

The Management of Fungal Infections

George H. Karam, M.D.

**Paula Garvey Manship Professor of Medicine
Louisiana State University School of Medicine
in New Orleans**

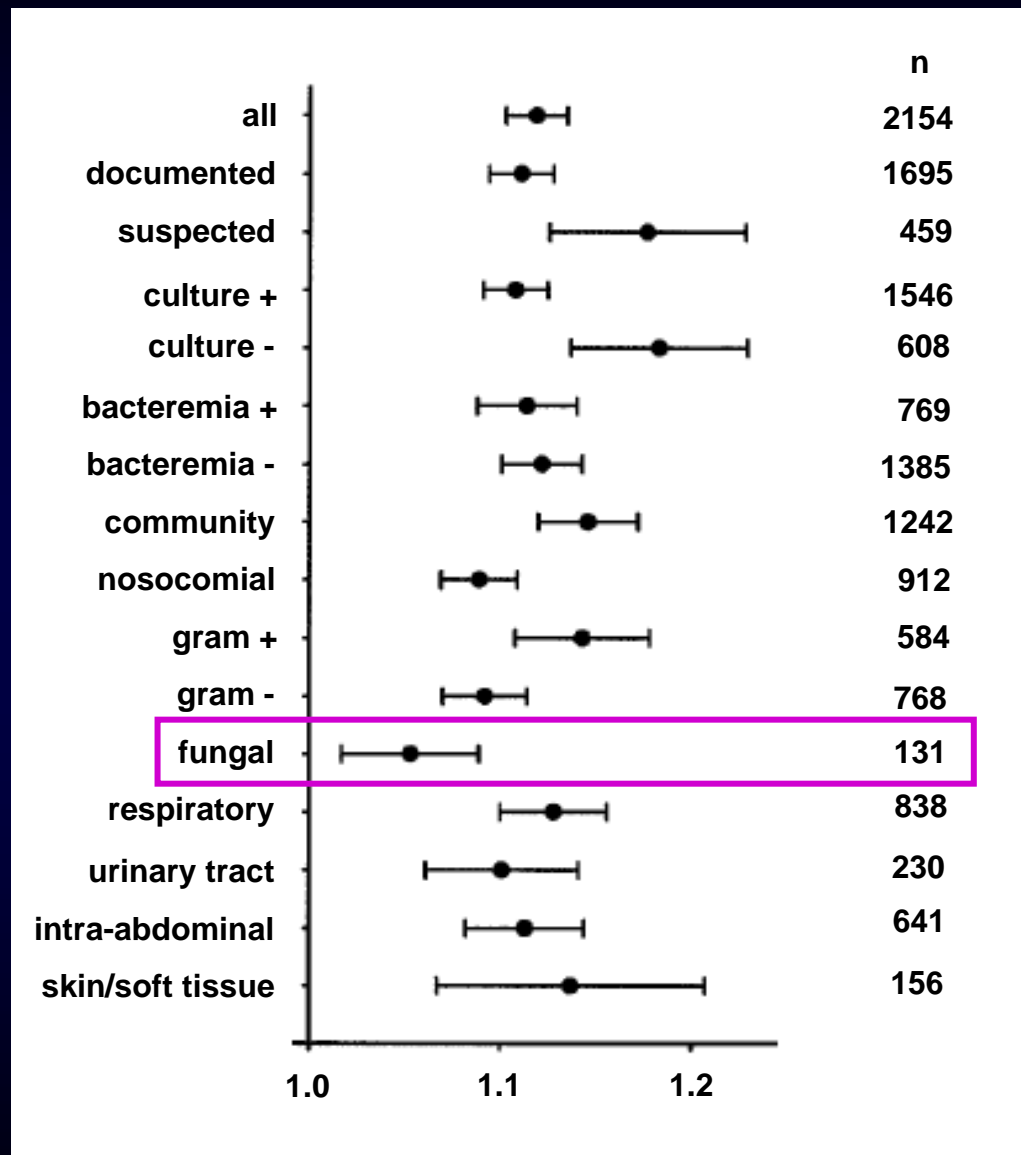
The Relevance of *Candida* for the Critical Care Physician

