

EPIDEMIOLOGY OF FUNGAL INFECTION

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MIG_INFECTIOUS DISEASE

ST Luc University Hospital

UCL



Candida species

C. albicans

C. glabrata

C. guilliermondii

C. kefyr

C. krusei

C. lusitanae

C. parapsilosis

C. rugosa

C. tropicalis

Other yeasts

Blastoschizomyces species

Cryptococcus neoformans

Malassezia species

Rhodotorula species

Saccharomyces species

Trichosporon species

Aspergillus species

A. flavus

A. fumigatus

A. niger

A. terreus

A. ustus

A. versicolor

Agents fongiques opportunistes potentiellement pathogènes

Zygomycetes

Absidia species

Cunninghamella species

Mucor species

Rhizomucor species

Rhizopus species

Saksenaea species

Other hyaline moulds

Acremonium species

Emmonsia species

Fusarium species

Paecilomyces species

Phialemonium species

Scedosporium species

Scopulariopsis species

Trichoderma species

Dematiaceous moulds

Alternaria species

Bipolaris species

Curvularia species

Cladophialophora species

Dactylaria species

Exophiala species

Phialophora species

Ramichloridium species

Wangiella species

Dimorphic fungi

Blastomyces dermatitidis

Coccidioides immitis

Histoplasma capsulatum

Paracoccidioides brasiliensis

Penicillium marneffeii

Sporothrix schenckii

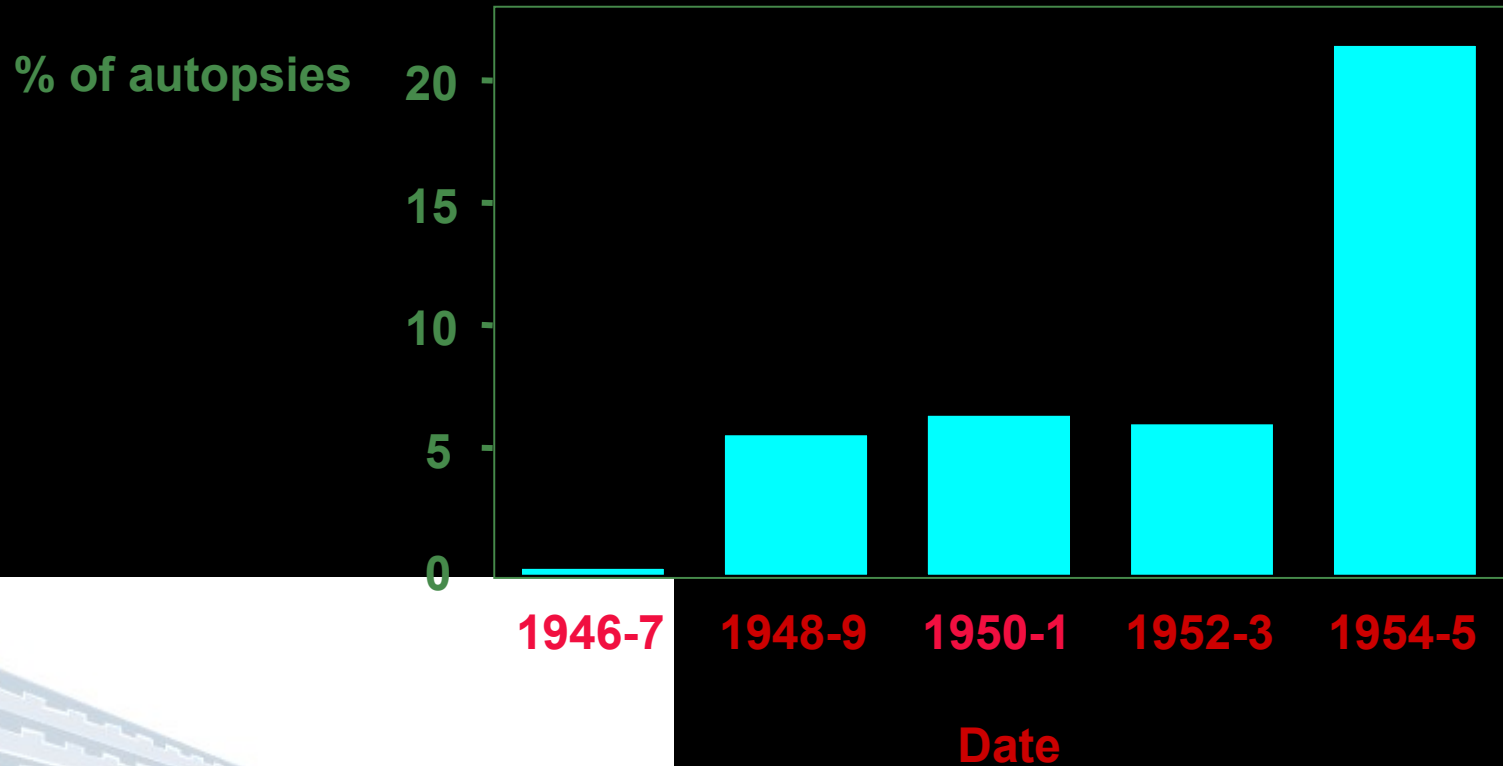
Other, *Pneumocystis jirovecii* (d)



“A conspicuous increase in the number of fungal infections has occurred in recent years.”



Invasive mycoses as percent of all autopsies



Ref: Keye & Magee, Am J

Total incidence of candidaemia in US ICUs

Trick et al/ CID 2002; 35: 627. NNIS data from 1116 ICUs/ 311 hospitals. From data for 3,041,585 patients

Candidaemia
per 10,000
CVC days

9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0



1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999

year

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TRICK ET AL, CID 2002

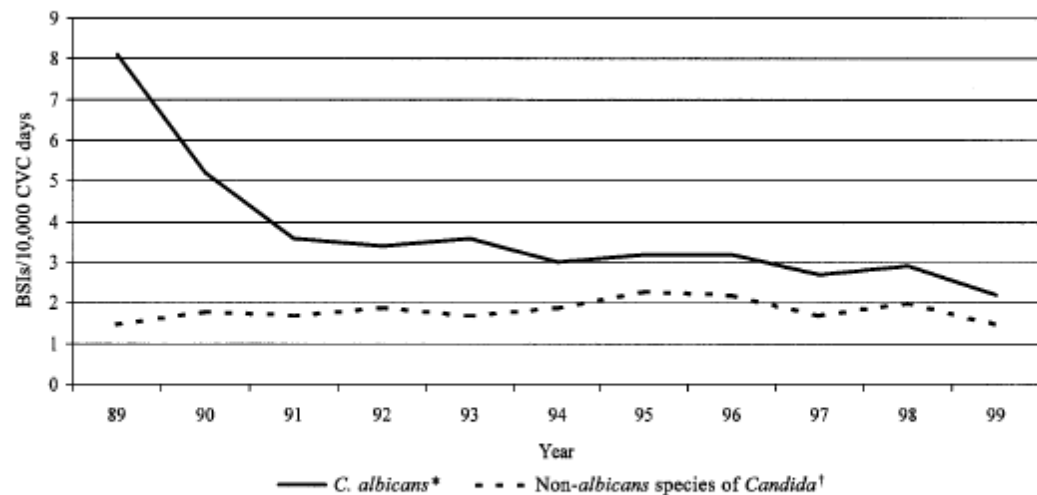


Figure 1. Incidence of hospital-acquired bloodstream infection (BSI) due to *Candida albicans* and non-albicans species of *Candida*, National Nosocomial Infections Surveillance system intensive care unit wards, 1989–1999. * $P < .001$ for the annual incidence of *C. albicans* BSI, determined using the χ^2 test for trend, 1989–1999. † $P = .53$ for the annual incidence of non-albicans species of *Candida* BSI, determined using the χ^2 test for trend, 1989–1999. CVC days, total no. of days in which a central venous catheter was in place.

IFI : Hématologie et greffes d'organe

Pathologie /agent	incidence
<i>Candida</i>	Baisse 70 à 42%
<i>Aspergillus</i>	doublée 13 à 29%
Non <i>aspergillus</i>	Triplée de 4 - 12%
Non identifiés	6%
<i>Cryptococcus</i>	4%
Dimorphiques	3%
<i>Pneumocystis</i>	2%

Occurrence of invasive mycoses is a function of
medical speciality
nature and severity of underlying disease
surgical and pharmaceutical management
[other factors, including local factors]



Table 1. Risk factors and conditions associated with invasive candidiasis

Primary risk factors	Associated conditions
Prolonged antibiotic use	Solid organ transplant
Central venous catheter	Bone marrow transplant
Prolonged length of stay in an ICU	Hematologic malignancy
Abdominal surgery	Very low birth weight neonate
Heavy colonization	Acid-suppressing medications
Hyperalimentation	Nasogastric tubes
Immunosuppression	Extensive burns
	Malnutrition
	Severe pancreatitis
	Acute renal failure
	Hemodialysis

Data from References 7, 24, 37, 144, and 145.

Table 1. Independent risk factors for the development of candidaemia in SICU patients

Independent variables	RR	OR
Prior abdominal surgery	7.3	—
Triple lumen catheter	5.4	—
Acute renal failure	4.2	—
Parenteral nutrition	3.6	—
Multiple antibiotics (3–5)	—	12.5
<i>Candida</i> isolated from other sites	—	10.4
Length of ICU stay >7 days	—	9.8

RR, relative risk; OR, odds ratio.

