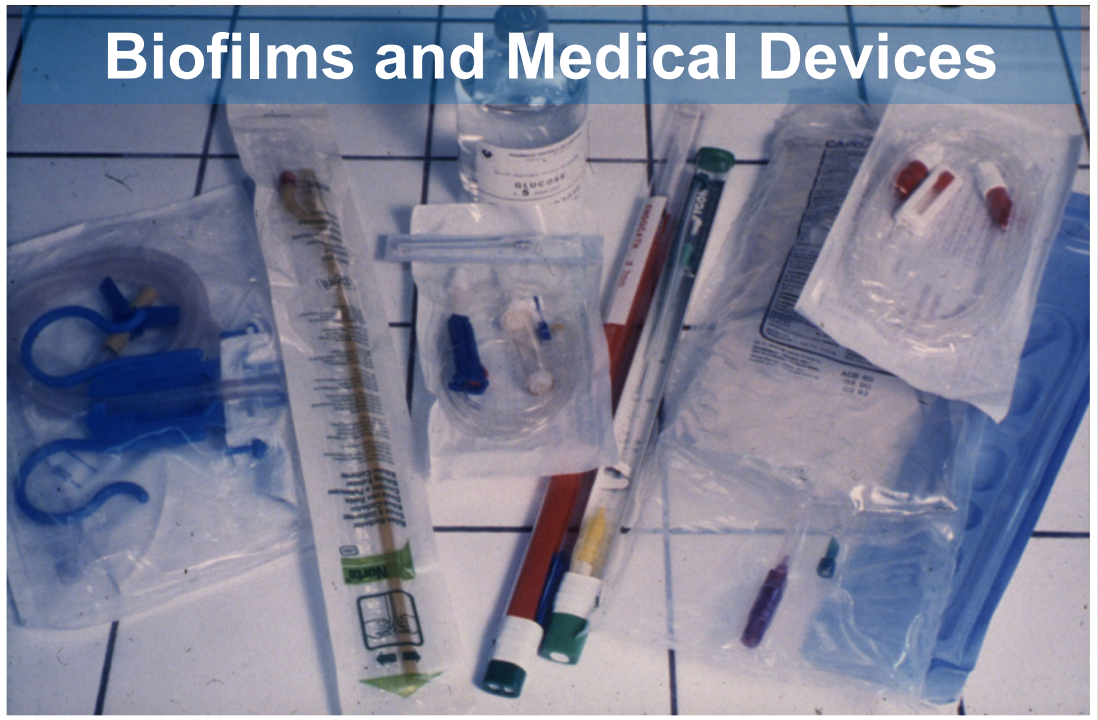
Biofilms and Medical Devices



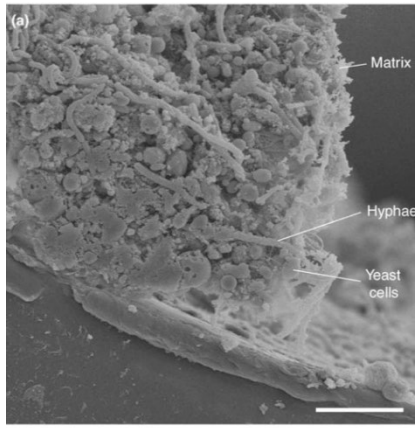
Candida biofilms on implanted biomaterials: a clinically significant problem

FEMS Yeast Res **6** (2006)

Gordon Ramage[1], José Pedro Martínez[2] & José Luis López-Ribot[3]

Table 1. Implantable devices in which *Candida* biofilms develop most frequently

Device	Usage per year	Infection risk (%)	Main *Candida* species
Central and peripheral venous catheters	5 million	3–8	*albicans* *glabrata* *parapsilosis*
Hemodialysis and peritoneal dialysis catheters	240 000	1–20	*albicans* *parapsilosis*
Urinary catheters	Tens of millions	10–30	*albicans* *glabrata*
Endotracheal tubes	Millions	10–25	*albicans*
Intracardiac prosthetic devices	400 000	1–3	*albicans* *glabrata* *parapsilosis* *tropicalis*
Breast implants	130 000	1–2	*albicans*
Prosthetic joints	600 000	1–3	*parapsilosis* *albicans* *glabrata*
Neurosurgical shunts	40 000	6–15	*albicans*
Voice prostheses	Thousands	50–100	*albicans* *tropicalis*
Dentures	> 1 million	5–10	*albicans* *glabrata*



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Current Opinion in Microbiology

Bacterial biofilm development as a multicellular adaptation: antibiotic resistance and new therapeutic strategies

César de la Fuente-Núñez, Fany Reffuveille, Lucía Fernández and Robert EW Hancock

Table 1

Examples of different bacterial species involved in infections associated with biofilm development in immunocompromised patients and medical devices

Biofilm bacterial species	Surface	Disease/infections
Aerobic/anaerobic bacteria	Surface/deep skin	Chronic wound
Burkholderia cepacia	Lungs	Cystic fibrosis
Enterococcus faecalis	Heart valves Central venous catheters Urinary catheters	Endocarditis
Escherichia coli	Urinary tract Middle ear Prostheses	Urinary tract infections Otitis media
Haemophilius influenzae	Middle ear	Otitis media
Klebsiella pneumoniae	Central venous catheters	
Mycobacterium tuberculosis	Lungs	Tuberculosis
Pseudomonas aeruginosa	Lungs Middle ear Contact lenses Central venous catheters Prostheses	Cystic fibrosis Otitis media Nosocomial infections
Staphylococcus aureus	Middle ear Bones Sutures Central venous catheters Prosthetic heart valves Prostheses	Otitis media Musculoskeletal infections Nosocomial infections
Staphylococcus epidermidis	Surface/deep skin Heart valves Central venous catheters Prostheses	Chronic wound Endocarditis
Streptococcus sp	Tooth surfaces	Dental caries

Adv Exp Med Biol - Advances in Microbiology, Infectious Diseases and Public Health
DOI 10.1007/5584_2016_196
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The Correlation Between Biofilm Production and Catheter Related Blood Stream Infections Sustained by *Candida*. A Case Control Study

Grazia Brunetti, Valeria Visconti, Maria Cristina Ghezzi, Alessandra Giordano, and Giammarco Raponi

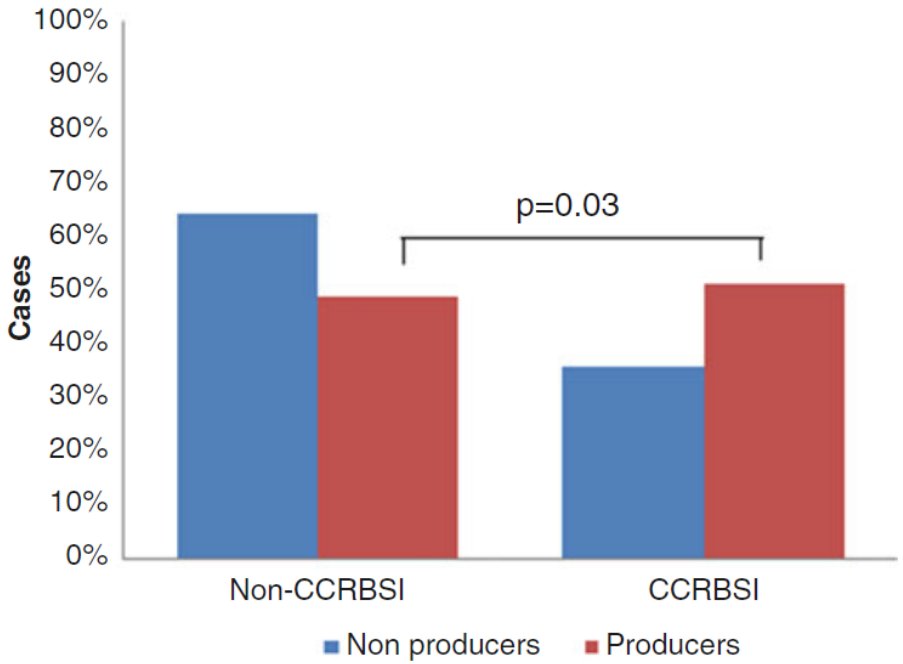
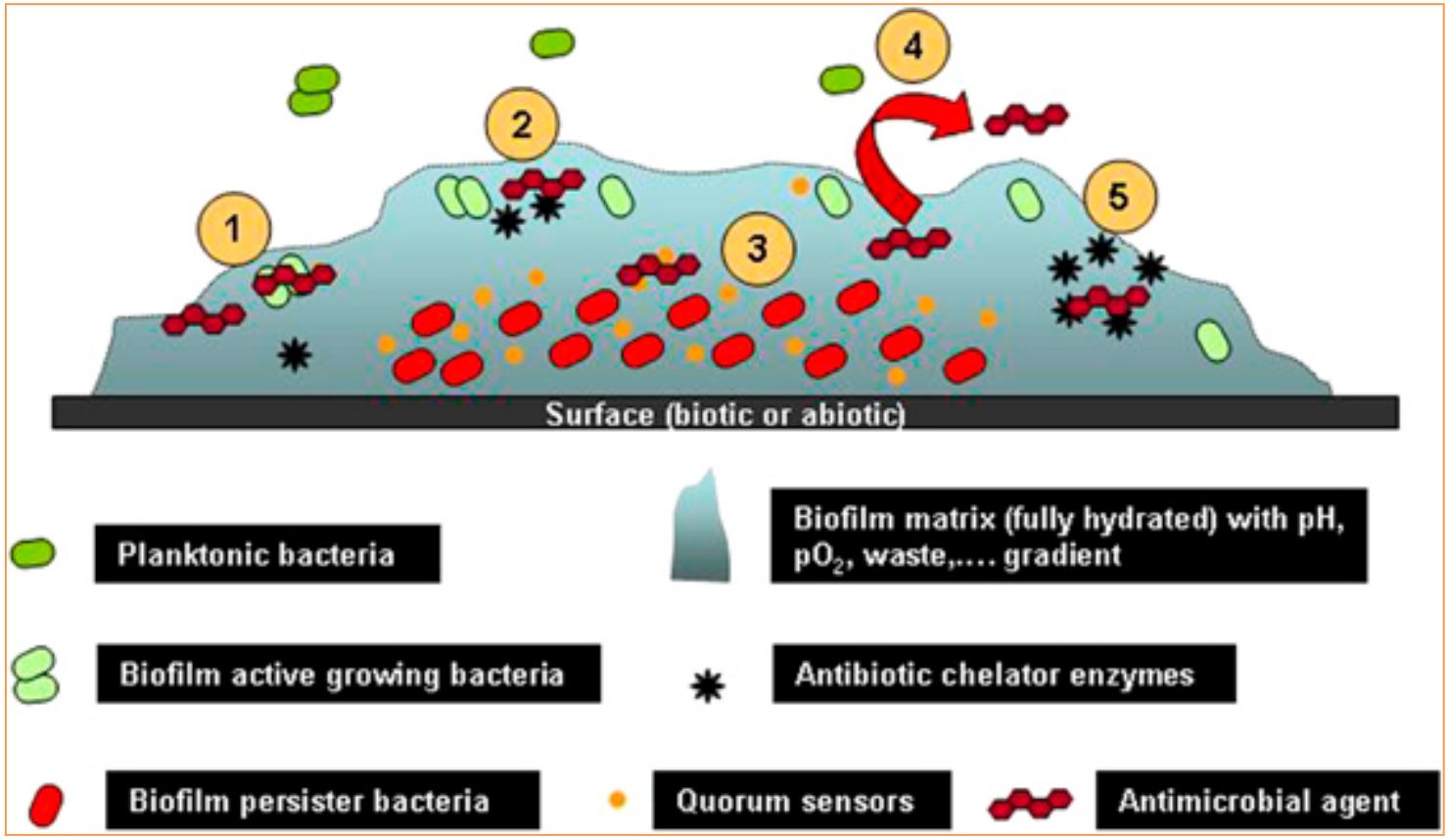


Fig. 2 Biofilm production by the strains isolated from the CCRBSI and non-CCRBSI study groups. The biofilm-producing strains were isolated more frequently, and with a significantly enhanced production in the CCRBSI group relative to the non-CCRBSI group ($\chi^2 = 4.25$, $p = 0.03$)

Difficult to treat - Candida biofilms



The Candida biofilm lifestyle results in antifungal drug resistance and protection of the fungus from host defenses, which carry important clinical complications.

Proposed-biofilm associated resistance mechanisms

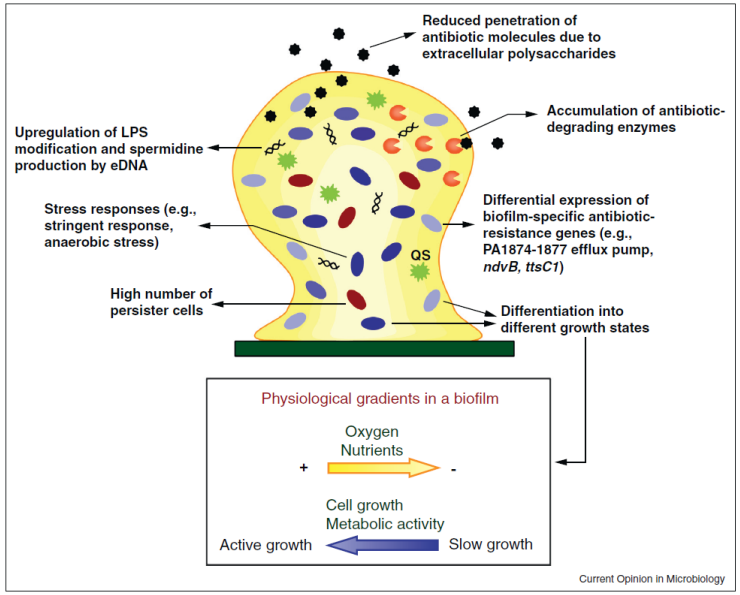
(1) Antimicrobial agents may fail to penetrate beyond the surface layers of the biofilm.

