

# **Approach to Candida Bloodstream Infections**

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# Issues

- Diseases
- Current epidemiology of infection
  - Incidence
  - Species distribution
- Diagnosis
- New Therapies

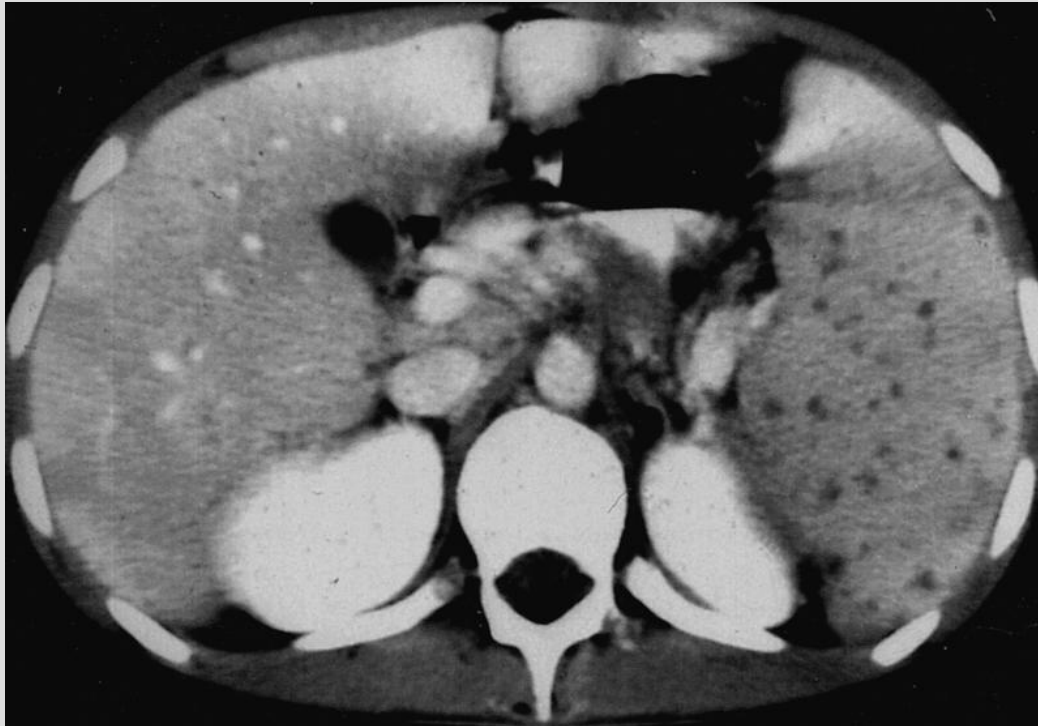
# Diseases

- Candidemia
- Deep-tissue infection
  - Acute invasive candidiasis
    - Abscess formation in the presence of hematogenous spread
    - Multiple organs involved
      - ◆ Endocarditis
      - ◆ Abscesses
      - ◆ Chorioretinitis
      - ◆ 30-40% attributable mortality



# Diseases

- Hepatosplenic candidiasis (chronic)
  - Different pathogenesis
    - ◆ Acquisition through portal vasculature
    - ◆ Little involvement from live organism; pathology from chronic inflammatory response

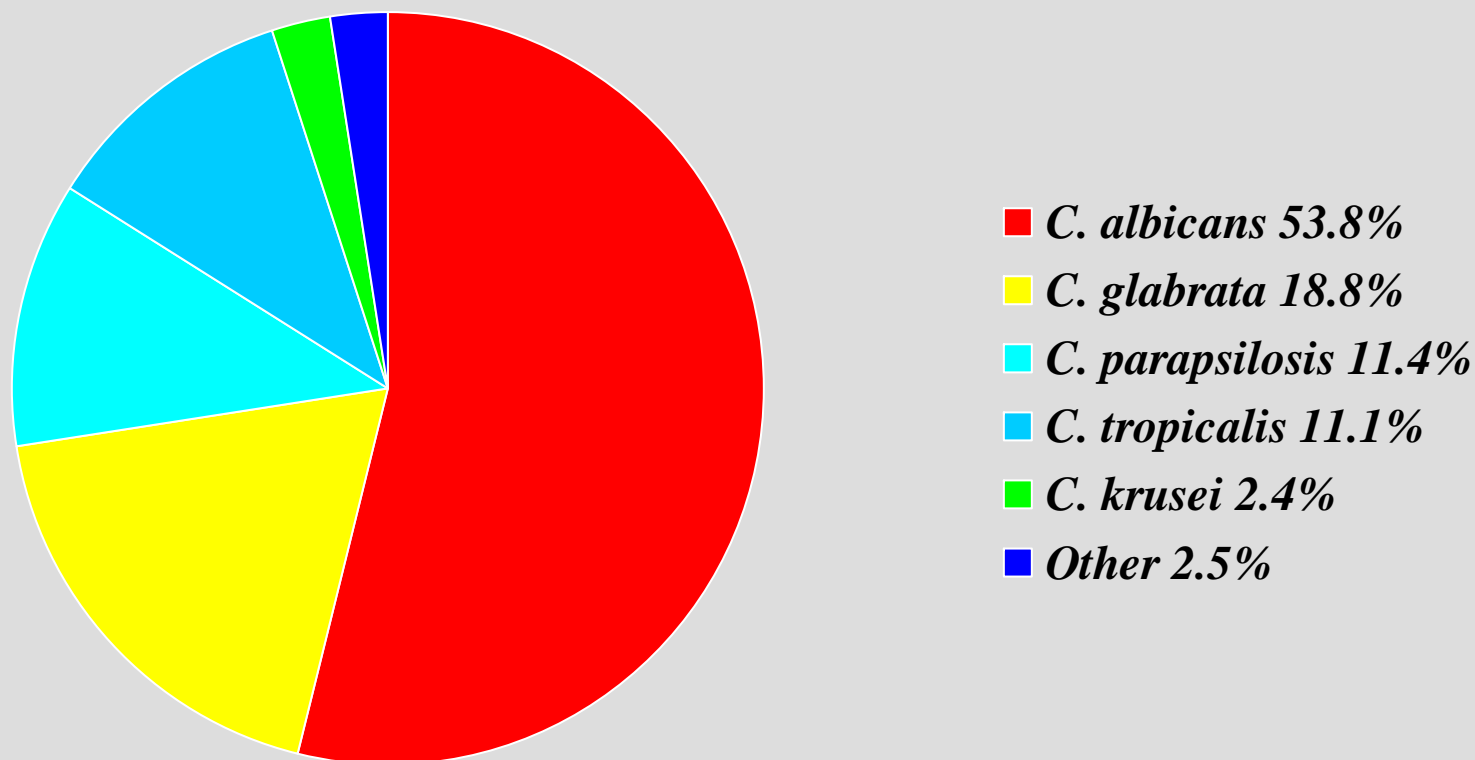


# Nosocomial Bloodstream Infections in US Hospitals: 1995-2002

Rank	Pathogen	BSI per 10,000 admissions	% BSI			% Crude Mortality		
			Total (n=20,978)	ICU (n=10,515)	Non-ICU (n=10,515)	Total	ICU	Non-ICU
1.	CoNS	15.8	31.3	35.9	26.6	20.7	25.7	13.8
2.	<i>S. aureus</i>	10.3	20.2	16.8	23.7	25.4	34.4	18.9
3.	<i>Enterococcus</i> spp.	4.8	9.4	9.8	9.0	33.9	43.0	24.0
4.	<i>Candida</i> spp.	4.6	9.0	10.1	7.9	39.2	47.1	29.0
5.	<i>E. coli</i>	2.8	5.6	3.7	7.6	22.4	33.9	16.9
6.	<i>Klebsiella</i> spp.	2.4	4.8	4.0	5.5	27.6	37.4	20.3
7.	<i>P. aeruginosa</i>	2.1	4.3	4.7	3.8	38.7	47.9	27.6
8.	<i>Enterobacter</i> spp.	1.9	3.9	4.7	3.1	26.7	32.5	18.0
9.	<i>Serratia</i> spp.	0.9	1.7	2.1	1.3	27.4	33.9	17.1
10.	<i>A. baumannii</i>	0.6	1.3	1.6	0.9	34.0	43.4	16.3