Modified from Blumberg *et al.*⁷ and Wey *et al.*⁸

Changes in host background for candidaemia

Surveys in the 1980s: ~50-80% of all patients with candidaemia were neutropenic

Recent surveys show very few neutropenic patients in the candidaemia cohorts



Changes in candidaemia host background

<u>Underlying condition</u>	<u>% 1992–93^a</u>	<u>% 1998–00^b</u>
-----------------------------	------------------------------	------------------------------

Age >65 years

Age <1 year

*a*Kao *et al.*, 1999; *Hajjeh et al.*, 2004

Table 2

Underlying pathology/medical care of patients with candidaemia ($n = 2089$; more than one may be present in each episode)

	No.	%
Surgery	1007	48.2
Intensive care	839	40.2
Solid tumour	471	22.5
Steroids	364	17.4
Haematological malignancy	257	12.3
Premature birth	125	6.0
HIV infection	63	3.0
Burns	29	1.4



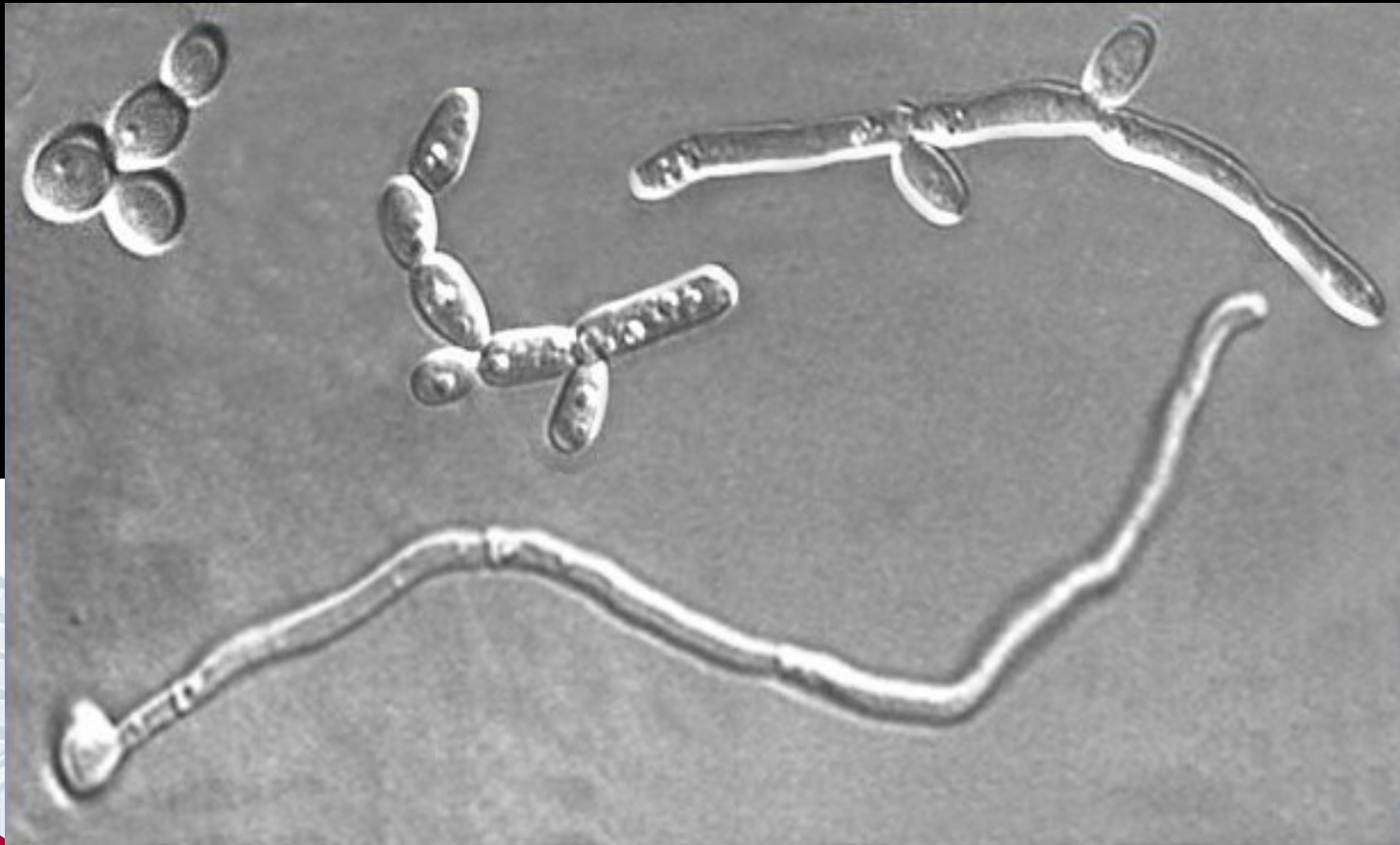
Table 3. Species-specific disease associations and risk factors seen in non-*albicans* candidiasis

Species	Disease association/risk factor
<i>Candida glabrata</i>	Azole prophylaxis HIV/AIDS Surgery Urinary and vascular catheters
<i>Candida guilliermondii</i>	Previous polyene use
<i>Candida krusei</i>	Azole prophylaxis Neutropenia Bone marrow transplant
<i>Candida lusitanae</i>	Previous polyene use
<i>Candida parapsilosis</i>	Central venous catheter Neonates Hyperalimentation
<i>Candida rugosa</i>	Burns
<i>Candida tropicalis</i>	Neutropenia Bone marrow transplant

Data from Reference 7.



Candida bloodstream infections



Candidaemia

Incidence



“*Candida* is now the fifth most common isolate recovered from blood in nosocomial septicemias”

1978 Edwards *et al.* Ann Intern Med 89: 91–106

“*Candida* species were the fourth most common cause [of nosocomial bacteremia]”

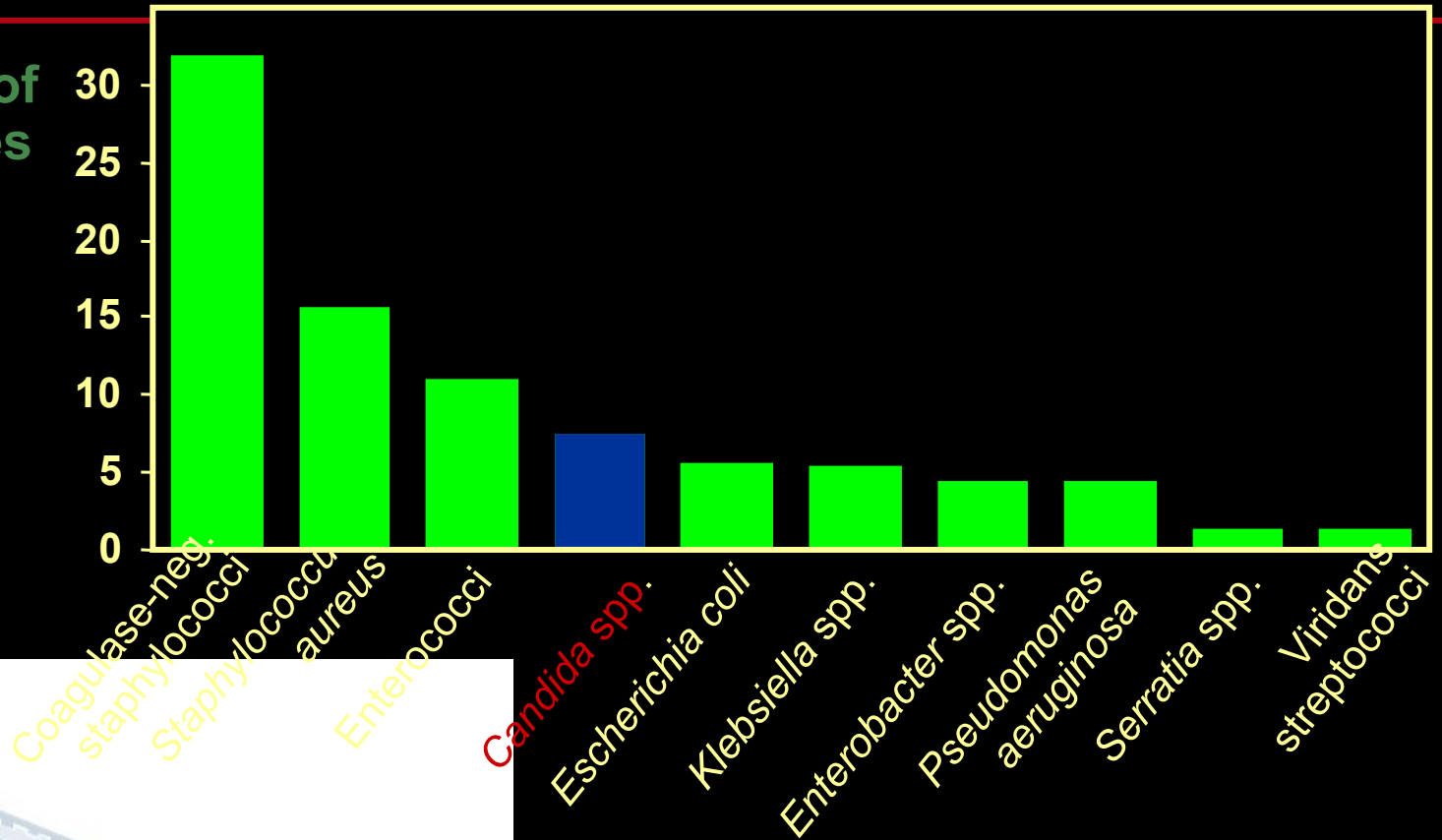
1999 Edmond *et al.* CID 29: 239–244

“Severe fungal infections have taken precedence over other bacterial infections.”