- Development of invasive candidiasis in 10% of patients residing in intensive care units

Impact of Timing of Antimicrobial Agents on Survival in Human Septic Shock

- Survival rate of 79.9% with administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension
- Each hour of delay in antimicrobial administration over the ensuing 6 hours associated with an average decrease in survival of 7.6%
- By multivariate analysis, time to initiation of effective antimicrobial therapy the single strongest predictor of outcome

Adjusted Odds Ratio of Death

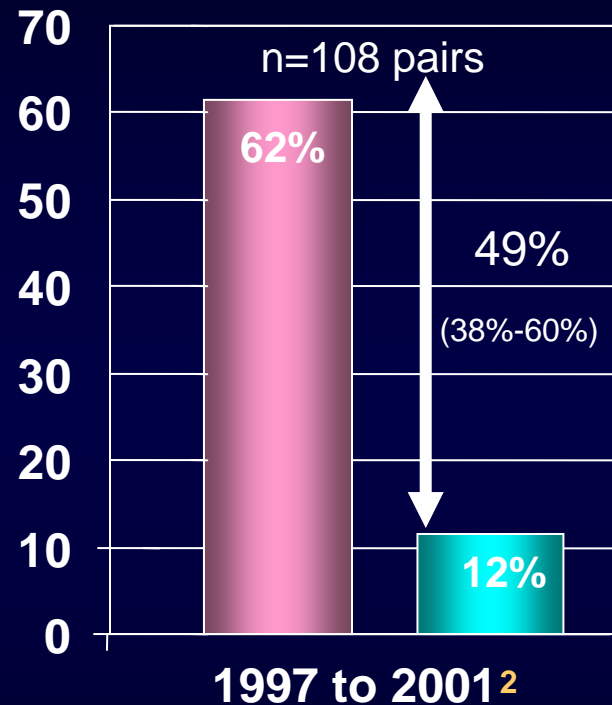
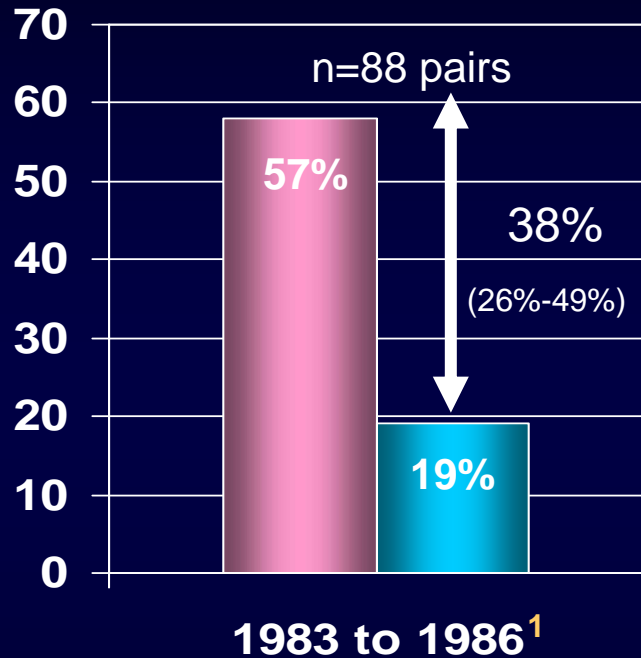


2008 Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock

- “Risk factors for candidemia should also be considered when choosing initial therapy.”
- “When deemed warranted, the selection of empirical antifungal therapy (e.g., fluconazole, amphotericin B, or echinocandin) will be tailored to the local pattern of the most prevalent *Candida* species and any prior administration of azoles drugs.”

