

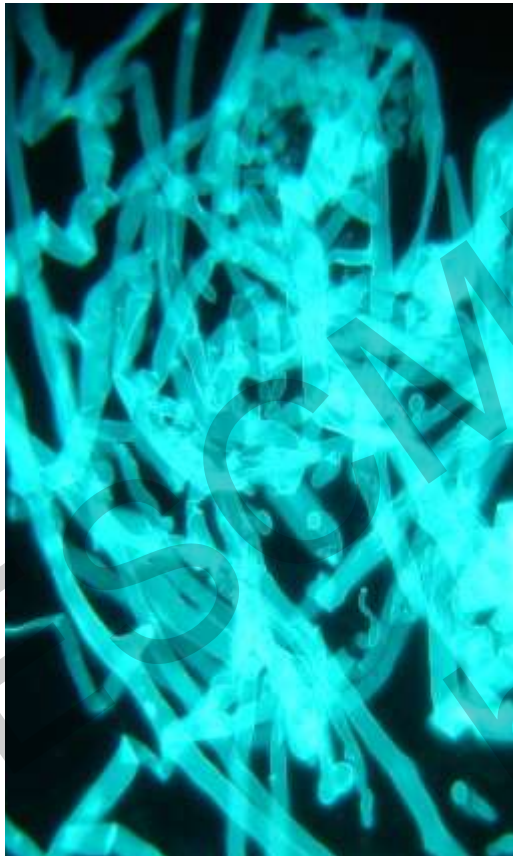


Multiple species Candidaemia

26th ECCMID
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Road map



Definitions

Epidemiology

Pathogenesis

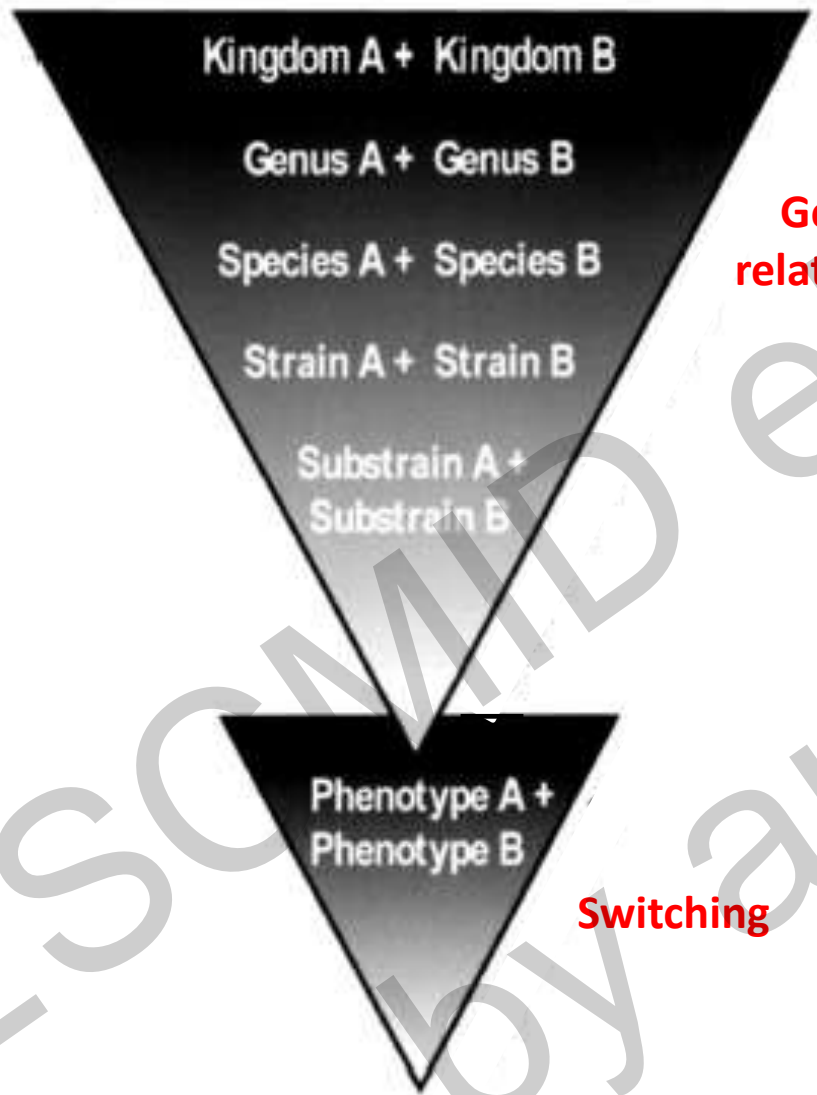
Risk factors

Clinical characteristics

Diagnosis

Outcome

Definitions: Polyfungal infections

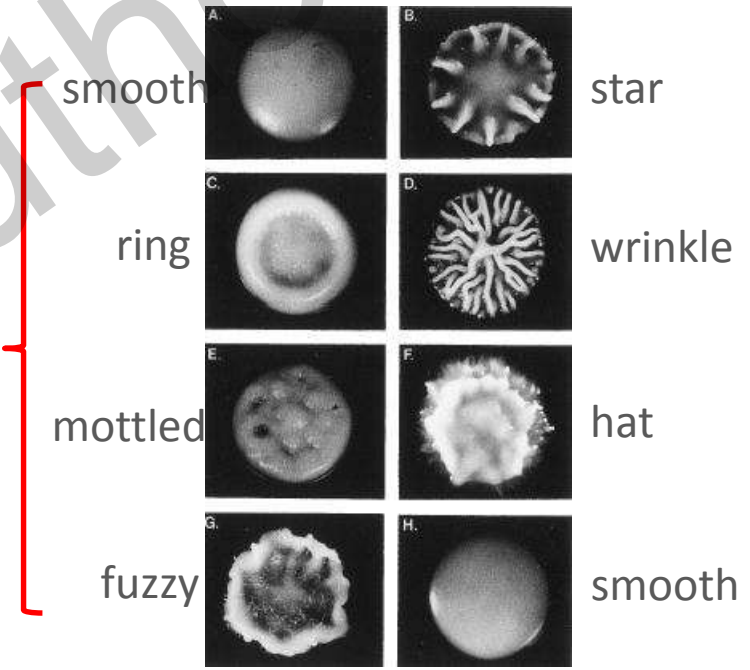


Genetic relatedness

- Bacteria & Fungi
- Aspergillus* & *Candida*
- C albicans* & *C krusei*
- Candida albicans*

C. albicans 3153A

Switching



A *Candida*-bloodstream infection is called candidemia.

Definitions



Multiple species candidemia: ≥ 2 different *Candida* species growing within the same blood culture bottle!

Candidemia

What we know

- Common (2nd in rank order in EU and NAM ICUs)
- Deadly (attributable mortality 49%)
- Expensive
- Management involves time-critical decision making
- Two species – worse outcome?