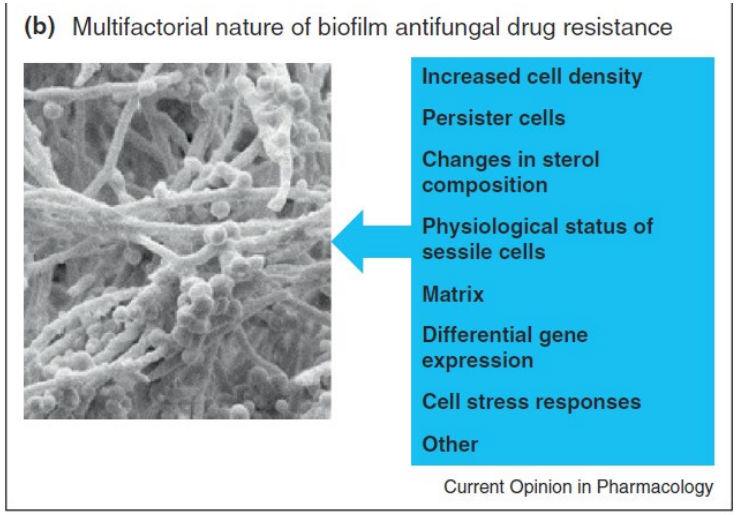
(2) Antimicrobial agents may be trapped and destroyed by enzymes in the biofilm matrix

(3) Altered growth rate inside the biofilm.

(4) Expression of biofilm-specific resistance genes

(5) Stress response to hostile environmental conditions





L Mathè *Curr Genet* 2013
CG Pierce *J Fungi (Basel)* 2017
CG Pierce *Current Opinion in Pharmacology* 2013
C de la Fuente-Nunez *Current Opinion in Microbiology* 2013

Adv Exp Med Biol - Advances in Microbiology, Infectious Diseases and Public Health
DOI 10.1007/5584_2016_9
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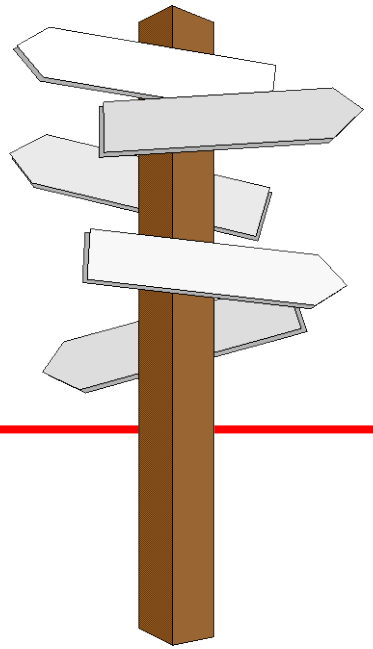
Diagnostic of Fungal Infections Related to Biofilms

Maurizio Sanguinetti and Brunella Posteraro

Despite newer and innovative approaches, the diagnosis of fungal infections related to biofilms, most notably those caused by the *Candida* and *Aspergillus* genera, remains difficult.

Candida and hospital stay

- Devices
- Colonization



- Biofilm
- Infection

Risk factors

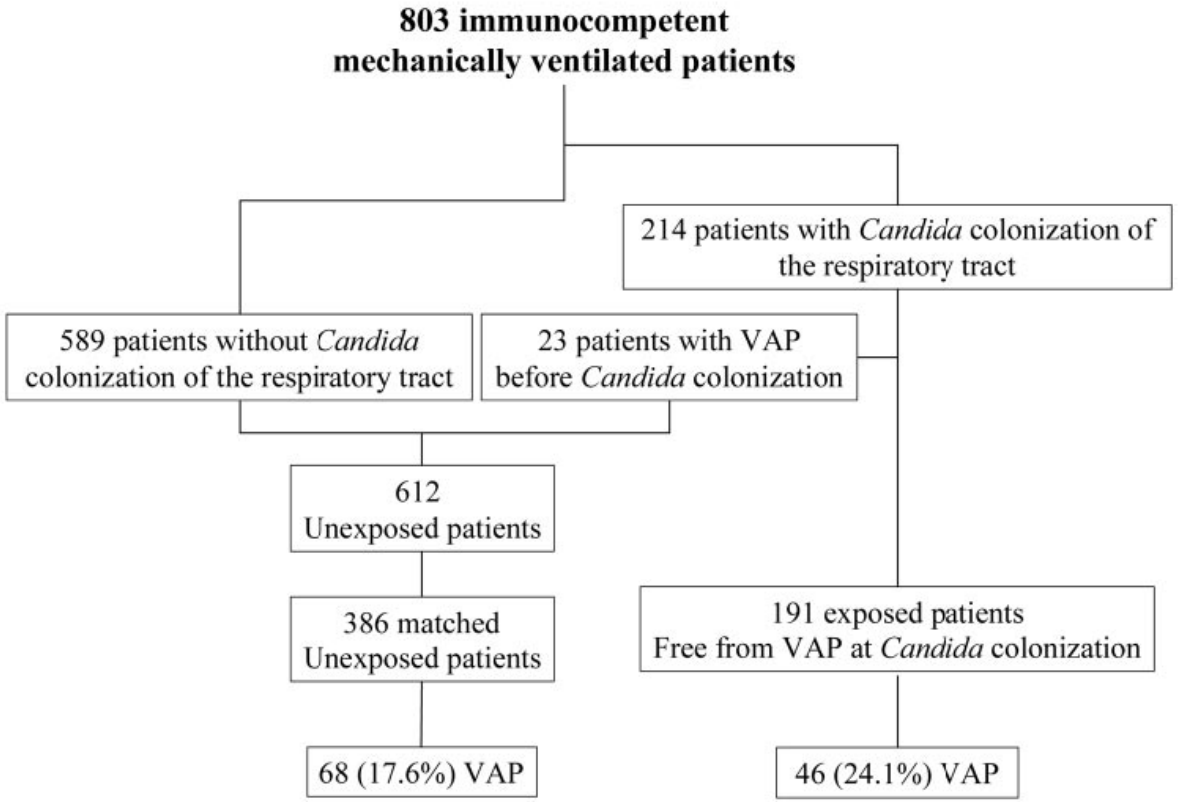
Candida colonization and biofilm production

- Is frequent in ICU patients
- The gut is the main portal of entry in neutropenic patients
- The skin is an important source of candidemia in non-neutropenic patients
- Tracheal colonization reflect oropharyngeal colonization and is not associated with candidal pneumonia in non- neutropenic ICU patients

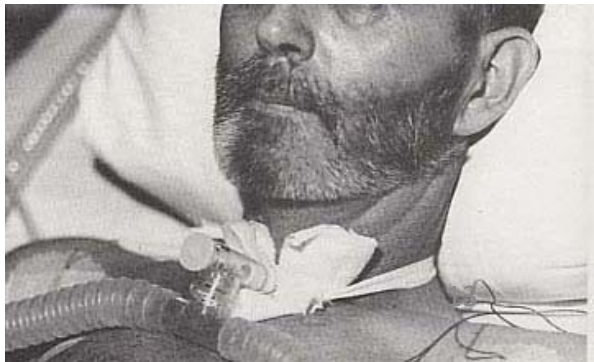
CHEST ONLINE

Candida Colonization of the Respiratory Tract and Subsequent Pseudomonas Ventilator-Associated Pneumonia*

Elie Azoulay, Jean-François Timsit, Muriel Tafflet, Arnaud de Lassence, Michael Darmon, Jean-Ralph Zahar, Christophe Adrie, Maité Garrouste-Orgeas, Yves Cohen, Bruno Mourvillier and Benoît Schlemmer



Candida colonization of the respiratory tract is common in patients receiving MV for > 2 days and is associated with prolonged ICU and hospital stays, and with an increased risk of Pseudomonas VAP



Gil-Perotin *et al. Critical Care* 2012, **16**:R93
http://ccforum.com/content/16/3/R93

CRITICAL CARE

RESEARCH Open Access

Implications of endotracheal tube biofilm in ventilator-associated pneumonia response: a state of concept

Table 2 Bacterial isolation in surveillance endotracheal aspirates

Microorganism	ETA n, %	Days until ETA+ (mean ± SEM)	ETA-ETT match (n, %)
Colonized patients	65, 87%	2.1 ± 0.4	36, 56%
Acinetobacter baumannii	20, 32%	7.8 ± 1.6	12, 60%
Pseudomonas aeruginosa	14, 22%	5.4 ± 2.1	9, 64%
Cocci (SCN, Streptococcus spp)	13, 20%	5 ± 0.9	4, 31%
Staphylococcus aureus (MSSA,MRSA)	10, 15%	2.2 ± 0.6	6, 60%
Candida albicans	29, 45%	2 ± 0.6	6, 21%
Candida no albicans	17, 26%	3.2 ± 0.5	1, 6%

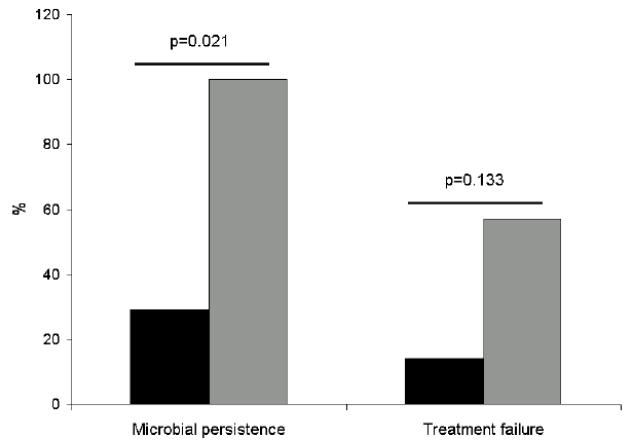


Figure 3 Relationship between biofilm, microbial persistence and treatment failure. Bar graph representative of the percentage of cases in which there was (gray) or not (black) bacterial survival on ETT biofilm despite appropriate treatment. Microbial persistence in respiratory samples and treatment failure were more frequent when bacterial growth was documented in ETT.

Biofilm was found in 95% of the ETTs.

19% of the patients developed VAP

Despite appropriate antibiotic treatment, microrganisms involved in VAP were found in biofilm (50%).

In this situation, microbial persistence and impaired response to treatment (treatment failure and relapse) were more frequent.

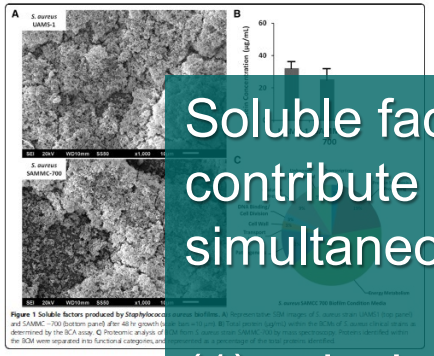
Sanchez *et al. BMC Musculoskeletal Disorders* 2013, **14**:187
http://www.biomedcentral.com/1471-2474/14/187

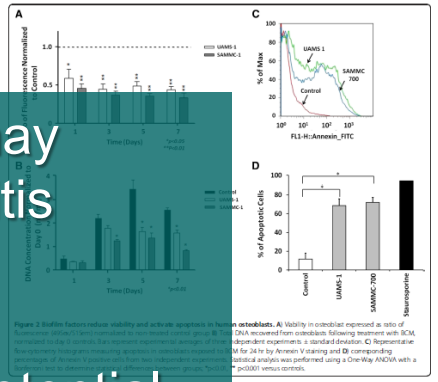
BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Staphylococcus aureus biofilms decrease osteoblast viability, inhibits osteogenic differentiation, and increases bone resorption *in vitro*

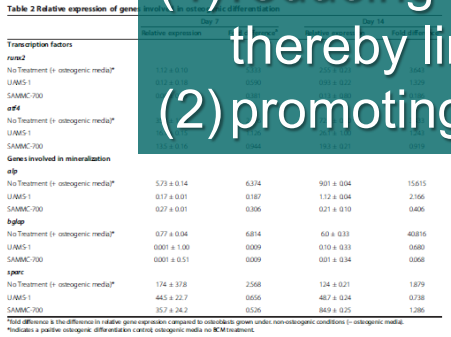
Carlos J Sanchez Jr*†, Catherine L Ward†, Desiree R Romano, Brady J Hurtgen, Sharanda K Hardy, Ronald L Woodbury, Alex V Trevino, Christopher R Rathbone and Joseph C Wenke

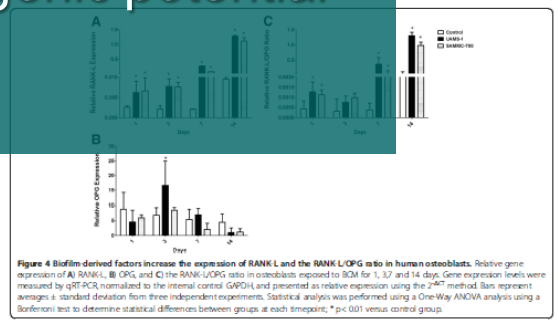




Soluble factors produced by *S. aureus* biofilms may contribute to bone loss during chronic osteomyelitis simultaneously by:

(1) reducing osteoblast viability and osteogenic potential thereby limiting new bone growth
(2) promoting bone resorption





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Diagnostic Microbiology and Infectious Disease 58 (2007) 325–331
DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
www.elsevier.com/locate/diagmicrobio

Mycology

Incidence, risk factors, and predictors of outcome of candidemia. Survey in 2 Italian university hospitals

Matteo Bassetti[a,*], Enrico Maria Trecarichi[b], Elda Righi[a], Maurizio Sanguinetti[c], Francesca Bisio[a], Brunella Posteraro[c], Ornella Soro[d], Roberto Cauda[b], Claudio Viscoli[a], Mario Tumbarello[b]

	P value	OR (95% CI)
Length of hospitalization	<0.001	1.04 (1.02-1.06)
Central venous catheter	0.001	3.46 (1.70-7.03)
Previous candidemia	0.008	5.47 (1.56-19.16)
Previous bacteremia	0.02	7.16 (1.26-40.68)
Parenteral nutrition	<0.001	4.81 (2.29-10.09)
Chronic renal failure	<0.001	4.48 (1.98-10.13)

Mycoses. 2012 Nov 1. doi: 10.1111/myc.12014. [Epub ahead of print]