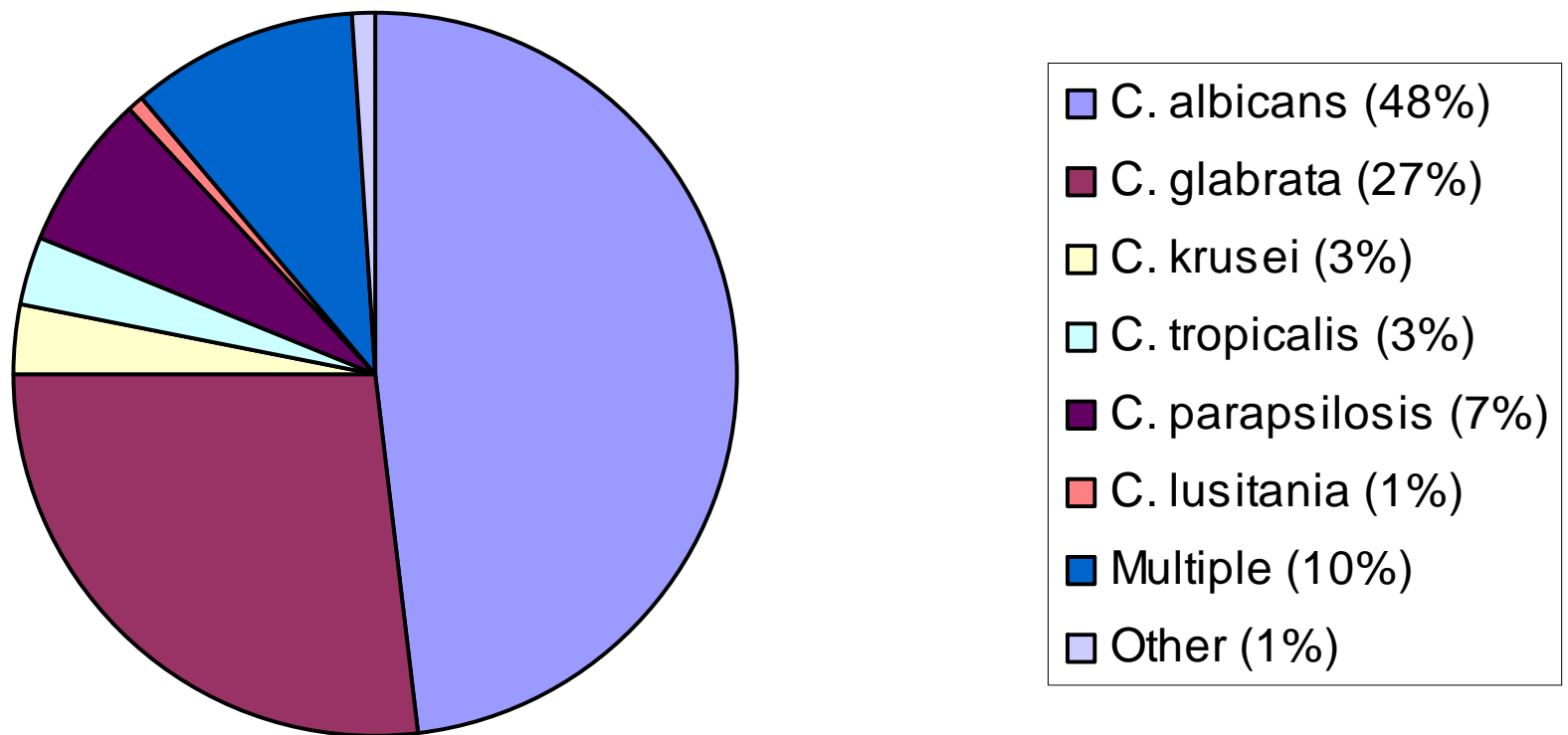
Wisplinghoff H, et al. *Clin Infect Dis.* 2004;39:309-317.