JAMA 2009;302:2323
CID 2003;37:1172
CMR 2007;20:133
CID 2012;54:1739

Epidemiology

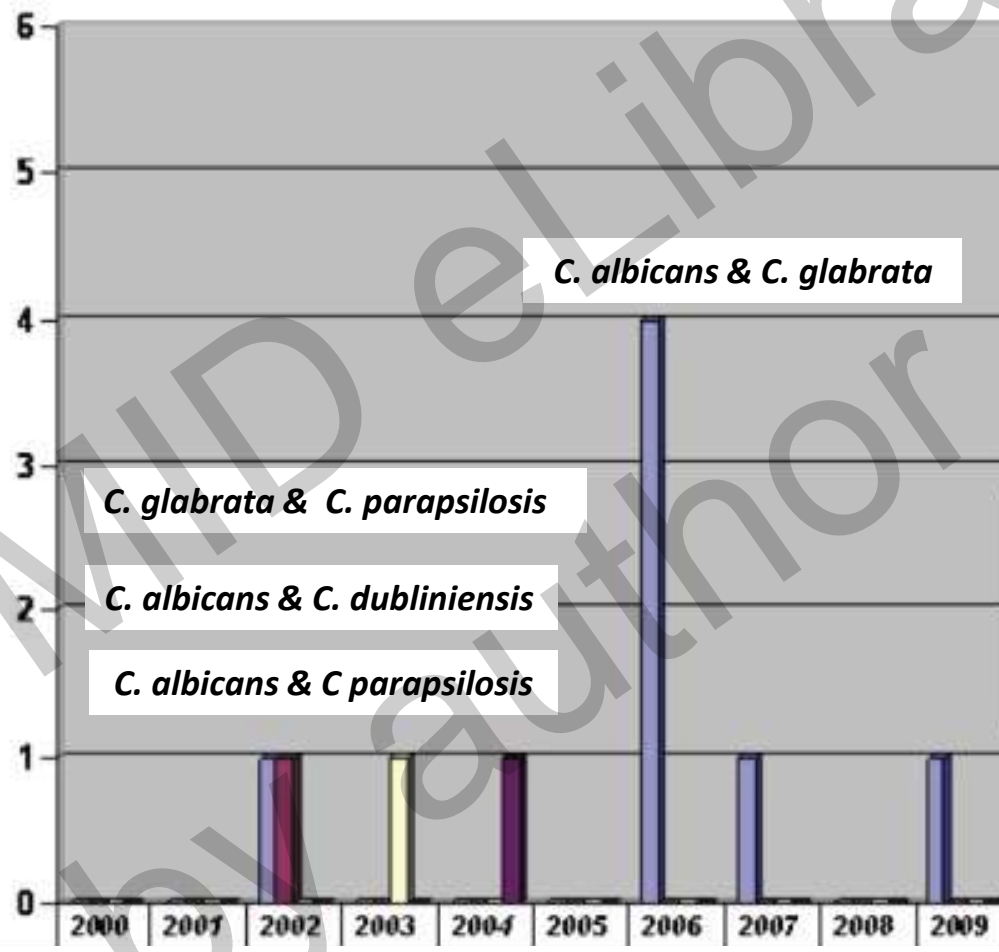


Among patients with candidemia exists a high rate of synchronous bacteremia!

Decade	Polymicrobial candidemia and bacteriemia/total candidemia (% of total)	Mixed Candida blood cultures/total candidemia (% of total)	References
1960s	5 cases reported		Bodey et al. 1965
1970s	5/70 (7%)	7/88 (8%)	Klein and Watanakunakorn 1979; Roselle and Watanakunakorn 1979
1980s	105/453 (23%)	34/1015 (3%)	Maksymiuk et al. 1984; Dyess et al. 1985; Guerra-Romero et al. 1989; Komshian et al. 1989
1990s	54/359 (15%)	60/1917 (3%)	Bryce et al. 1992; Fraser et al. 1992; Nguyen et al. 1996; Abi-Said et al. 1997; Anaissie et al. 1998; Launay et al. 1998; Tumbarello et al. 1999; Viscoli et al. 1999; Yamamura et al. 1999
2000s	168/698 (24%)	158/2762 (6%)	Luzzati et al. 2000; Ahmad et al. 2002; Pulimood et al. 2002; Viudes et al. 2002; Antoniadou et al. 2003; Pappas et al. 2003; Boktour et al. 2004
2007s	100/372 (27%)	12/372 (3%)	8 Veterans Affairs Hospital & 1 Tertiary Care Hospitals: Klotz et al. 2007
TOTAL	432/1882 (23%)	271/6154 (4%)	<i>Candida</i> spp. invasion carries the risk of dissemination of other microbes!