2002 Kumar & Kulkarni Bioorg Med Chem 10: 1153–1170

Causes of bacteraemia/fungaemia, USA 1995–98

Percent of all causes

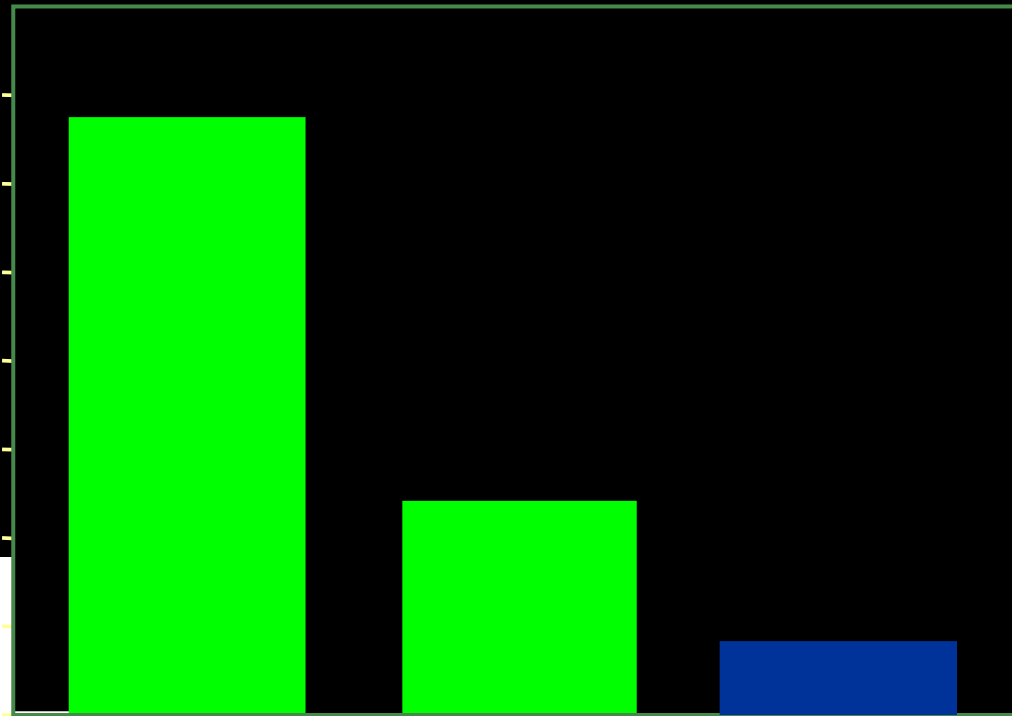


Source: Edmonds *et al*, CID 1999; 29: 239–44

Causes of bacteraemia/fungaemia, USA 1995–98

Percent of all causes

70
60
50
40
30
20
10
0



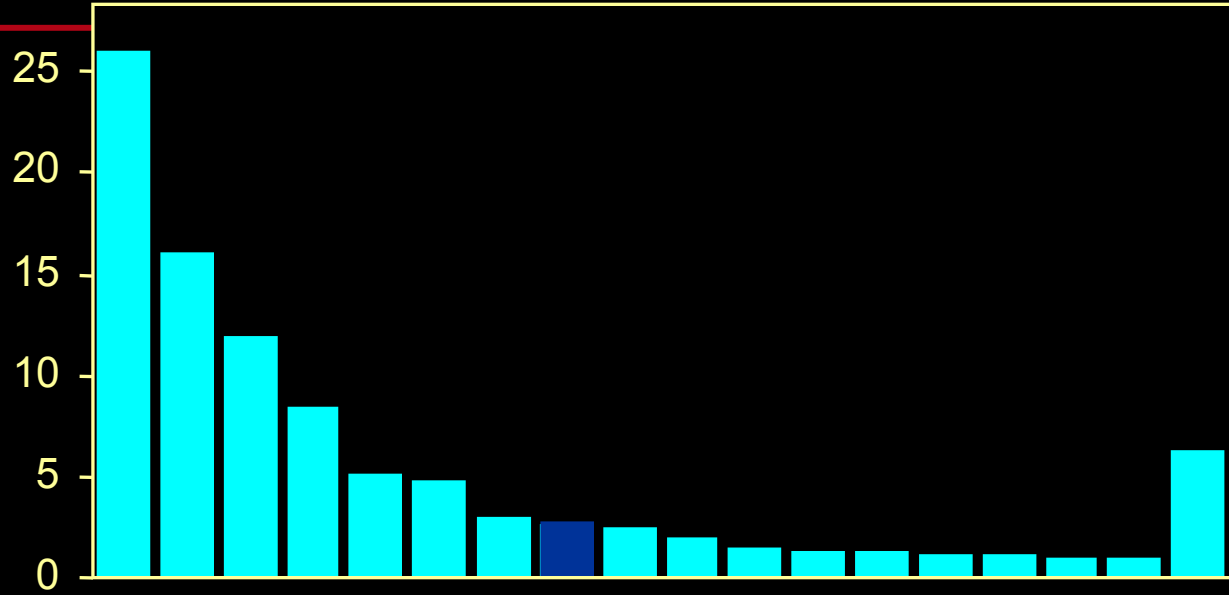
Gram +ve
cocci

Coliforms

Candida
spp.

Causes of bacteraemia/fungaemia, UK 1997–2002

Percent of all isolates



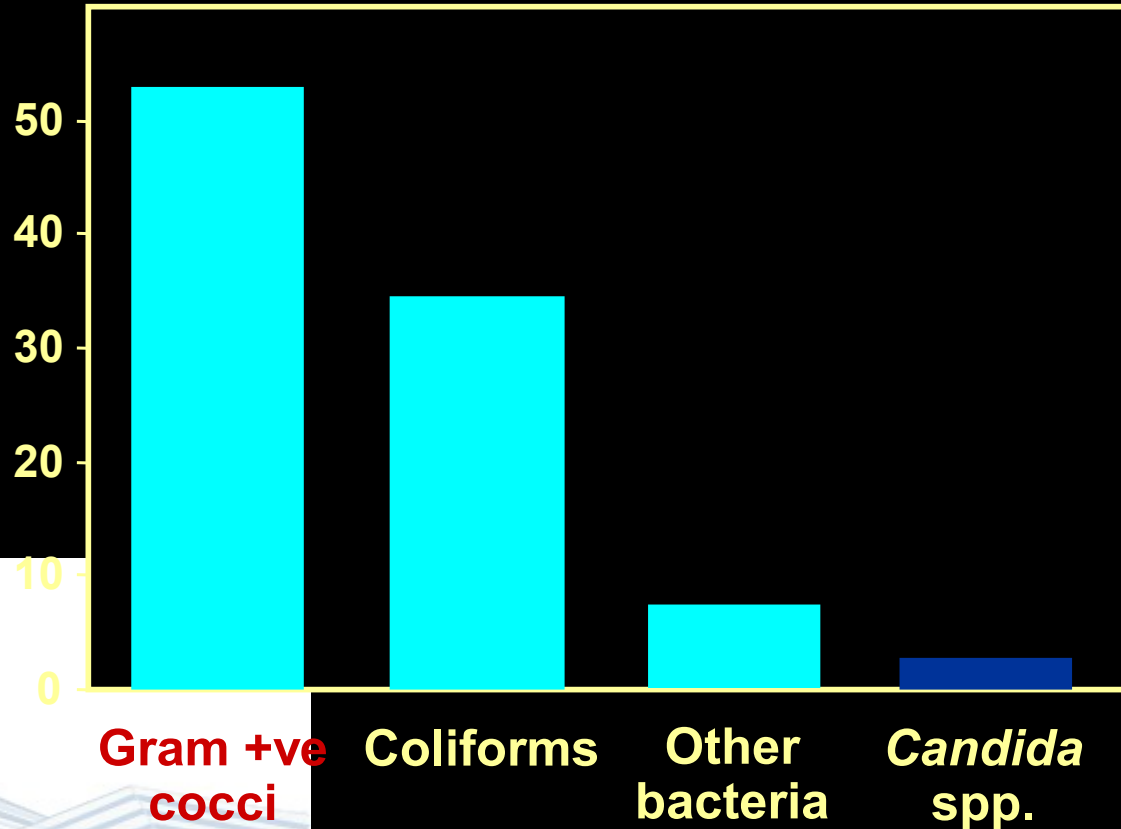
Staphylococcus aureus
 Coagulase-negative staphylococci
 Escherichia coli
 Enterococcus spp.
 Klebsiella spp.
 Enterobacter spp.
 Pseudomonas aeruginosa
 Candida spp.
 Coliforms (unspecified)
 Proteus spp.
 Pseudomonas spp.
 Acinetobacter spp.
 Streptococcus pneumoniae
 Streptococcus — other spp.
 Serratia spp.
 Bacteroides spp.
 Citrobacter spp.
 Other isolates