# Distribution of *Candida* species

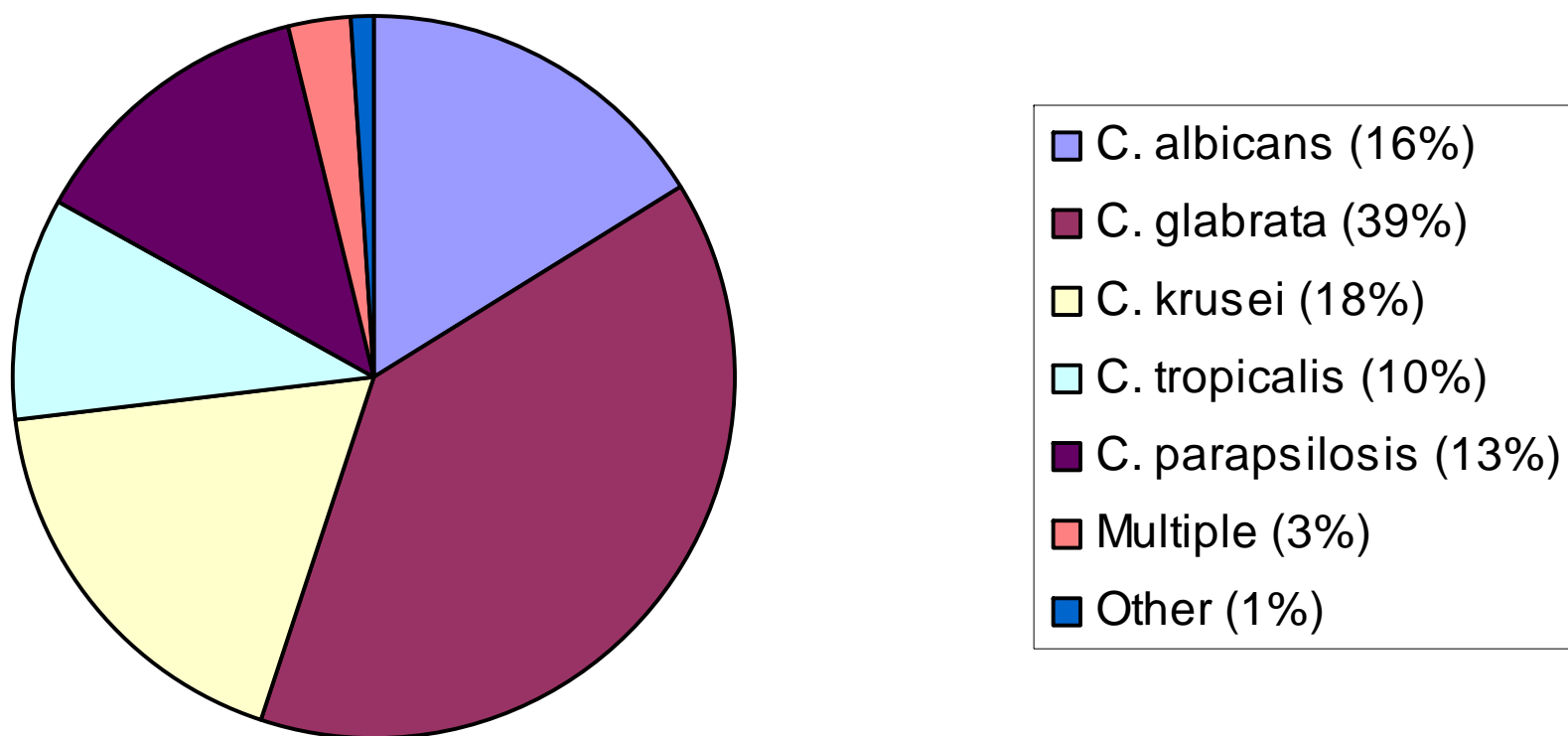


**N= 1890; 1995-2002**

# Invasive *Candida* spp. in OTRs: Data From TRANSNET

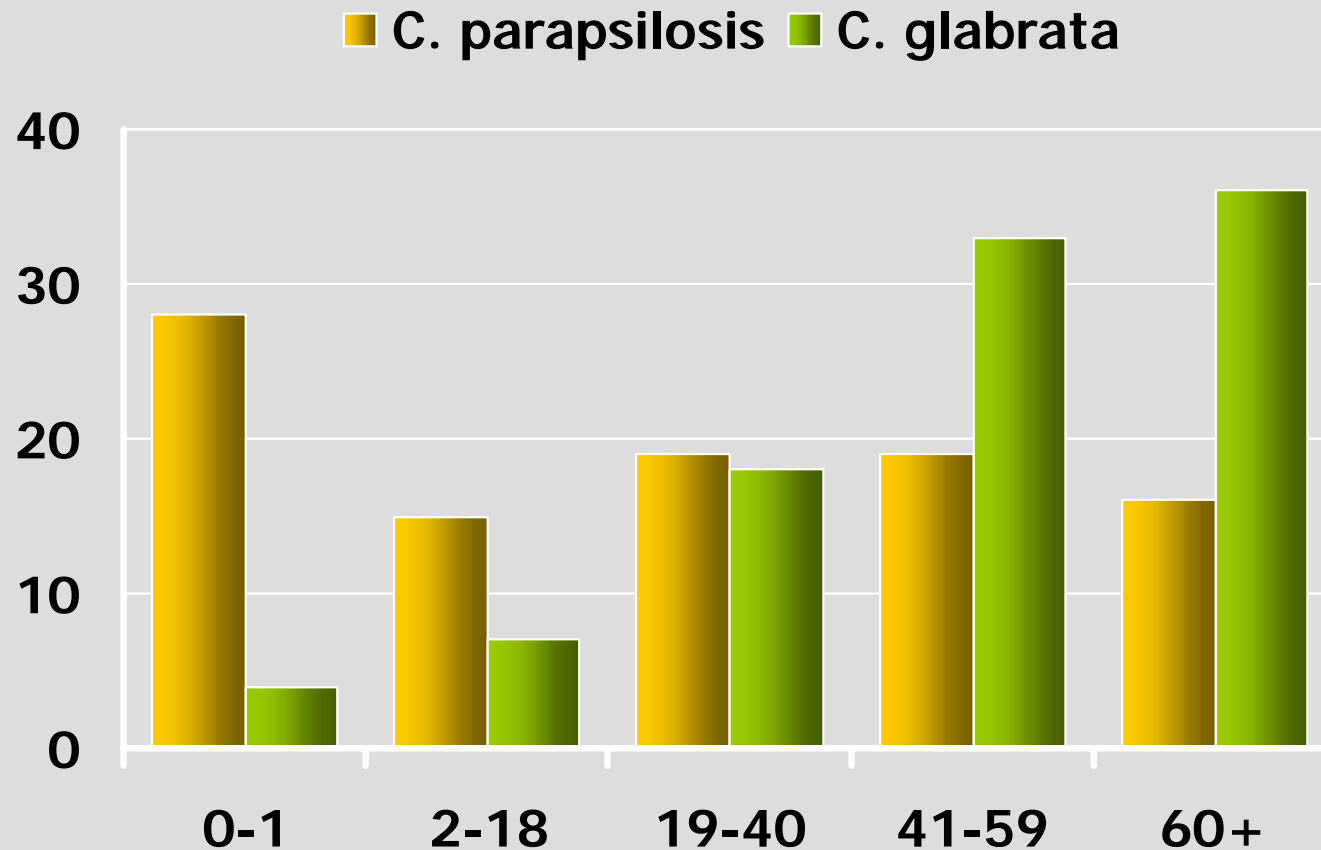


# Invasive *Candida* spp. in SCTs: Data From TRANSNET





# Incidence of *C. parapsilosis* and *C. glabrata* by Patient Age



Data from University of Michigan, 1988-1999.  
Malani PN, et al. Mycoses. 2001;44:446-449.

# Epidemiology

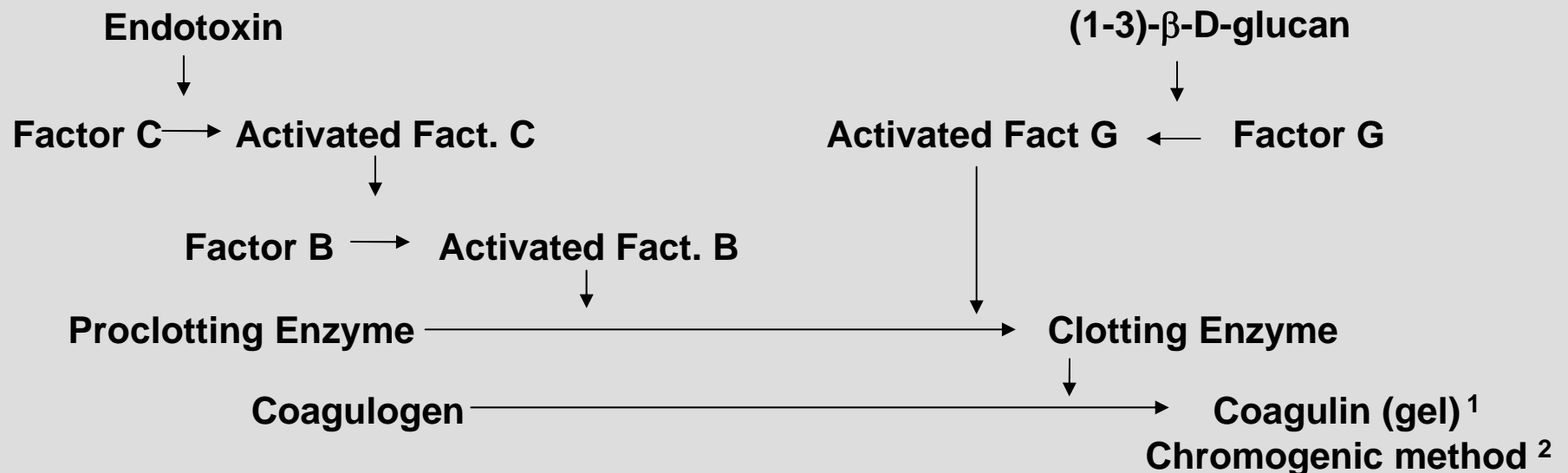
- Candida infections are important and associated with a high crude mortality rate
- Species are clearly different with regards to disease potential and susceptibility to antifungal drugs
- Outcomes and efficacy of antifungal drugs should be interpreted with this in consideration

# Diagnosis

- Culture improved, but still insensitive
- Numerous patients die with post-mortem diagnoses

# Diagnostic tests relying on identification of (1-3)- $\beta$ -D-Glucan

- Activates *Limulus* amoebocyte lysate
- Factor G initiates cascade. Output measured by
  - Turbidity after gel clot: WB003 (Wako Pure Chem. Indust.)<sup>1</sup>
  - Chromogenic substrate: Fungitec G test (Seikagaku) and Fungitell, (Assoc. Cape Cod)<sup>2</sup>



## INVASIVE FUNGAL INFECTIONS

Early Detection =  
Improved Patient Outcomes



# Introducing Fungitell™

## A New FDA-Cleared Diagnostic Test to Detect Invasive Fungal Infections

- Fungitell detects very low (picogram/mL) levels of (1-3)- $\beta$ -D-Glucan in serum in one hour (glucan is a component of most medically important fungi including *Candida* and *Aspergillus*)\*
- In a recent study, Fungitell positives were observed a **median of 10 days earlier than conventional diagnosis**<sup>1</sup>
- Fungitell has demonstrated 100% sensitivity in patients with proven or probable fungal infection. When the test was negative, 100% Negative Predictive Value<sup>1</sup> was observed.
- Fungitell is indicated as an adjunct to diagnosis of IFI, particularly in high risk, immunosuppressed patient populations (e.g. transplant recipients, chemotherapy patients, AIDS patients and others)



### CORPORATE HEADQUARTERS

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\* Fungitell does not detect certain species of fungus that either do not produce (1,3)- $\beta$ -D-Glucan or produce very low levels such as *Cryptococcus* and *Zygomycetes*.