Distribution of mixed-species candidemia according to year, 10-year review

Number of episodes with mixed species: 4%

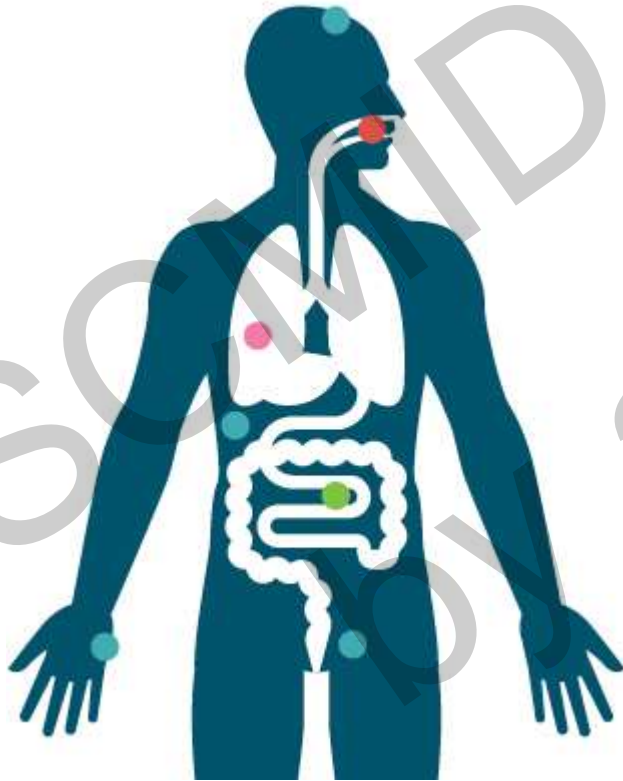


Bloodstream infections: multispecies incident episodes



Pathogenesis: origin of infection?

Keynote Lecture:
The fungal Microbiome and human health

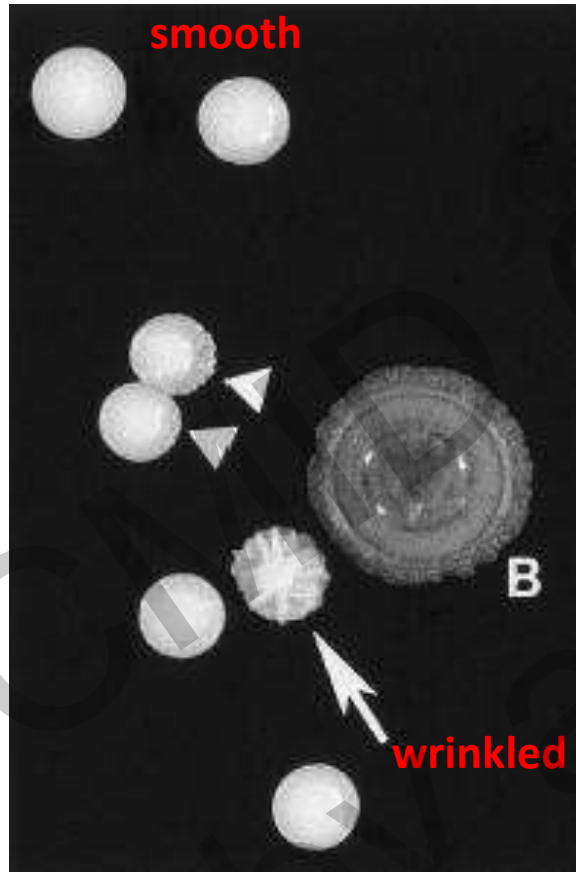


- ✓ Identified 101 fungal species, each person harboring between 9 and 23 fungal species in their mouth.
- ✓ **Fungal species inhabit the mammalian body, alongside diverse commensal bacteria. And when one microbial community is knocked out, another can cause illness.**

The Mycobiome

Mahmoud Ghannoum | The scientists, 2016

Pathogenesis: Pathogen interactions?



Primary culture from the vaginal secret:

- bacterial colony (B) alters the morphology of closely associated *C. albicans* by inducing hypha and pseudohypha formation.
- Altered portions of colonies (arrowheads) and an entirely altered colony (arrow) are indicated.

Risik factors



Risk factors for fungemia in ICUs due to multiple species in reference to fungemia due to *C. albicans*

	Mixed infections		
	Adj. OR	95 % IC	P
Male gender	1.06	0.52-2.19	0.865
Between 45 – 64 years	1.27	0.39-4.07	0.691
Between 65 – 79 years	1.46	0.43-5.00	0.543
80 years and more	4.19	1.15-15.31	0.030
Central venous catheter	1.47	0.58-3.70	0.412
Arterial catheter	0.92	0.44-1.95	0.832
Surgery within 30 days	1.28	0.60-2.71	0.528
Hematological malignancy	1.23	0.33-4.58	0.757
Solid tumor	1.68	0.74-3.83	0.215
Solid organ transplantation	1.45	0.45-4.64	0.530
HIV infection	1.19	0.21-6.84	0.848
Intravenous drug addiction	13.71	1.77-106.28	0.012
Caspofungin pre-exposure	12.51	1.05-149.70	0.046
Fluconazole pre-exposure	0.77	0.10-6.02	0.800

Multivariate multinomial regression analysis, YEASTS program, Paris area, October 2002 to September 2010

