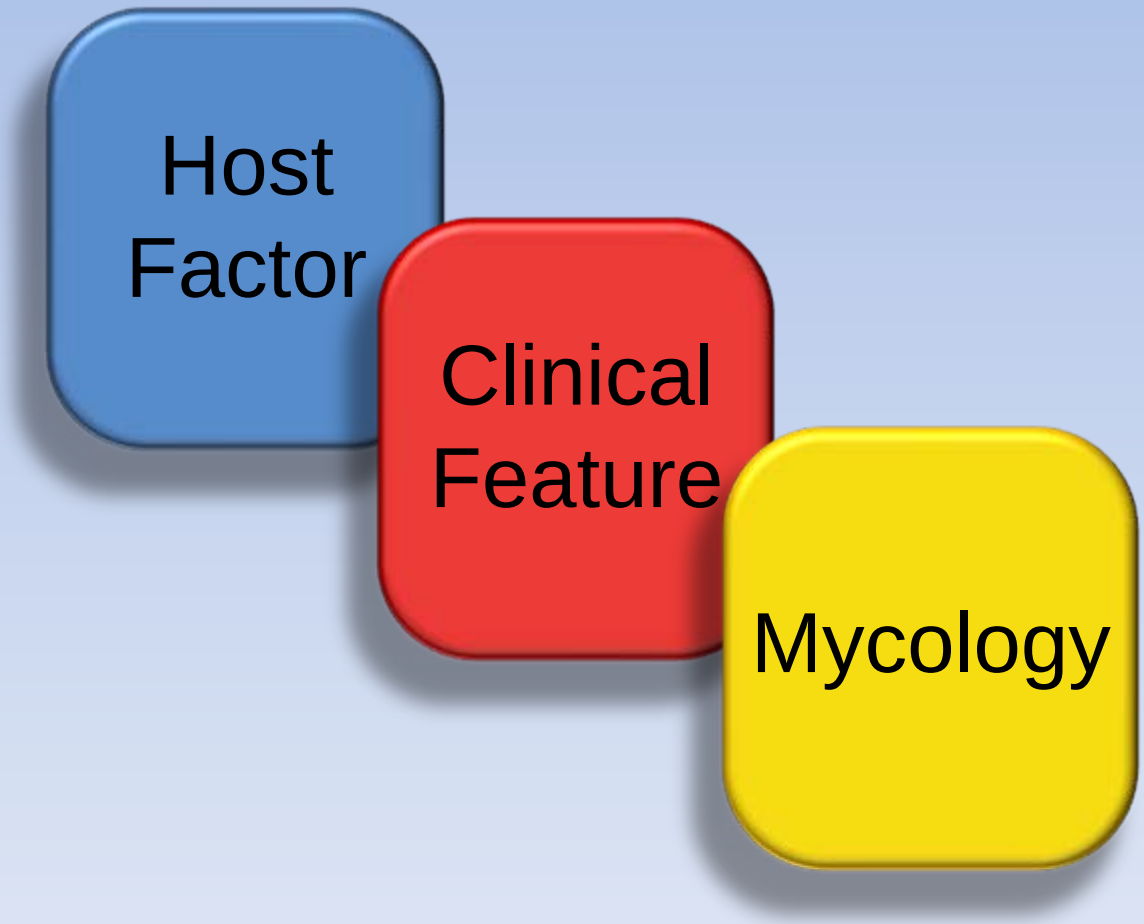
Fungal Infections in ICU

QEH ICU
Chairperson: Dr Osburga Chan

What is it ?

Defining invasive fungal infection



Ascioglu *et al* 2002
Clin Infect Dis 34: 7 - 14

Host Factors

>3 weeks corticosteroids

neutropenia

Host Factor

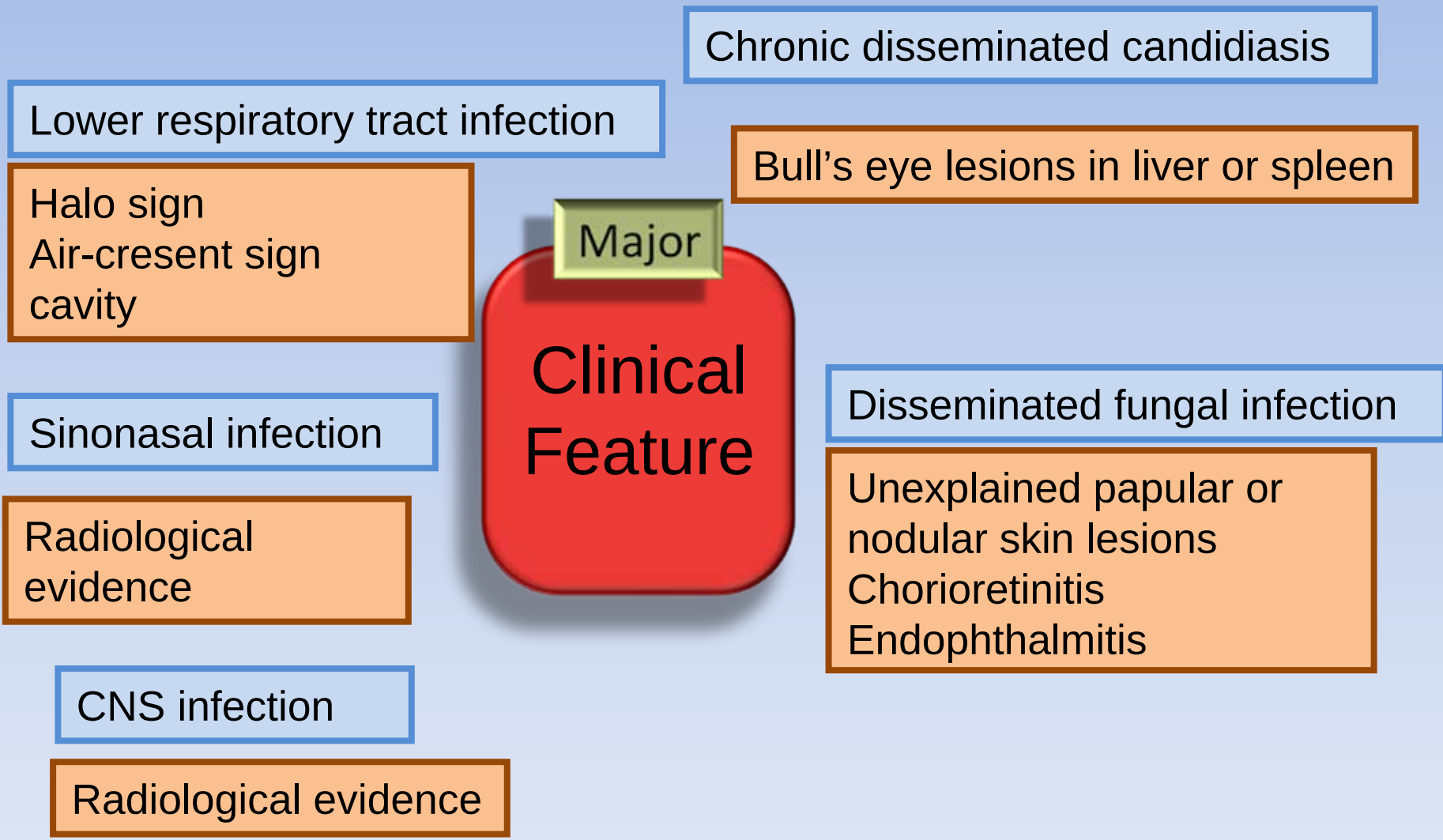
>4 days unexplained fever despite broad spectrum antibiotics

< 36°C or > 38°C and
- Prior mycosis
- AIDS
- Immunosuppressives
- > 10 daysneutropenia

Graft versus Host Disease

Ascioglu *et al* 2002
Clin Infect Dis 34: 7 - 14

Clinical features



Ascioglu *et al* 2002
Clin Infect Dis 34: 7 - 14

Clinical features

Minor

Clinical Feature

Lower respiratory tract infection

Cough, chest pain, haemoptysis, dyspnoea
Physical finding of pleural rub
Any new infiltrate not fulfilling major criteria

Sinonasal infection

Nasal discharge, stuffiness
Nose ulceration, eschar or epistaxis
Periorbital swelling
Maxillary tenderness
Black necrotic lesions or perforation of the hard-palate

CNS infection

CSF
- No pathogens
- No malignant cells
- abnormal biochemistry
- abnormal cell count

Focal neurological
- Seizures
- Hemiparesis
- Cranial nerve palsy

Mental changes
Meningeal irritation

Ascioglu *et al* 2002
Clin Infect Dis 34: 7 - 14

Mycology

Culture of mould from tissue, aspirate BAL or sputum

Mould seen in sinus aspirate

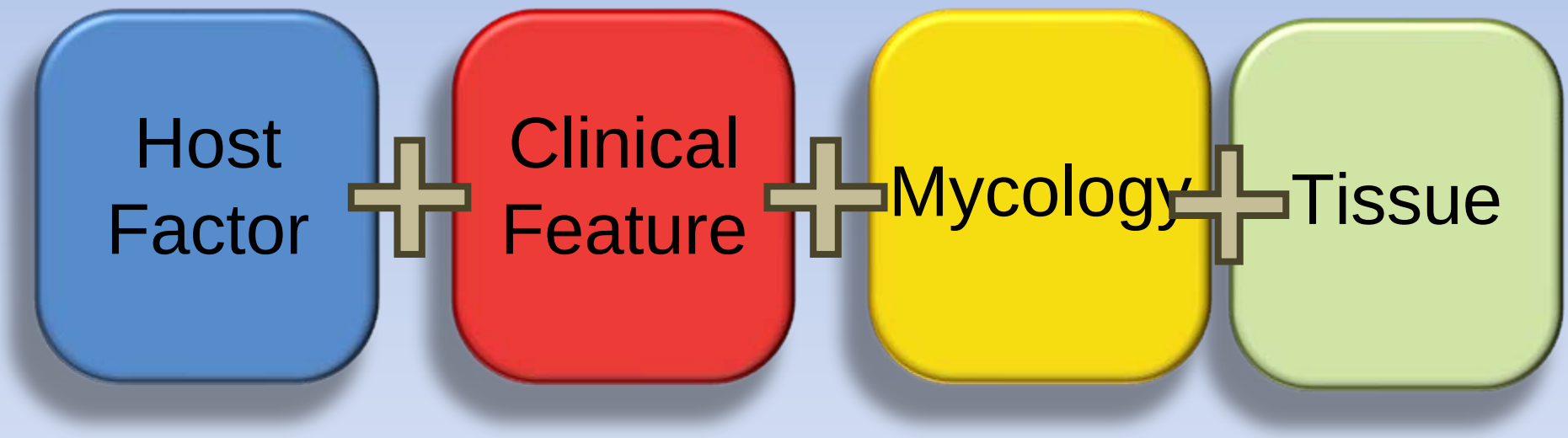
Mycology

Antigen in BAL, CSF or blood

Fungi seen in tissue or sterile body fluids

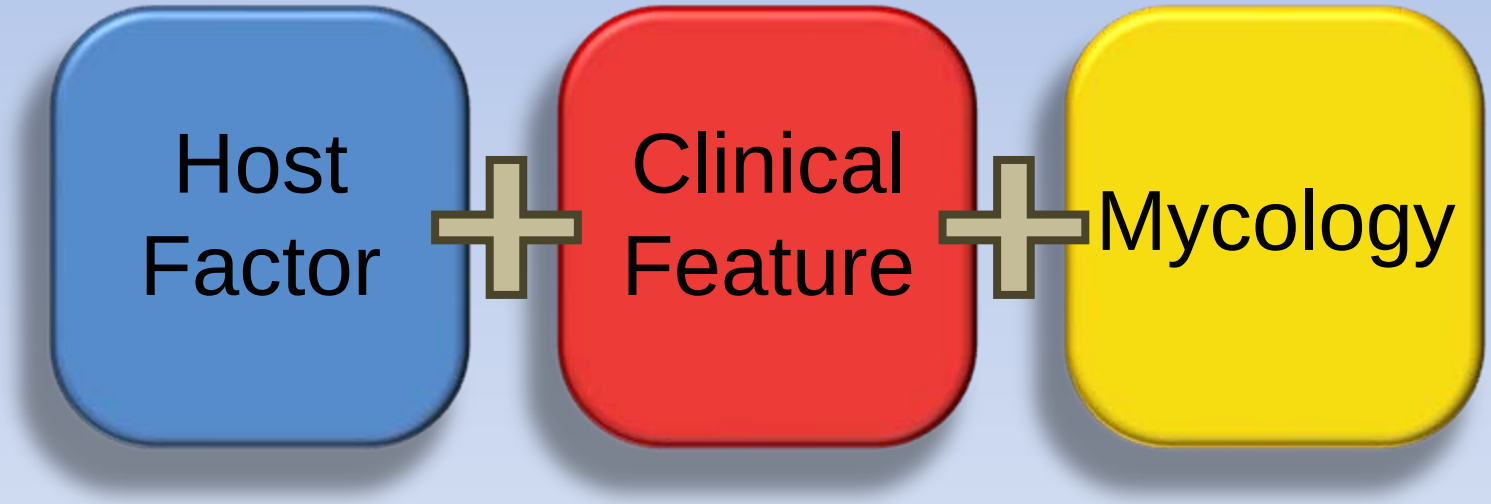
Ascioglu *et al* 2002
Clin Infect Dis 34: 7 - 14

Proven invasive fungal infective disease



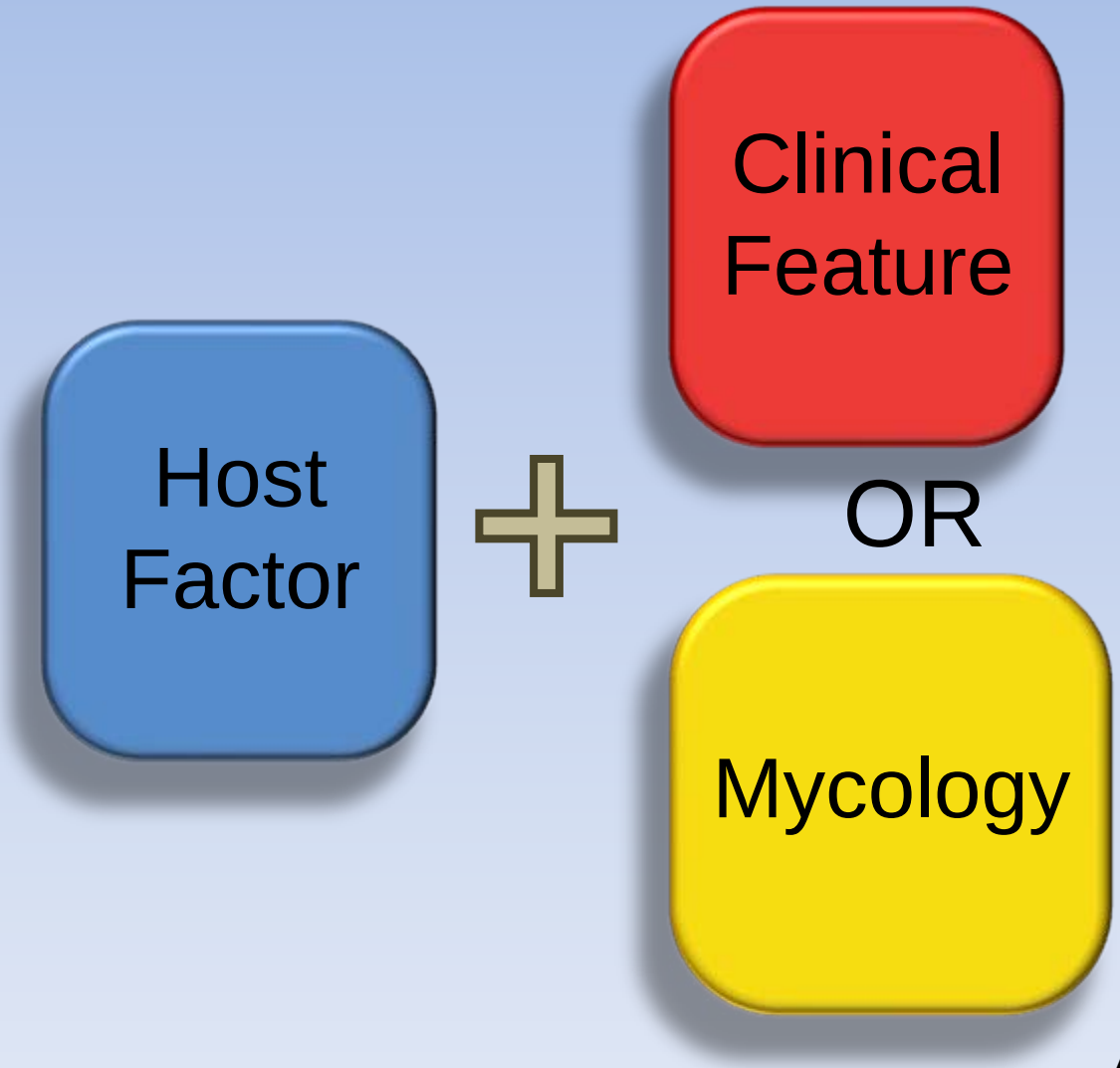
Ascioglu *et al* 2002
Clin Infect Dis 34: 7 - 14

Probable invasive fungal infective disease



Ascioglu *et al* 2002
Clin Infect Dis 34: 7 - 14

Possible fungal infective disease



Ascioglu *et al* 2002
Clin Infect Dis 34: 7 - 14

Why is it IMPORTANT ?