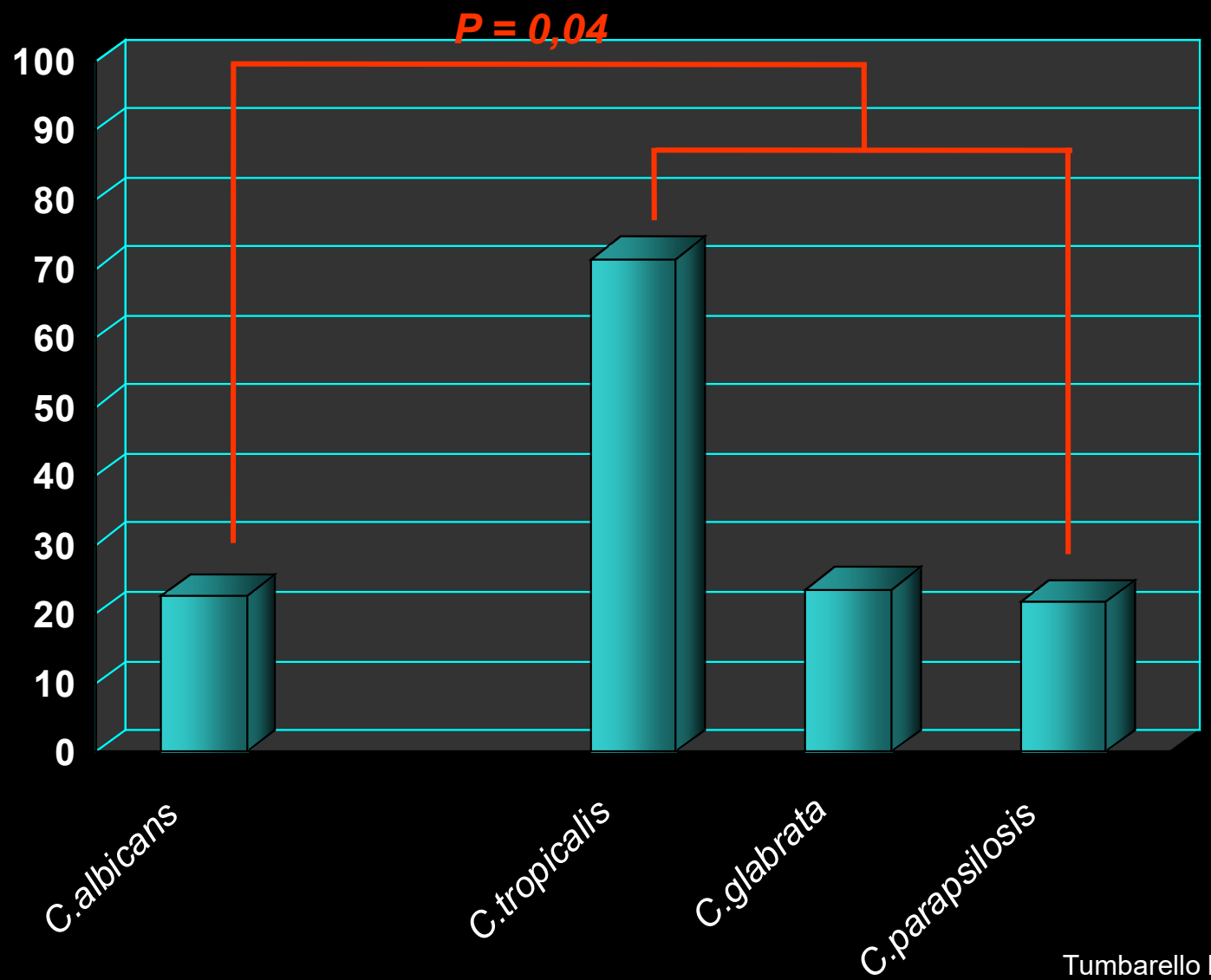
Prevalence of biofilm formation in clinical isolates of Candida species causing bloodstream infection.

Pannanusorn S, Fernandez V, Römling U.

Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden Department of Parasitology, Mycology and Environmental Microbiology, Swedish Institute for Infectious Disease Control, Solna, Sweden.

- 40% of the *C. albicans* isolates formed biofilm compared to 88.7% of the non-albicans Candida isolates ($P<0.0001$).
- Among non-albicans Candida spp., biofilm formation was most commonly observed in *C. tropicalis* and *C. lusitaniae* (100%), followed by *C. glabrata* (95%), *C. dubliniensis* (85.7%) and *C. parapsilosis* (66.7%).
- A quantitative correlation was observed between the amount of biofilm observed microscopically, and that determined by metabolic activity measurements.
- These results suggest that biofilm formation as a virulence factor might have a higher significance for non-albicans Candida species than for *C. albicans*.

Biofilm Production by *Candida* spp



Tumbarello M et al JCM 2007

The Changing Epidemiology of Invasive Candidiasis

Candida Glabrata *and* Candida Krusei *as the Leading Causes of Candidemia in Hematologic Malignancy*

CANCER June 1, 2008 / Volume 112 / Number 11

Ray Hachem, MD
Hend Hanna, MD
Dimitrios Kontoyiannis, MD
Ying Jiang, MS
Issam Raad, MD

TABLE 4
Distribution of Different Candida Species Causing Candidemia Among Patients With Hematologic Malignancies During 2 Periods: 1988-1992 Versus 1993-2003*

	No. of patients (%)		
Candida species	1988–1992, n = 230	1993–2003, n = 281	*P*
C. albicans	79 (34.4)	38 (13.5)	<.0001
C. glabrata	28 (12.2)	86 (30.6)	<.0001
C. krusei	17 (7.4)	68 (24.2)	<.0001
C. parapsilosis	33 (14.4)	39 (13.9)	.88
C. tropicalis	53 (23.0)	27 (9.6)	<.0001
C. guillermondii	2 (0.9)	4 (1.4)	.7
C. lusitaniae	3 (1.3)	3 (1.1)	>.99
Mixed *Candida* species	12 (5.2)	16 (5.7)	.81

* Data from Pittet 1996[34] based on a study on the epidemiology of Candidemia in 1988-1992 at the University of Texas M. D. Anderson Cancer Center. Fluconazole was introduced in 1989 and came into heavy prophylactic use after 1993.

TABLE 3
Multiple Logistic Regression Analysis of Independent Variables Predisposing Patients to Candidemia Caused by Different Species

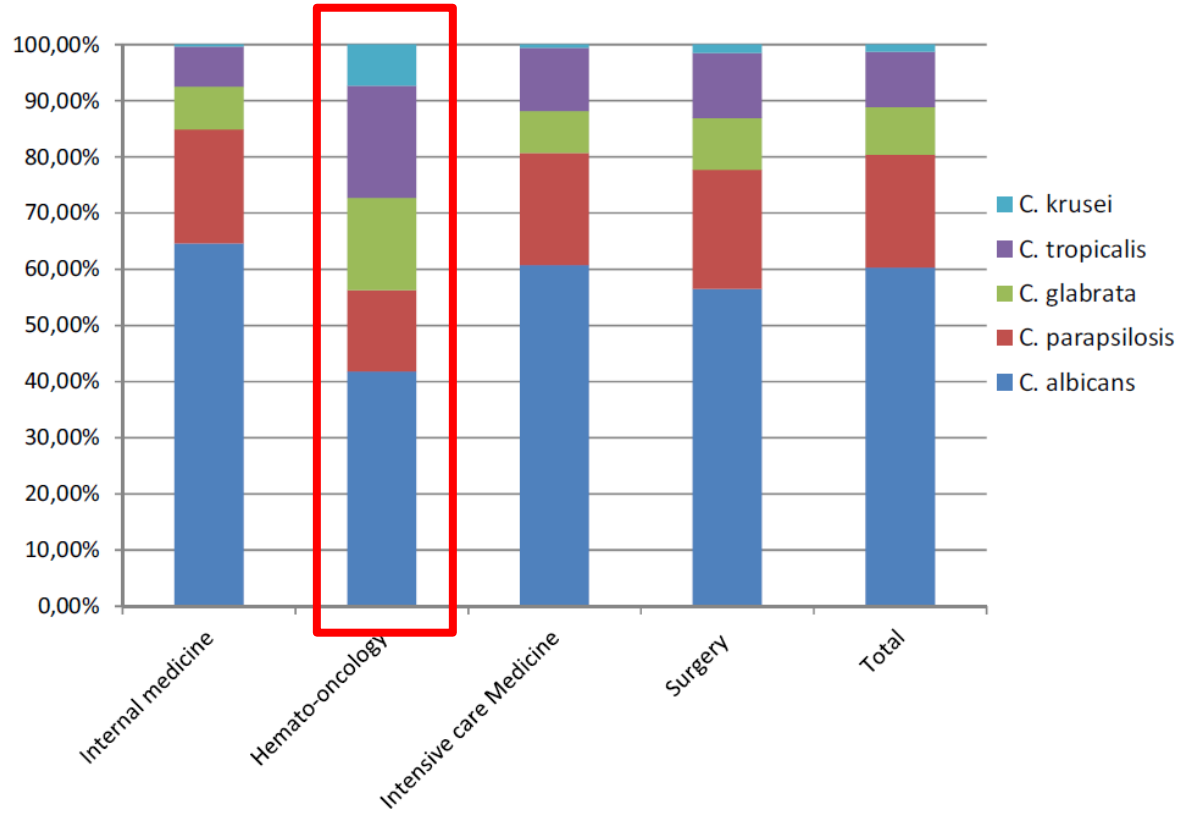
Candida species	Independent risk factor	OR	95% CI
C. albicans	No neutropenia	1.560	1.200–2.440
	No fluconazole prophylaxis	3.330	2.040–5.560
	Presence of solid tumor	2.500	1.540–4.000
C. tropicalis	Neutropenia	2.325	1.287–4.202
C. glabrata	Fluconazole prophylaxis	2.041	1.361–3.060
C. krusei	Fluconazole prophylaxis	5.260	2.922–9.468
	Neutropenia	5.378	2.696–10.727
C. parapsilosis	Catheter-related candidemia	2.470	1.587–3.845

OR indicates odds ratio; 95% CI, 95% confidence interval.

JCM Journals.ASM.org 2013

Epidemiology, Species Distribution, Antifungal Susceptibility, and Outcome of Candidemia across Five Sites in Italy and Spain

Matteo Bassetti,[a] Maria Merelli,[a] Elda Righi,[a] Ana Diaz-Martin,[b] Eva Maria Rosello,[c] Roberto Luzzati,[d] Anna Parra,[e] Enrico Maria Trecarichi,[f] Maurizio Sanguinetti,[g] Brunella Posteraro,[h] Jose Garnacho-Montero,[b] Assunta Sartor,[i] Jordi Rello,[j] Mario Tumbarello[f]



Distribution (%) of *Candida* species according to underlying pathology or medical care

Predictors of candidaemia caused by non-*albicans Candida* species: results of a population-based surveillance in Barcelona, Spain

D. Rodríguez[1], B. Almirante[1], M. Cuenca-Estrella[2], J. L. Rodríguez-Tudela[2], J. Mensa[3], J. Ayats[4], F. Sanchez[5], A. Pahissa[1] and the Barcelona Candidemia Project Study Group*

Article published online: 6 March 2010
Clin Microbiol Infect 2010; **16**: 1676–1682

TABLE 3. Multivariate analysis of risk factors associated with non-*albicans Candida* infection among all patients with candidaemia

Variable	OR	95% CI	p
Haematological transplant recipient	10.8	1.31–90.01	0.027
Previous fluconazole use[a]	4.47	2.12–9.43	<0.001
Neonatal intensive care unit admission	4.42	1.63–12.04	0.004
Previous antibiotic use[b]	0.42	0.21–0.85	0.017
Previous *Candida albicans* colonization	0.33	0.19–0.57	<0.001

[a]At least 3 days of fluconazole treatment within 30 days prior to candidaemia.
[b]At least 3 days of any antibiotic treatment within 30 days prior to candidaemia.

JOURNAL OF CLINICAL MICROBIOLOGY, June 2007, p. 1843–1850 Vol. 45, No. 6
0095-1137/07/$08.00+0 doi:10.1128/JCM.00131-07
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Biofilm Production by *Candida* Species and Inadequate Antifungal Therapy as Predictors of Mortality for Patients with Candidemia[▽]

Mario Tumbarello,[1] Brunella Posteraro,[2] Enrico Maria Trecarichi,[1] Barbara Fiori,[2] Marianna Rossi,[1] Rosaria Porta,[2] Katleen de Gaetano Donati,[1] Marilena La Sorda,[2] Teresa Spanu,[2] Giovanni Fadda,[2] Roberto Cauda,[1] and Maurizio Sanguinetti[2]*

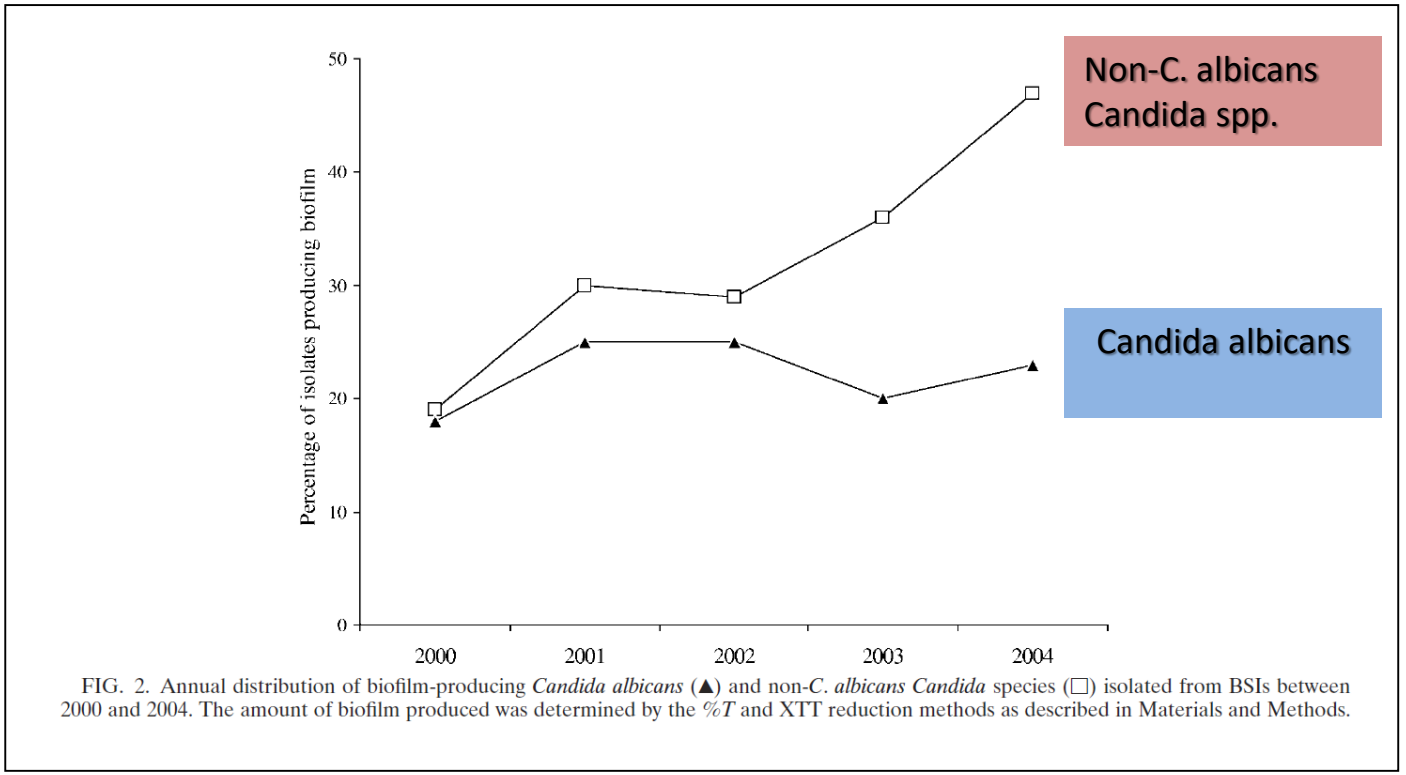

FIG. 2. Annual distribution of biofilm-producing *Candida albicans* (▲) and non-*C. albicans Candida* species (□) isolated from BSIs between 2000 and 2004. The amount of biofilm produced was determined by the *%T* and XTT reduction methods as described in Materials and Methods.