Adj. OR, adjusted odds ratio for year; 95 % CI odds ratio, 95 % confidence interval

Comparison of the epidemiological characteristics of patients with mixed fungemia with those of patients with monomicrobial fungemia

Factor	Mixed fungemia (n = 15)	Monomicrobial fungemia (n = 30)	P
Age, median years ± SD	41.5 ± 25	48.3 ± 32	
Sex			
Male	11 (79.3)	20 (77)	.64
Female	4 (26.7)	10 (33)	
Risk factor			
In intensive care unit	5 (33)	14 (47)	.66
Experienced neutropenia	1 (6.7)	3 (10)	.71
Underwent surgery	9 (60)	8 (27)	.03
Received parenteral nutrition	6 (40)	21 (70)	.05
Had intravenous line	2 (80)	30 (100)	.01
Had bladder catheter	11 (73)	24 (80)	.61
Previous receipt of antimicrobial agents	11 (73)	27 (90)	.14
Previous receipt of antifungal agents	5 (33)	6 (20)	.32
Receipt of corticosteroids	5 (33)	6 (20)	.32

Data are no. (%) of patients, unless otherwise indicated

Cinical characteristics



Patient demographics and clinical characteristics

Variable	No. of patients (%)		P value ^a
	Multiple-species candidemia (n = 33)	Candida albicans candidemia (n = 66)	
Mean age ± SD (yrs)	53 ± 20	51 ± 18	NS
Males/females	17/16	30/36	NS
Acute leukemia or myelodysplastic syndrome	11 (33)	5 (8)	0.001
Solid tumor	17 (52)	51 (77)	NS
Lymphoma/melanoma	5 (15)	10 (15)	NS
Bone marrow transplantation within past years	4 (12)	2 (3)	NS
ICU stay during infection	16 (48)	29 (44)	NS
Mean duration of ICU stay ± SD (days)	12 ± 14	12 ± 12	NS
Duration of candidemia ≥ 5 days^b	16 (48)	13 (20)	0.003
Mean duration of candidemia episode ± SD (days)	5.0 ± 5.0	2.7 ± 4.0	NS
Neutropenia (< 500 mm ³) ^c	13 (39)	16 (24)	NS
Neutropenia (< 500 mm ³) ^d	19 (58)	18 (27)	NS

SD, standard deviation; NS, not statistically significant; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation

^a Univariate analysis; ^b calculated as the duration between the first and last candidemia-positive blood cultures; ^c within 30 days before the first candidemia-positive blood culture or at study entry; ^d at study entry (i.e., on the day of the first candidemia-positive blood cultures)

Patient demographics and clinical characteristics

Variable	No. of patients (%)		P value ^a
	Multiple-species candidemia (n = 33)	Candida albicans candidemia (n = 66)	
Growth factor use	15 (46)	16 (24)	NS
Chemotherapy use	23 (70)	28 (42)	NS
Corticosteroid use	14 (42)	19 (29)	NS
APACHE II score $\geq 16^d$	15 (45)	17 (26)	NS
Antifungal therapy during previous month	11 (33)	7 (11)	0.006
Fluconazole prophylaxis	9 (27)	7 (11)	0.03
Breakthrough candidemia	6 (18)	3 (5)	0.04
Catheter-related candidemia	10 (30)	25 (38)	NS

SD, standard deviation; NS, not statistically significant; APACHE, Acute Physiology and Chronic Health Evaluation

^a Univariate analysis; ^b calculated as the duration between the first and last candidemia-positive blood cultures; ^c within 30 days before the first candidemia-positive blood culture or at study entry; ^d at study entry (i.e., on the day of the first candidemia-positive blood cultures)

Comparison of the epidemiological characteristics of patients with mixed fungemia with those of patients with monomicrobial fungemia

Factor	Mixed fungemia (n = 15)	Monomicrobial fungemia (n = 30)	P
Age, median years ± SD	41.5 ± 25	48.3 ± 32	
Sex			
Male	11 (79.3)	20 (77)	.64
Female	4 (26.7)	10 (33)	
Underlying disease			
Cancer	5 (33)	9 (30)	.82
Hematological disease	0 (0)	2 (7)	.30
HIV infection	3 (20)	3 (10)	.35
Injection drug use	3 (20)	3 (10)	.35
Transplantation	2 (13)	0 (0)	.04