It is getting more common …

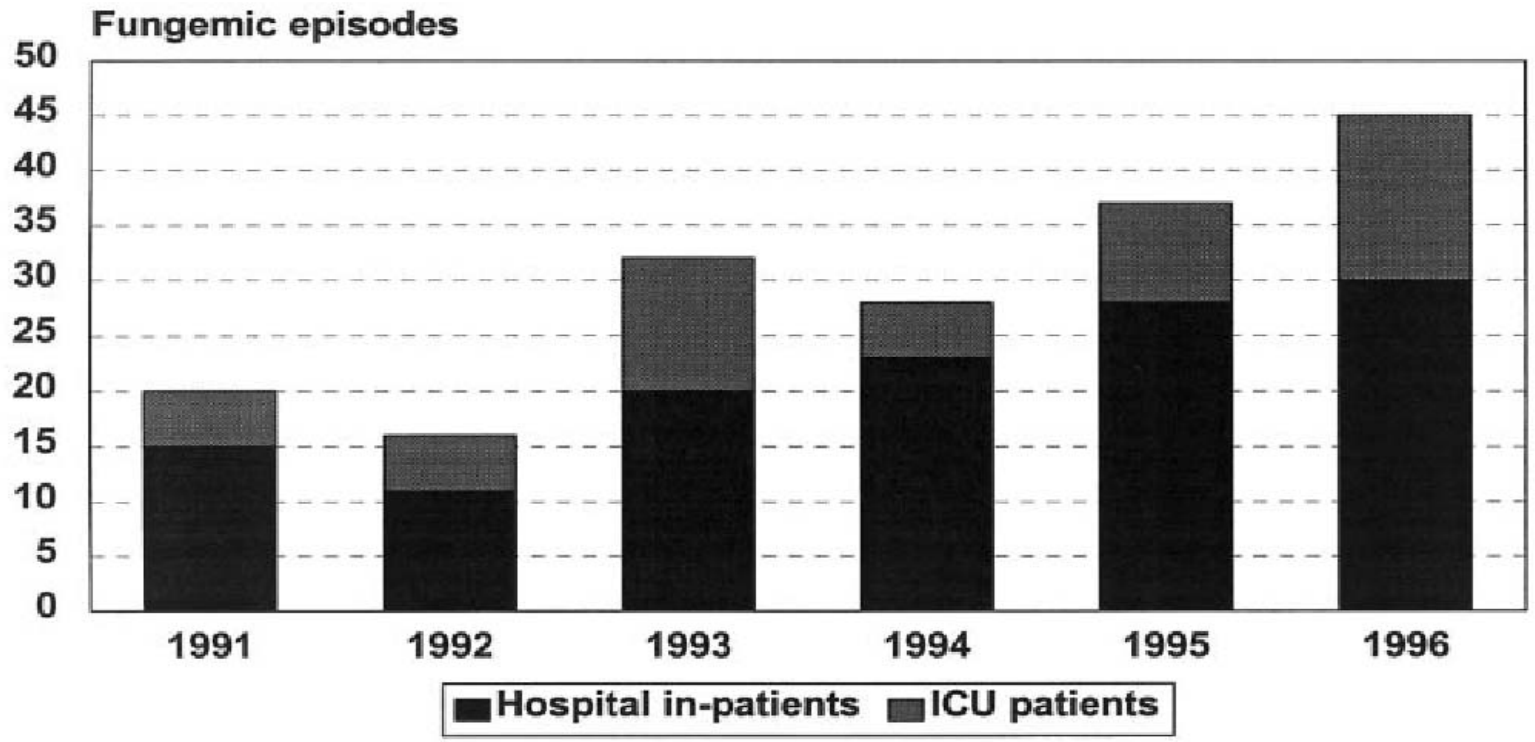


Fig. 1. Evolution of fungaemias in Hospital General Universitario "Gregorio Marañón" from 1991–1996 according to place of admission (general beds or ICU).

International Journal of Antimicrobial Agents Jan 2000

It is getting more common …

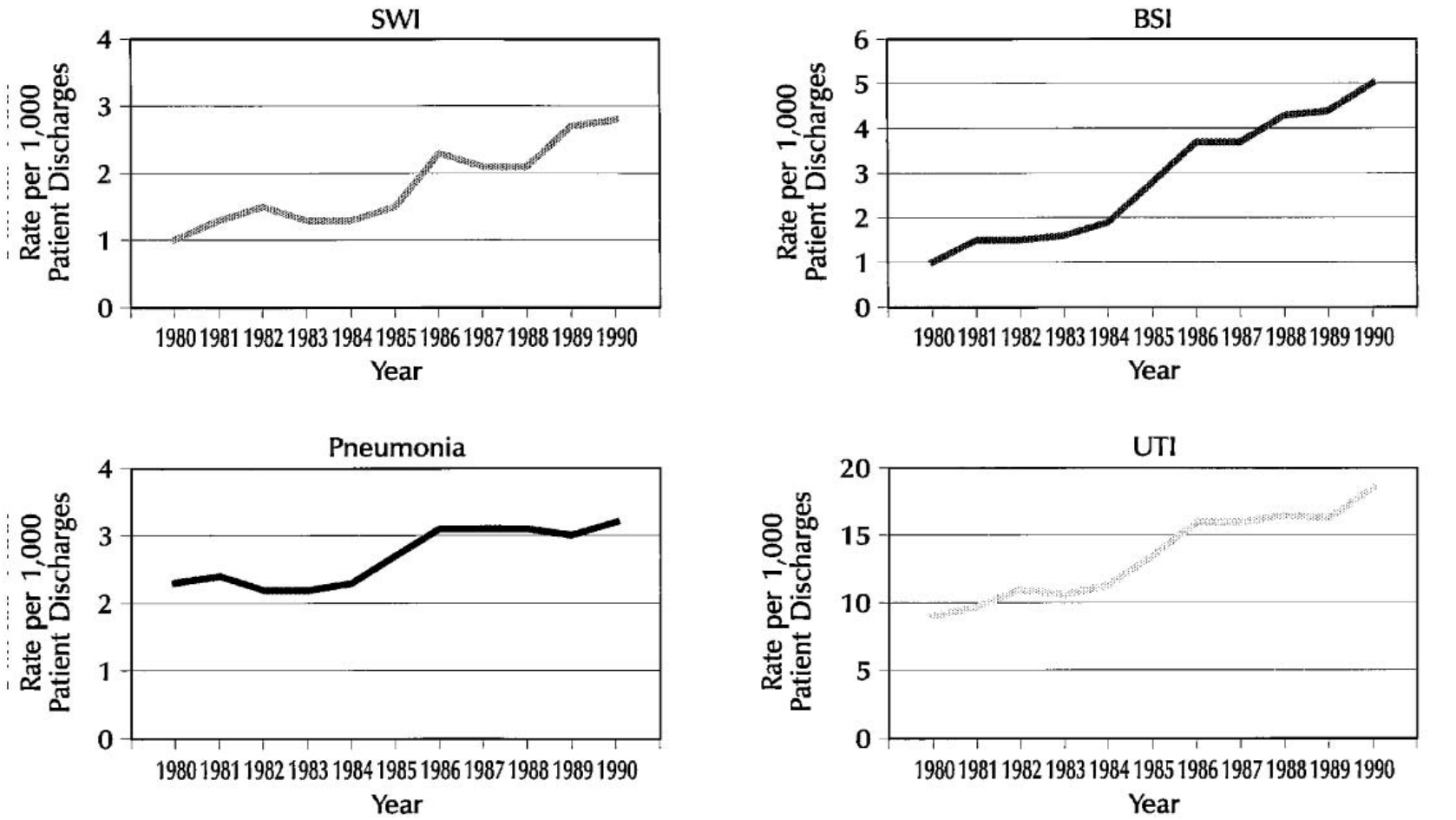


FIG. 1. Secular trend in the nosocomial fungal infection rate at U.S. hospitals, including surgical wound infection (SWI), bloodstream infection (BSI), urinary tract infection (UTI), and pneumonia, as reported to the NNIS system, by the site of infection, 1980 to 1990. Data from reference 8.

Clinical Microbiology Reviews, Oct 1996 p499-511

It is getting more common

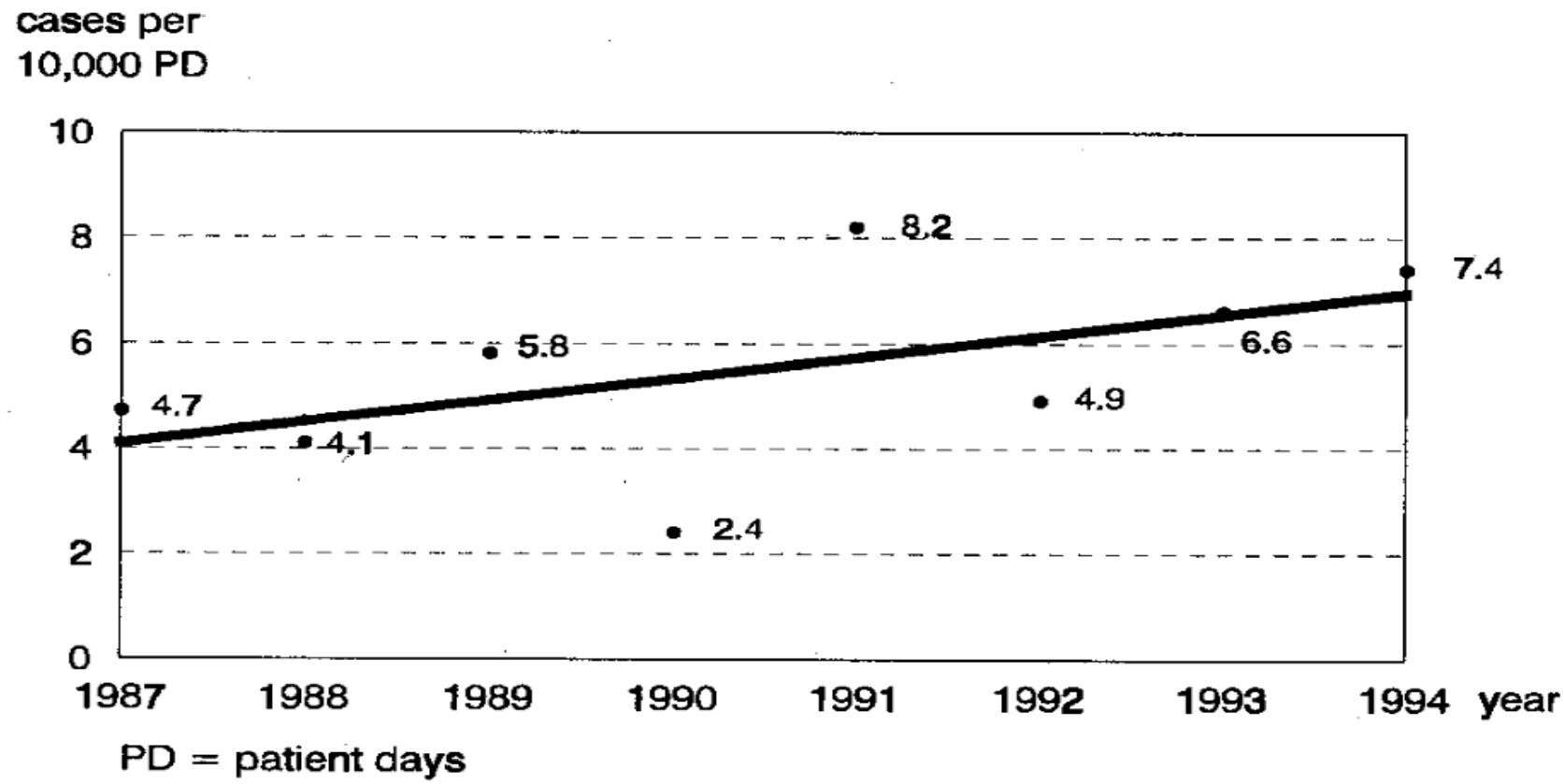


Figure 1: Incidence of *Candida* bloodstream infections 1987–1994.

Infection 25 (1997) No.1

It is getting more common …

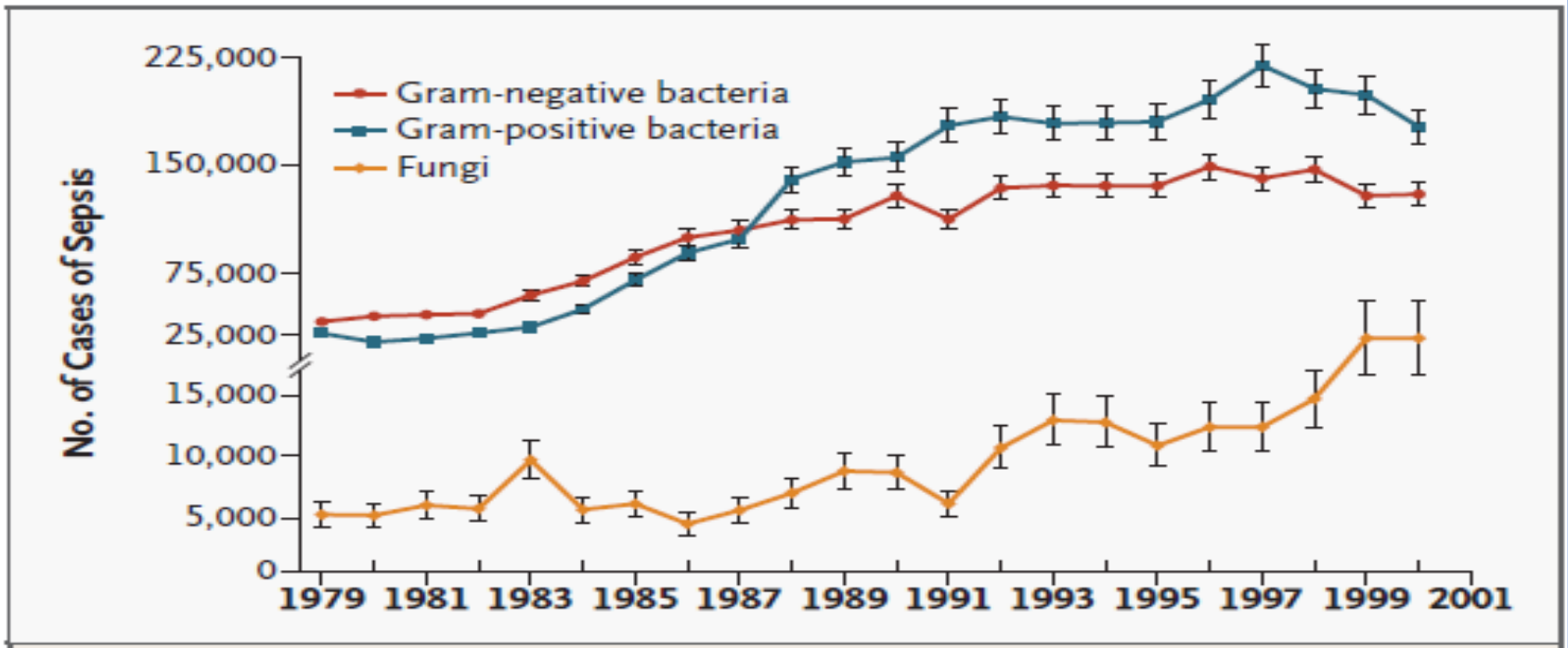


Figure 3. Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979–2000.