<sup>1</sup> Odabasi, et al. (2004) Clinical Infectious Diseases. 39:199-205.

# (1-3)- $\beta$ -D-Glucan Detection

- Different reagents (different genera of horseshoe crabs)
  - Defined appropriate cut-off-- 60 pg/mL
- Studied population of patients at risk-antifungal prophylaxis trial in patients with MDS, leukemia
  - 283 neutropenic subjects with 7.3 sera over 3 week (2070 samples)

No. of BG-positive serum samples	Proven or probable IFI				Proven, probable, or possible IFI			
	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %
1 specimen	100	90	43	100	70	96	79	93
$\geq 2$ sequential specimens	65	96	57	97	38	99	87	87
$\geq 3$ sequential specimens	60	99	80	96	28	100	100	85

NOTE. EORTC-MSG criteria are from [18].

# (1-3)- $\beta$ -D-Glucan Detection

- Multicenter (6 sites) case-control study
  - 163 cases / 170 controls
  - Performance of one sample
    - At 60 pg/mL cut-off: 80-100% sensitivity for candidemia (species dependent)

Table 3. Performance of the (1 $\rightarrow$ 3)- $\beta$ -D-glucan (BG) assay for detection of invasive fungal infection in 333 subjects.

BG cutoff value, pg/mL	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
40	79.1	79.4	78.7	79.9
50	73.0	82.9	80.4	76.2
60	69.9	87.1	83.8	75.1
80	64.4	92.4	89.0	73.0
100	62.6	94.7	91.9	72.5
125	60.1	96.5	94.2	71.6
150	57.1	97.6	95.9	70.3

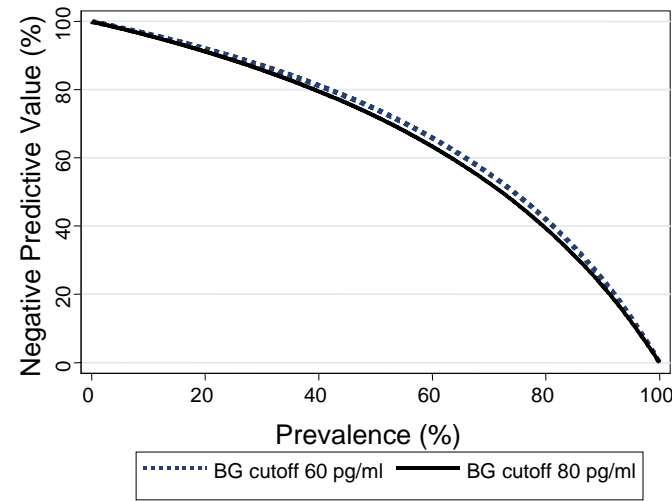
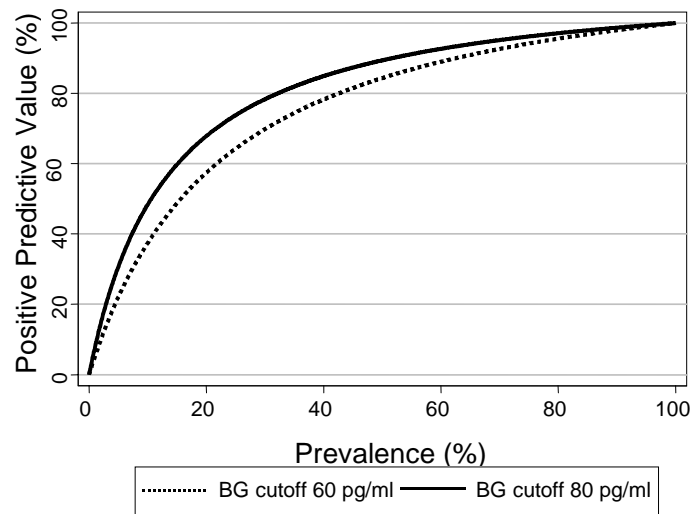
NOTE. Proven or probable IFI was determined according to European Organization for the Research and Treatment of Cancer/Mycoses Study Group criteria.

Ostrosky-Zeichner et al.  
Clin Infect Dis 2005;  
41:654

# (1-3)- $\beta$ -D-Glucan Detection

## ■ Problems

- No matching of cases and controls
  - 50% of controls were “healthy” people
- Predictive values calculated based on inappropriate prevalence (case / control design)





# (1-3)- $\beta$ -D-Glucan Detection

- 279 patients with variable diagnoses
  - Case control design with variable control groups

Parameter <sup>a</sup>	IFI patient groups and subgroups/control groups			
	Total IFI patients/ blood donors	Total IFI patients/ patients at risk	Pulmonary aspergillosis/ corresponding patients at risk	Bloodstream infections/ corresponding patients at risk
No. of patients	117/40	117/122	70/100	27/101
No. of patients with a BG $\geq$ 80 pg/ml	91/3	91/36	48/27	23/36
Sensitivity (95% CI)	77.8 (70.2–85.3)	77.8 (70.2–85.3)	68.6 (57.7–79.5)	85.2 (71.8–98.6)
Specificity (95% CI)	92.5 (84.3–1.0)	70.5 (62.4–78.6)	73.0 (64.3–81.7)	64.4 (55.0–73.7)
LR <sup>+</sup> (95% CI)	10.4 (3.5–30.9)	2.64 (1.97–3.53)	2.54 (1.77–3.64)	2.39 (1.76–3.24)
LR <sup>–</sup> (95% CI)	0.24 (0.17–0.34)	0.32 (0.22–0.45)	0.43 (0.30–0.62)	0.23 (0.09–0.57)
Yule Q	0.95	0.79	0.71	0.82

# (1-3)- $\beta$ -D-Glucan Detection

Patient no.	HIV status	Days from serum sampling to microscopic diagnosis in BAL <sup>a</sup> fluid	BG level (pg/ml)
1	Positive	-7	>500
2	Positive	-5	156
3	Positive	-5	455
4	Positive	-2	>500
5	Positive	-1	>500
6	Positive	-1	>500
7	Positive	-1	>500
8	Positive	0	>500
9	Positive	0	>500
10	Positive	1	>500
11	Positive	2	>500
12	Positive	3	203
13	Positive	4	176
14	Positive	5	397
15	Positive	6	103
16	Positive	22	>500
17	Negative (two lung grafts)	0	115
18	Negative (cerebral lymphoma)	0	>500
19	Negative (dermatomyositis ARDS) <sup>a</sup>	1	>500
20	Negative (pulmonary neoplasia)	2	>500

<sup>a</sup> BAL, bronchoalveolar lavage.

<sup>b</sup> ARDS, acute respiratory distress syndrome.