Data are no. (%) of patients, unless otherwise indicated

Comparison of the epidemiological characteristics of patients with mixed fungemia with those of patients with monomicrobial fungemia

Factor	Mixed fungemia (n = 15)	Monomicrobial fungemia (n = 30)	P
Clinical manifestations			
Fever	14 (93)	24 (80)	.24
Shock	1 (6)	11 (37)	.03
Renal insufficiency	4 (27)	2 (7)	.06
Skin	2 (13)	2 (7)	.45
Chorioretinitis	1 (7)	0 (0)	.15
Source			
Catheter	9 (60)	11 (37)	.13
Unknown	3 (20)	13 (43)	.12
Urine	2 (13)	1 (3)	.20
Abdomen	1 (7)	4 (13)	.50
Received therapy	13 (87)	25 (84)	.77
Mortality	3 (20)	16 (53)	.03
Related mortality	3 (20)	12 (40)	.18

Data are no. (%) of patients, unless otherwise indicated

Diagnosis



Culture

- Recovery of *Candida* species from sterile sites (ex. blood, peritoneal fluid) is diagnostic of IC
- Blood culture is positive in about 50% of patients with autopsy proven IC

Serological methods

- Early diagnosis ex. 1,3 beta D glucan assay
- Mannan plus Antimannan: *C. parapsilosis* and *C. guilliermondii* fungemias were not detected by the Platelia Candida Ag Plus assay

Histopathologic & microscopic methods

- Proof of infection
- Multiple species?

Molecular methods

- Early species identification, peptide nucleic acid fluorescence in situ hybridisation technology (PNA FISH): evaluated for five *Candida* species showed sensitivity of 99.3% and specificity 100%.



S epiderm & C glabrata & C albicans

Pure (single species) culture?
Multiple species?
Polymicrobial?

Discordant results between phenotypic assay and real-time PCR

Number of isolates	Phenotypic identification	Multiprobe Real-time PCR
1	<i>C. tropicalis</i>	<i>C. glabrata</i> & <i>C. tropicalis</i>
1	<i>C. albicans</i>	<i>C. glabrata</i> & <i>C. albicans</i>
2	<i>C. zeylanoides</i>	<i>C. parapsilosis</i>
2	<i>C. krusei</i>	<i>C. glabrata</i>
1	<i>C. albicans</i>	<i>Candida</i> spp.
1	<i>C. glabrata</i>	<i>Candida</i> spp.
1	<i>Candida</i> spp.	<i>Candida</i> spp.
1	<i>C. parapsilosis</i>	<i>Candida</i> spp.
1	<i>Candida</i> spp.	<i>Candida</i> spp.

Laboratory data of patients with positive PCR

G	Age	Underlying disease	BSAT	CVC	AFT	Outcome	Blood cultures	Nested PCR multiples
M	19 d	Ichthyosis, prematurity	Yes	Yes	Yes	Died	<i>C. parapsilosis</i>	<i>C. parapsilosis</i>
M	14 d	Prematurity	Yes	Yes	Yes	Survived	<i>C. albicans</i>	<i>C. albicans</i>
F	44 d	Esophageal atresia	Yes	Yes	Yes	Survived	<i>C. albicans</i>	<i>C. albicans</i>
F	20 m	Acute lymphoblastic leukemia	Yes	Yes	Yes	Died	<i>C. tropicalis</i>	<i>C. tropicalis</i>
M	20 m	Non-Hodgkin lymphoma	Yes	Yes	Yes	Survived	<i>C. albicans</i>	<i>C. albicans</i>
F	11 m	Hydrocephalus	Yes	Yes	Yes	Survived	<i>C. albicans</i>	<i>C. albicans</i>
M	5 y	Disseminated medulloblastoma	Yes	Yes	Yes	Died	<i>C. krusei</i>	<i>C. krusei</i>
F	16 m	Hydrocephalus	Yes	Yes	Yes	Died	<i>C. albicans</i>	<i>C. albicans</i>
M	3 y	Bone marrow transplantation, neuroblastoma	Yes	Yes	Yes	Died	Negative	<i>C. tropicalis</i> and <i>C. parapsilosis</i>^a
F	15 y	Osteosarcoma, septic shock	Yes	Yes	Yes	Died	Negative	<i>C. parapsilosis</i> ^a
M	35 d	Congenital diaphragmatic hernia	Yes	Yes	Yes	Survived	Negative	<i>C. tropicalis</i> ^a
M	9 d	Congenital diaphragmatic hernia	Yes	Yes	Yes	Survived	Negative	<i>C. tropicalis</i> and <i>C. parapsilosis</i>^a
M	55 d	Necrotizing enterocolitis	Yes	Yes	Yes	Died	Negative	<i>C. tropicalis</i> and <i>C. parapsilosis</i>^a