Points represent the number of cases for the given year, and I bars the standard error.

The New England Journal of Medicine 2003; 348: 1546-1554

It happens in ICU !

Table 1 Most common pathogens in 2064 ICU-acquired infections in the EPIC study [8]

Pathogen	Incidence (% of ICU-acquired infections)
Enterobacteriaceae	34.4 %
Staphylococcus aureus	30.1 %
Pseudomonas aeruginosa	28.7 %
Coagulase-negative staphylococci	19.1 %
Fungi	17.1 %

Intensive Care Medicine (1998) 24 : 206-216

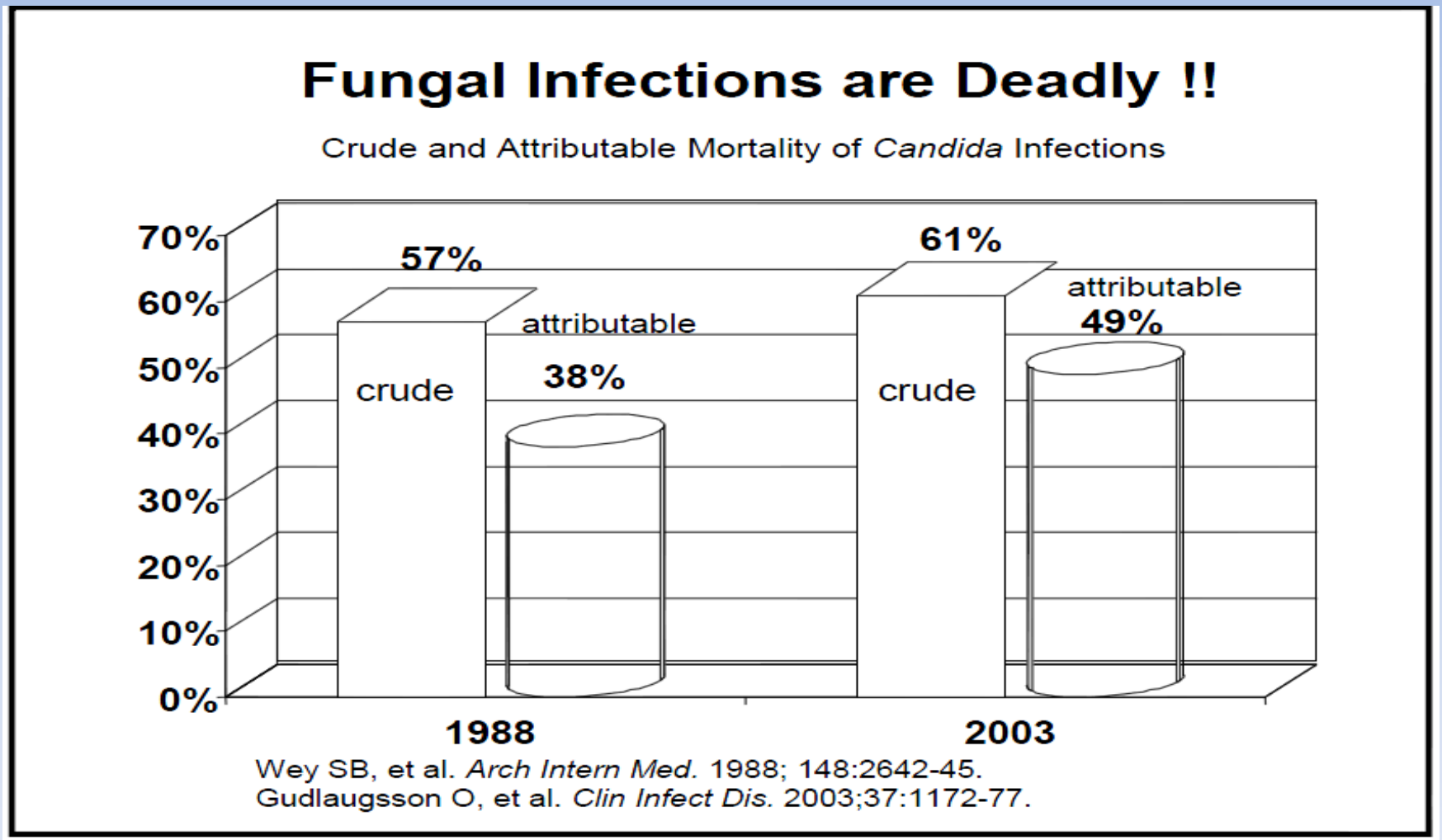
It happens in ICU !

Incidence Rates of Nosocomial BSIs (SCOPE)

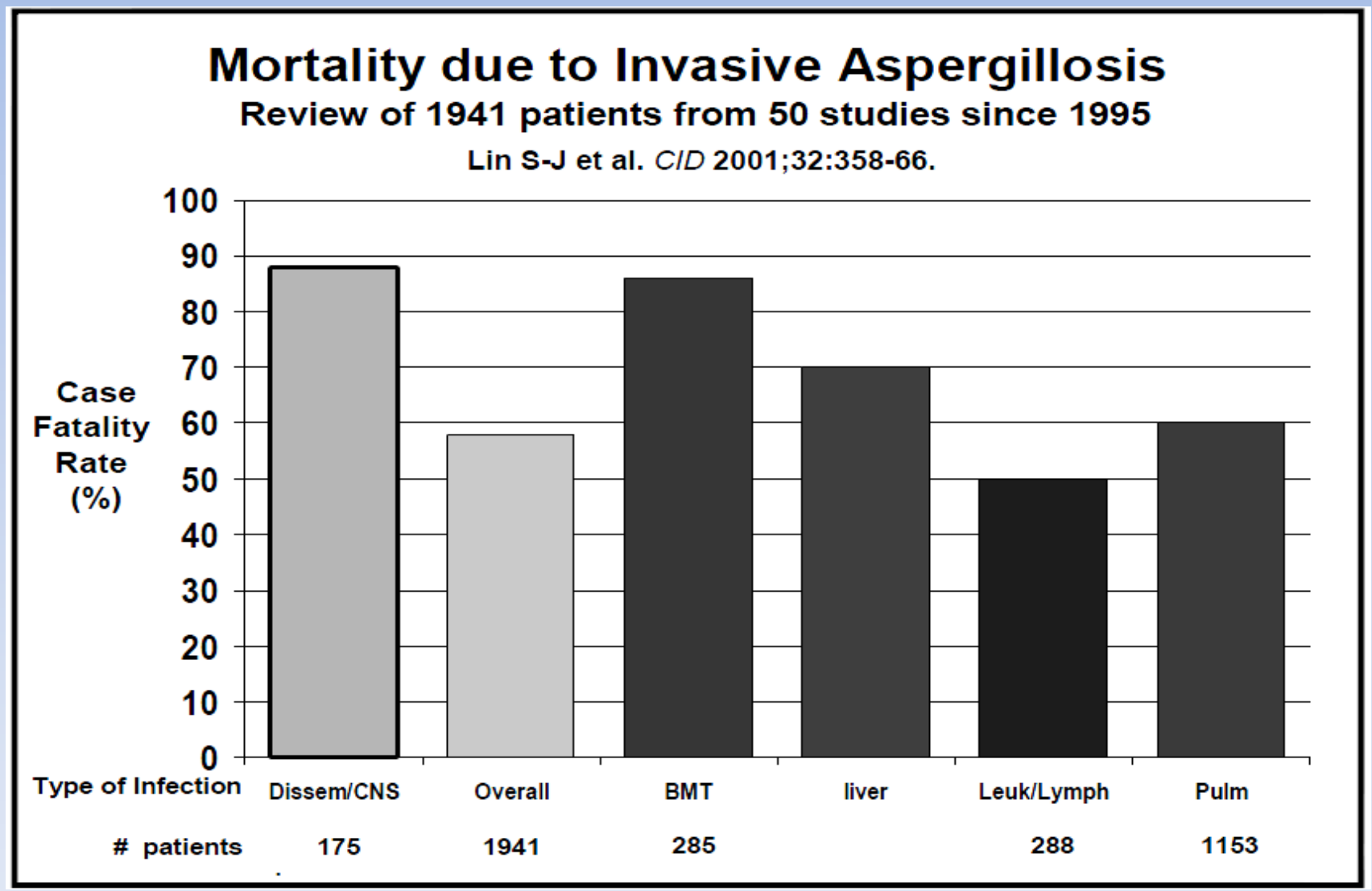
Pathogen	Percentage of BSIs		
	Total	*ICU*	*Non-ICU*
CoNS	31.3	35.9	26.6
S. aureus	20.2	16.8	23.7
Enterococcus	9.4	9.8	9.0
Candida	***9.0***	***10.1***	***7.9***
E. coli	5.6	3.7	7.6
Klebsiella spp.	4.8	4.0	5.5
P. aeruginosa	4.3	4.7	3.8

Wisplinghoff et al. *Clin Infect Dis* 2004; 39: 309-17.

Its mortality is high …



Its mortality is high …



Its mortality is high …

Table 2.

Mortality Rates for Specific Organism in IFIS.

Organism	Mortality (%)	Organism	Mortality (%)
Aspergillus species		**Fusarium species**	
Overall case fatality rate	**58**	Immunocompromised	70 – 87
AIDS	86	Histoplasma capsulatum	
HSCT	32 – 87	Disseminated	<25
Leukemia / Lymphoma	49	**Trichosporon species**	
Blastomyces dermatitidis		Geotrichum capitatum	57
Immunocompromised	30 – 49	Trichosporon spp	65 – 70
Candida species		**Zygomycetes**	
Overall	**10 – 49**	**Overall**	**54**
Neutropenic	48	Diabetes	44
Coccidioides species		Malignancy	66
AIDS	40 – 85	SOT	48
Dematiaceous fungi		Deferoxamine therapy	83
CNS disease	73	HSCT	91
Disseminated disease	79	**Cryptococcus species**	
Pre-existing immunodeficiency	84	SOT	42
		Scedosporium infection in HSCT or SOT	**58**

AIDS: acquired immunodeficiency syndrome; CNS: Central nervous system; HSCT: hematopoietic stem cell transplant; SOT: solid organ transplantation

Infection 36 . 2008 . No. 4

Its cost is enormous …

Table 3. Outcomes attributable to candidemia in the United States, 2000.

Variable	Pediatric patients			Adult patients		
	With candidemia (n = 1118)	Without candidemia (n = 2062)	Attributable increase (95% CI)	With candidemia (n = 8949)	Without candidemia (n = 17,267)	Attributable increase (95% CI)
Mortality, %	15.8	5.9	10.0 (6.2–13.8)	30.6	16.1	14.5 (12.1–16.9)
Length of stay, mean no. of days per patient	44.8	23.7	21.1 (14.4–27.8)	18.6	8.5	10.1 (8.9–11.3)
Total charges, mean US$ per patient	183,645	91,379	92,266 (65,058–119,474)	66,154	26,823	39,331 (33,60–45,602)

NOTE. Patients with candidemia hospitalized in the United States in 2000 are compared with propensity score–matched control patients without candidemia.

Clinical Infectious Disease 2005; 41 : 1232-1239

Its cost is enormous …

ICU LOS, Hospital LOS, Daily costs, Hospital costs, Hospital mortality

Table 1

Demographic characteristics of severe sepsis patients with and without invasive fungal infection

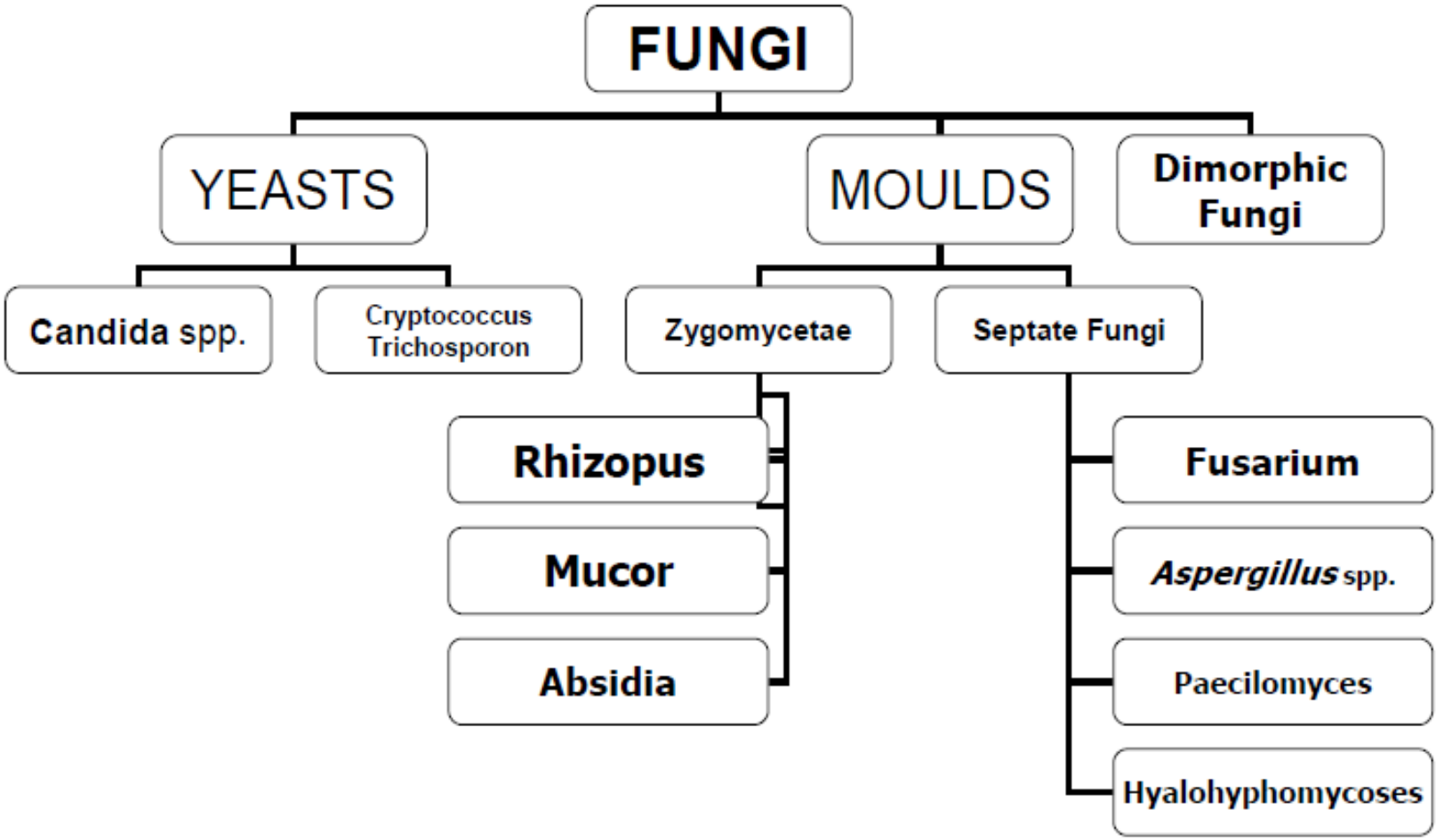
Variables	Severe sepsis patients with IFI ($n = 90$)	Severe sepsis patients without IFI ($n = 228$)	*P* value
Baseline descriptors			
Age (years)	65 (50–76.25)	61.5 (45–73)	NS
Sex (male; *n* [%])	57 (63.3%)	149 (65.4%)	NS
Admission APACHE II score (mean [IQR])	21 (17–27)	18 (13–23)	0.001
Admission SOFA score(mean [IQR])	8 (6–12)	8 (5–11.75)	NS
Comorbidity (*n* [%])	71 (78.9%)	165 (72.4%)	NS
Cancer (*n* [%])	14 (15.6%)	24 (10.5%)	NS
Diabetes mellitus (*n* [%])	15 (16.7%)	26 (11.4%)	NS
Interventions			
Mechanical ventilation (*n* [%])	71 (78.9%)	75 (32.9%)	<0.001
Central venous catheterization (*n* [%])	74 (82.2%)	122 (53.5%)	<0.001
Urinary catheterization (*n* [%])	84 (93.3%)	137 (60.1%)	<0.001
Arterial catheterization (*n* [%])	51 (56.7%)	112 (49.1%)	NS
Total parenteral nutrition (*n* [%])	49 (54.4%)	99 (43.4%)	NS
Corticosteroids or immunodepressant drugs (*n* [%])	22 (24.4%)	45 (19.7%)	NS
Renal replacement therapy (*n* [%])	21 (23.3%)	28 (12.3%)	0.024
Outcomes			
ICU LOS (days; mean [IQR])	16 (7.75–31)	5 (2–10)	<0.001
Hospital LOS (days; mean [IQR])	29.5 (17.75–50.25)	19 (10.25–36)	<0.001
Daily costs ($; mean ± SD)	520 ± 319	481 ± 437	NS
Hospital costs ($; mean ± SD)	17,051 ± 14,183	8,474 ± 9,484	0.001
Hospital mortality	61 (67.8%)	94 (41.2%)	<0.001

APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IQR, interquartile range; IFI, invasive fungal infection; LOS, length of stay; NS, not significant; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

Critical Care 2008 12: R5

Who are the Players ?