JOURNAL OF CLINICAL MICROBIOLOGY, June 2007, p. 1843–1850 Vol. 45, No. 6
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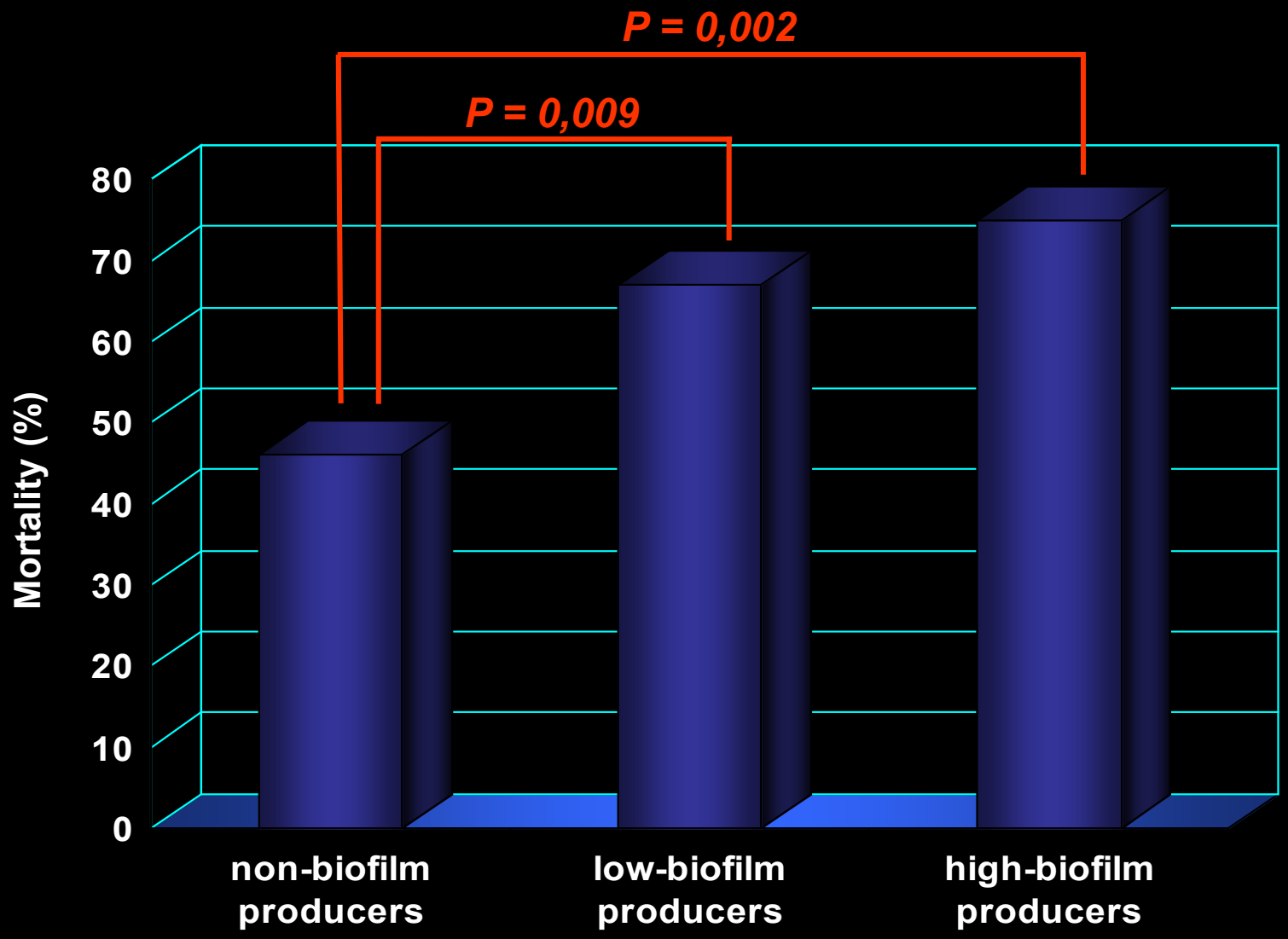
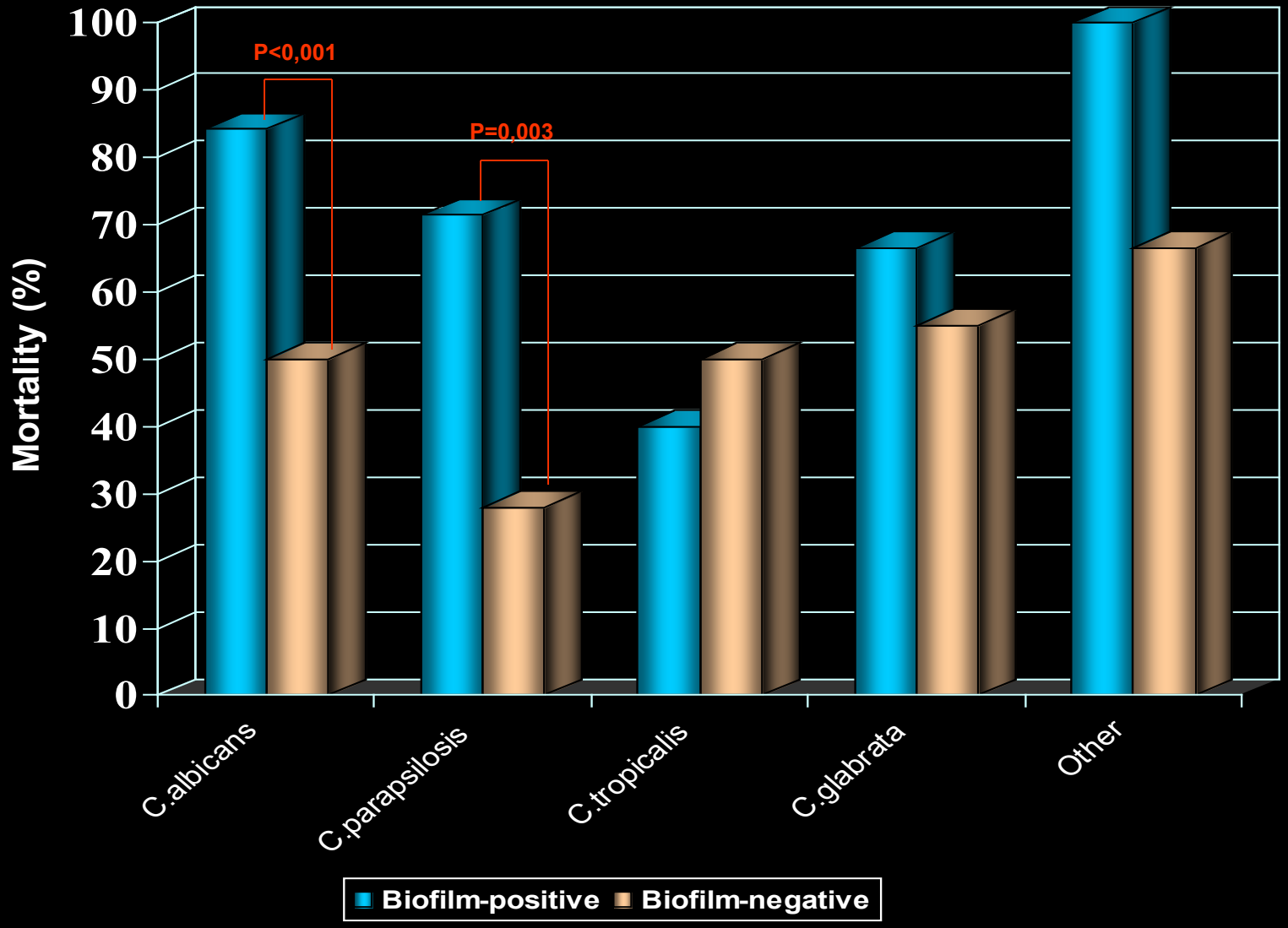
Variables associated with mortality in 294 patients with candidemia	OR (95% CI)	*P*
Inadequate antifungal therapy	2.35 (1.09-5.10)	*0.03*
Infection biofilm-forming *Candida* species	2.33 (1.26-4.30)	*0.007*
APACHE score	1.03 (1.01-1.15)	*0.001*

Mortality in Relation to the Amount of Biofilm Production



Tumbarello M et al JCM 2007

Mortality by Biofilm-Producing Isolates



Tumbarello M et al JCM 2007

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PLoS one

Risk Factors and Outcomes of Candidemia Caused by Biofilm-Forming Isolates in a Tertiary Care Hospital

Mario Tumbarello[1]*, Barbara Fiori[2], Enrico Maria Trecarichi[1], Patrizia Posteraro[3], Angela Raffaella Losito[1], Alessio De Luca[4], Maurizio Sanguinetti[2], Giovanni Fadda[2], Roberto Cauda[1], Brunella Posteraro[5]

For the case-case-control study, BF-CBSI and NBF-CBSI patients, were compared with a common control group, consisting of randomly selected patients who had been hospitalized in our center during the same periods of time and in the same wards as the case patients, but who did not have evidence of CBSI

Table 2. Logistic regression analysis of risk factors for candidemias by biofilm-forming (BF) and non-biofilm-forming (NBF) isolates.

Variable	OR (95% CI)
BF CBSI	
CVC in place at time of positive blood culture	6.44 (3.21–12.92)
Total parenteral nutrition	5.21 (2.59–10.48)
Diabetes mellitus	4.47 (2.03–9.83)
Urinary catheter in place at time of positive blood culture	2.40 (1.18–4.91)
NBF CBSI	
Total parenteral nutrition	8.41 (3.70–19.08)
CVC in place at time of positive blood culture	5.73 (2.55–12.84)
Antibiotic therapy in previous 30 days	4.48 (1.55–12.93)
Surgery in previous 30 days	2.45 (1.04–5.81)

NOTE. CBSI, *Candida* bloodstream infection; CVC, central venous catheter.

doi:10.1371/journal.pone.0033705.t002

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PLoS one

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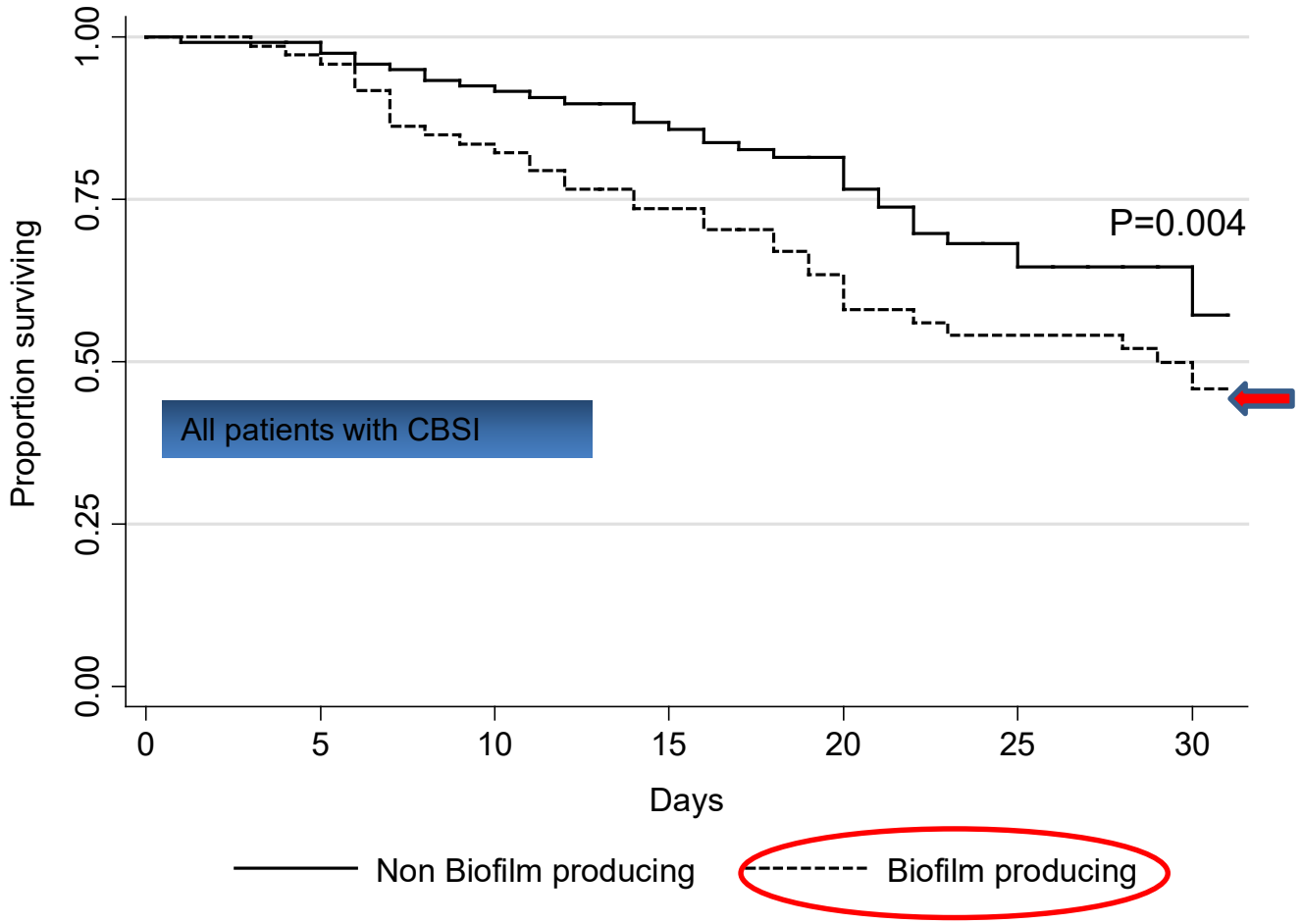
73 (86.9%) of 84 patients with BF-CBSI have been matched to 73 patients with NBF-CBSI, based on age, sex, APACHE III score, and adequateness of antifungal therapy.