Patient no.	Fungus isolated in hemoculture	Days from serum sampling to first positive hemoculture	BG level (pg/ml)	M level ( $\mu$ g/ml)
1	<i>C. parapsilosis</i>	-8	77	<0.250
2	<i>C. glabrata</i>	-4	49	<0.250
3	<i>C. guilliermondii</i>	-4	>500	1.47
4	<i>C. albicans</i>	-3	>500	>2
5	<i>C. albicans</i>	-2	>500	>2
6	<i>C. glabrata</i>	-1	>500	1.121
7	<i>C. krusei</i>	-1	46	1.071
8	<i>C. albicans</i>	0	247	<0.250
9	<i>C. guilliermondii</i>	0	358	<0.250
10	<i>C. albicans</i>	1	>500	<0.250
11	<i>C. albicans</i>	1	>500	>2
12	<i>C. glabrata</i>	1	181	<0.250
13	<i>C. lusitaniae</i>	1	>500	1.026
14	<i>C. guilliermondii</i>	2	289	<0.250
15	<i>C. tropicalis</i>	2	>500	1.436
16	<i>C. guilliermondii</i>	3	151	1.2
17	<i>C. guilliermondii</i>	3	282	<0.250
18	<i>C. albicans</i>	4	160	<0.250
19	<i>C. albicans</i>	5	21	NA
20	<i>C. tropicalis</i>	5	>500	NA
21	<i>C. glabrata</i>	5	312	0.62
22	<i>C. krusei</i>	6	>500	<0.250
23	<i>C. albicans</i>	7	83	<0.250
24	<i>C. glabrata</i>	7	198	1.650
25	<i>C. krusei</i>	8	210	<0.250
26	<i>C. albicans</i>	14	>500	NA
27	<i>G. capitatum</i>	-4	>500	<0.250*

<sup>a</sup> NA, not available; \*, GM test = 0.68.

# Antifungals

## Sites of Action of Systemic Antifungal Agents

### Cell membrane

#### Polyenes:

Amphotericin B  
Lipid formulations of amphotericin B  
Nystatin

### Cell wall

#### Echinocandins:

Caspofungin  
Micafungin  
Anidulafungin

### Cytoplasm

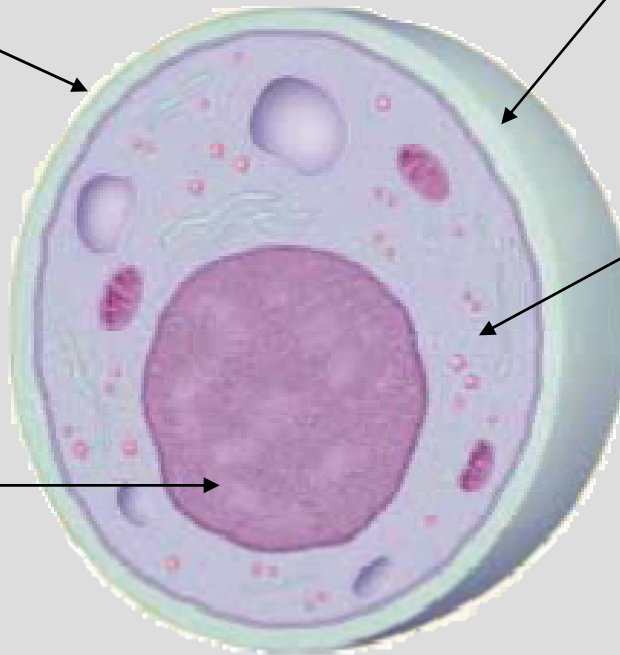
#### Azoles:

Fluconazole  
Ketoconazole  
Itraconazole  
Voriconazole  
Posaconazole

### DNA

#### Antimetabolites:

5-fluorocytosine



# IDSA Guidelines for Candidemia

Choice of therapy depends on clinical status of the patient and knowledge of species

1) Remove all lines, if feasible

2) Therapy: Fluconazole  $\geq 6\text{mg/kg/d}$  (400mg)

or Amphotericin B 0.6-1.0 mg/kg/d

Micafungin,  
Anidulafungin or Caspofungin 50mg/d  
or Amphotericin B plus Flu 800mg 5-7d,  
then Flu

3) Treat 2 weeks after last positive blood culture and resolution of signs/symptoms of infection

# Fluconazole for Candidemia

- Non-neutropenic patients with candidemia
- 237 patients: AmB 0.5-0.6 mg/kg/day vs. fluconazole 400 mg/day
- Success: 79% AmB vs. 70% Fluconazole  
(95% CI -5%, 23%)

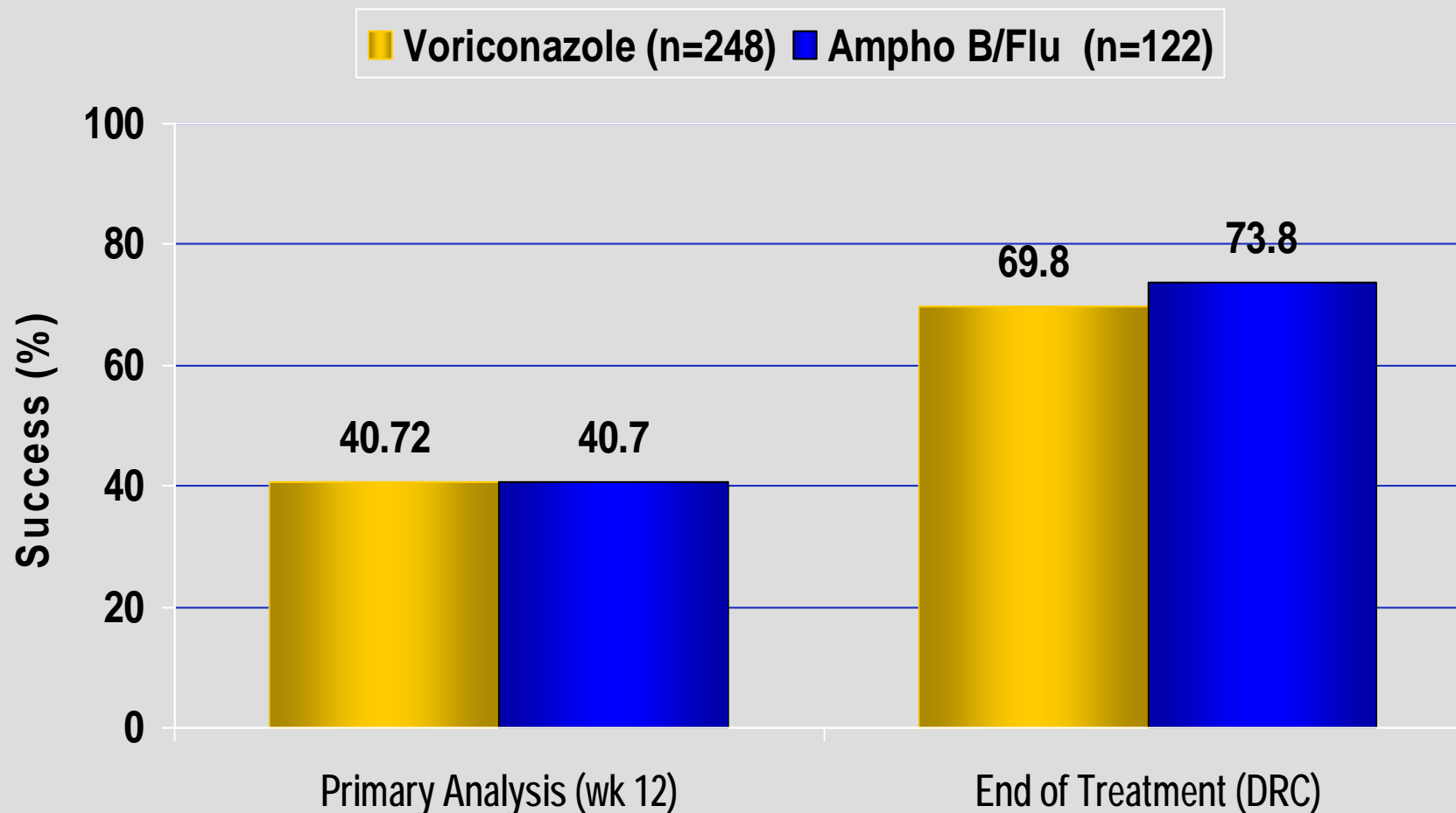
Rex JH, et al. *N Engl J Med.* 1994;331:1325-1330