Source: UK Nosocomial Infection National Surveillance Service, 2005

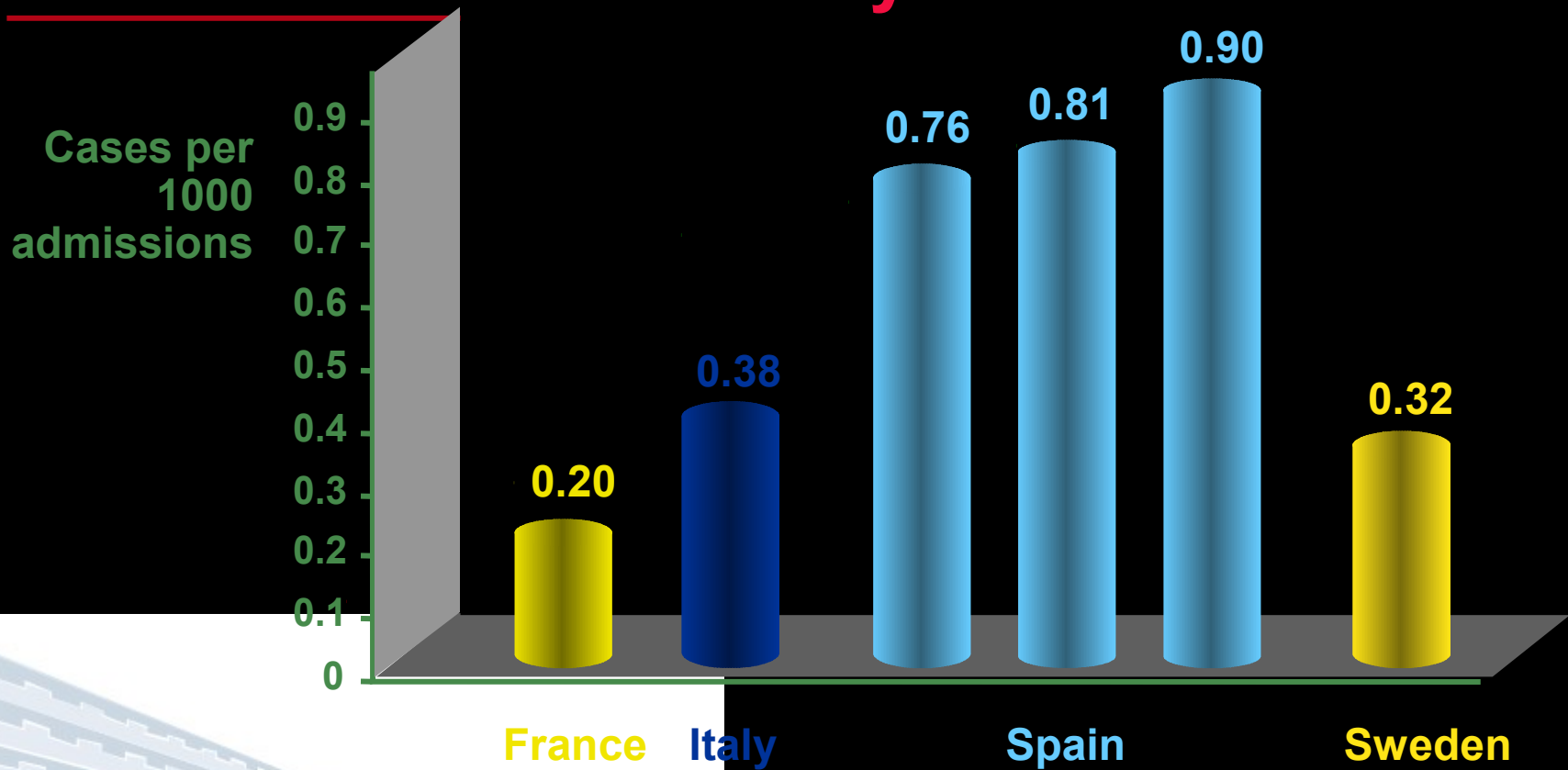


Causes of bacteraemia/fungaemia, UK 1997–2002

Percent of all causes

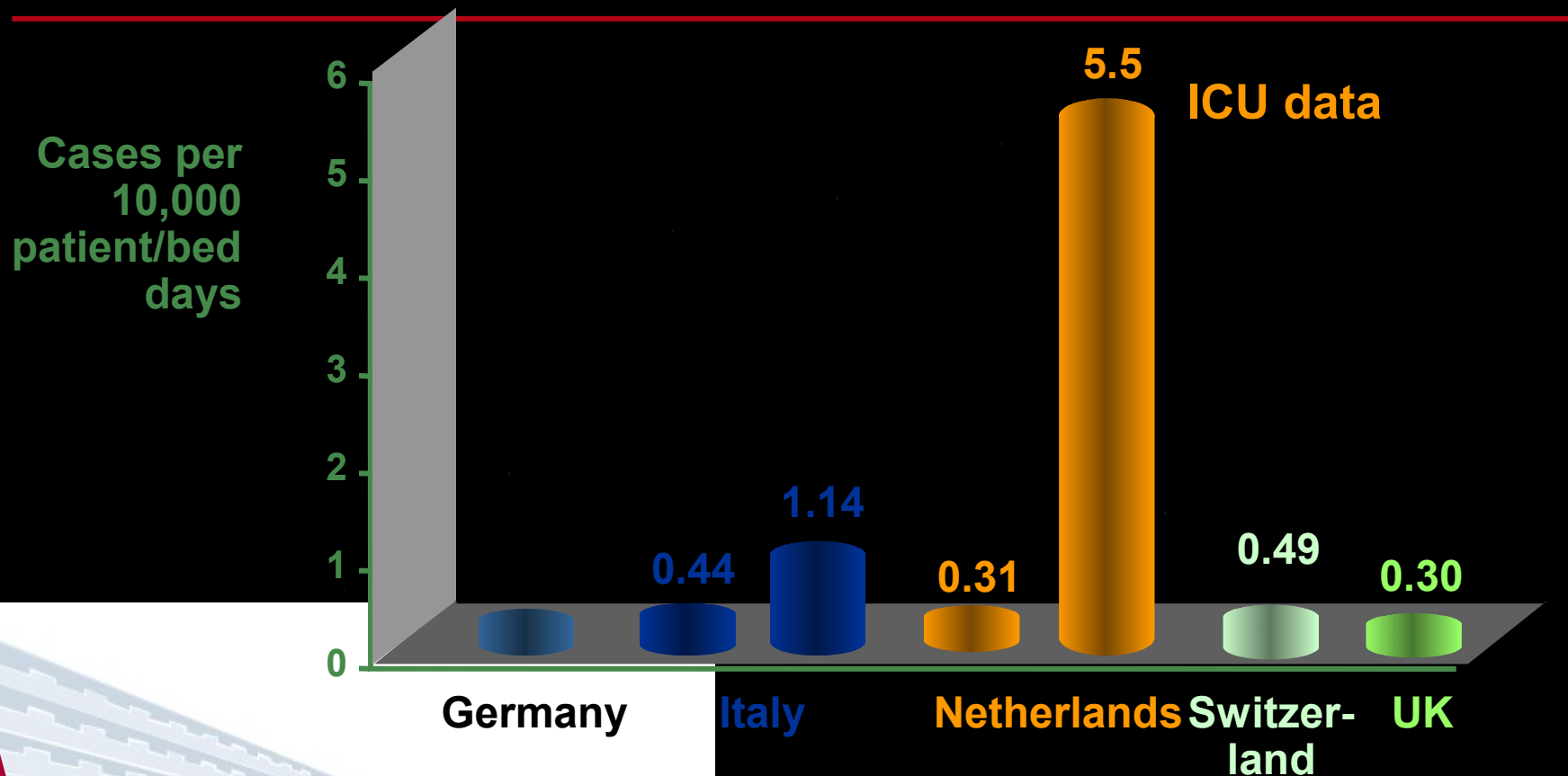


Candidaemia incidence in hospital surveys



Sources: Tortorano *et al.* 2004; Alonso-Valle *et al.*, 2003; Viudes *et al.*, 2002; Gomez *et al.*, 2001

Candidaemia incidence in hospital surveys



Sources: Tortorano *et al.* 2004; Kibbler *et al.* 2003; Luzzati *et al.* 2000; Voss *et al.* 1996, 1997; Marchetti *et al.* 2004

**Six reviews on candidaemia
epidemiology from the same search
all claimed the incidence of
candidaemia was *increasing***