Table 3. Comparison between patients with biofilm-forming (BF) candidemia or non-biofilm-forming (NBF) candidemia in the matched cohort study.

Variable	BF-CBSI group ($n=73$)	NBF-CBSI group ($n=73$)	P-value
Outcome parameters			
Initial treatment failure[f]	26 (35.6)	15 (20.5)	0.04
Hospital LOS after CBSI, days	29±31	19±5	0.007
Hospital mortality	39 (53.4)	22 (30.1)	0.004
Infection-related mortality	32 (43.8)	18 (24.6)	0.01
Antifungal therapy cost	€ 11,371±6544	€ 6108±4106	0.02

Kaplan-Meier survival curves in patients with CBSI according to biofilm production.



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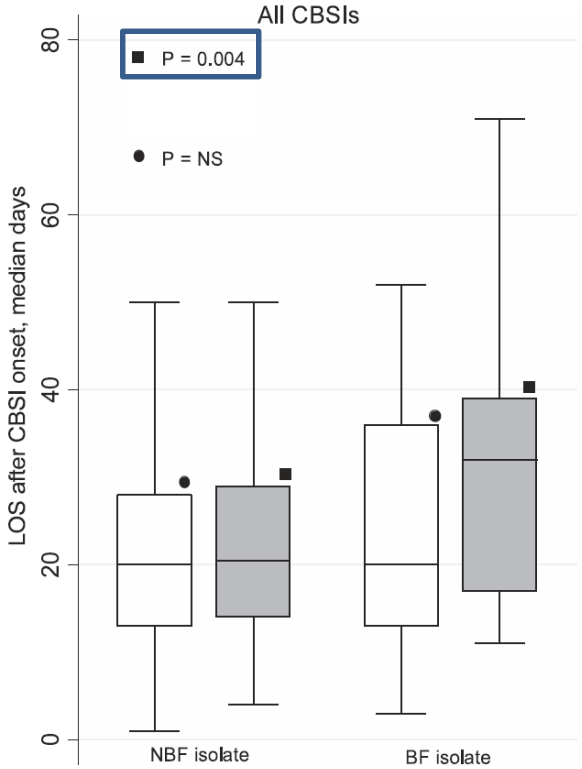
PLoS one

Risk Factors and Outcomes of Candidemia Caused by Biofilm-Forming Isolates in a Tertiary Care Hospital

Mario Tumbarello[1]*, Barbara Fiori[2], Enrico Maria Trecarichi[1], Patrizia Posteraro[3], Angela Raffaella Losito[1], Alessio De Luca[4], Maurizio Sanguinetti[2], Giovanni Fadda[2], Roberto Cauda[1], Brunella Posteraro[5]

The median (range) **post-CBSI hospital LOS** did not significantly differ between BF-CBSI group (20 days [3–189]) and NBF-CBSI group (19 days [1–105]) (p = 0.16), by considering all case patients.



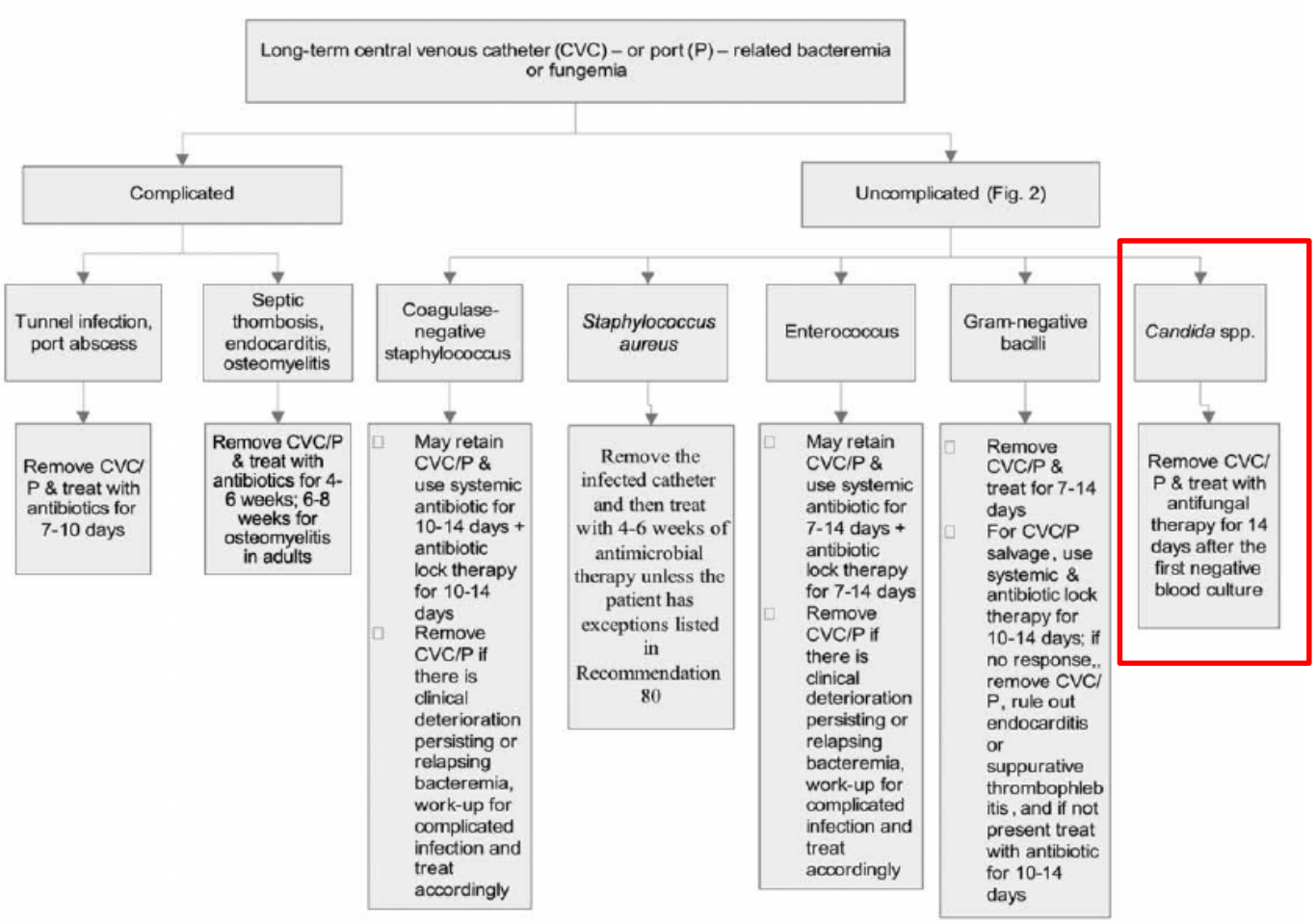
This difference between the groups reached statistical significance when calculated only among patients who survived (32 days [11–189] vs. 20.5 days [4–105], respectively, p = 0.004).

Figure 2. Hospital length of stay (LOS) following the *Candida* bloodstream infection (CBSI) onset in all (white box-plots) or surviving (grey box-plots) patients. Patients were grouped according to the biofilm-forming (BF) or non-biofilm-forming (NBF) *Candida* isolate (for all CBSIs), and according to receiving of highly active anti-biofilm (HAAB) or non-HAAB antifungal therapy (for BF CBSIs only). Lines inside the boxes indicate the median values, whereas upper and lower limits of the boxes and whiskers indicate the interquartile and total ranges, respectively. P-values for statistically significant differences between the groups are shown.
doi:10.1371/journal.pone.0033705.g002

Clinical Infectious Diseases 2009; 49:1–45

Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America

Leonard A. Mermel,[1] Michael Allon,[2] Emilio Bouza,[3] Donald E. Craven,[3] Patricia Flynn,[4] Naomi P. O'Grady,[5] Issam I. Raad,[6] Bart J. A. Rijnders,[10] Robert J. Sherertz,[7] and David K. Warren[8]



Early Removal of Central Venous Catheter in Patients with Candidemia Does Not Improve Outcome: Analysis of 842 Patients from 2 Randomized Clinical Trials

Clinical Infectious Diseases 2010; 51(3):295–303

Marcio Nucci,[1] Elias Anaissie,[2] Robert F. Betts,[3] Bertrand F. Dupont,[5] Chunzhang Wu,[4] Donald N. Buell,[4] Laura Kovanda,[4] and Olivier Lortholary[5,6]

Table 5. Multivariate Analysis of the Effect of Early Removal of the Central Venous Catheter (CVC) on Treatment Success and Survival at 28 and 42 Days after Treatment Initiation in 842 Patients with Candidemia

	Treatment success		Survival at 28 days		Survival at 42 days	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
CVC removal within 24 h after treatment initiation						
CVC removal	NT	NT	1.15 (0.79–1.67)	.45	1.19 (0.84–1.67)	.33
Persistent neutropenia	NT	NT	0.36 (0.15–0.88)	.03	0.38 (0.16–0.90)	.03
Surgery	NT	NT	1.46 (0.87–2.47)	.16	1.97 (1.23–3.18)	.005
Older age	NT	NT	0.98[a] (0.97–0.99)	.02	0.98[a] (0.97–0.99)	.02
CVC removal within 48 h after treatment initiation						
CVC removal	1.20 (0.86–1.69)	.26	1.23 (0.85–1.75)	.27	1.25 (0.88–1.75)	.20
Receipt of corticosteroids	0.64 (0.44–0.94)	.02	0.77 (0.51–1.16)	.21	0.70 (0.47–1.02)	.06
Persistent neutropenia	0.42 (0.18–0.98)	.04	0.36 (0.15–0.89)	.03	0.38 (0.16–0.90)	.03
Higher APACHE II score	0.93[a] (0.91–0.96)	<.001	0.90[a] (0.88–0.93)	<.001	0.91[a] (0.89–0.93)	<.001
Liver failure	NT	NT	0.22 (0.07–0.72)	.01	NT	NT
Surgery	1.25 (0.80–1.95)	.33	1.46 (0.86–2.46)	.16	1.96 (1.22–3.17)	.006
Older age	0.99[a] (0.98–1.01)	.31	0.98[a] (0.97–0.99)	.02	0.98[a] (0.97–0.99)	.02

All patients were treated with Micafungin, caspofungin, or liposomal Amphotericin B

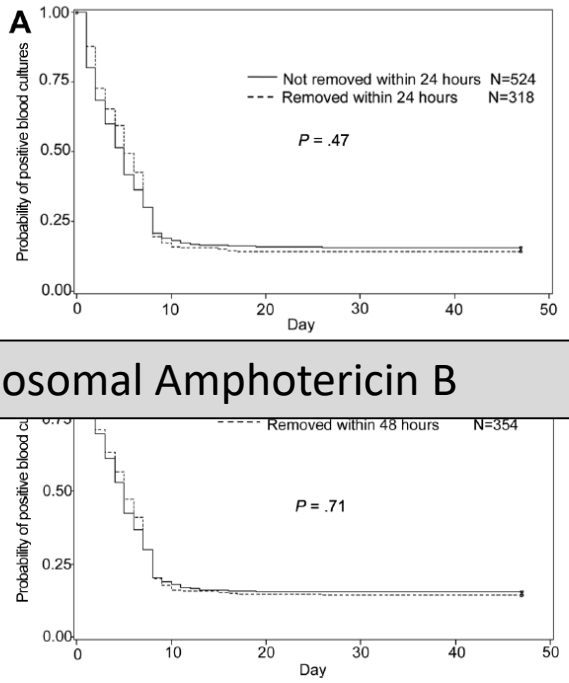


Figure 2. Time to mycological eradication for patients whose central venous catheter (CVC) was removed within 24 h (*A*) or 48 h (*B*) after initiation of antifungal therapy, compared with patients whose CVC was not removed within this time frame.

ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients

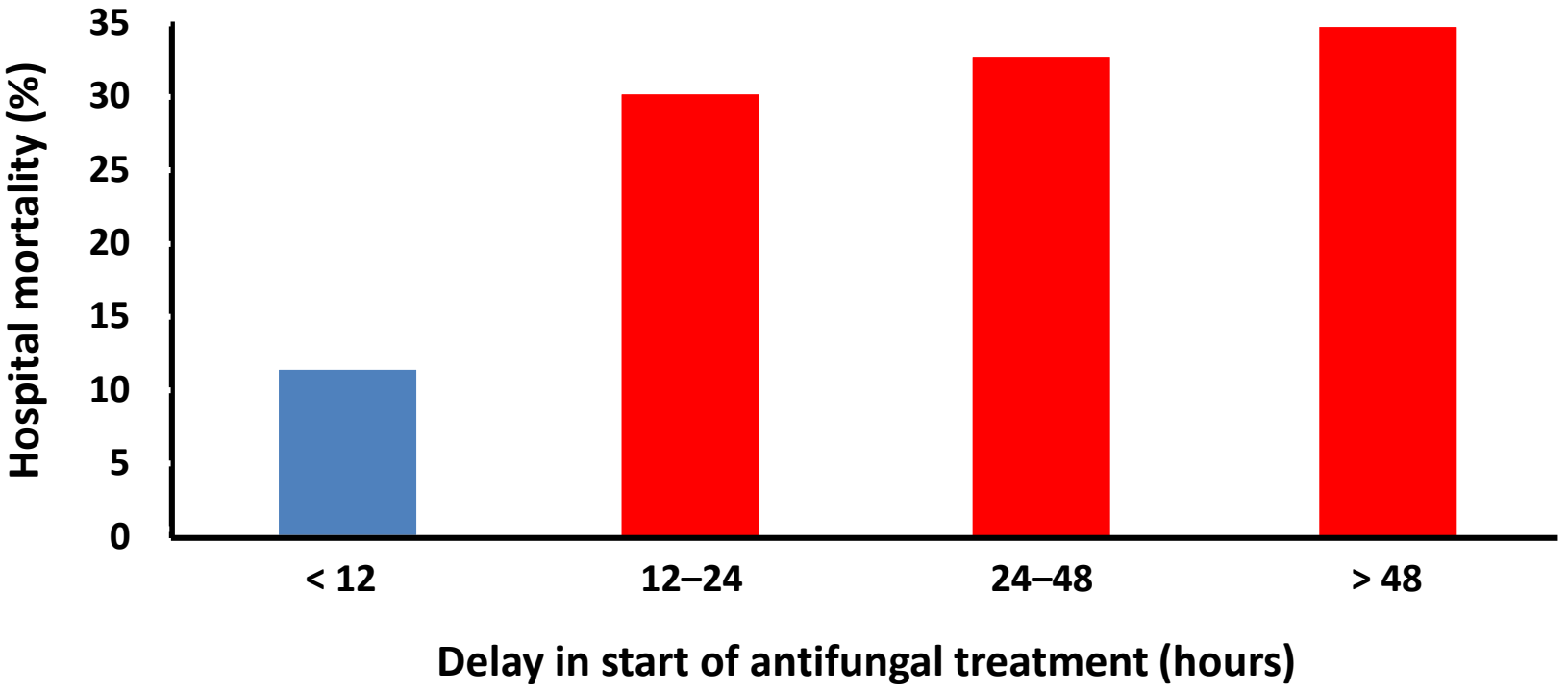
O. A. Cornely[1†], M. Bassetti[2†], T. Calandra[3†], J. Garbino[4†], B. J. Kullberg[5†], O. Lortholary[6,7†], W. Meersseman[8†], M. Akova[9], M. C. Arendrup[10], S. Arikan-Akdagli[11], J. Bille[3], E. Castagnola[12], M. Cuenca-Estrella[13], J. P. Donnelly[5], A. H. Groll[4], R. Herbrecht[15], W. W. Hope[16], H. E. Jensen[17], C. Lass-Flörl[18], G. Petrikkos[19], M. D. Richardson[20], E. Roilides[21], P. E. Verweij[5], C. Viscoli[22] and A. J. Ullmann[23] for the ESCMID Fungal Infection Study Group (EFISG)

TABLE 7. Recommendations on catheter management in candidaemia

Population	Intervention	SoR	QoE	References
Central venous catheter can be removed	Remove indwelling lines (not over a guidewire)	A	II_r	[98]
Central venous catheter cannot be removed	Echinocandin, liposomal amphotericin B or amphotericin B lipid complex	B	II_r	[98] [90] [89] [91] [93] [92]
	Azole or amphotericin B deoxycholate	D	II_r	[95] [98] [73] [97] [96] [94]

Interventions are intended to clear candidaemia and to improve survival.

Hospital mortality and timing of antifungal treatment



Morrell M, *et al*. *Antimicrob Agents Chemother* 2005

JOURNAL OF CLINICAL MICROBIOLOGY, June 2007, p. 1843–1850 Vol. 45, No. 6
0095-1137/07/$08.00+0 doi:10.1128/JCM.00131-07
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Biofilm Production by *Candida* Species and Inadequate Antifungal Therapy as Predictors of Mortality for Patients with Candidemia[▽]

Mario Tumbarello,[1] Brunella Posteraro,[2] Enrico Maria Trecarichi,[1] Barbara Fiori,[2] Marianna Rossi,[1] Rosaria Porta,[2] Katleen de Gaetano Donati,[1] Marilena La Sorda,[2] Teresa Spanu,[2] Giovanni Fadda,[2] Roberto Cauda,[1] and Maurizio Sanguinetti[2]*

Variables associated with mortality in 294 patients with candidemia	OR (95% CI)	*P*
Inadequate antifungal therapy	**2.35 (1.09-5.10)**	***0.03***
Infection biofilm-forming *Candida* species	**2.33 (1.26-4.30)**	***0.007***
APACHE score	**1.03 (1.01-1.15)**	***0.001***

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3591–3593 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.01701-10
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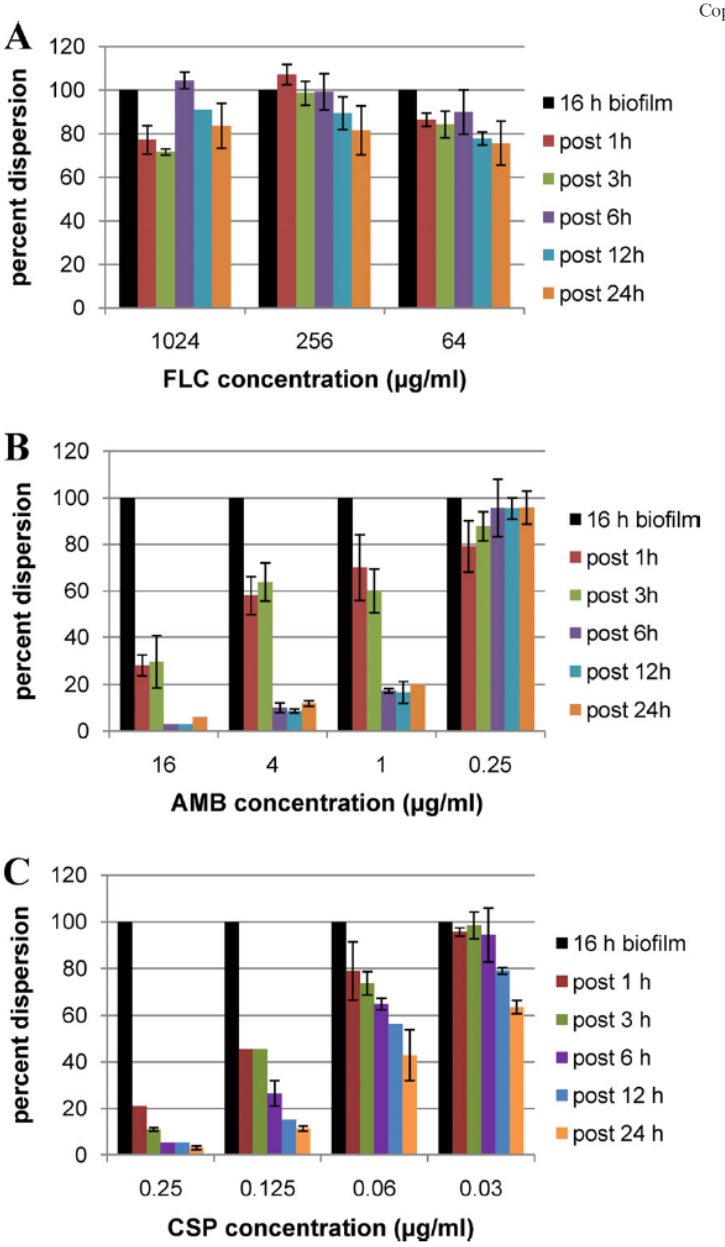
Effects of Fluconazole, Amphotericin B, and Caspofungin on *Candida albicans* Biofilms under Conditions of Flow and on Biofilm Dispersion[▽]

Priya Uppuluri,[1,2] Anand Srinivasan,[3] Anand Ramasubramanian,[2,3] and Jose L. Lopez-Ribot[1,2]*

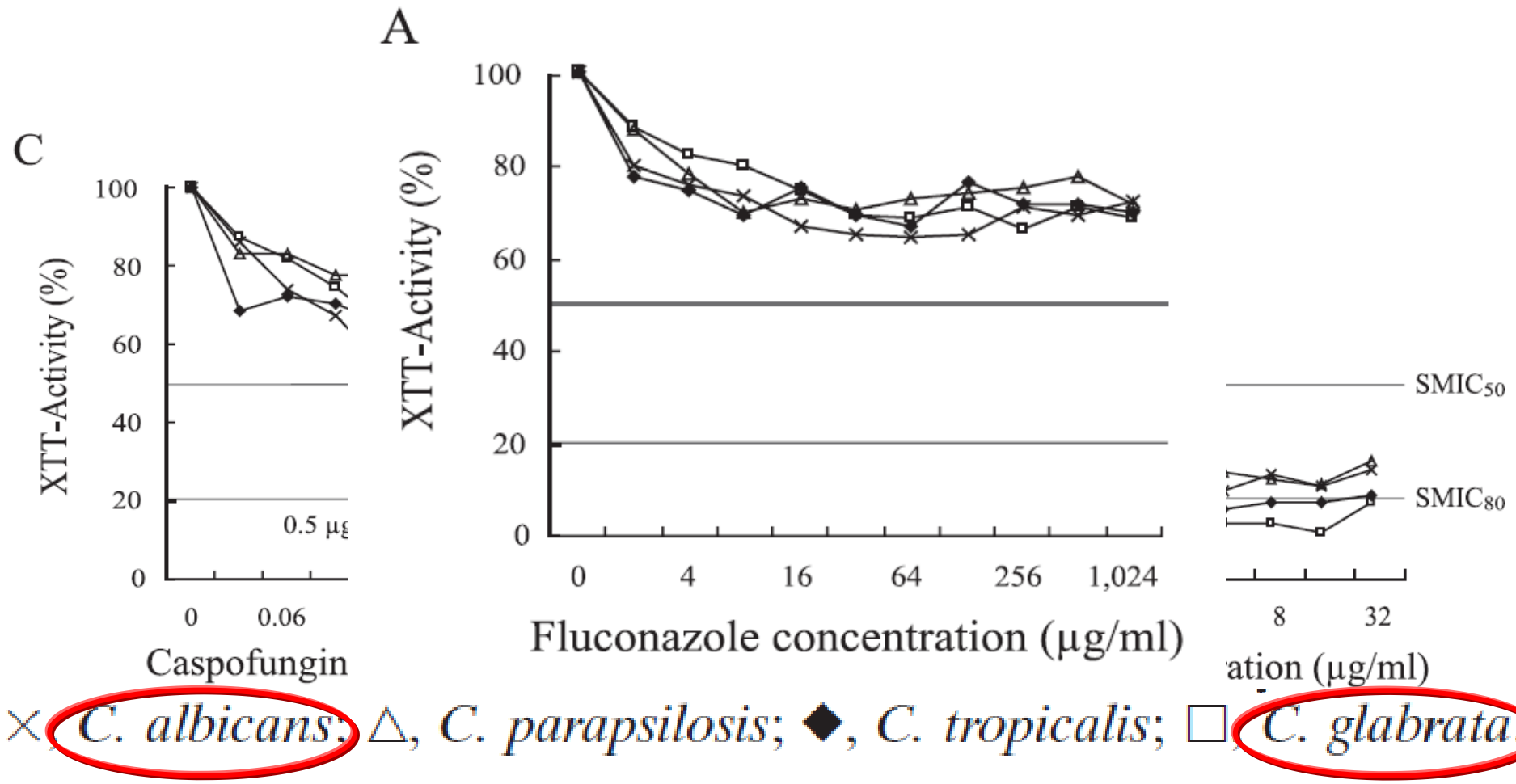


Biofilms displayed high levels of resistance to Fluconazole, and this antifungal exerted minor effects on dispersion levels.

Amphotericin B proved effective in reducing viability of cells within the biofilms and dispersion, but only at high concentrations.

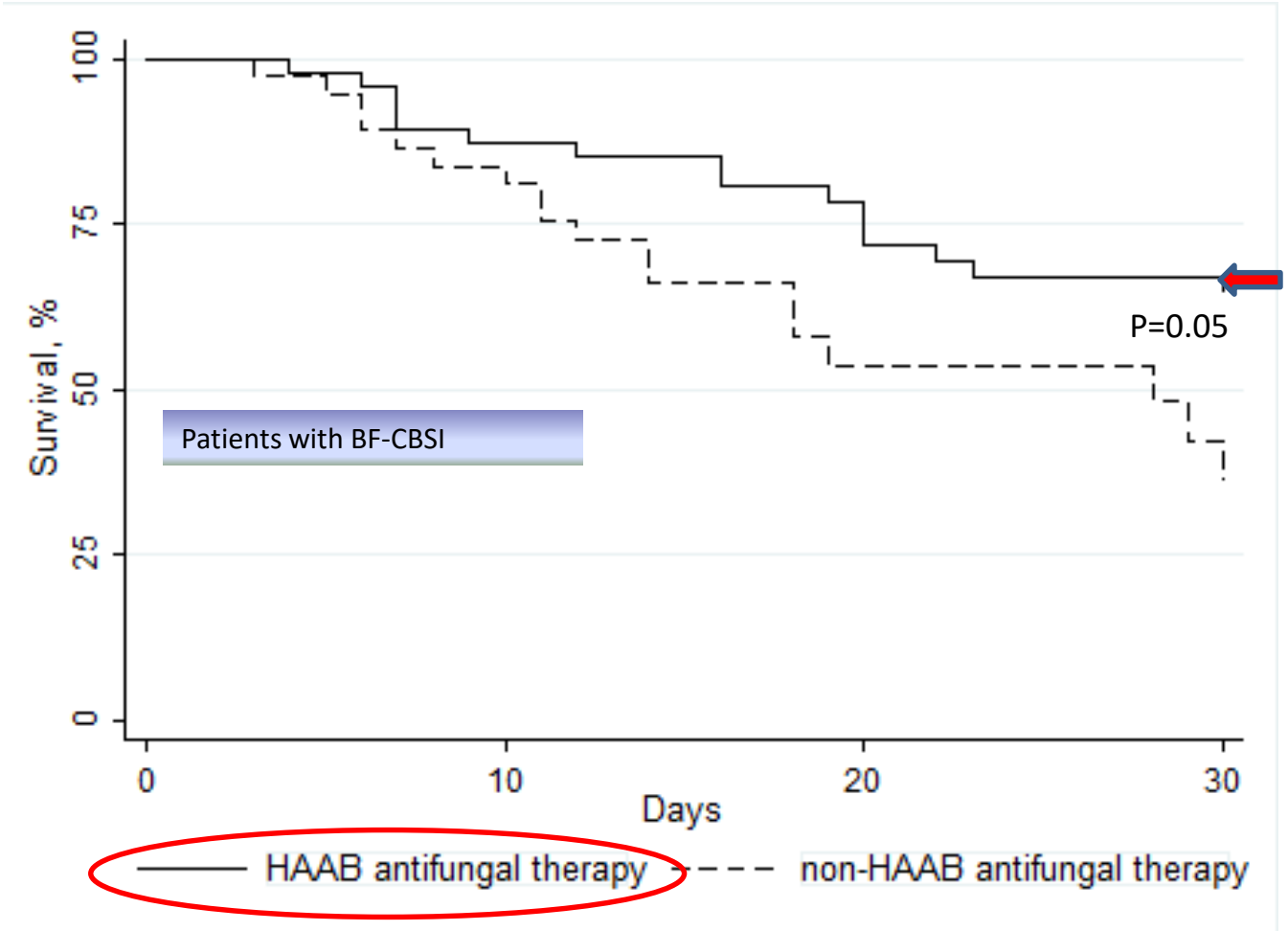
Under flow conditions, Caspofungin exhibited potent activity against biofilms and drastically reduced biofilm dispersion.