The Fungal World

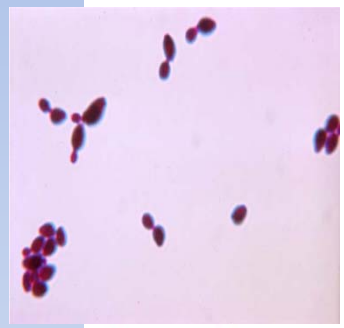


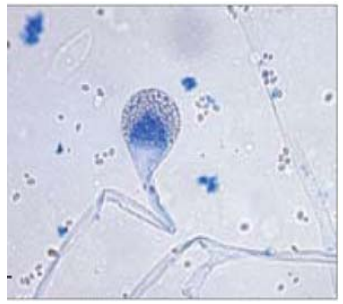
Opportunistic Fungal Pathogens

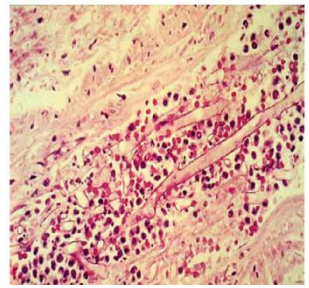
Table 1. Spectrum of opportunistic fungal pathogens[a]

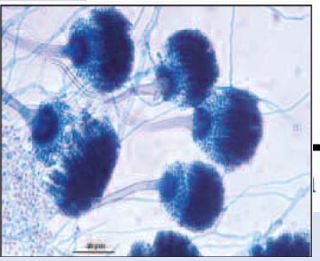
Candida spp.	*C. albicans*	Other yeasts	*Blastoschizomyces* spp.
	C. glabrata		*Cryptococcus neoformans*
	C. guilliermondii		*Malassezia* spp.
	C. kefyr		*Rhodotorula* spp.
	C. krusei		*Saccharomyces* spp.
	C. lusitaniae		*Trichosporon* spp.
	C. rugosa	Zygomycetes	*Absidia* spp.
	C. parapsilosis		*Cunninghamella* spp.
	C. tropicalis		*Mucor* spp.
Aspergillus spp.	*A. fumigtus*		*Rhizomucor* spp.
	A. niger		*Rhizopus* spp.
	A. flavus	Dematiaceous moulds	*Alternaria* spp.
	A. terreus		*Bipolaris* spp.
Other hyaline moulds	*Acremonium* spp.		*Curvularia* spp.
	Fusarium spp.		*Cladophialophora* spp.
	Paecilomyces spp.		*Exophiala* spp.
	Scedosporium spp.		*Phialophora* spp.
	Scopulariopsis spp.		
	Trichoderma spp.		

reference [109].









European Society of Clinical Microbiology and Infectious Diseases, 14 (Suppl. 4), 5-24

Which appears more ?

TABLE 3. Relative proportions of common and emerging nosocomial fungal infections, by pathogen, 1980 to 1990[a]

Fungal pathogen	Estimated percentage
Candida albicans	61
Non-*albicans Candida* spp.	19
C. parapsilosis	
C. tropicalis	
C. krusei	
C. lusitaniae	
Torulopsis glabrata[b]	8
Aspergillus spp.	1
Other	11
Yeasts (*Malassezia* and *Trichosporon* spp.)	
Zygomycosis (*Mucor* and *Rhizopus* spp.)	
Hyalohyphomycosis (*Fusarium* and *Acremonium* spp.)	
Phaeohypomycosis (*Alternaria*, *Bipolaris*, and *Curvularia* spp.)	

88%

[a] Data are from reference 8. The list of "other" pathogens is not all-inclusive.
[b] Also referred to as *C. glabrata*.

Epidemiology of Nosocomial Fungal Infections Vol.9 No. 4

Which appears more ?

Table 2

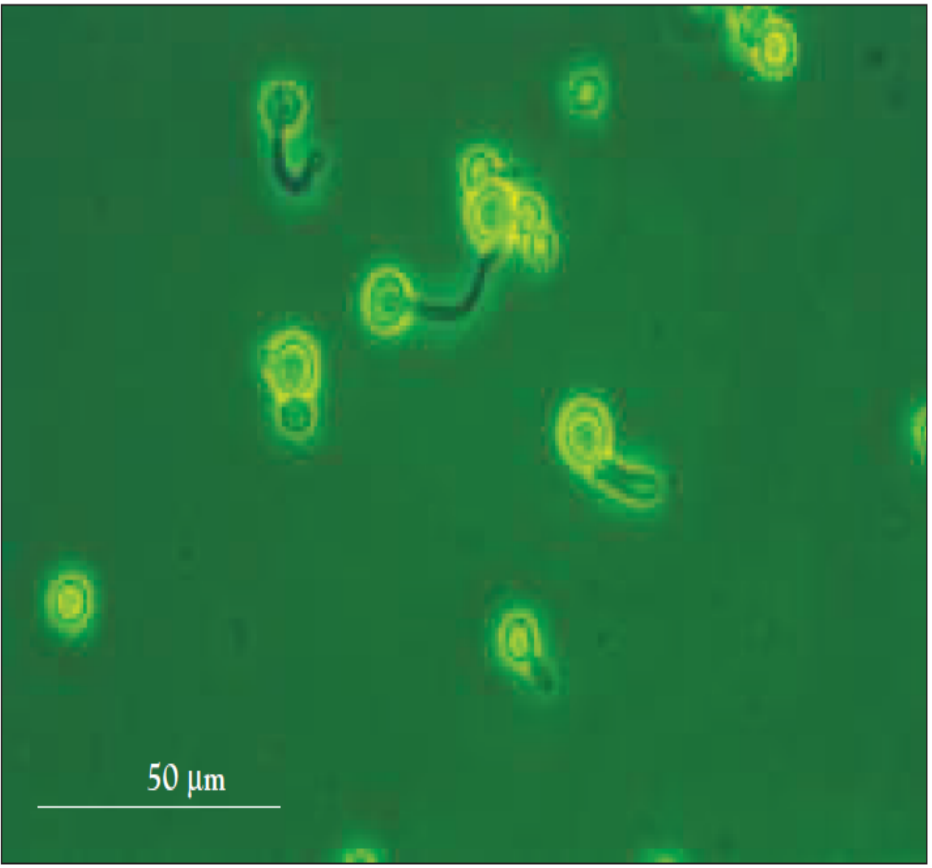
Characteristics of fungal infection

Characteristics	Episodes (*n* [%])
Pathogens	
Candida albicans	58 (58.0)
Candida tropicalis	17 (17.0)
Candida glabrata	15 (15.0)
Candida parapsilosis	3 (3.0)
Aspergillus	3 (3.0)
Others or unclassified	4 (4.0)
Site of infection	
Lung	62 (56.4)
Abdomen	25 (22.7)
Bloodstream or catheter related	15 (13.6)
Other sites	8 (7.3)

93%

Critical Care 2008, 12 : R5

The *Candida*



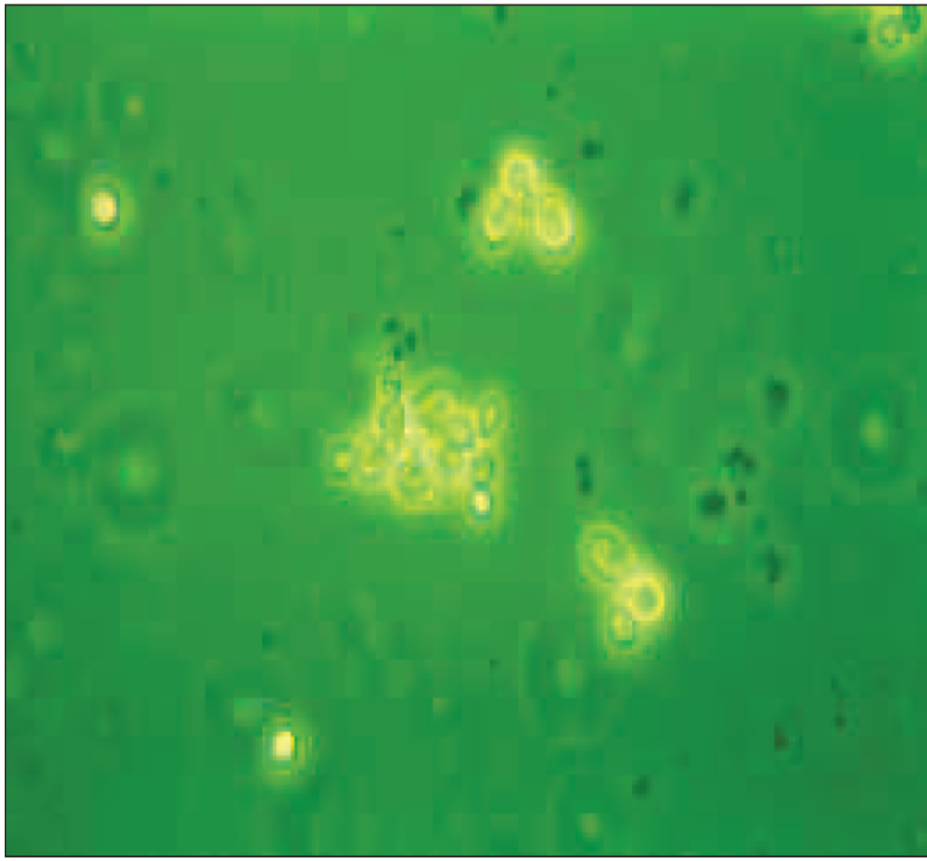
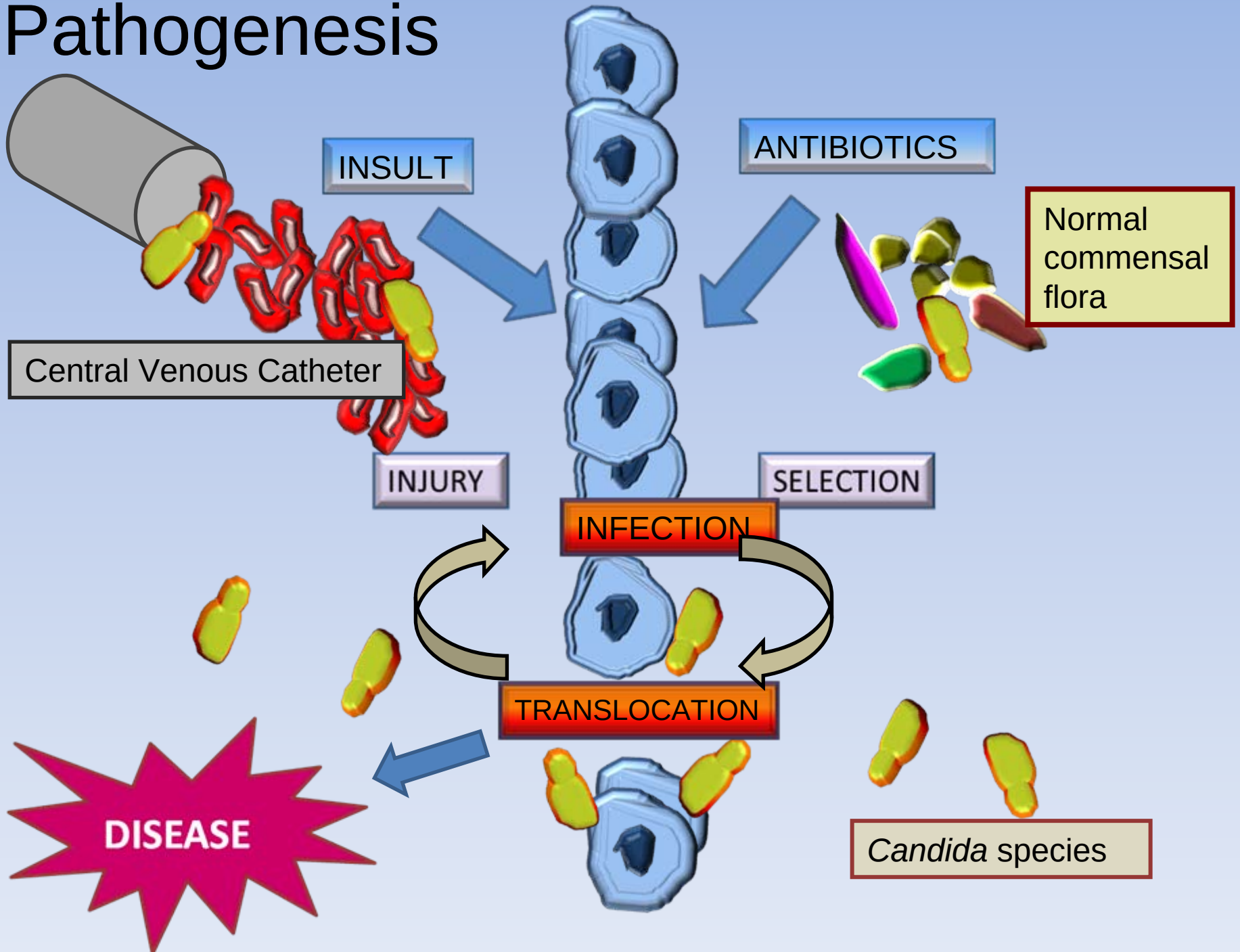