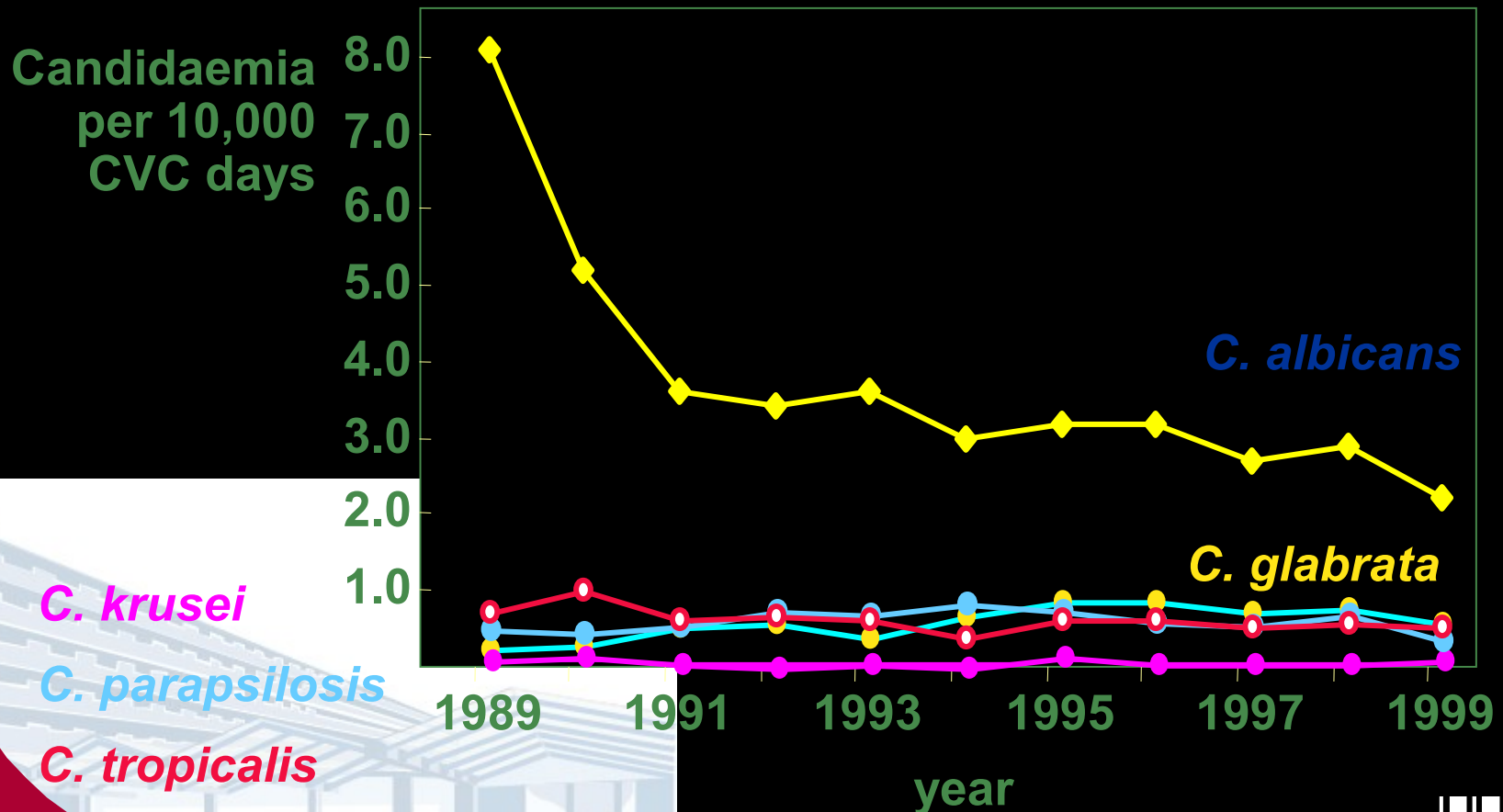
Candidaemia

Causative species



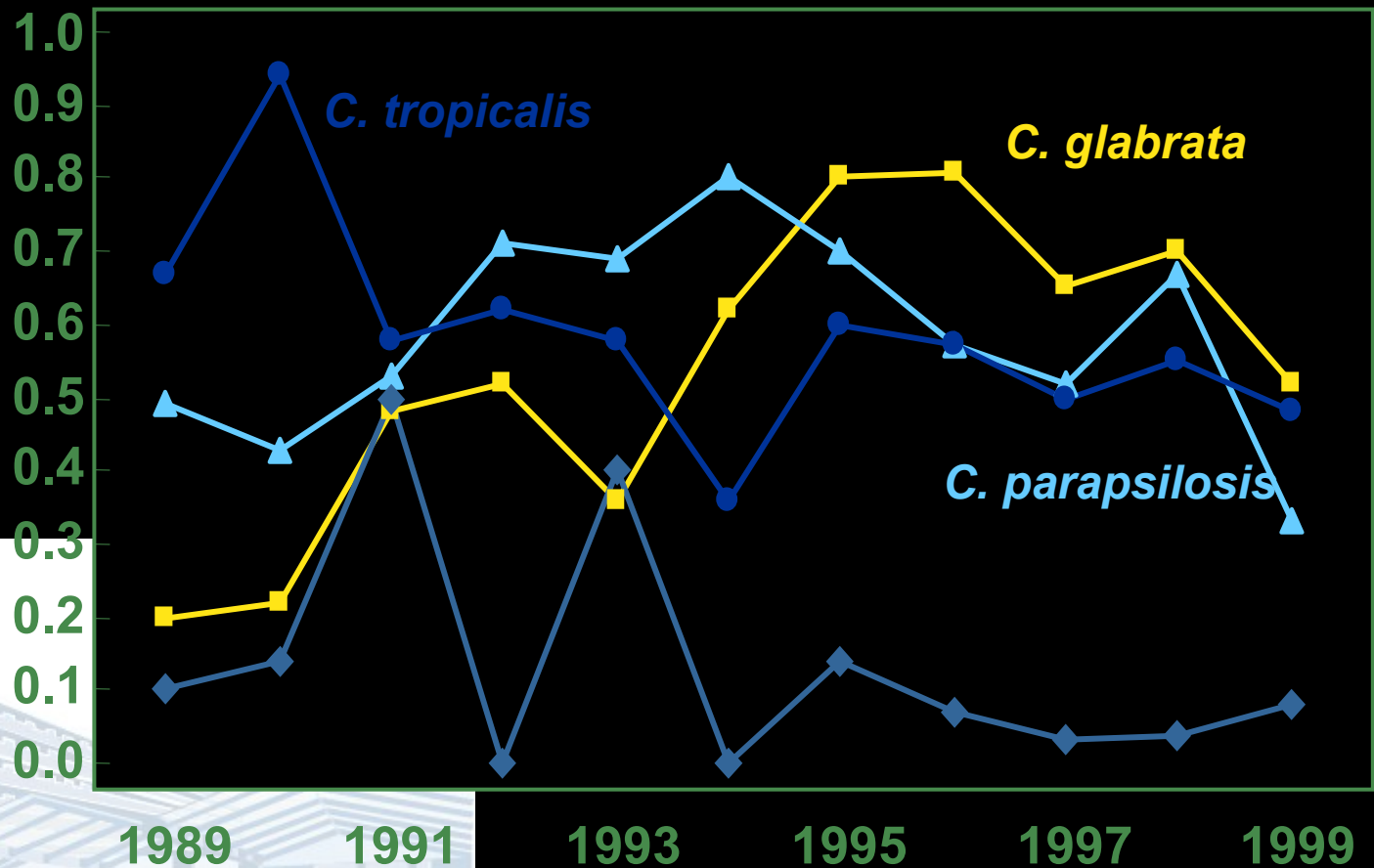
Incidence of candidaemia in US ICUs, 1989–99

Trick *et al* CID 2002; 35: 627. NNIS data from 1116 ICUs / 311 hospitals / 3,041,585 patients



Source: Trick et al, CID 2000;35:627

Candidaemias per 10,000 CVC days



EN EUROPE



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INCIDENCE en Fonction des pathologies

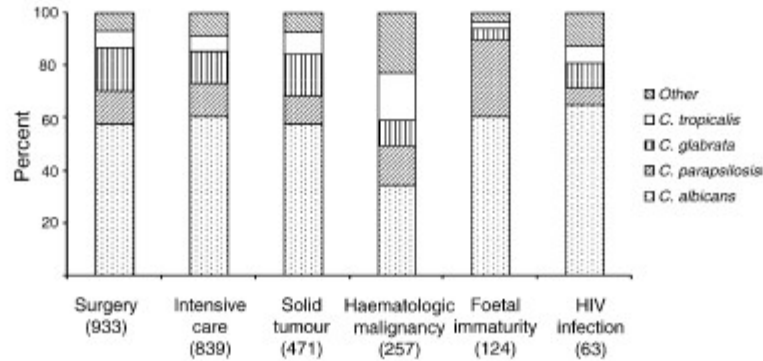
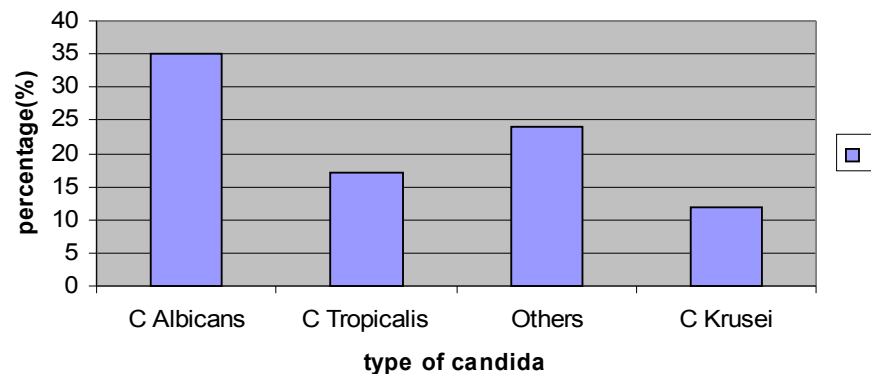


Fig. 1. European Confederation of Medical Mycology (ECMM) survey: distribution of the four most frequently isolated *Candida* species according to underlying pathology/medical care.

cases of candida in haematology malignancies



***C. krusei* is the only *Candida* species with a high propensity to azole resistance.**

Susceptibility surveys show it also tends to be resistant to flucytosine and amphotericin B



INCIDENCE EN FONCTION DES PAYS

362

A.M. Tortorano et al. / International Journal of Antimicrobial Agents 27 (2006) 359–366

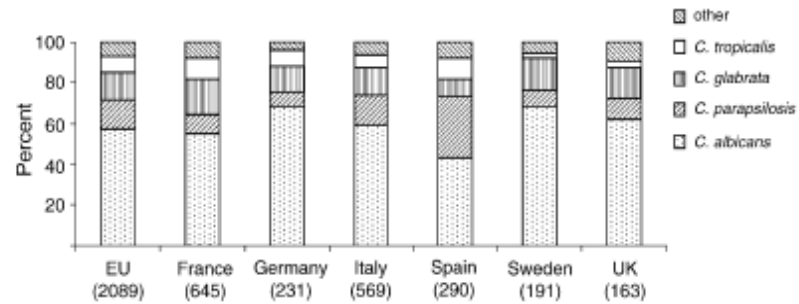


Fig. 2. European Confederation of Medical Mycology (ECMM) survey: *Candida* species causing candidaemia by country.