G, gender; M, male; F, female; d, days; m, months; y, years; BSAT, broad spectrum antibiotic therapy; CVC, central venous catheter; AFT, presumptive antifungal therapy after blood sample collection

^a Sequencing analysis showed 99-100 % identity with *C. parapsilosis stricto sensu* and 99-100% identity with *C. tropicalis*

Outcome



ESCMID eLibrary
by author

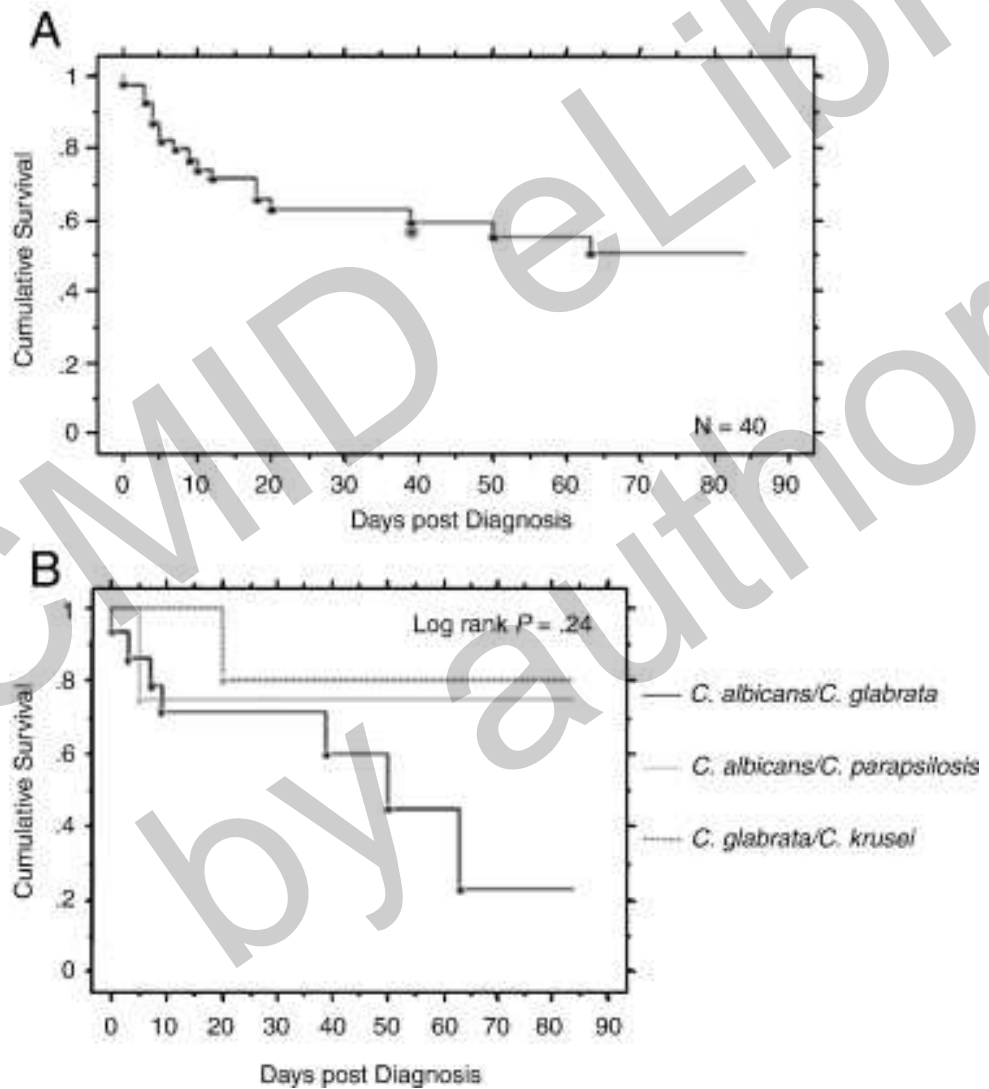
Therapy and Outcome Data for Patients with MSC and Patients with *Candida albicans* Candidemia