# Fluconazole + AmB for Candidemia

- Study Arms
  - FLU+Placebo: FLU 800 mg/day plus MVI
  - FLU+AmB: FLU 800 mg/day+0.7 mg/kg dAmB
- Placebo/AmB x 3-8 days & was blinded
- Results: FLU + AmB...
  - Was favored overall ( $P= .04$  to  $.08$ )
    - Was more nephrotoxic (no surprise)
  - Gave lowest rate persistent +BC ever seen
    - 7% vs. 17%: this is better than any previous study

Rex JH, et al. Clin Infect  
Dis 2004

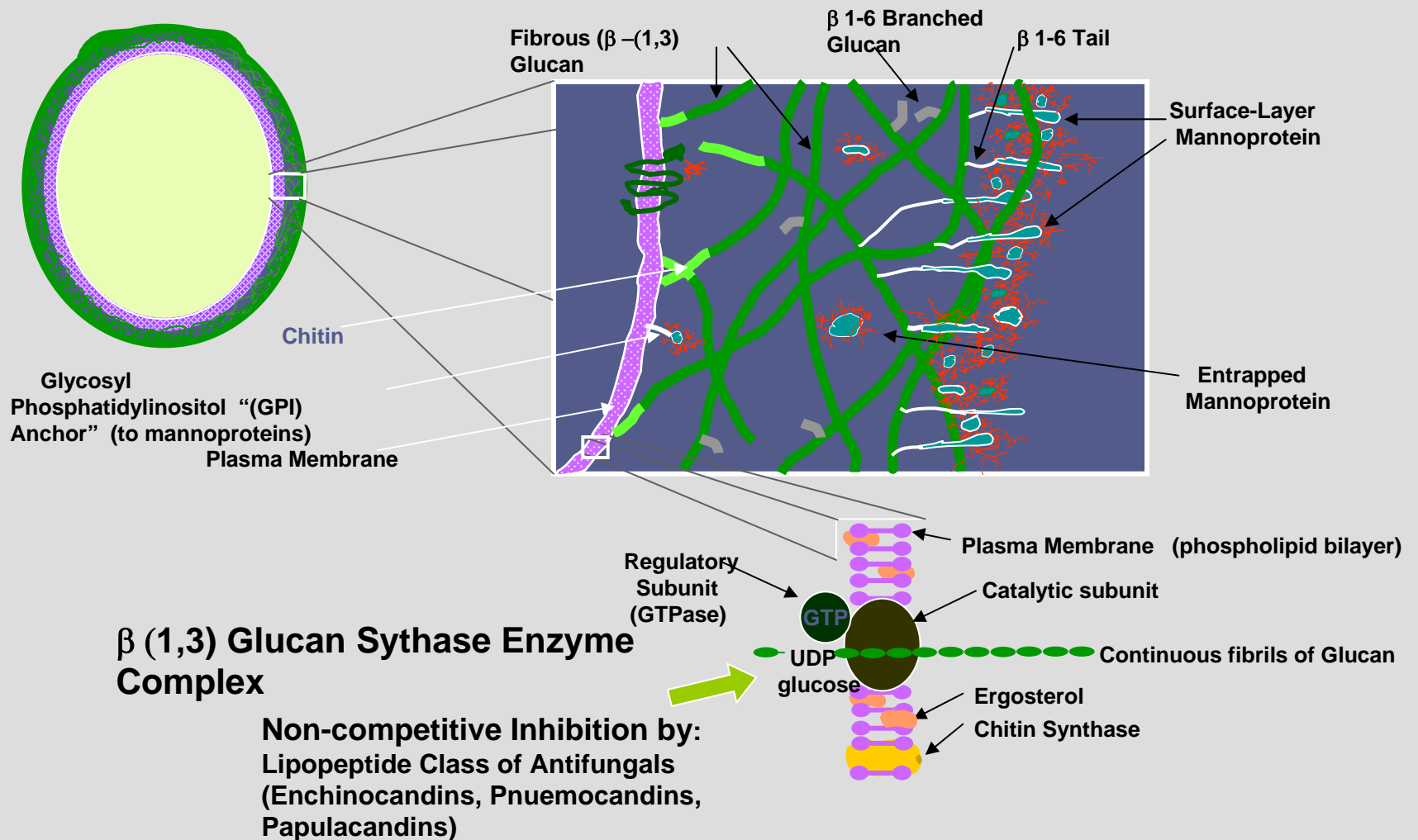
# Global Comparative Candidemia Study: Success at wk 12 & End of Treatment (EOT)



# Echinocandins

## Fungal Cell Wall

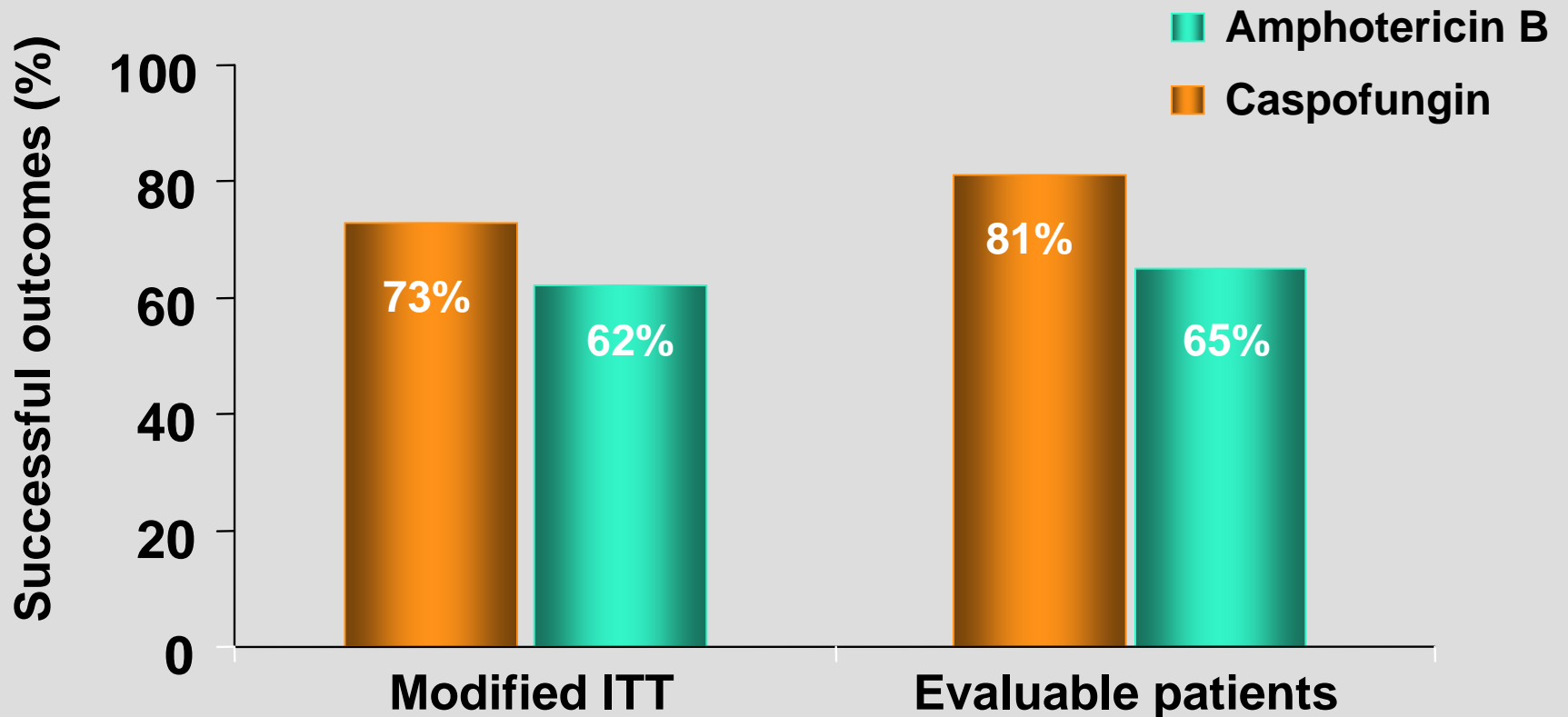
Adapted from: Kurtz, MB, ASM News, Jan 98, Vol 64, No 1, pp. 31-9.  
Walsh, TJ. The Oncologist, 2000;5:120-135