Candidemia in French hospitals: incidence rates and characteristics

H. Richet¹, P. Roux², C. Des Champs³, Y. Esnault⁴, A. Andremont⁵ and the French Candidemia Study Group*

Table 6 Yeast species most frequently isolated in blood cultures from patients hospitalized in French public hospitals in 1995

	Teaching Hospitals (n ^a = 107) % ^b	General Hospitals (n ^a = 27) % ^b	Cancer referral centres (n ^a = 22) % ^b	Total (n ^a = 156) % ^b
<i>C. albicans</i>	51.4	59.3	50.0	52.5
<i>C. parapsilosis</i>	16.5	14.8	13.6	15.8
<i>C. glabrata</i>	9.2	18.5	13.6	11.4
<i>C. krusei</i>	4.6	3.7	4.6	4.4
<i>C. tropicalis</i>	11.9	0	9.1	9.5
<i>C. pseudotropicalis</i>	1.8	0	1.3	1.3
Other yeasts ^c	4.6	3.7	9.1	5.0

^aNumber of different strains detected in patients with candidemia.

^bMore than one species in some patients.

^cNon-identified yeasts (mostly) or other yeasts identified.

Clin Microbiol Infect 2002; 8: 405–412

EN ESPAGNE

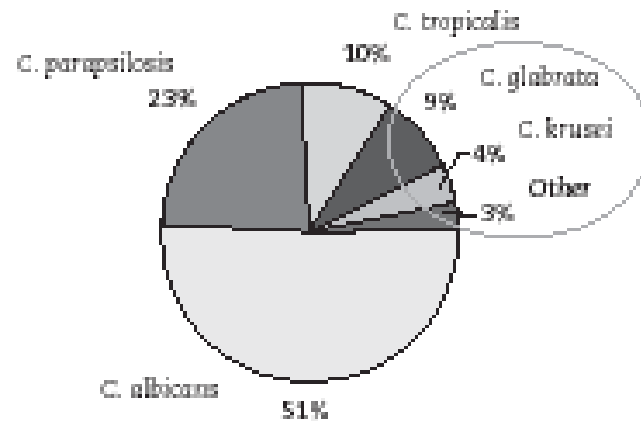


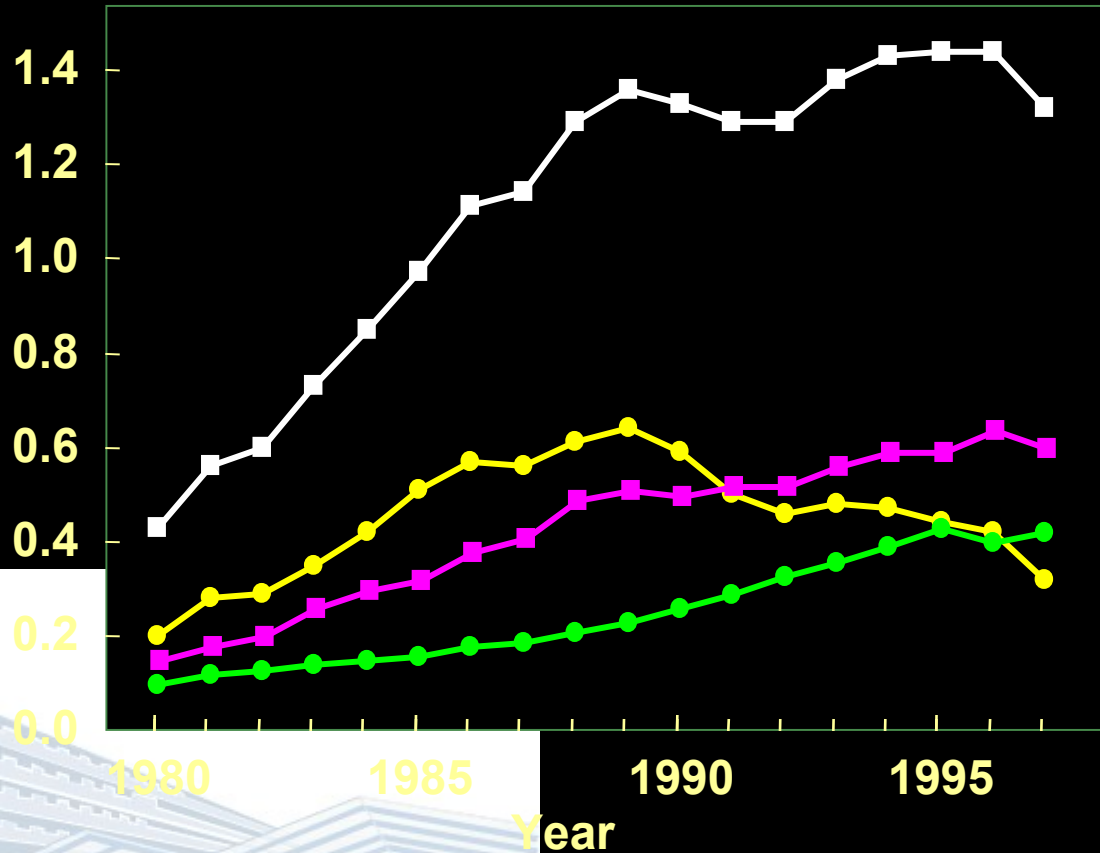
Fig. 3. Distribution of *Candida* species causing fungemia in a study reported by Almirante et al from Barcelona, Spain [8].

OUTCOMES



Mortality from fungal disease, USA, 1980–97

Mortality
per 100,000
population



All mycoses

Other mycoses

Aspergillosis

Candida infection

source: McNeil et al, CID 2001; 33: 64

OUTCOMES

Table 4
Outcome of *Candida* bloodstream infections at Day 30

<i>Candida</i> species	ECMM survey [6]		Barcelona area survey [26]	
	No. of episodes	Mortality rate, % (range) ^a	No. of episodes	Mortality rate (%)
<i>C. albicans</i>	1090	38.5 (29–45)	83	47
<i>C. glabrata</i>	269	45.0 (25–64)	14	50
<i>C. parapsilosis</i>	263	25.9 (0–34)	22	28
<i>C. tropicalis</i>	140	41.4 (20–44)	19	59
<i>C. krusei</i>	38	55.3 (20–67)	5	46
Total	1942 ^b	37.9 (27–40)	150	44

ECMM, European Confederation of Medical Mycology.

^a Range reflects data from all participating countries.

^b Includes 142 other less common *Candida* species not reported in detail.

Table 5 Outcome of 1,942 episodes of *Candida* bloodstream infection at day 30 according to aetiologic agent, underlying conditions and age groups

Parameter	No. of episodes	Percent mortality	<i>P</i> value ^a
Aetiologic agent			
<i>C. albicans</i>	1,090	38.5	0.65
<i>C. glabrata</i>	269	45.0	0.02
<i>C. parapsilosis</i>	263	25.9	<0.001
<i>C. tropicalis</i>	140	41.4	0.42
Underlying condition			
Surgery	892	35.3	0.26
Intensive care	791	42.4	0.02
Solid tumor	442	49.2	<0.001
Haematological malignancy	247	44.9	0.03
HIV infection	61	23.4	0.03
Premature birth	123	26.8	0.02
Age group			
<1 y	142	26.0	0.006
1–19 y	148	22.3	<0.001
20–69 y	1,096	36.6	0.46
≥70 y	556	47.7	<0.001
Total	1,942	37.9	

^aCalculated against overall crude mortality

Table 3. Thirty-day mortality rate of patients with fungaemia: comparison between episodes caused by *Candida albicans* and non-*albicans* *Candida* spp.

	Candidaemia episodes in 86 patients, <i>n</i> (mortality rate %)	<i>p</i>
<i>C. albicans</i> vs. non- <i>albicans</i> spp.	38 (21.1) vs. 56 (42.8)	0.029
<i>C. albicans</i> vs. <i>C. parapsilosis</i>	38 (21.1) vs. 21 (33.3)	0.300
<i>C. albicans</i> vs. <i>C. tropicalis</i>	38 (21.1) vs. 15 (60.0)	0.006
<i>C. albicans</i> vs. <i>C. glabrata</i>	38 (21.1) vs. 12 (50.0)	0.052
<i>C. albicans</i> vs. other species ^a	38 (21.1) vs. 8 (25.0)	0.806

^a*C. krusei* (*n* = 3), *C. lusitaniae* (*n* = 2), *C. guilliermondii* (*n* = 2), *C. pelliculosa* (*n* = 1).