Nosocomial Candidemia

Attributable Mortality



■ Cases ■ Controls

Estimates from 2009 IDSA guideline³

- 15-25% for adults
- 10-15% for neonates & children

¹Wey SB et al. *Arch Intern Med* 1988;148:2642-2645

²Gudlaugsson O et al. *Clin Infect Dis* 2003;37:1172-1177

³Pappas PG et al. *Clin Infect Dis* 2009;48:503-535

Falagas ME et al. *Eur J Clin Microbiol Infect Dis* 2006;25:419-425

Delaying Empirical Treatment of Positive *Candida* Bloodstream Infections Until Positive Cultures Are Available

- Retrospective cohort analysis of 157 patients with candidemia
 - Death in 50 (31.8%) of patients
- Definition of “inappropriate treatment” in this study
 - “the absence of antifungal agents at the time that fungus-positive blood samples for culture were drawn”
 - “fluconazole treatment with the subsequent isolation of either *Candida krusei* or *Candida glabrata*”
- Timing of the administration of antifungal therapy
 - Within 12 h in 9 (5.7%) patients
 - Between 12 and 24 h in 10 (6.4%) patients
 - Between 24 and 48 h in 86 (54.8%) patients
 - Greater than 48 h in 52 (33.1%) patients

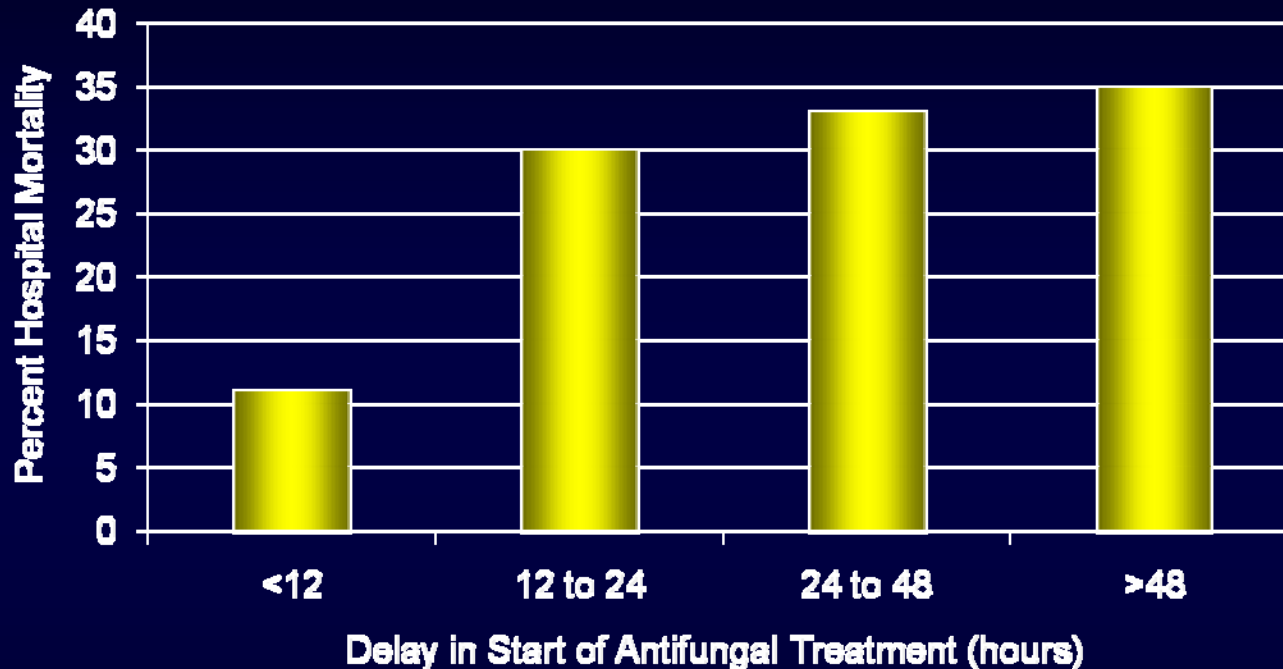
12.1%

Candida Bloodstream Infection in 245 Patients at BJH Who Received Antifungal Therapy 2004–2006

- Percent of patients who received antifungal therapy within 24 hours of a positive blood culture being drawn
 - 30%

Delaying Empirical Treatment of Positive *Candida* Bloodstream Infections Until Positive Cultures Are Available