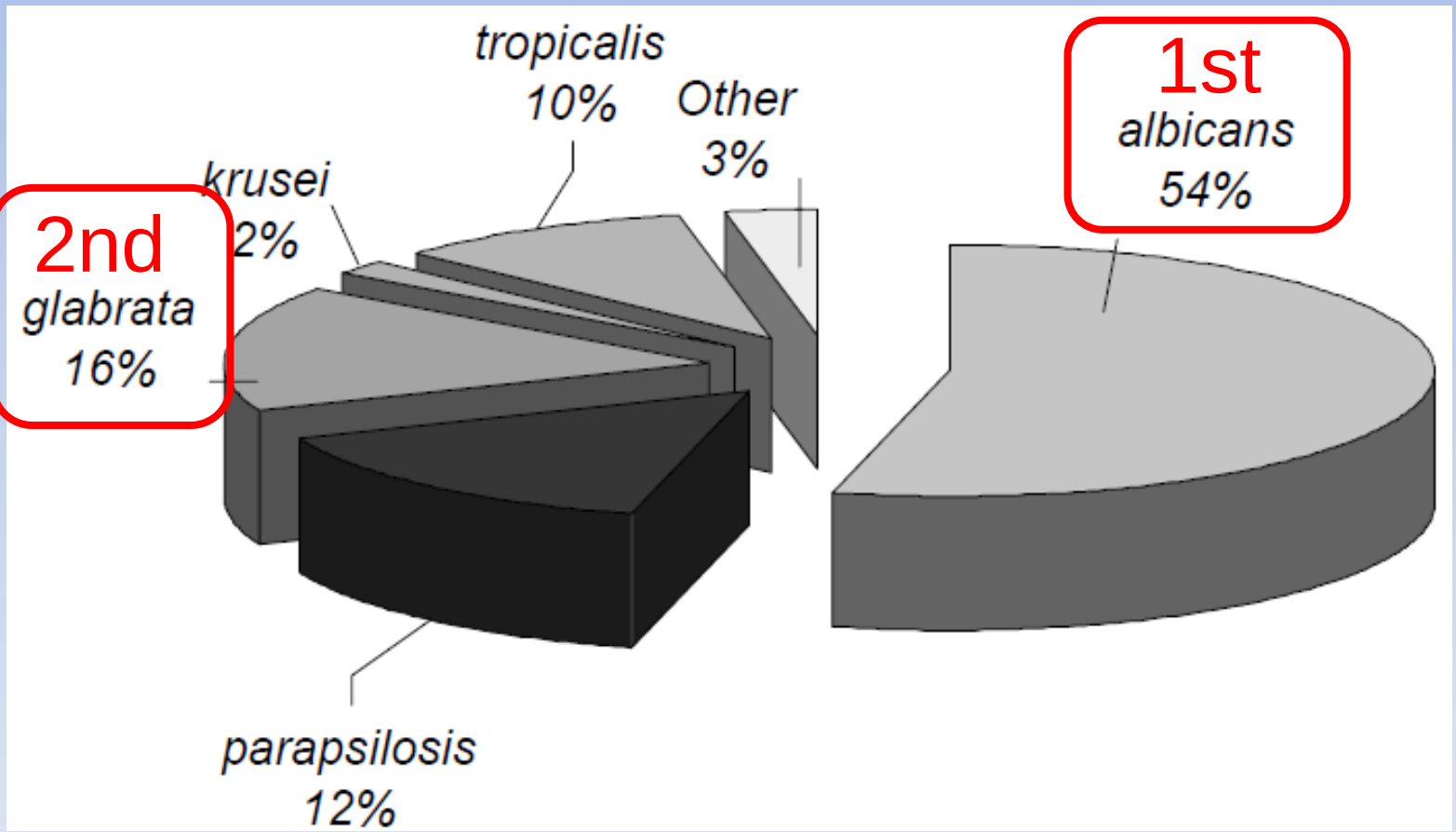
Figure 3. *Candida albicans*, with characteristic germ tubes at left. Non-*albicans Candida*, germ-tube negative at right. Source: Mycology Online http://www.mycology.adelaide.edu.au

C. albicans can be differentiated from other *Candida* species by its characteristic germ tube production after incubation at 37 C for 2-3 hours

Pathogenesis



Epidemiology of Candidemia



J Clinical Micro 2002;40:852-856
Medicine 2003 ; 309-321

Epidemiological Differences

Surgical ICU

- *C. albicans* 48%
- *C. glabrata* 24%
- *C. tropicalis* 19%
- *C. parasilosis* 7%
- Other species 2%

Neonatal ICU

- *C. albicans* 63%
- *C. parasilosis* 29%
- *C. glabrata* 6%
- Other species 3%

Clinical Infectious Disease 199;29(2):253-8

Increasing non *C. albicans*

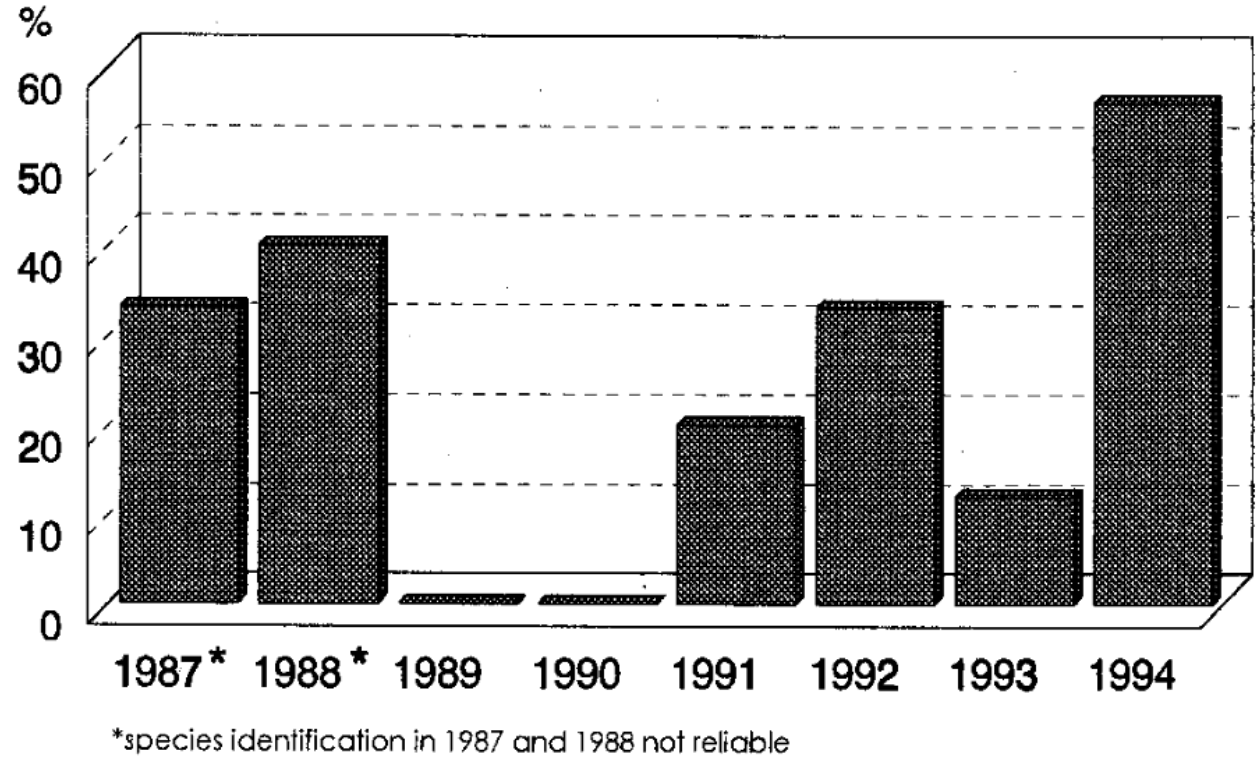
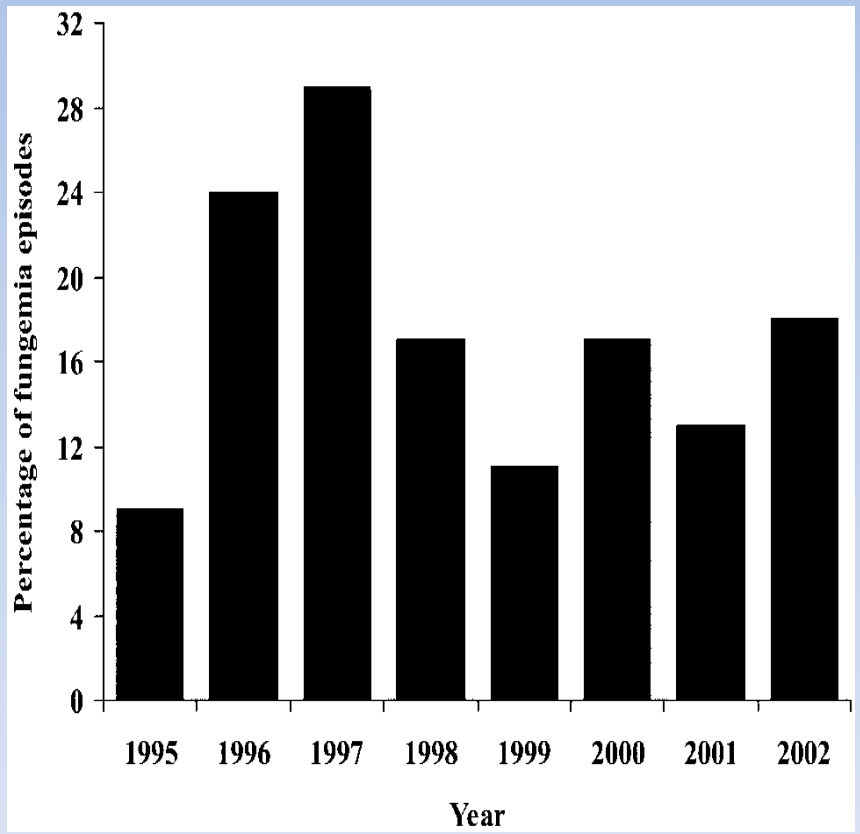
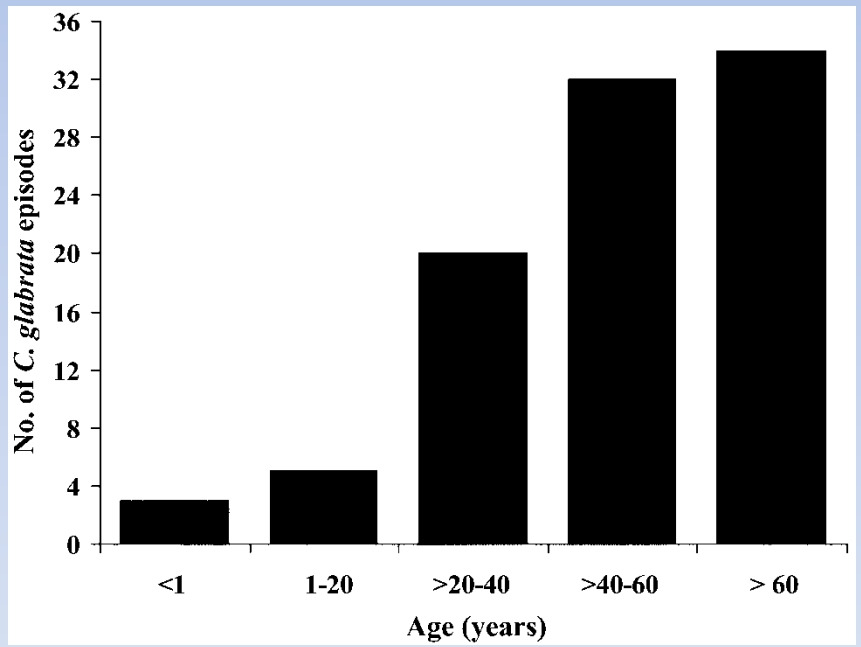


Figure 3: Proportion of non-*Candida albicans* species causing bloodstream infections 1987–1994.

Infection 25 (1997) No.1

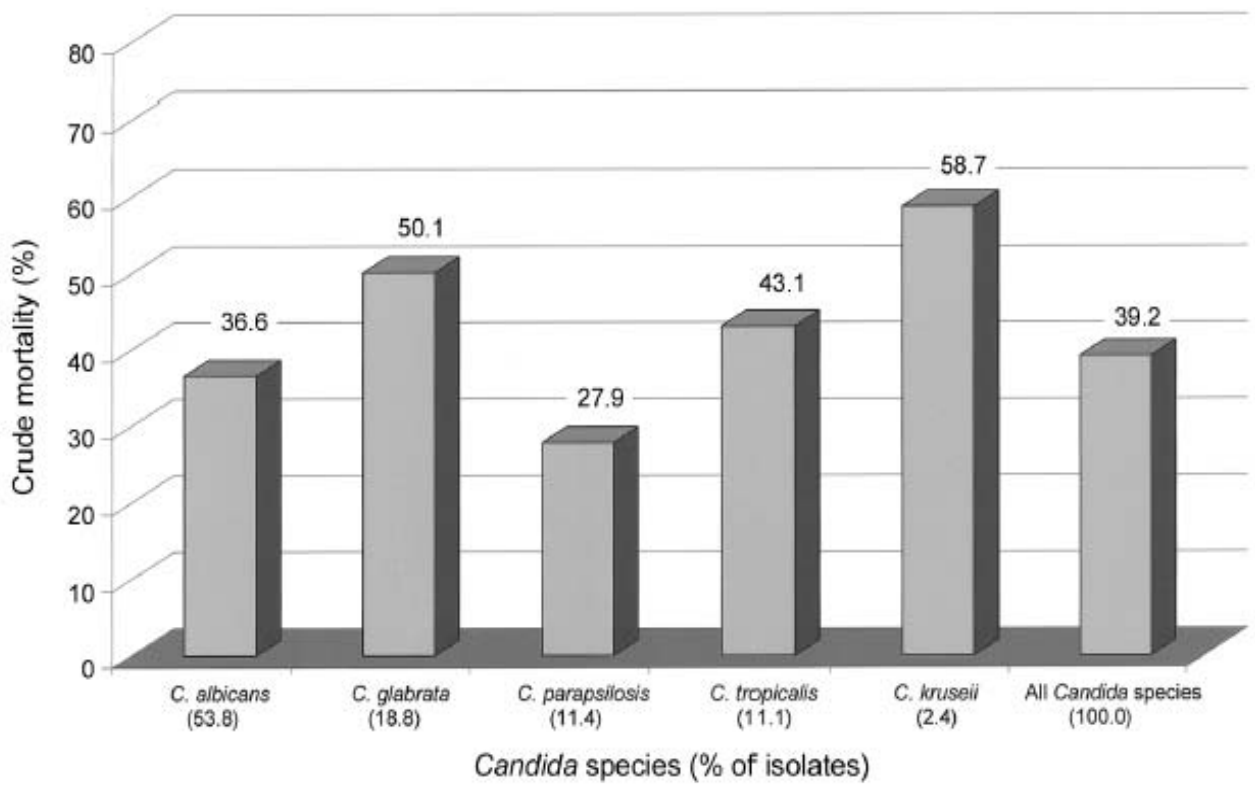
Candida glabrata





Clinical Infectious Diseases 2005; 41 : 975-981

Mortality Differences



3. Distribution of *Candida* species in 1890 cases of *Candida* bloodstream infection and associated crude mortality

Clinical Infectious Disease 2004 : 39 : 309-317

Susceptability Patterns Differences

Table 3. General patterns of susceptibility of *Candida* species.

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Flucytosine	Amphotericin B	Candins
Candida albicans	S	S	S	S	S	S	S
Candida tropicalis	S	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S	S to R[a]
Candida glabrata	S-DD to R	S-DD to R	S-DD to R	S-DD to R	S	S to I	S
Candida krusei	R	S-DD to R	S	S	I to R	S to I	S
Candida lusitaniae	S	S	S	S	S	S to R	S

NOTE. I, intermediately susceptible; R, resistant; S, susceptible; S-DD: susceptible dose-dependent.

[a] Echinocandin resistance among *C. parapsilosis* isolates is uncommon.

From 47th Annual Meeting of Infectious Diseases Society of America

Who are at risk ?

Risk Factors for Candidal Bloodstream Infections in Surgical Intensive Care Unit Patients: The NEMIS Prospective Multicenter Study

Procedure undergone	No. (%) of patients		Infection rate[a]	RR (95% CI)	*P*
	All	Case patients			
Intubation					
No	1021 (24)	2 (5)	0.30	—	
Yes	3255 (76)	40 (95)	1.12	2.7 (0.6–11.2)	.18
Central venous catheter					
No	1330 (31)	1 (2)	0.11	—	
Yes	2946 (69)	41 (98)	1.23	8.1 (1.1–59.6)	.04
Triple-lumen catheter					
No	2050 (48)	3 (7)	0.21	—	
Yes	2226 (52)	39 (93)	1.40	5.1 (1.5–16.8)	.01
Foley catheter					
No	675 (16)	4 (10)	0.71	—	
Yes	3601 (84)	38 (90)	1.04	1.3 (0.5–3.8)	.59
Hemodialysis					
No	4106 (96)	34 (81)	0.86	—	
Yes	170 (4)	8 (19)	2.79	2.6 (1.2–5.6)	.02
Surgery					
Any					
No	1075 (25)	1 (2)	0.11	—	
Yes	3201 (75)	41 (98)	1.22	8.7 (1.2–63.5)	.03

Clinical Infectious Diseases 2001;33:177-86

Who are at risk ?