# Caspofungin versus Amphotericin B for Invasive Candidiasis

Analysis of all patients (non-stratified)



Successful outcome = symptom resolution and microbiological clearance

# Micafungin vs Liposomal Amphotericin B in Candidemia

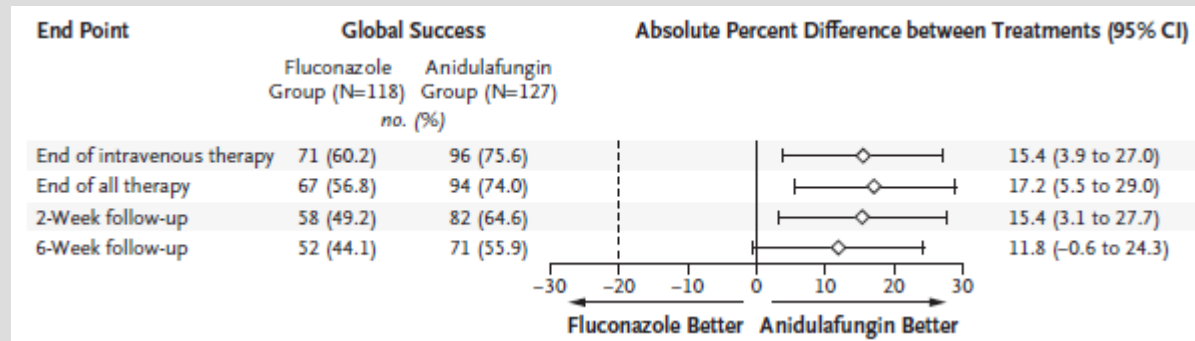
	Micafungin		Liposomal amphotericin B		Difference in proportion (95% CI)
	Number of patients	Number treated successfully (%)	Number of patients	Number treated successfully (%)	
Overall	247	183 (74.1%)	247	172 (69.6%)	4.5% (-3.5 to 12.4)
Complete response*		159 (64.4%)		150 (60.7%)	
Partial response*		24 (9.7%)		22 (8.9%)	
Neutropenic status at baseline					4.9% (-3.0 to 12.8)†
<500 cells per µL	32	19 (59.4%)	25	14 (56.0%)	
≥500 cells per µL	215	164 (76.3%)	222	158 (71.2%)	

\*Both mycological eradication and a complete clinical response were necessary to be deemed a complete response. For a partial response, an improvement in clinical symptoms and any radiographic abnormalities had to be demonstrated in addition to a mycological response. †Stratified by neutropenic status.

Table 3: Treatment success in the modified intention-to-treat population

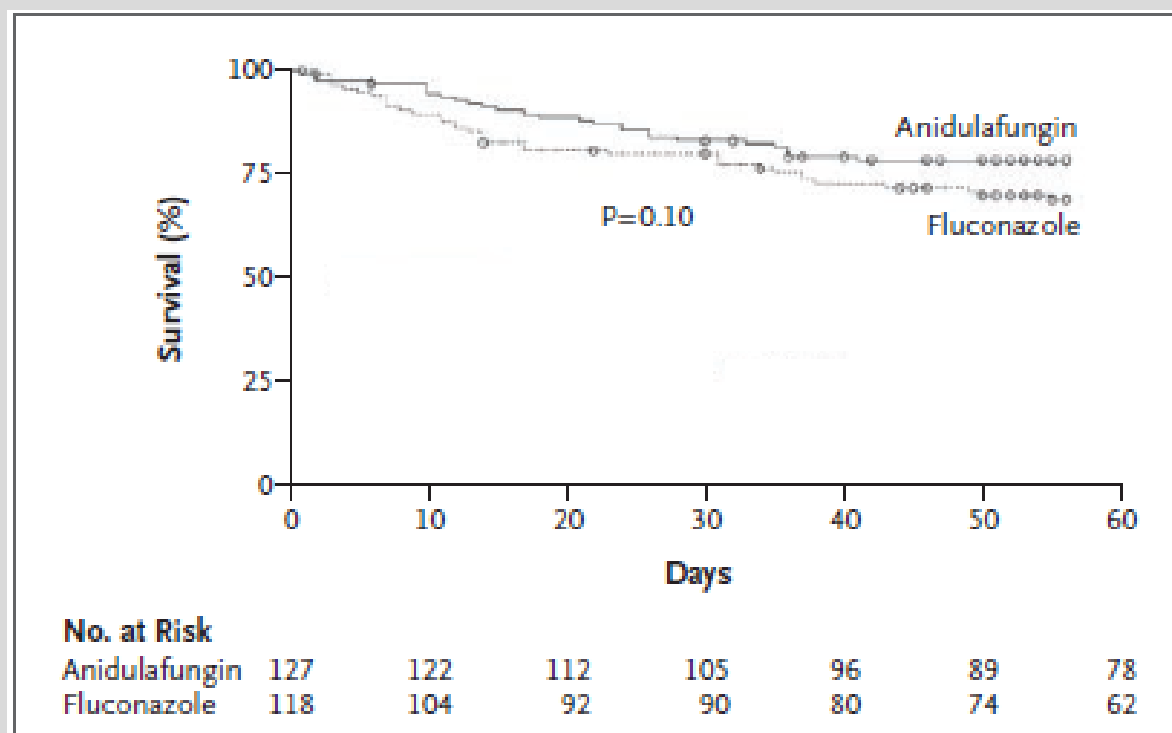
- Micafungin 100 mg/kg/d (n=264) vs L-AmB 3 mg/kg/d (n=267)
- No difference in success across species
- More infusion related toxicity and renal abnormalities in L-AmB

# Anidulafungin vs Fluconazole for Invasive Candidiasis & Candidemia



- Primary endpoint end of IV therapy
  - Anidulafungin non-inferior to fluconazole
    - Difference: 15.4 (95 % CI [3.85, 26.99])
- Secondary endpoints favor anidulafungin
- Trend to worse clearance of *C. parapsilosis*

# Anidulafungin vs Fluconazole for Invasive Candidiasis & Candidemia



Reboli A, et al New Eng J Med 2007; 356: 2472-82

# Caspofungin vs. Micafungin

- Randomized to caspofungin (70 / 50 mg) vs. micafungin (150 mg) vs. micafungin (100 mg)
  - Non-inferiority of caspofungin and micafungin established
  - No difference between micafungin doses
- Caspofungin dose escalation (150 mg vs. 50 mg)
  - No difference in adverse events
  - No difference in treatment efficacy