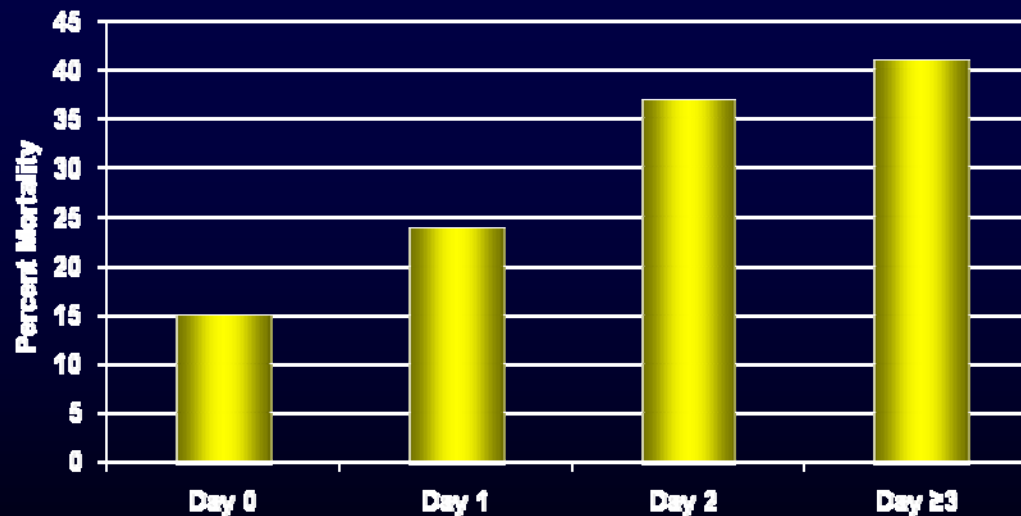
- Hospital mortality based on timing of antifungal therapy



- Independent determinants (by multivariate analysis) of hospital mortality
 - APACHE II score (one-point increments) ($P < 0.001$)
 - Prior antibiotic treatment ($P = 0.028$)
 - Administration of antifungal treatment 12 hours after having the first positive blood sample for cultures ($P = 0.018$)

Impact on Mortality of Candidemia Based on Time to Initiation of Antifungal Therapy

- Retrospective cohort study of 230 patients from 4 medical centers
- 162 patients (70%) with nonsurgical hospital admission
- *C. albicans* most commonly isolated (56% of patients)
- 192 patients with no previous fluconazole treatment
- Mortality rates based on time of initiation of fluconazole ($P = .0009$ for trend)



Mortality in Septic Shock Caused by *Candida**

Etiology		All cases	0-2 hour delay	2-12 hour delay	>12 hour delay
Bacteria	Number (#)	2686	701	1279	706
	% of total #		26.1	47.6	26.3
	% survival	47.7	77.3	48.2	16
<i>Candida</i>	Number	308	16	62	230
	% of total #		5.2	20.1	74.7
	% survival	17.5	81.3	41.9	6.5

*median time to initiation of effective antimicrobial therapy in septic shock:
 5.5 hours for bacteria versus 35.1 hours for *Candida*
 Kumar A et al. 47th ICAAC, Chicago, September 17-20, 2007. K-2174

Risk Factors for Candidemia

- Broad-spectrum antibacterial antibiotics
- Use of central venous catheters
- Receipt of parenteral nutrition
- Receipt of renal replacement therapy by patients in ICUs
- Neutropenia
- Implantable prosthetic devices
- Receipt of immunosuppressive agents

Risk Factors for Candidemia

- Prolonged use of antibacterial antibiotics
- Presence of central venous catheters
- Hyperalimentation
- Prolonged ICU stay
- Surgery (especially that which transects the gut wall)
- Colonization by *Candida* of multiple nonsterile sites

Candida As a Risk Factor for Mortality in Peritonitis

- Multicenter retrospective case-control study in ICU patients
- Isolation of *Candida* spp. appeared to be an independent risk factor for mortality in nosocomial peritonitis (48% vs 28%, $P < .05$)
 - *Candida* in community-acquired peritonitis not demonstrated to be mortality risk factor but sample size small
- Upper GI tract perforation demonstrated to be a risk factor for nosocomial peritonitis with isolation of *Candida*
- Curative antifungal treatment not prescribed in all patients after identification of *Candida* but mortality rates similar between treated and untreated patients

The Interpretation of Positive Cultures for *Candida* from Sputum or Bronchial Secretions