Variable	No. of patients (%)		P value ^a
	Multiple-species candidemia (n = 33)	<i>Candida albicans</i> candidemia (n = 66)	
Antifungal therapy use	30 (91)	54 (82)	NS
Fluconazole	12	37	0.02
AMB deoxycholate	4	7	NS
Lipid formulation of AMB	10	7	0.05
Combination (polyene plus fluconazole)	4 (12)	3 (5)	NS
Had response to antifungal therapy	14 (47)	40 (74)	0.01
Had response to primary singl-agent therapy	9 (35)	35 (69)	0.004
Had response to combination therapy (polyene plus fluconazole)	3 (75)	2 (67)	NS
30-day mortality	15 (45)	22 (33)	NS

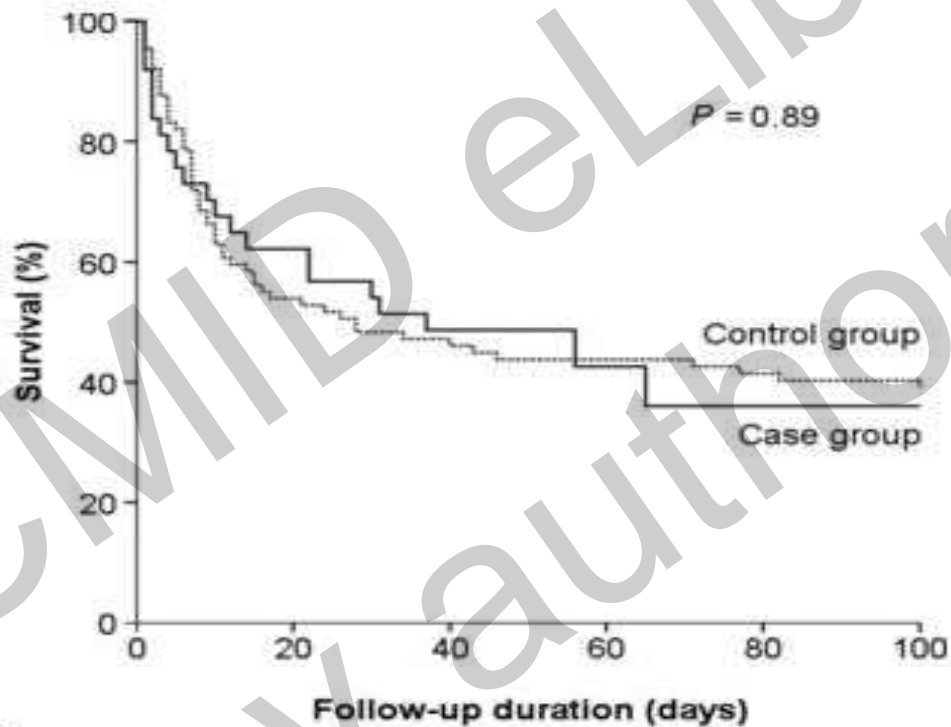
AMB, amphotericin B; NS, not statistically significant; MSC, multiple-species candidemia

^a Univariate analysis

Kaplan–Meier survival curves at 12-week follow-up for patients with MSC (A) overall and (B) based on most commonly observed species combinations.



Kaplan-Meier estimates of survival in patients with mixed Candida/bacterial bloodstream infection and monomicrobial candidaemia: no difference!



Candida sp. (4%)

Candida sp. & Bacteria (23%)

No. at risk

	0	20	40	60	80	100
Case group	37	23	18	14	11	11
Control group	89	48	41	38	36	33

Take home message

Multi-species infections: 3-8%

More often *Candida* sp. plus bacteria (25%)

C. albicans & *C. glabrata* are most often

Diagnosis: culture, serology and molecular

Risk factors: AM pre-exposition

Outcome: no major differences

Small number of patients – inhomogenous groups



Thank you for your attention!