Treatment or drug received	No. (%) of patients: All	Case patients	Infection rate[a]	RR (95% CI)	*P*
Parenteral nutrition					
No	3376 (79)	12 (29)	0.43	—	
Yes	900 (21)	30 (71)	2.04	3.8 (1.9–7.6)	<.001
Intralipid agents					
No	3514 (82)	20 (48)	0.67	—	
Yes	762 (18)	22 (52)	1.80	2.2 (1.2–4.0)	.02
Vancomycin					
No	2954 (69)	15 (36)	0.67	—	
Yes	1322 (31)	27 (64)	1.35	1.5 (0.8–2.8)	.26
Anti-anaerobic agents					
No	2600 (61)	10 (24)	0.50	—	
Yes	1676 (39)	32 (76)	1.44	2.2 (1.1–4.6)	.03

[a] Cases of candidal bloodstream infection per 1000 days in the surgical intensive care unit.

Clinical Infectious Diseases 2001;33:177-

Who are at risk ?

Antifungal agent administered	No. (%) of patients: All	Case patients	Infection rate[a]	RR (95% CI)	*P*
Any					
No	3222 (75)	26 (62)	1.06	—	
Yes	1054 (25)	16 (38)	0.90	0.6 (0.3–1.1)	.09
Amphotericin B					
No	4107 (96)	40 (95)	1.05	—	
Yes	169 (4)	2 (5)	0.50	0.3 (0.1–1.4)	.14
Azole					
No	3774 (88)	31 (74)	0.98	—	
Yes	502 (12)	11 (26)	1.03	1.0 (0.5–2.1)	.86
Nystatin					
No	3791 (89)	35 (83)	1.01	—	
Yes	485 (11)	7 (17)	0.93	0.7 (0.3–1.7)	.48

Clinical Infectious Diseases 2001;33:177-86

Who are at risk ?

Table 5. Clinical diagnoses assigned to 4276 surgical intensive care unit patients and their risk for candidal bloodstream infection (BSI).

Diagnosis	No. (%) of patients: All	No. (%) of patients: Case patients	Infection rate[a]	RR (95% CI)	*P*
Acute renal failure					
No	3848 (90)	19 (45)	0.54	—	
Yes	428 (10)	23 (55)	3.09	4.7 (2.5–8.8)	<.001
Shock					
No	3458 (81)	17 (40)	0.57	—	
Yes	818 (19)	25 (60)	2.00	2.9 (1.5–5.4)	.001
ARDS					
No	3728 (87)	25 (60)	0.80	—	
Yes	548 (13)	17 (40)	1.55	1.5 (0.8–2.8)	.23
DIC					
No	3675 (86)	23 (55)	0.67	—	
Yes	601 (14)	19 (45)	2.31	3.0 (1.6–5.5)	<.001
Bacterial BSI					
No	3860 (90)	27 (64)	0.85	—	
Yes	416 (10)	15 (36)	1.44	1.2 (0.6–2.3)	.58

Clinical Infectious Diseases 2001;33:177-86

Who are at risk ?

Table 6. Fungal colonization among the 4276 surgical intensive care unit patients and their risk of candidal bloodstream infection.

Isolate and site of colonization	No. (%) of patients: All	No. (%) of patients: Case patients	Infection rate[a]	RR (95% CI)	*P*
Candida species					
In urine					
No	3649 (85)	25 (60)	0.79	—	
Yes	627 (15)	17 (40)	1.62	1.6 (0.9–3.1)	.13
In stool					
No	2996 (70)	16 (38)	0.70	—	
Yes	1280 (30)	26 (62)	1.34	1.4 (0.7–2.7)	.29
In both urine and stool					
No	3823 (89)	30 (71)	0.90	—	
Yes	453 (11)	12 (29)	1.35	1.1 (0.6–2.1)	.78
Candida albicans					
In stool					
No	2029 (71)	22 (58)	1.09	—	
Yes	820 (19)	16 (42)	1.25	1.0 (0.5–1.9)	.98
In urine					
No	3908 (91)	32 (76)	0.89	—	
Yes	368 (9)	10 (24)	1.59	1.4 (0.7–3.0)	.32

Clinical Infectious Diseases 2001;33:177-

Who are at risk ?

Table 7. Multivariate analyses of risk factors for candidal bloodstream infections in surgical intensive care unit (SICU) patients with and without prior surgery.

Model, risk factor	RR[a] (95% CI)	*P*
Model 1[b]		
Antifungal medication	0.3 (0.1–0.6)	<.001
Acute renal failure	4.2 (2.1–8.3)	<.001
Parenteral nutrition	3.6 (1.8–7.5)	<.001
Any surgery	7.3 (1.0–53.8)	.05
Model 2[c]		
Antifungal medication	0.2 (0.1–0.5)	<.001
Acute renal failure	3.8 (1.9–7.4)	<.001
Parenteral nutrition	2.8 (1.3–5.8)	.01
Neurological surgery	0.2 (0.04–0.7)	.02
Ear/nose/throat surgery	0.3 (0.1–0.9)	.02
Triple-lumen catheter	5.4 (1.2–23.6)	.03

Clinical Infectious Diseases 2001;33:177-86

Risk Factors $\neq$ Mortality

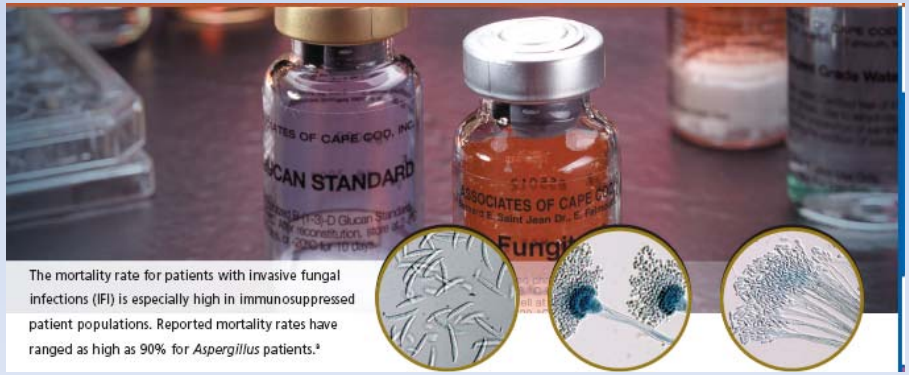
Table 2: Underlying diseases and co-morbidity by survival group.

	Survivors (n = 17)	Non-survivors (n = 23)	Odds ratio (95% CI)
Abdominal surgery	1	11	3.2 (1.0–10.5)
Acute hemodialysis	1	11	1.8 (1.2–2.7)
Antibacterial use	17	23	
• > 7 days	12	18	1.3 (0.5–3.9)
• > 2 classes	7	11	1.1 (0.7–2.0)
ARDS	0	21	10.8 (2.9–40.9)
COPD	0	1	1.0 (0.9–1.1)
CVC	15	23	0.9 (0.7–1.0)
Diabetes mellitus	0	1	1.0 (0.9–1.1)
Malignancy	5	6	1.0 (0.6–1.4)
MODS	2	21	10.1 (2.7–38.6)
Pneumonia	2	4	1.0 (0.8–1.4)
Splenectomy	3	2	0.9 (0.7–1.2)
Steroid use	4	8	1.2 (0.8–1.7)
TPN	14	20	1.4 (0.3–5.9)

ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease: CVC = central venous catheter; MODS = multi-organ dysfunction syndrome; TPN = total parenteral nutrition; 95% CI = confidence interval.

Infection 25 (1997) No.1

Diagnosis
The Problems & Ways



The mortality rate for patients with invasive fungal infections (IFI) is especially high in immunosuppressed patient populations. Reported mortality rates have ranged as high as 90% for *Aspergillus* patients.[a]

The need of Early Diagnosis

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

Article

Treatment of Invasive Aspergillosis: Relation of Early Diagnosis and Treatment to Response

JOSEPH AISNER, M.D.; STEPHEN C. SCHIMPFF,

1 May 1977 | Volume 86 Issue 5 | Pages 539-543

17 Cases
Rx within 96 hr : 3 complete resolution, 3 partial response
Rx delayed / not given : 11 died !

Abstract

Aspergillus infections in patients with cancer are difficult to diagnose, and such diagnoses are frequently made at necropsy. Earlier therapy has been proposed to provide better response. We reviewed 17 consecutive patients with documented aspergillosis to determine the impact of earlier diagnosis and prompt treatment with amphotericin B. Sixteen had hematologic malignancies, and all had marked granulocytopenia. Six were diagnosed and treated within 96 h of the appearance of infiltrates. Three of these six had complete resolution of all signs and symptoms of aspergillus infection. The other three had a partial response to therapy despite continued granulocytopenia. All 11 patients in whom antifungal therapy was either delayed (six) or not given (five) for at least 2 weeks after the infiltrate was present died with progressive aspergillosis. Aggressive diagnostic methods to establish the diagnosis of aspergillosis are warranted so that antifungal therapy can be started early, which may then be successful in resolving these potentially fatal infections.

The need of early diagnosis

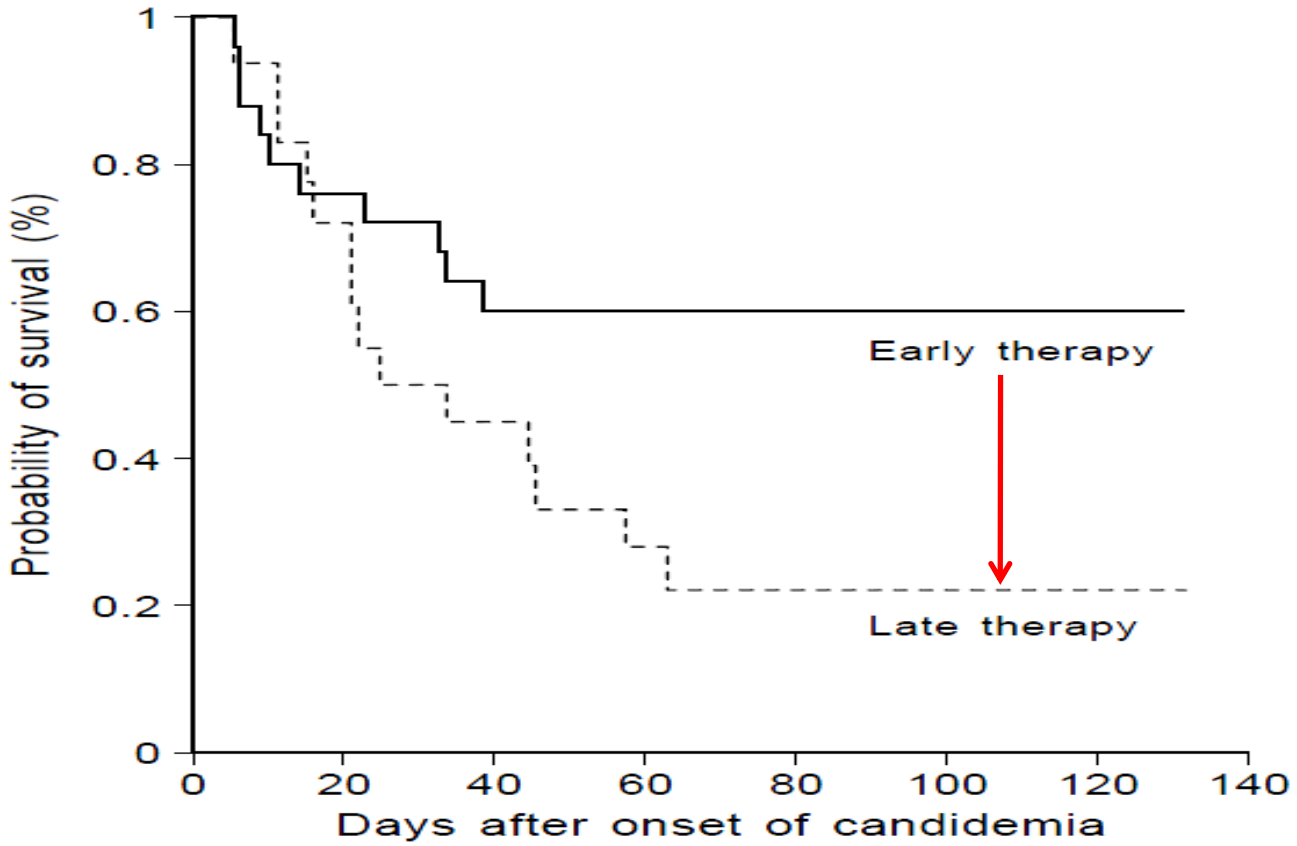


Fig. 2 Kaplan-Meier estimated probability of survival after first blood culture positive for *Candida* according to the time that elapsed between the episode of candidemia and the start of antifungal therapy ("early": ≤ 2 days vs "late": > 2 days)

Intensive Care Med (1997) : 23:23-30

The need of early diagnosis

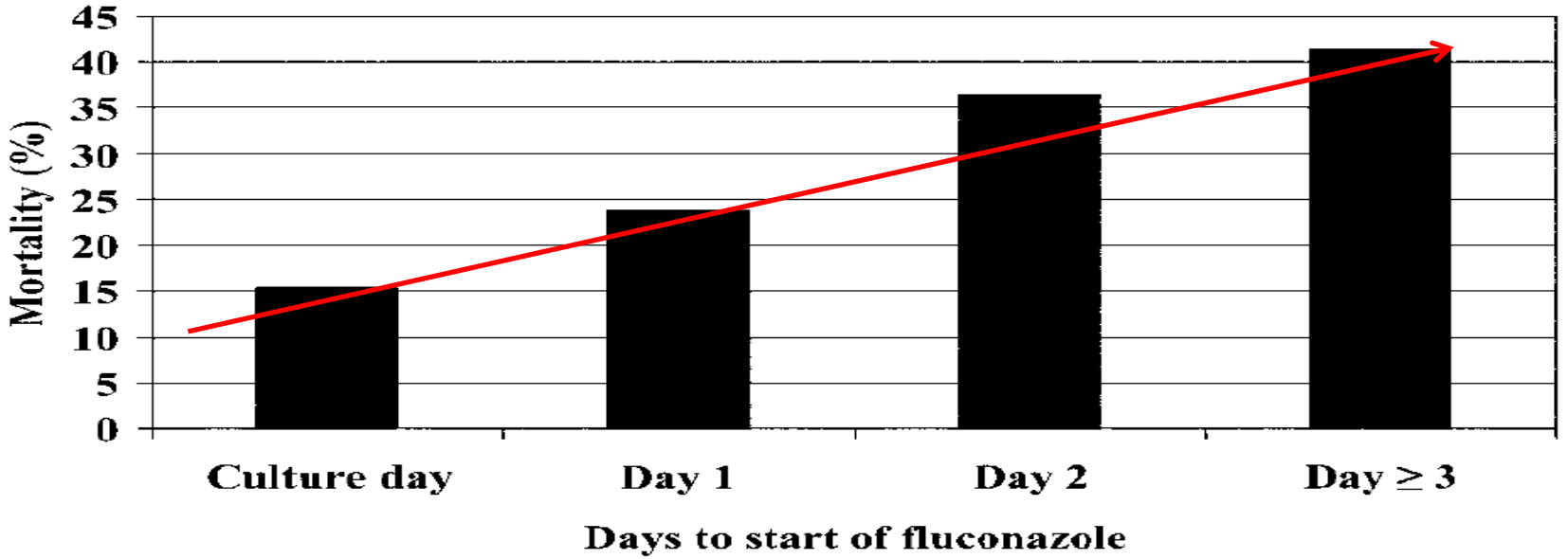
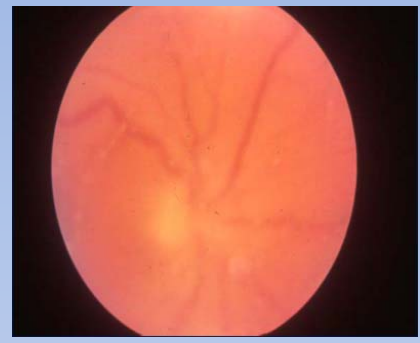


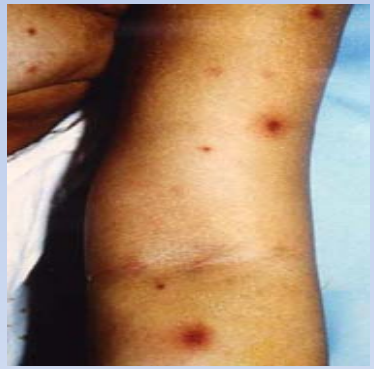
Figure 2. Relationship between hospital mortality and the number of days to initiation of fluconazole therapy. We calculated the days to the start of fluconazole therapy by subtracting the start date of fluconazole therapy from the culture date of the first blood sample positive for yeast ($P = .0009$ for trend, using the Mantel-Haenszel χ^2 test).