Biofilm activity of antifungals vs different species



Choi HW et al. *AAC* 2007

Kaplan-Meier survival curves in patients with BF-CBSI according to antifungal therapy.



Tumbarello et al. PLoS ONE 2012

Zilberberg *et al. BMC Infectious Diseases* 2010, **10**:150
http://www.biomedcentral.com/1471-2334/10/150

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Inappropriate empiric antifungal therapy for candidemia in the ICU and hospital resource utilization: a retrospective cohort study

Marya D Zilberberg*[1,2], Marin H Kollef[3], Heather Arnold[3], Andrew Labelle[3], Scott T Micek[3], Sm Andrew F Shorr[5]

Table 3: Unadjusted Outcomes

	Inappropriate (n = 80)	Appropriate (n = 10)	P value*
ICU LOS (days)			
Mean ± SD	10.8 ± 10.8	9.1 ± 10.1	
Hospital LOS (days) following onset of CBSI			
Mean ± SD	18.4 ± 17.0	10.7 ± 9.4	
Median (IQR 25, 75)	13 (8, 22)	8 (3, 16)	0.062
Hospital mortality	23 (28.8%)	0	0.059

*Derived using Mann Whitney U test for continuous variables and Fisher's exact test for categorical variable

Table 4: Utilization outcomes attributable to inappropriate antifungal treatment

Outcome	Point estimate	95% CI	P value
Excess hospital LOS (days) following onset of CBSI*	7.7	0.6-13.5	0.015
Excess hospital costs ($)†	$13,398	$1,060-$26,736	0.033

Based on generalized linear models with gamma distribution
*Generalized linear model, adjusted for all covariates with $p < 0.2$ in the univariate analysis plus age, APACHE II score, need for mechanical ventilation and need for pressors; manual backwards elimination to arrive at most parsimonious model
†Generalized linear model, adjusted for all covariates with $p < 0.2$ in the univariate analysis plus age and time from hospital admission to CBSI onset, APACHE II score, need for mechanical ventilation and need for pressors; manual backwards elimination to arrive at most parsimonious model

DISPATCHES

Biofilm-Forming Capability of Highly Virulent, Multidrug-Resistant *Candida auris*

Leighann Sherry, Gordon Ramage, Ryan Kean, Andrew Borman, Elizabeth M. Johnson, Malcolm D. Richardson, Riina Rautemaa-Richardson

Table 1. Planktonic susceptibility profiles of 7 antifungals against *Candida auris* yeast

	Planktonic MIC*			
Drug	Strain 2	Strain 6	Strain 10	Strain 12
Fluconazole	>32	>32	>32	>32
Voriconazole	8	8	32	1
Caspofungin	32	32	2	>32
Micafungin	0.5	≤0.0625	<0.06	≤0.0625
Liposomal amphotericin B	0.25	0.25	0.5	1
Amphotericin B	0.25	0.25	0.5	0.5
Chlorhexidine, %	≤0.02	≤0.02	≤0.02	≤0.02

*Values are mg/L except as indicated. All MIC tests were performed on 3 independent occasions, showing identical results each time.

Table 2. Sessile susceptibility profiles of 7 antifungals against *Candida auris* yeast

	Sessile MIC*			
Drug	Strain 2	Strain 6	Strain 10	Strain 12
Fluconazole	>32	>32	>32	>32
Voriconazole	>32	>32	>32	>32
Caspofungin	>32	>32	>32	>32
Micafungin	>32	>32	0.25	>32
Liposomal amphotericin B	2	8	16	16
Amphotericin B	2	4	2	4
Chlorhexidine, %	≤0.02	≤0.02	≤0.02	≤0.02

*Values indicate mg/L except as indicated. Sessile MICs are defined as a 90% inhibition of the metabolic dye XTT, 2,3-Bis(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide inner salt (Sigma-Aldrich, Dorset, UK) compared with the untreated control; MIC tests were performed on 3 independent occasions and showed identical results each time.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2011, p. 532–538 Vol. 55, No. 2
0066-4804/11/$12.00 doi:10.1128/AAC.01128-10
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Recent Exposure to Caspofungin or Fluconazole Influences the Epidemiology of Candidemia: a Prospective Multicenter Study Involving 2,441 Patients[▽]

Olivier Lortholary,[1,2,3] Marie Desnos-Ollivier,[1,2] Karine Sitbon,[1,2] Arnaud Fontanet,[4] Stéphane Bretagne,[1,2,5] Françoise Dromer,[1,2*] and the French Mycosis Study Group†

Risk of being infected with an isolate with decreased susceptibility to **fluconazole** was independently associated with
•age ≥15 years
•recent preexposure to fluconazole

Risk of being infected with an isolate with decreased susceptibility to **caspofungin** was independently associated with
•age <15 years
•recent preexposure to caspofungin

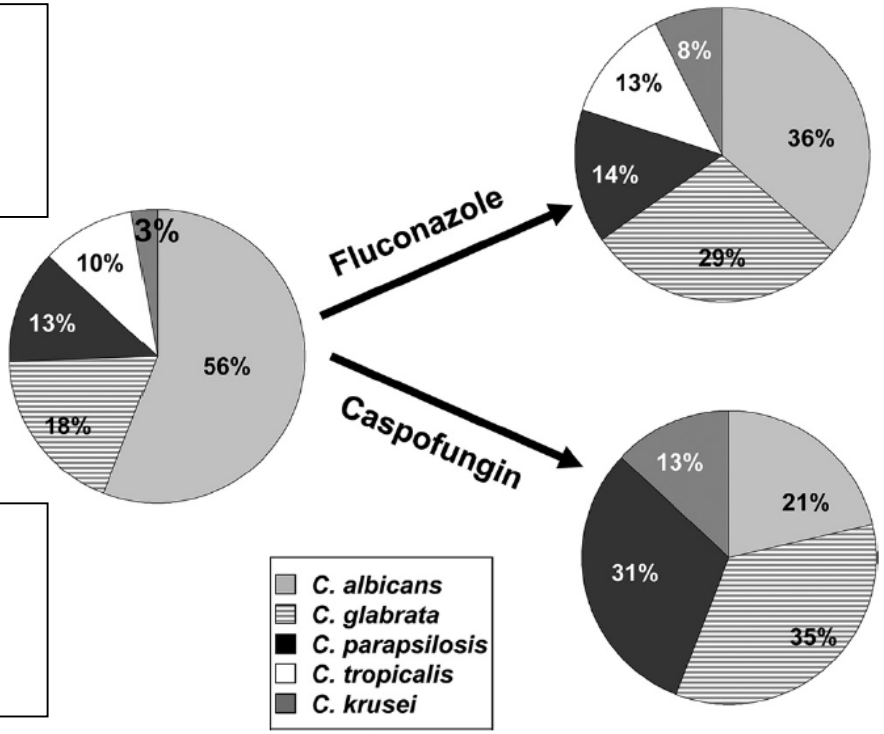
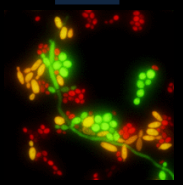
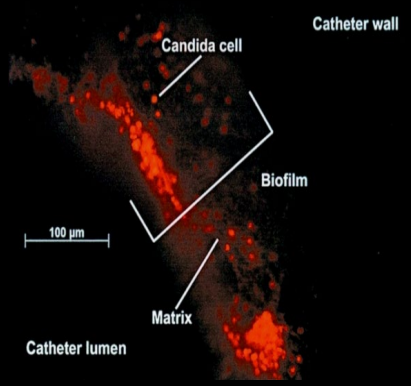


FIG. 2. Proportion of the five major *Candida* species responsible for fungemia in patients with (n = 159) or without (n = 2,289) prior exposure to fluconazole (P = 0.001) or with (n = 61) or without (n = 2,387) prior exposure to caspofungin (P < 0.001) (incident episodes and recurrences are included).

One of the Candida species most frequently forming biofilm

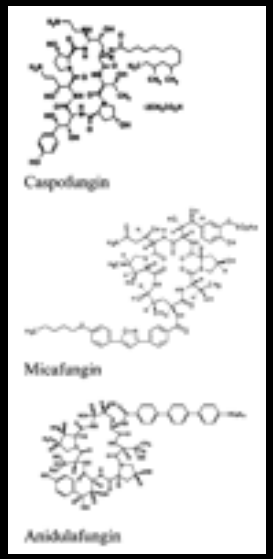


Candida parapsilosis



Biofilm

The less effective antifungal drug



Echinocandins

The most effective antifungal drug

Comparative Efficacy of Echinocandins and Nonechinocandins for the Treatment of *Candida parapsilosis* Infections: A Meta-analysis

Pramodini B. Kale-Pradhan, Pharm.D., Geoffrey Morgan, Sheila M. Wilhelm, Pharm.D., and Leonard B. Johnson, M.D.

The success rates of treating C. parapsilosis were similar for the echinocandin group versus other antifungal treatment groups.
The combined risk ratio demonstrated that echinocandins are not significantly different from other antifungal agents for the treatment of candidemia or invasive candidiasis due to C. parapsilosis.

CONCLUSION: Echinocandins are as effective as comparator drugs for the treatment of candidemia or invasive candidiasis due to C. parapsilosis.

Study or Subgroup	Echinocandins Events	Total	Other Antifungals Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Colombo 2003	14	20	13	20	17.6%	1.08 [0.70, 1.66]
Kuse 2007	33	37	26	30	38.9%	1.03 [0.86, 1.23]
Mora-Duarte 2002	14	21	13	21	17.6%	1.08 [0.69, 1.69]
Queiroz-Telles 2008	10	13	11	17	12.9%	1.19 [0.75, 1.88]
Reboli 2007	7	11	10	12	13.0%	0.76 [0.46, 1.28]
Total (95% CI)		**102**		**100**	**100.0%**	**1.03 [0.88, 1.21]**
Total events	78		73			

Heterogeneity: Chi² = 1.76, df = 4 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.39 (P = 0.69)

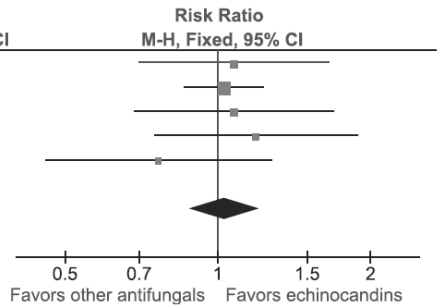


Figure 3. Forest plot of the five studies included in the meta-analysis of echinocandins versus comparator antifungals for the treatment o *Candida parapsilosis* candidemia or invasive candidiasis. M-H = Mantel-Haenszel; CI = confidence interval.

Study or Subgroup	Echinocandins Events	Total	Other Antifungals Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Colombo 2003	61	81	55	89	18.0%	1.22 [0.99, 1.50]
Kuse 2007	156	175	149	166	25.2%	0.99 [0.92, 1.07]
Mora-Duarte 2002	51	73	53	86	16.9%	1.13 [0.91, 1.42]
Queiroz-Telles 2008	28	32	27	28	21.3%	0.91 [0.78, 1.05]
Reboli 2007	85	108	55	94	18.5%	1.35 [1.11, 1.64]
Total (95% CI)		**469**		**463**	**100.0%**	**1.09 [0.94, 1.27]**
Total events	381		339			

Heterogeneity: Tau² = 0.02; Chi² = 19.16, df = 4 (P = 0.0007); I² = 79%
Test for overall effect: Z = 1.15 (P = 0.25)

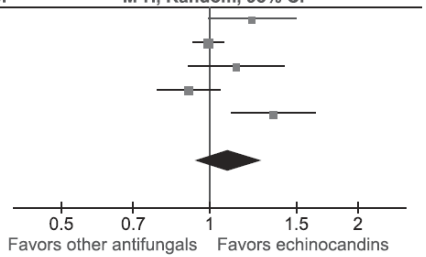


Figure 4. Forest plot of the five studies included in the meta-analysis of echinocandins versus comparator antifungals for the treatment of non–*Candida parapsilosis* candidemia or invasive candidiasis. M-H = Mantel-Haenszel; CI = confidence interval.

(Pharmacotherapy 2010;30(12):1207–1213)

Microbiologic and clinical characteristics of biofilm-forming *Candida parapsilosis* isolates associated with fungaemia and their impact on mortality☆

S. Soldini [1,6], B. Posteraro [2,6], A. Vella [1], E. De Carolis [1], E. Borghi [4], M. Falleni [5], A.R. Losito [3], G. Maiuro [3], E.M. Trecarichi [3], M. Sanguinetti [1,*], M. Tumbarello [3]

2017

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID

Regression analysis of variables associated with 30-day mortality.