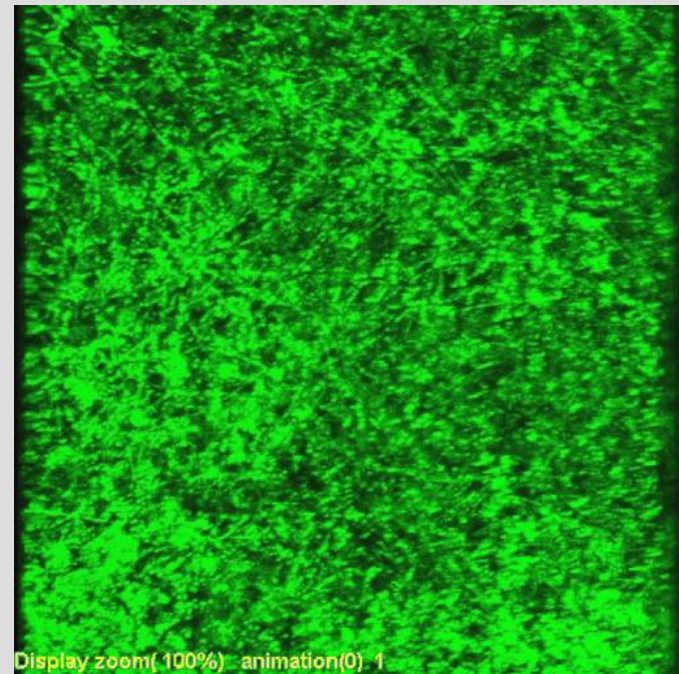
Pappas et al. Clin Infect Dis  
2007

Betz et al. ICAAC 2008

# Clinical Relevance of Biofilms

- *Candida* spp. adhere to inert and biological surfaces – associated with virulence
  - Catheter-related infections
  - Biomaterial surfaces (implants, dentures, prostheses)
  - Biofilm-associated infections (endocarditis, oropharyngeal candidiasis)
- High level of antifungal resistance
  - Fluconazole & polyene resistance
  - Echinocandin susceptibility

**3D view of a *C. albicans* biofilm**



Bachmann SP, et al. Antimicrob Agents Chemother 2002;46:3591-6;  
Ramage G, et al. Antimicrob Agents Chemother 2002;46:3634-6

## Slide 30

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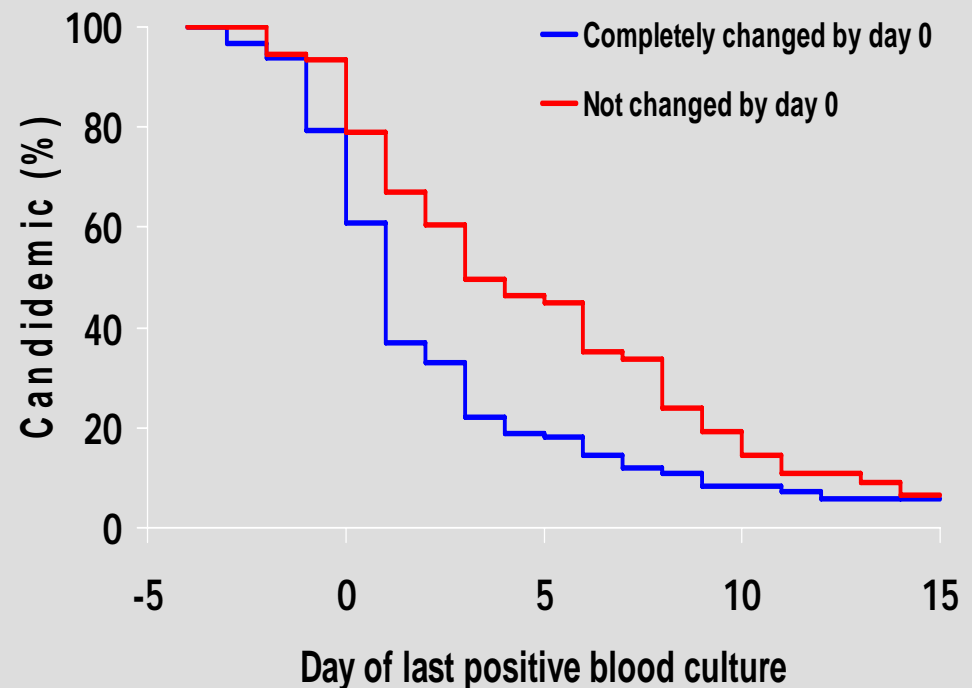
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Thomas F Patterson MD, 12/9/2005

# Vascular Catheter Removal

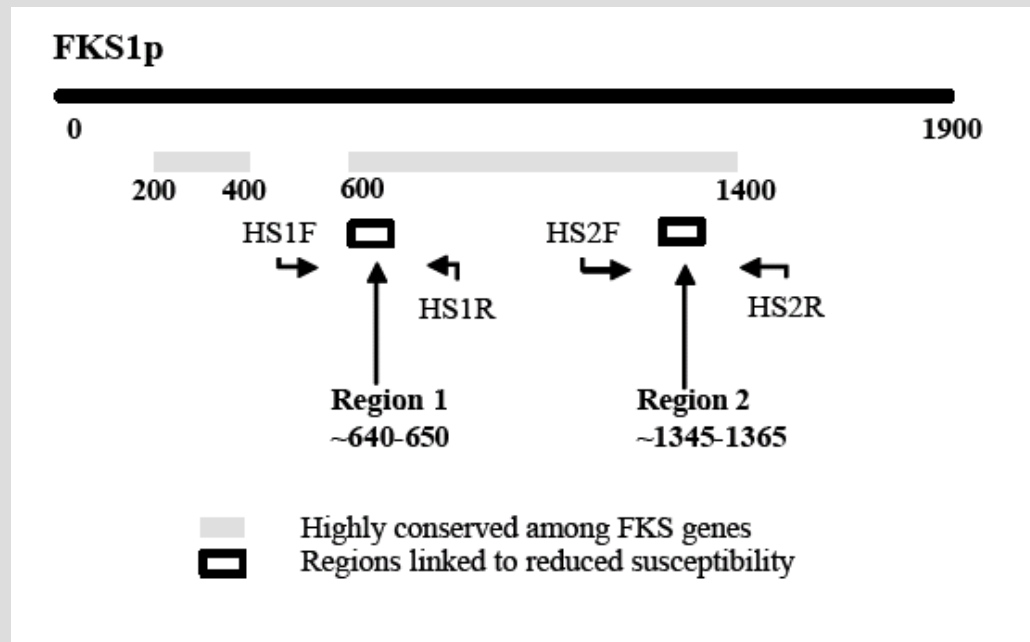
- Non-neutropenic patients
  - Catheter frequently implicated—change indicated
    - Unless other obvious source (urine, abscess)
- Neutropenic patients
  - Mucositis: gut source
  - Tunneled line removal may be difficult & benefit less clear
- *Candida parapsilosis*
  - Strongly catheter-associated
  - *Very* difficult to eradicate without line removal





# Resistance

- Resistance to CAS generated in *Candida albicans* isolates in the laboratory
  - Mapped to *FKS* gene (*C. albicans*)



- Clinical isolates
  - *C. albicans*, *C. krusei*, *C. parapsilosis*

Park et al. Antimicrob  
Agents Chemother 2005

# Conclusions

- Candidemia is a persistent, common problem
- Species differ with respect to ability to cause disease, susceptibility to antifungal drugs
- Many new treatment options
  - Echinocandins most promising in clinical trials
- Resistance is becoming apparent
  - Echinocandins- target alteration
  - Cross-resistance to azoles primarily efflux pump mediated
    - Exception: *C. krusei*