Clinical Infectious Diseases 2006 : 43, 25-31

Diagnosis



- Clinical
  - Variable clinical course
  - Look for Candida endophthalmitis/chorioretinitis
    - Rare 9-15% of candemic patients
  - Others : skins lesions, arthritis
    - Even rarer



- Blood Culture
  - Sensitivity <50%, becomes positive only late in diseases
  - Mean time to +ve culture is 48 to 72 hours

Diagnosis

- Radiological
  - Non specific and occur late and thus limited usefulness for early diagnosis
- Pathological
  - Not always feasible in critically ill patients

Diagnosis

- Serological tests
  - Detection of components of fungal cell walls
    - Galactomannan
    - Beta-(1,3)-D-glucan level

J

Diagnosis

Diagnosis of Invasive Aspergillosis Using a Galactomannan Assay: A Meta-Analysis

Christopher D. Pfeiffer,[1] Jason P. Fine,[2] and Nasia Safdar[1]

Departments of [1]Medicine and [2]Biostatistics, University of Wisconsin Medical School, Madison, Wisconsin

27 studies from 1996 to 2005

Sensitivity 0.71

Specificity 0.89

Clinical Infectious Disease 2006 : 42

Diagnosis

- Measurement of beta-(1,3)-D-glucan level
  - Sensitvity 69%-97%, Specificity 87-100%
  - Positive Predictive Value : 59-96%
  - Negative Predictive Value : 75%-97%
  - Application in ICU setting ?

Serum glucan levels did not show a correlation with presence of fungal infections, not specific, may be useful as –ve predictor of infection

Serum Glucan Levels Are Not Specific for Presence of Fungal Infections in Intensive Care Unit Patients

Justin Digby, John Kalbfleisch, Andy Glenn, Angie Larsen, William Browder, and David Williams*

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Received 24 February 2003/Returned for modification 31 March 2003/Accepted 7 July 2003

Fungal infections in the critically ill patient are difficult to diagnose and are associated with a high mortality rate. A major obstacle to managing fungal infection is the lack of a reliable clinical assay that will rapidly identify patients with fungal sepsis. Glucans are polymers of glucose that are found in the cell wall of fungi and certain bacteria. Glucans are also released from the fungal cell wall into the extracellular milieu. Several studies have reported that detection of fungal glucan in serum or plasma is useful in the diagnosis of mycoses. However, recent studies have questioned the clinical utility of this assay. In this study, we examined serum glucan levels in intensive care unit (ICU) patients and attempt to correlate serum glucan levels with the presence of fungal infection. Following attainment of informed consent, serum was harvested from 46 ICU patients with confirmed fungal infections, confirmed bacterial infections, or no evidence of infection. Sera from eight healthy volunteers served as control. Serum glucan was assayed with a glucan-specific *Limulus* assay. Serum glucan levels were increased (69.6 ± 17 pg/ml; $P < 0.001$) in ICU patients versus the normal (11.5 ± 1.3 pg/ml) and noninfected ICU (27.4 ± 17 pg/ml) controls. However, serum glucan levels were not different in patients with confirmed fungal infections versus those with confirmed bacterial infections. Thus, serum glucan levels did not show a correlation with the presence of fungal infections and do not appear to be specific for fungal infections. However, the assay may be useful as a negative predictor of infection.

Clinical & Diagnostc Lab Immunology Seot

Diagnosis

- Molecular Diagnostic Testing
  - Detection of Candida DNA in either blood or tissue
  - Few data on their performance in high risk critically ill patients however

Difficulties

- Clinical manifestations are non specific
- Diagnostic tests are insensitive, positive late in infection
- Invasive procedures are not always possible to perform, esp in critically ill patients

Treatment

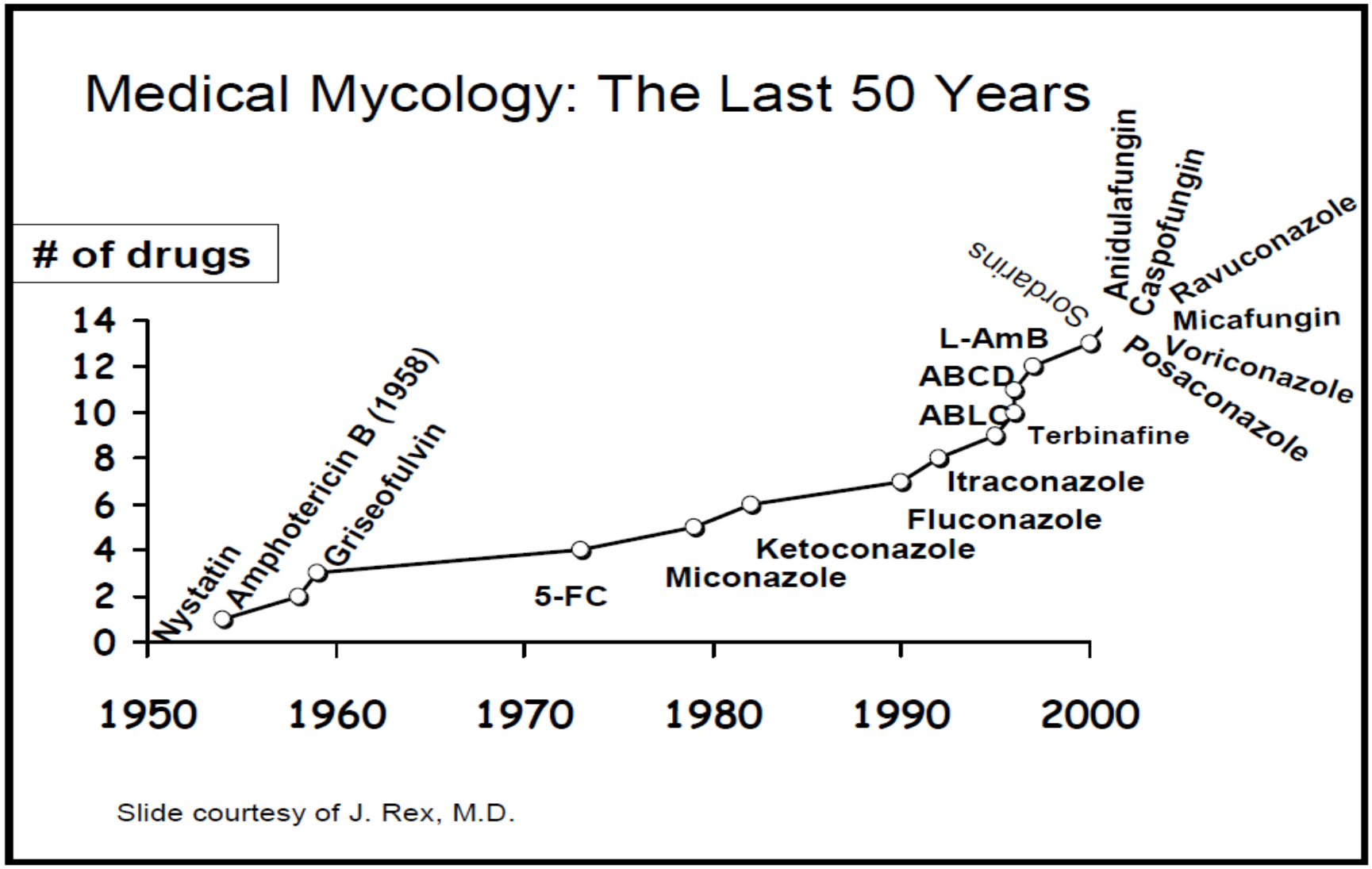
Defining Success

Table 2. Responses to antifungal therapy in patients with candidemia and other forms of invasive candidiasis.

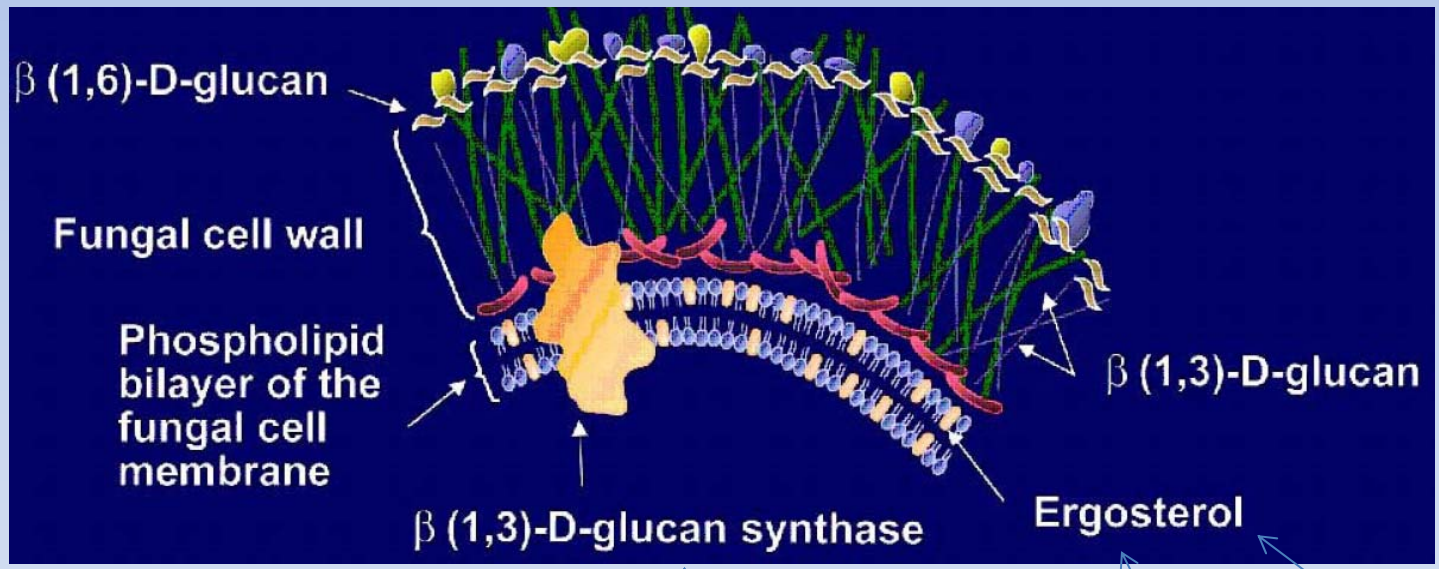
Outcome, response	Criteria
Success	
Complete response	Survival and resolution of all attributable symptoms and signs of disease; plus
	Documented clearance of pathogen from the blood in cases of candidemia; plus
	Documented clearance of infected sites that are accessible to repeated sampling (e.g., CSF)
	If additional cultures are not feasible (e.g., in cases of candidiasis involving visceral organs), survival and resolution of all attributable symptoms and signs of disease and radiological resolution can be equated with a complete response
Partial response	Survival and improvement of attributable symptoms and signs of disease[a]; plus
	Documented clearance of blood in cases of candidemia; plus
	Documented clearance of infected sites that are accessible to repeated sampling (e.g., CSF).
	If additional cultures are not feasible, survival and resolution of attributable symptoms and signs of disease and radiological improvement or stabilization can be equated with a partial response[b]
Failure	
Stable response	Survival and minor or no improvement in attributable symptoms and signs of disease; plus
	Persistent isolation of *Candida* species from blood specimens or specimens from other sterile sites; or
	If additional cultures are not feasible, radiological stabilization can be equated with a stable response[b]
Progression of disease	Persistent isolation of *Candida* species from blood specimens or specimens from other sterile sites in association with worsening clinical symptoms or signs of disease (e.g., septic shock, progression of hematogenous cutaneous candidiasis); or
	New sites of disease or worsening of preexisting lesions radiologically (e.g., those observed in chronic disseminated candidiasis) in association with clinical deterioration
Death	Death during the prespecified period of evaluation regardless of attribution

Clinical Infectious Diseases 2008; 47:674–83

The Weapons


Medical Mycology: The Last 50 Years
# of drugs
14
12
10
8
6
4
2
0
1950
1960
1970
1980
1990
2000
Nystatin
Amphotericin B (1958)
Griseofulvin
5-FC
Miconazole
Ketoconazole
Fluconazole
Itraconazole
Terbinafine
ABLC
ABCD
L-AmB
Sordarins
Anidulafungin
Caspofungin
Ravuconazole
Micafungin
Voriconazole
Posaconazole
Slide courtesy of J. Rex, M.D.

The Weapons

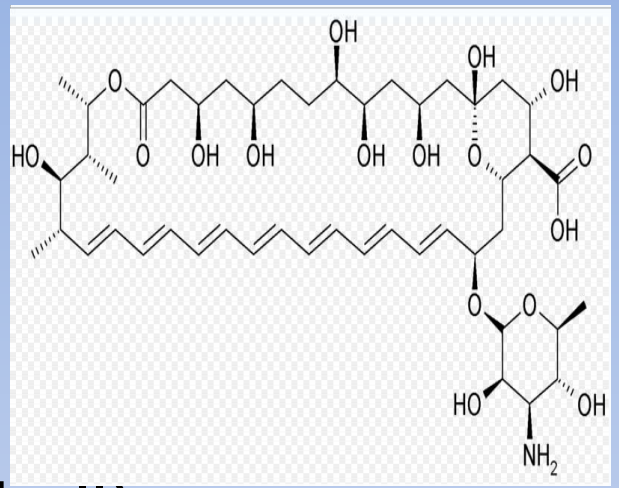


Azoles

Echinocandins

Amphotericin B

Amphotericin B



- Very board spectrum
  - Nearly all Candida species (not all)
  - Effective vs invasive moulds
- Side effects especially nephrotoxicity

Authors	Rate of nephrotoxicity
1998 White	64%
1999 Walsh	49%
1999 Wingard	53%

Lipid Formulation Ampho B

- Lipid Formulations
  - ABELCET : lipid complex
  - AMPHOTEC : colloidal dispersion
  - AMBISOME : liposomal amphotericin

- Overall, rate of successful response with standard doses of lipid based AMB preparations and conventional AMB indistinguishable

NEJM 1999 : 340 : 764

Less Side Effects & Better Tolerated

Table 1.

Frequency (%) of Reactions Related to Infusion of Amphotericin B Formulations[a]

Adverse Effect	Amphotericin B Lipid Complex[27]	Comparison Study[28]		Comparison Study[29]	
		Amphotericin B Colloidal Dispersion	Conventional Amphotericin B	Liposomal Amphotericin B	Conventional Amphotericin B
Chills	18	77	53	20	56
Fever	14	55	47	18	43
Nausea	9	7	7	13	10
Vomiting	8	11	8	6	7
Dyspnea	7	9	4	4.7	7.3
Hypertension	5	7	6	2.3	11.3
Hypotension	8	12	6	3.5	8.1
Tachycardia	NA	9	5	2.3	12.5
Hypokalemia	5	26	29	42.9	50.6
Hypomagnesemia	NA	6	11	20.4	25.6

[a]NA = not available.