Characteristic	OR	95% CI
HBF/MBF *Candida parapsilosis* infection	3.85	1.88–7.87
Presentation with septic shock	3.78	1.63–8.75

Therapeutic measures affecting 30-day mortality rate in 106 patients with HBF/MBF *Candida parapsilosis* fungaemia

Characteristic	Died ($n = 61$)	Alive ($n = 45$)	OR (95% CI) for mortality
Initial antifungal therapy			
Azole based	36 (59.0%)	11 (24.4%)	4.63 (1.83–12.03)
Non-azole based[a]	24 (39.3%)	34 (75.5%)	0.21 (0.08–0.54)
Switch to azole therapy[b]	4/24 (16.7%)	14/34 (41.2%)	0.29 (0.05–1.14)
Causes of inadequate antifungal therapy			
Initiation beyond first 48 hours	43 (70.5%)	18 (40.0%)	3.58 (1.47–8.75)
No antifungal therapy	1 (1.6%)	0 (0.0%)	—
CVC removal (≤48 hours)[c]	36/47 (76.6%)	39/41 (95.1%)	0.17 (0.02–0.86)

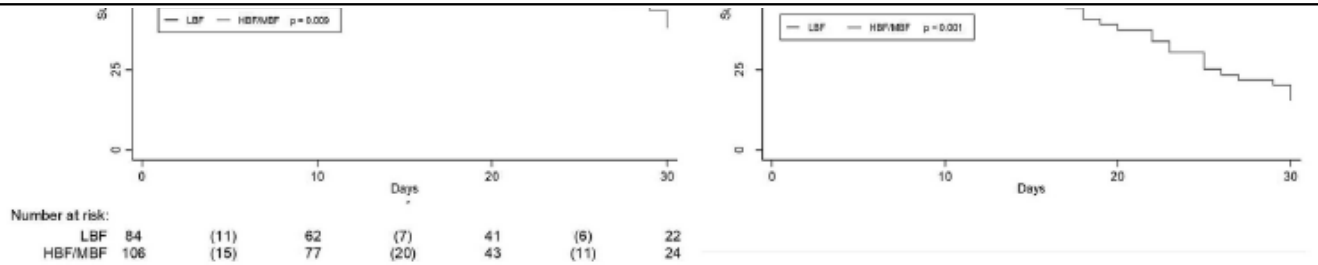
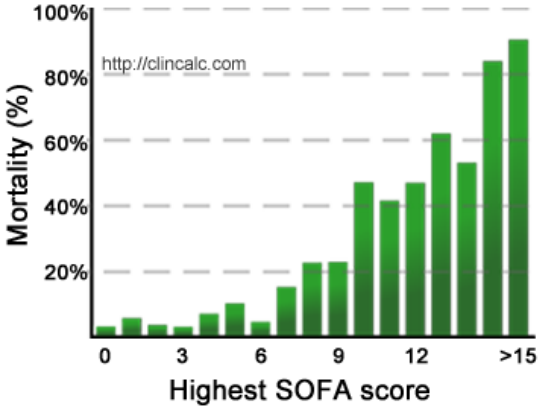
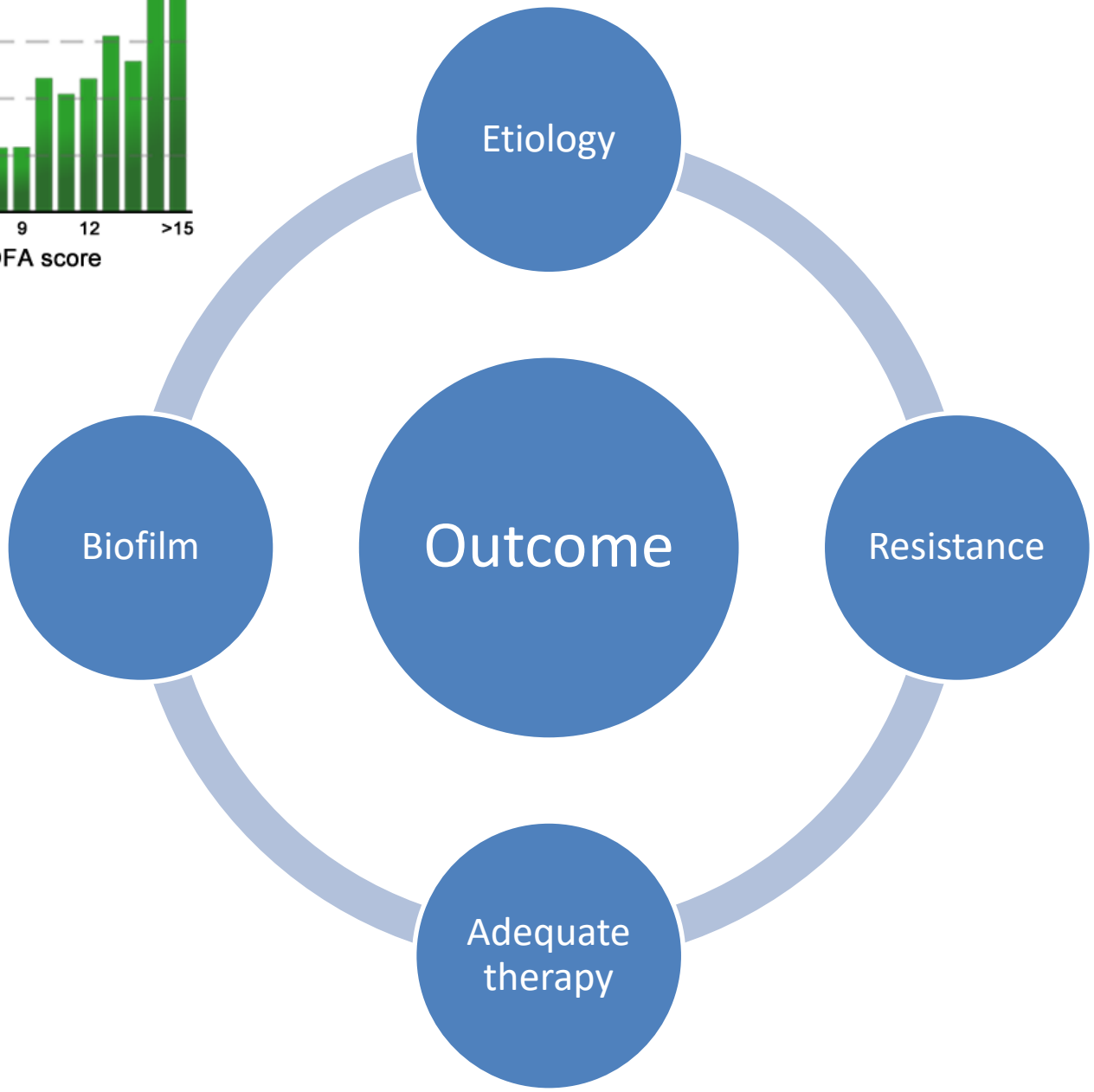


Fig. 3. Survival of patients with either LBF or HBF/MBF *Candida parapsilosis* fungaemia who were monitored over 30 days from first positive blood culture. (a) Kaplan-Meier survival curve. (b) Kaplan-Meier survival curve adjusted for presentation with septic shock, receipt of adequate antifungal therapy (≤48 hours) and removal of central venous catheter (≤48 hours). Comparison between these curves showed statistically significant difference in mortality rate. Shown are number of patients in both LBF and HBF/MBF groups who were available for follow-up at beginning of each interval (10, 20, and 30 days) of survival curves depicted in (a). HBF, high biofilm formation; LBF, low biofilm formation; MBF, moderate biofilm formation.


100%
80%
60%
40%
20%
Mortality (%)
http://clincalc.com
0
3
6
9
12
>15
Highest SOFA score


Etiology
Biofilm
Outcome
Resistance
Adequate therapy


WHAT'S NEW?

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REVIEW

Future therapies targeted towards eliminating *Candida* biofilms and associated infections

H.M.H.N. Bandara[a*], V. H. Matsubara [b,c*] and L. P. Samaranayake[a,d]

Table 2. Antifungal activity of natural compounds against a variety of fungal strains.

Natural compound	Origin	Effective against	Reference
Saponins	Different plant families	*C. albicans*	[188]
Lichochalcone-A	Licorice roots of *Glycyrrhiza* species	*C. albicans*	[189]
Carbohydrate-derived fulvic acid (CHD-FA)	Humic acids (humic substances)	*C. albicans*	[190]
Plant peptide (Tn-AFP1)	*Trapa natans* fruits	*C. tropicalis*	[191]
Human peptide (ApoEdpLW)	Human Apolipoprotein E	*C. albicans, C. parapsilosis, C. tropicalis, C. glabrata*	[192]
Tea polyphenols	Green tea	*C. albicans*	[193]
Cinnamon oil	*Cinnamomum zeylanicum*	*C. orthopsilosis* and *C. parapsilosis*	[194]
	Cinnamomum aromaticum (*Cinnamomum cassia*)	*C. albicans, C. glabrata*, and *C. krusei*	[195]
Sesamol	Sesame oil	*C. albicans*	[196]
Asarones	*Acorus calamus*	*C. albicans* and *C. tropicalis*	[197]
Garlic extract (allyl alcohol)	*Allium sativum*	*C. albicans*	[198]
Acteoside (polyphenolic compounds)	*Colebrookea oppositifolia*	*C. albicans, Cryptococcus neoformans*, and *Aspergillus fumigatus*	[199]

Vargas-Blanco *et al. Ann Clin Microbiol Antimicrob (2017) 16:41*
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RESEARCH Open Access

A pre-therapeutic coating for medical devices that prevents the attachment of *Candida albicans*

Diego Vargas-Blanco, Aung Lynn, Jonah Rosch, Rony Noreldin, Anthony Salerni, Christopher Lambert and Reeta P. Rao*

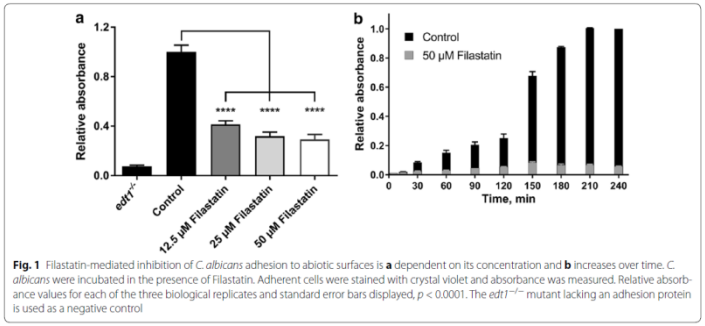

Fig. 1 Filastatin-mediated inhibition of *C. albicans* adhesion to abiotic surfaces is **a** dependent on its concentration and **b** increases over time. *C. albicans* were incubated in the presence of Filastatin. Adherent cells were stained with crystal violet and absorbance was measured. Relative absorbance values for each of the three biological replicates and standard error bars displayed, $p < 0.0001$. The *edt1*$^{-/-}$ mutant lacking an adhesion protein is used as a negative control

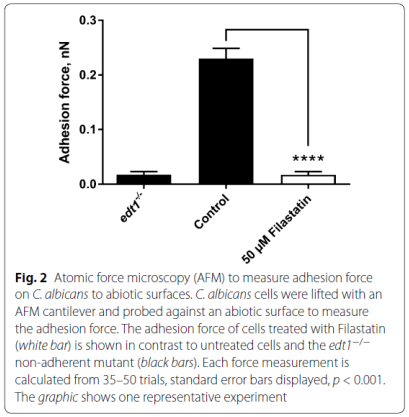

Fig. 2 Atomic force microscopy (AFM) to measure adhesion force on *C. albicans* to abiotic surfaces. *C. albicans* cells were lifted with an AFM cantilever and probed against an abiotic surface to measure the adhesion force. The adhesion force of cells treated with Filastatin (*white bar*) is shown in contrast to untreated cells and the *edt1*$^{-/-}$ non-adherent mutant (*black bars*). Each force measurement is calculated from 35–50 trials, standard error bars displayed, $p < 0.001$. The *graphic* shows one representative experiment

Conclusion: We demonstrate that Filastatin treated medical devices prevented adhesion of Candida, thereby reducing nosocomial infections.

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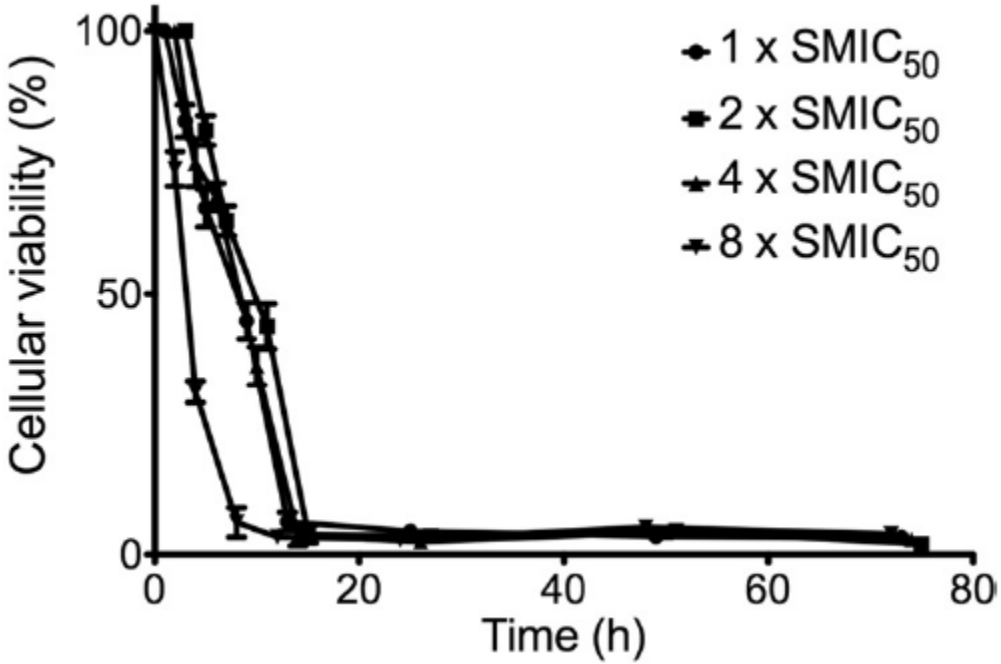
February 2013

Liposomal Amphotericin B Displays Rapid Dose-Dependent Activity against *Candida albicans* Biofilms

Gordon Ramage,[a] Anto Jose,[a] Leighann Sherry,[a] David F. Lappin,[a] Brian Jones,[b] Craig Williams[c]



Biofilms formed by *Candida albicans* bloodstream isolates on catheters are an important clinical problem. Devising chemotherapeutic strategies to treat these in situ is an attractive option. Liposomal amphotericin effectively kills C. albicans biofilms rapidly (12 h) and effectively (>90%) in a dose-dependent manner. This study has implications for considering the effective doses of antifungal agents used for catheter lock therapy

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