Bedin, Clinical Microbiology and Infection, 2006, 12 : 75 80

Table 1 Demographic, risk factors and clinical data on a cohort of 186 patients with candidemia

Variables	Total no.	Mortality	OR	95% CI	P value
Population	186 (100%)	79 (42%)			
Age	48 year (5 days-91 years)				
Male/female	112/74 (60%/40%)	43/36 (42%/43%)	0.65	0.36-1.19	0.82
Broad-spectrum anti-bacterial chemo therapy	164 patients (88.6%)	73 (44%)	2.14	0.8-5.74	0.07
Chemotherapy	35 (19%)	11 (31%)	0.56	0.26-1.22	0.15
Neutropenia	26 (14%)	10 (37%)	0.82	0.35-1.93	0.4
Steroids	48 (26%)	23 (48%)	1.35	0.7-2.61	0.34
Immunosuppression	3 (1.6%)	0 (0%)	0.07	0.0-10.23	0.13
Hyperalbuminemia	60 (32%)	30 (50%)	1.57	0.85-2.92	0.15
Prior surgery	76 (41%)	32 (42%)	0.97	0.54-1.76	0.93
ICU stay	103 (70%)	52 (50%)	2.11	1.16-3.85	0.01
Thrombocytopenia	37 (20%)	24 (65%)	3.11	1.49-6.70	0.002
Renal failure	26 (14%)	18 (70%)	3.65	1.50-8.91	0.001
Ventilatory support	102 (59%)	55 (54%)	2.93	1.58-5.40	0.0005
Inotropic support	58 (31%)	45 (78%)	9.57	4.61-19.88	0.005
Central venous catheters	125 (67%)	57 (46%)	1.49	0.79-2.79	0.21
Arterial lines	86 (46%)	47 (55%)	2.56	1.41-4.64	0.18
Anti-fungal therapy	110 (59%)	31 (29%)	0.24	0.13-0.45	0.0002
Time to initiation of anti-fungal therapy	2.9 days (1-10 days)				
Treatment initiation	2 days (1-4 days)				
Treatment duration	13 days (1-45 days)				
Amphotericin B	96 (52%)	34 (35%)	0.55	0.30-0.99	0.028
Fluconazole	14 (7.5%)	4 (29%)	0.52	0.16-1.71	0.03

The P value refers to univariate statistical analysis of categorical variables. OR, odds ratio; CI, confidence interval.

Table 2. Commonly reported species distribution (%) of *Candida* bloodstream isolates and general susceptibility of *Candida* species to antifungal agents

Species	Frequency	Fluc	Itra	Vori	5FC	Ampho	Caspo
<i>C. albicans</i>	48.0–59.0	S	S	S	S	S	S
<i>C. glabrata</i>	12.0–34.0	S-DD to R	S-DD to R	S to S-DD	S	S to I	S
<i>C. parapsilosis</i>	7.0–11.0	S	S	S	S	S	S (to I)
<i>C. tropicalis</i>	5.8–19.0	S	S	S	S	S	S
<i>C. krusei</i>	1.0–5.0	R	S-DD to R	S to S-DD	I to R	S to I	S
<i>C. lusitanae</i>	<1%	S	S	S	S	S to R	S
Other <i>Candida</i> spp.	2.0–6.9	V	V	V	V	V	V

Data from Reference 95. Frequency data from the EIERO (146), NEMIS (147), NNIS (148), SENTRY (149), and SCOPE (28) surveillance studies.

Abbreviations: Fluc, fluconazole; Itra, itraconazole; Vori, voriconazole; 5FC, flucytosine; Ampho, amphotericin-B; Caspo, caspofungin; S, susceptible; S-DD, susceptible dose dependent; I, intermediate; R, resistant; V, variable.

ASPERGILLOSIS



Filamenteux : Aspergillus

– Implantation

– Colonisation

– Sensibilisation ABPA

– Aspergillome

– Aspergillose invasive

– Autres

organes

sinus – poumon

sinus - poumons

cavité préexistante

poumon –SNC – peau – os –cœur ...

Oreille, œil , cutanée (brûlés, plaies...),

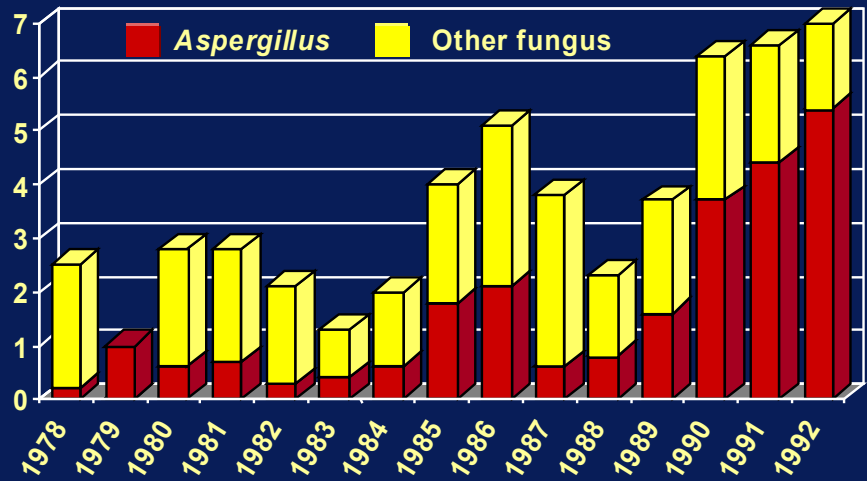
Les autres filamenteux de l'environnement :

Fsarium, Mucor, Scedosporium, Paecylomyces....

INCIDENCE

Invasive aspergillosis at autopsy (N=8124)

Prevalence at necropsy (%)

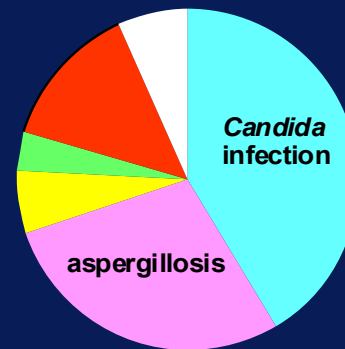


Groll et al *J Infect* 1996;33:23-32

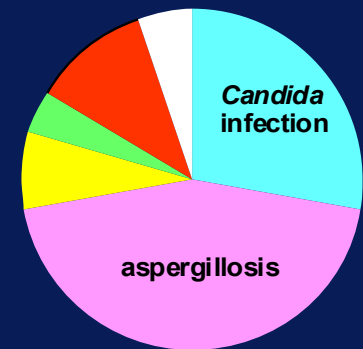
Visceral fungal diseases in Japan

Data from autopsy records

1990, N=863



1994, N=629



Ref: Yamazaki *et al.*, J. Clin. Microbiol. 1999;37:1732–1736

The host is the most important factor determining incidence of invasive mycoses

General changes in the human condition that lead to higher numbers of patients at risk of invasive mycosis

higher age (longevity)
more complex interventions
more cytotoxic therapy
more immunosuppressive therapy
less mortality from other causes

(List stolen from B. de Pauw)

In aspergillosis...

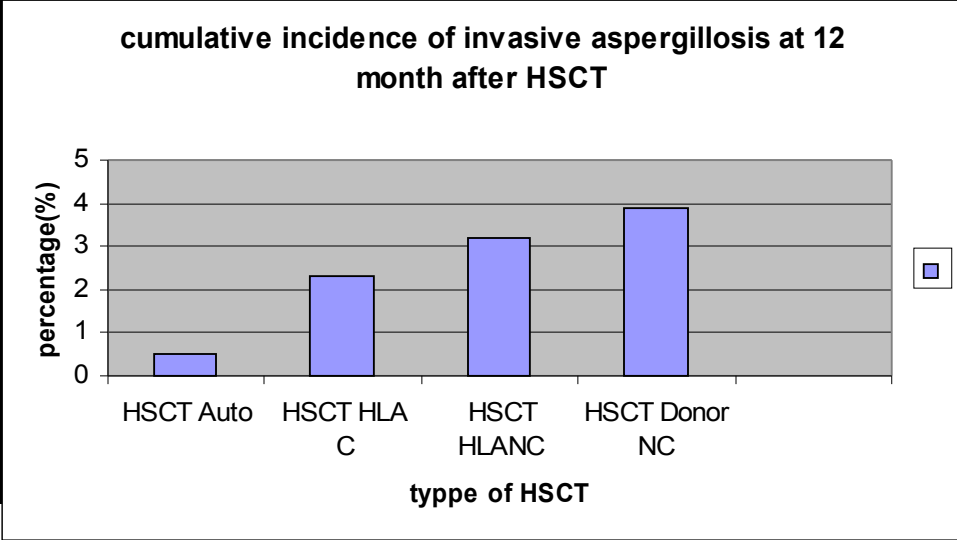
Incidence rose with increasing lung Tx

Incidence rose with increasing BMT

Incidence rose with switch to HSTC



References : Morgan et al , Med Mycol 2005 ; 43 :S49-58
Mortalité influencée par : corticothérapie , neutropenie
Lymphopénie, GVHD
CMV disease