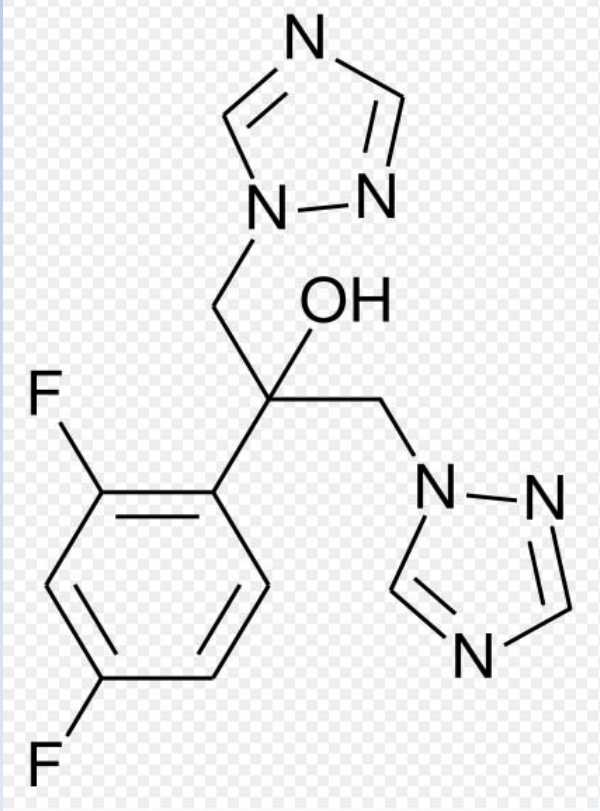
Am J Health Syst Pharm Vol 59 Jan 1, 2002

Azoles

- Fluconazole, itraconazole, voriconazole, posaconazole
- Fluconazole : advantages
  - Safe, excellent penetration
  - Effective and board spectrum
  - *C. albicans* resistance continues to be rare
  - Inexpensive
  - Can switch to oral with excellent absorption

Fluconazole : what is not covered

- *C. krusei*
- +/- *C. glabrata*
- *Aspergillus* and other moulds



Voriconazole

- Oral (well absorbed) and IV formulations
- Spectrum of activity:
  - *Candida spp, Aspergillus, Fusarium, Pseudoallescheria / Scedosporium, C. neoformans*
  - Not active vs Zygomycosis, Sporothrix
- Therapy of choice: *Aspergillus*
- Increasingly used as prophylaxis and empiric therapy in neutropenia and bone marrow / stem cell transplant
  - Are we selecting for Zygomycosis infections?
    - Marty et al. ICAAC 2003; Abstract M985
- Adverse drug effects:
  - Hepatotoxicity – follow LFTs
  - Viual disturbances
  - Avoid IV in patients with CrCl < 50 ml/min

Any Problems With Voriconazole

- >expensive than fluconazole
- ½ life 6 hr – dose b.i.d.
- IV not in presence of renal failure
- Does not get into urine
- > side-effects than fluconazole e.g. visual / photopsia
- >drug interactions e.g. rifampin

Echinocandins

- Caspofungin, Anidulafungin, Micafungain
  - Only available in parental form
  - Once daily administration
  - No need dose adjustment for renal insufficiency
  - Effective for invasive candidiasis

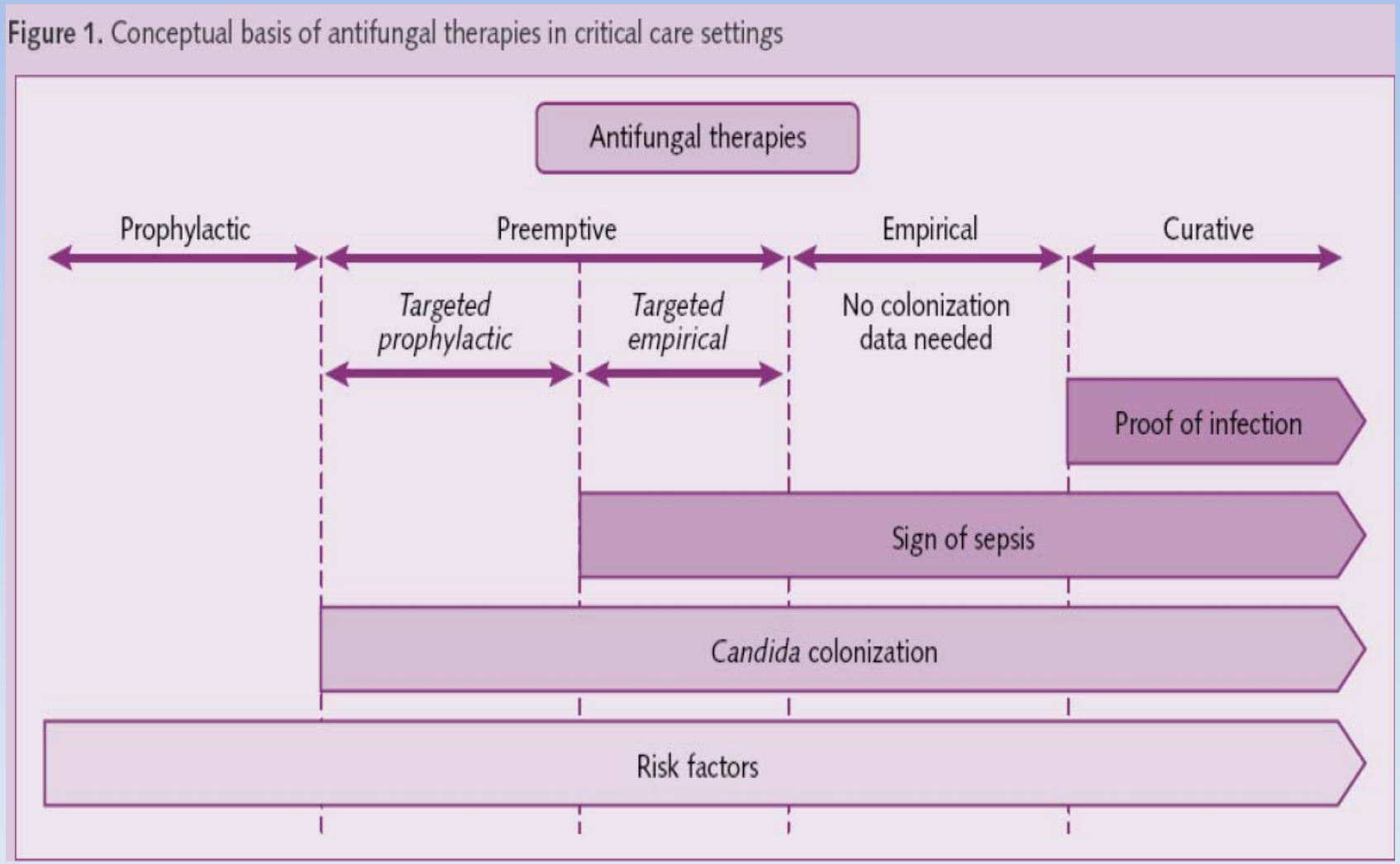
Considerations during Pregnancy

- Amphotericin B
- Azoles to be avoided because of possible birth defects
- Echinocandins : few data

Selection of Drugs

- Clinical trials
  - Not available for all bugs / infections
  - Several agents may be deemed “equivalent”
- Spectrum of activity vs suspected or known pathogens
- Penetration of specific body sites?
- Drug side effects
- Drug interactions
- Other patient factors (renal or hepatic dysfunction, concomitant medications)

When to Treat ?



Antifungal Prophylaxis

- No evidence of fungal infection or colonization but considered at high risk of fungal infection

Antifungal Prophylaxis

- Identifying High Risk Patients
  - Procedures :
    - Central Venous Catheter
    - Surgery
  - Treatments & Medications
    - Parenteral Infections
    - Intralipid agents
    - Anti-anaerobic agents
  - Clinical Diagnosis
    - Acute Renal Failure
    - Shock
    - DIC

Antifungal Prophylaxis

Infection: ↓ by 1/2
Mortality: ↓ by 1/4

Antifungal agents for preventing fungal infections in non-neutropenic critically ill and surgical patients: systematic review and meta-analysis of randomized clinical trials

E. Geoffrey Playford[1,2]*, Angela C. Webster[3,4], Tania C. Sorrell[2,5] and Jonathan C. Craig[3,4]

Objectives: This study aims to systematically identify and summarize the effects of antifungal prophylaxis in non-neutropenic critically ill adult patients on all-cause mortality and the incidence of invasive fungal infections.

Conclusions: Prophylaxis with fluconazole or ketoconazole in critically ill patients reduces invasive fungal infections by one-half and total mortality by one-quarter. Although no significant increase in azole-resistant *Candida* species associated with prophylaxis was demonstrated, trials were not powered to exclude such an effect. In patients at increased risk of invasive fungal infections, antifungal prophylaxis with fluconazole should be considered.

Journal of Antimicrobial Chemotherapy Dec 2005

Limitations of prophylaxis

- Unnecessary toxicity
- Selection of resistant organisms
- Drugs interactions
- Is correct group being targeted ?

Current Guildlines : 2009 IDSA

- Fluconazole 400mg (6mg/kg) daily is recommended for *high risk patients* in adult units that have *a high incidence* of invasive candidiasis

Empiric Treatment

For

- Delay in treatment associated with higher mortality
- Blood cultures not very sensitive
- Symptoms and signs are non specific

Against

- Increased antifungal resistance
- Toxicity, costs, no good end point

Empiric Treatment in ICU Candidiasis

- Proper Patient
- Colonization
  - CVC
  - GI tract

Empirical Treatment

Mortality: ⬇ at an acceptable cost

Empirical Anti-*Candida* Therapy among Selected Patients in the Intensive Care Unit: A Cost-Effectiveness Analysis

Yoav Golan, MD; Michael P. Wolf, MD; Stephen G. Pauker, MD; John B. Wong, MD; and Susan Hadley, MD

Background: Mortality from invasive candidiasis is high. Low culture sensitivity and treatment delay contribute to increased mortality, but nonselective early therapy may result in excess costs and drug resistance.

Objective: To determine the cost-effectiveness of anti-*Candida* strategies for high-risk patients in the intensive care unit (ICU).

Design: Cost-effectiveness decision model.

Data Sources: Published data to 10 May 2005, identified from MEDLINE and Cochrane Library searches, ICU databases, expert estimates, and actual hospital costs.

Target Population: Patients in the ICU with suspected infection who have not responded to antibacterial therapy.

Time Horizon: Lifetime.

Perspective: Societal.

Interventions: Fluconazole, caspofungin, amphotericin B, or lipid formulation of amphotericin B given as either empirical or culture-based therapy and no anti-*Candida* therapy.

Outcome Measures: Incremental life expectancy and incremental cost per discounted life-year (DLY) saved.

Results of Base-Case Analysis: Ten percent of the target population will have invasive candidiasis. Empirical caspofungin therapy is the most effective strategy but is expensive ($295 115 per DLY saved). Empirical fluconazole therapy is the most reasonable strategy ($12 593 per DLY saved) and decreases mortality from 44.0% to 30.4% in patients with invasive candidiasis and from 22.4% to 21.0% in the overall target cohort.

Results of Sensitivity Analysis: Empirical fluconazole therapy is reasonable for likelihoods of invasive candidiasis greater than 2.5% or fluconazole resistance less than 24.0%. For higher resistance levels, empirical caspofungin therapy is preferred. For low prevalences of invasive candidiasis, culture-based fluconazole is reasonable. For prevalences exceeding 60%, empirical caspofungin therapy is reasonable. For caspofungin to be reasonable at a prevalence of 10%, its cost must be reduced by 58%.

Limitations: Less severe illness and limited use of broad-spectrum antimicrobial agents, typical of smaller hospitals, could result in a lower risk for invasive candidiasis.

Conclusions: In patients in the ICU with suspected infection who have not responded to antibiotic treatment, empirical fluconazole should reduce mortality at an acceptable cost. The use of empirical strategies in low-risk patients is not justified.

Ann Intern Med. 2005;143:857-869.
For author affiliations, see end of text.
www.annals.org

Current Guildlines : IDSA 2009

- Fluconazole (loading dose of 800mg [12mg/kg], then 400mg [6mg/kg] daily)
- caspofungin (loading dose of 70mg, then 50mg daily), anidulafungin (loading dose of 200mg, then 100mg daily), or
- micafungin (100mg daily)

Initial therapy

- An *echinocandin is preferred* for patients who have had *recent azole exposure*, whose *illness is moderately severe or severe*, or who are at *high risk of infection due to C. glabrata or C. krusei*.

Current Guildlines : IDSA 2009

- *AmB-d (0.5-1.0mg/kg daily) or LFAmB (3-5mg/kg daily) are alternatives* if there is intolerance to other antifungals or limited availability of other antifungals.

- Empirical antifungal therapy should be considered for critically *ill* patients *with risk factors* for invasive candidiasis and *no other known cause of fever*, and it should be based on clinical assessment of risk factors, serologic markers for invasive candidiasis, and/or culture data from nonsterile sites.

Current Guildlines : IDSA 2009 Candidemia in Non Neutropenic Patients

- Fluconazole (loading dose of 800mg [12mg/kg], then 400mg [6mg/kg] daily) or an echinocandin (caspofungin: loading dose of 70mg, then 50 mg daily; micafungin: 100mg daily; anidulafungin: loading dose of 200mg, then 100mg daily) is recommended as initial therapy for most adult patients.
- The Expert Panel favors an *echinocandin* for patients with *moderately severe to severe illness* or for patients who have had *recent azole exposure*.
- Fluconazole is recommended for patients who are less critically ill and who have had no recent azole exposure.

Current Guildlines : IDSA 2009 Candidemia in Non Neutropenic Patients

- Transition from an echinocandin to fluconazole is recommended for patients who have *isolates that are likely to be susceptible to fluconazole* (e.g., *Candida albicans*) and who *are clinically stable*.

- ***For infection due to Candida glabrata, an echinocandin is preferred***. Transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility. For patients who have initially received fluconazole or voriconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of an azole to completion of therapy is reasonable.

Current Guildlines : IDSA 2009 Candidemia in Non Neutropenic Patients

- For infection due to *Candida parapsilosis*, treatment with *fluconazole* is recommended. For patients who have initially received an echinocandin, are clinically improved, and whose follow-up culture results are negative, continuing use of an echinocandin is reasonable.

- *Amphotericin B* deoxycholate (AmB-d) administered at a dosage of 0.5-1.0mg/kg daily or a lipid formulation of AmB (LFAmB) administered at a dosage of 3-5 mg/kg daily are ***alternatives*** if there is intolerance to or limited availabiligy of other antifungals . Transition from AmB-d or LFAmB to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole and who are clinically stable.

Current Guildlines : IDSA 2009 Candidemia in Non Neutropenic Patients

- Voriconazole administered at a dosage of 400 mg (6mg/kg) twice daily for 2 doses and then 200 mg (3mg/kg) twice daily thereafter is effective for candidemia , but it *offers little advantage over fluconazole* and is recommended as stepdown oral therapy for selected cases of candidiasis due to *Candida krusei* or voriconazole-susceptible *C. glabrata*.
- The recommended duration of therapy for candidemia *without* obvious metastatic complications is for **2 weeks *after*** documented clearance of *Candida* from the bloodstream and resolution of symptoms attributable to candidemia.
- Intravenous catheter removal is strongly recommended for nonneutropenic patients with candidemia.

Prevention

- Reducing frequency and duration of antibiotics administration in ICU

- Compliance with basic control practices such as wash hands frequently and effectively
  - *Candida spp* could be transmitted via hands of healthcare workers

Conclusions and Thanks

- Candida infection is not uncommon in ICU
- Changing epidemiology
- Limitations of existing diagnostic modalities
- Treatment dilemma
- Clinical Suspicious and Clinical Judegement