FUNGAL INFECTION IN SOLID ORGAN TRANSPLANTATION

Aspergillosis in transplantation: prevalence and outcome

Type	Invasive (%)	Colonized (%)	Mortality (%)	Attributable deaths (%)
Lung	8.4	10.4	55	9.3
Heart	6.2	No data	78	15.4
Liver	1.7	0.5	87	16.9
Renal	0.7	1.7	75	No data
Pancreas	1.0	No data	100	No data
Bone marrow	6.4	2.2	92	10.0

Adapted from Singh (2)

Table 2

Patterson : Fungal infections in solid organ transplantation

Timing of fungal infections in solid organ transplantation

Early (<1 month)

Uncommon except in liver transplant

Nosocomial intensive care unit *Candida* infections

Endogenous

Exogenous

Intermediate (1–6 months, especially 2 months)

Candida

Aspergillus

Other filamentous fungi

Zygomycoses

Dematiaceous fungi

Late (>6 months)

Associated with late rejection

Aspergillus

Cryptococcus

Other endemic fungi

Histoplasma capsulatum

Sporothrix schenckii

Table 1



INVASIVE PULMONARY ASPERGILLOSIS IN ICU

Table 1 Risk factors for IPA in non-neutropenic critically ill patients in the ICU

Risk factor	Reference
COPD in combination with prolonged corticosteroid use	[1, 24–26]
High-dose systemic corticosteroids > 3 weeks (e. g. prednisone equivalent > 20 mg/day)	[2, 31, 33]
Chronic renal failure with RRT	[8, 35]
Liver cirrhosis/acute hepatic failure	[2–4, 34]
Near-drowning	[4, 36–38]
Diabetes mellitus	[2, 3, 31, 33]

COPD, Chronic obstructive pulmonary disease; *RRT*, renal replacement therapy

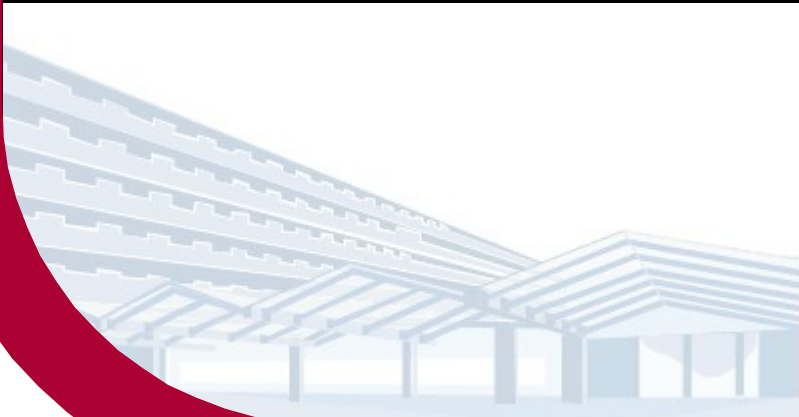
INCIDENCE : 0.3 à 5.8 %
MORTALITE : 80%



CAUSATIVES SPECIES

Anecdotal case reports suggest a recent rise in *A. flavus* and *A. terreus* infections

There is no doubt that invasive infections due to other moulds such as *Fusarium* spp., *Scedosporium* spp. and Zygomycetes are occurring with greater frequency than before



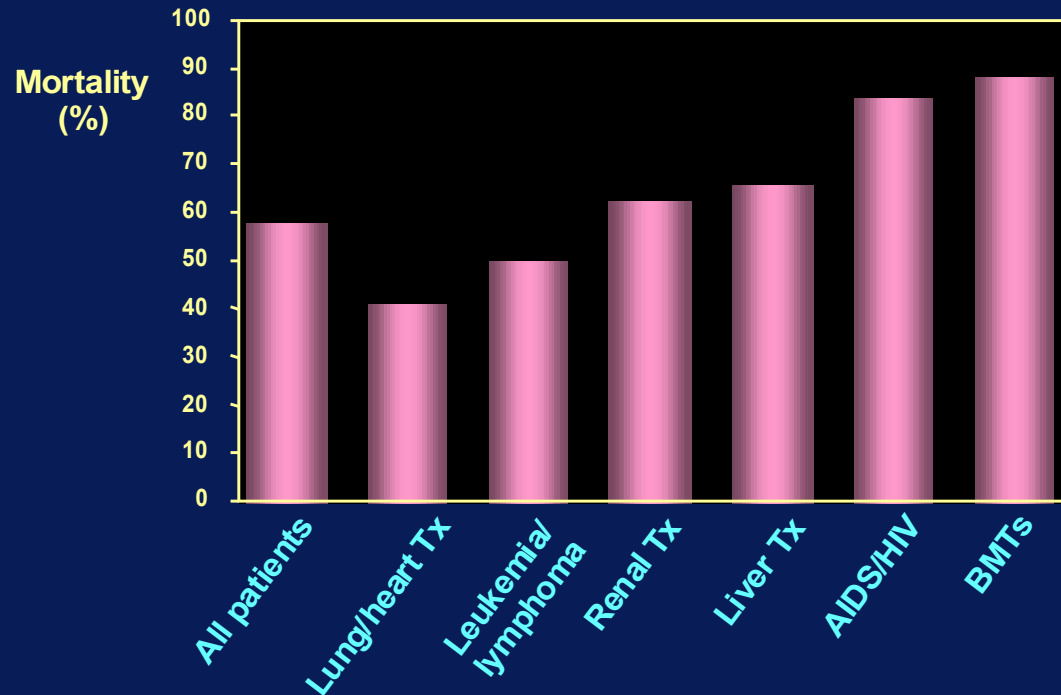
Les Aspergillus

<i>Aspergillus</i>	IF %	Caractéristiques
<i>fumigatus</i> possible .	60-70	IFI+++ , très S. mais hte CMF
<i>flavus</i> polyènes	10-20	Sinus + peau, baisse de la S./
<i>terreus</i> Candines	3-12	SD- R/AmB , S /MRC, POS,
<i>niger</i> <i>nidulans,</i>	0-4	IFI , Asie++ réservoir = sol Sensible , Otomycose +++ →
<i>Ustus</i> <i>versicolor</i>	0-2	S variable à la multi- R <i>A,lentulus</i> mime <i>A.fumigatus</i> IFI
<i>lentulus</i>		



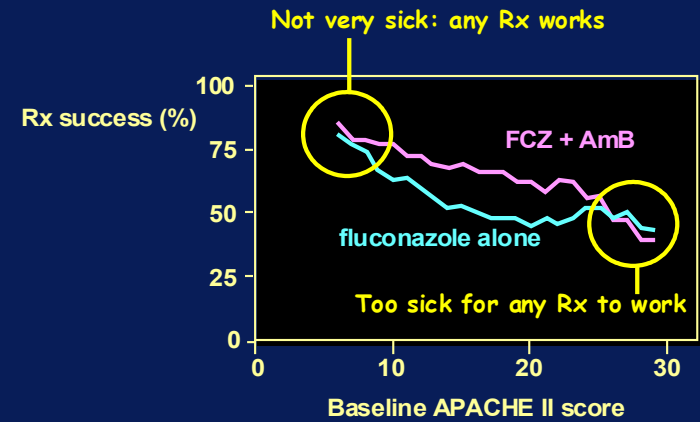
MORTALITY

Mortality from invasive aspergillosis



Lin et al *CID* 2001;32:358-366

Host status influences outcome in invasive mycoses



Rex *et al* CID 2003;36:1221



CLINIQUES UNIVERSITAIRES

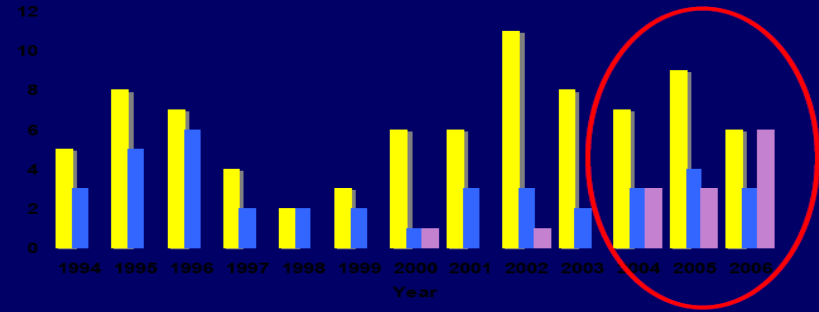


ZYCOMYCOSES



Zygomycoses : épidémiologie

■ *Asp.spp* ■ *A.terreus* ■ zygomycosis



Lass-Flörl, Innsbrück, données non publiées



Pathogènes fongiques émergents

Pourquoi? Trous de spectre

	<i>Polyenes</i>	<i>Fluco</i>	<i>Itraco</i>	<i>Vorico</i>	<i>Posaco</i>	<i>Candins</i>
<i>C albicans</i>	+	+	+	+	+	+
<i>C krusei</i>	+	-	-	+	+	+
<i>C glabrata</i>	+	-	-	+	+	+
<i>Cryptococcus</i>	+	+	+	+	+	-
<i>Aspergillus</i>	+	-	+	+	+	+
<i>Zygomycetes</i>	+	-	-	-	+	-
<i>Fusarium</i>	+/-	-	-	+/-	+/-	-

CONCLUSIONS

- Augmentation des mycoses émergentes
- *Candida albicans* reste agent principal
- Mortalité reste très élevée
- De plus en plus de situations à risque de DVPT de fungémie
- De nouvelles armes surtout thérapeutiques