- Literature rates of empiric antifungal therapy based on positive cultures for *Candida* from respiratory sites
 - In 34% of patients from a multicenter study of surgical intensive care units (Garey KW et al. *Mycoses* 2006;49:226–231)
 - In 24% of patients from a Dutch audit in two hospitals (Natsch S et al. *J Antimicrob Chemother* 2001;48:303-310)
- Comments from the 2004 IDSA *Candida* guidelines (Pappas PG et al. *Clin Infect Dis* 2004;38:161-189)
 - “Benign colonization of the airway with *Candida* species and/or contamination of the respiratory secretions with oropharyngeal material is much more common than either form (aspiration or hematogenous) of true *Candida* pneumonia.”
 - “Definitive diagnosis of *Candida* pneumonia requires histopathological confirmation.”

Sensitivity of Automated Blood Culture Systems for Detecting *Candida* Growth Rates

55% to 70%

(according to statistics of surveyed
manufacturers of automated blood culture
systems and the published literature)

Recent Literature About the Role of Non-Invasive Markers for Identifying Invasive Candidiasis

- 1,3- β -D-glucan antigenemia for early diagnosis of invasive fungal infections in neutropenic patients with acute leukemia (Senn L et al. *Clin Infect Dis* 2008;46:878-885)
- Real-time PCR assay for the diagnosis of candidemia in nonneutropenic, critically ill patients (McMullan R et al. *Clin Infect Dis* 2008;46:890-896)
 - Editorial response: “best viewed as a proof of principle, a project definitely worth further study” (Bennett J. *Clin Infect Dis* 2008;46:897-898)

Clinical Prediction Rule for Nosocomial Invasive Candidiasis

- Rule used in 303 of 2,859 patients (10.6%), of whom 88 had invasive candidiasis (bacteremia in 72, sterile site in 16)

Either any antibiotic use (day 1 – 3) or CVC (day 1 – 3)
plus

At least 2 of the following

- Any surgery (day -7 – 0)
 - Immunosuppressive use (day -7 – 0)
 - Pancreatitis (day -7 – 0)
 - TPN (day 1 – 3)
 - Any dialysis (day 1 – 3)
 - Steroid use (day -7 – 3)
- Rate of invasive candidiasis in patients meeting rule – 9.9%
 - Captured 34.1% invasive candidiasis (sensitivity 0.34)

Metastatic Sites of *Candida* Infection

- Findings from 63 surgical patients
 - 51 of 63 patients with fungemia as a late complication of intraperitoneal infection
 - 7 of 21 untreated or partially treated patients who died and at autopsies had evidence of visceral microabscesses, with 6 having kidney lesions

Concept Maps for Treatment of Candidemia

- 2004 IDSA guidelines for treatment of candidemia¹
 - Non-neutropenic patients
 - Neutropenic patients

- 2006 approach of a panel of infectious disease specialists, clinical microbiologists, and hospital epidemiologists from the 5 Swiss university hospitals²
 - Recent exposure to azoles
 - Neutropenia
 - Severe sepsis and septic shock

- 2009 IDSA guidelines for treatment of candidemia³
 - History of azole exposure
 - Severity of illness
 - Risk of infection with azole-resistant *Candida* species

¹Pappas PG et al. *Clin Infect Dis* 2004;38:161-189

²Flückiger E et al. *Swiss Med Wkly* 2006;136:447-463

³Pappas PG et al. *Clin Infect Dis* 2009;48:503-535

Treatment of Invasive Candidiasis in Non-Neutropenic Patients

- Minor roles
 - Amphotericin B and the lipid preparations
 - Voriconazole

- Preferred choices
 - Fluconazole
 - Echinocandins

Candida Bloodstream Infection in 245 Patients at BJH Who Received Antifungal Therapy 2004–2006

Multivariate Analysis of Mortality Risk Factors

	Hospital Cohort		
	Adjusted Odds Ratio	95% CI	P Value
APACHE II score (1-point increments)	1.18	1.11–1.25	.003
CVC retention	4.85	2.54–9.29	.015
Corticosteroid use	3.41	1.96–5.93	.027
Inadequate initial fluconazole dosing*	3.31	1.83–6	.044

*Inadequate fluconazole dosing in 41 patients

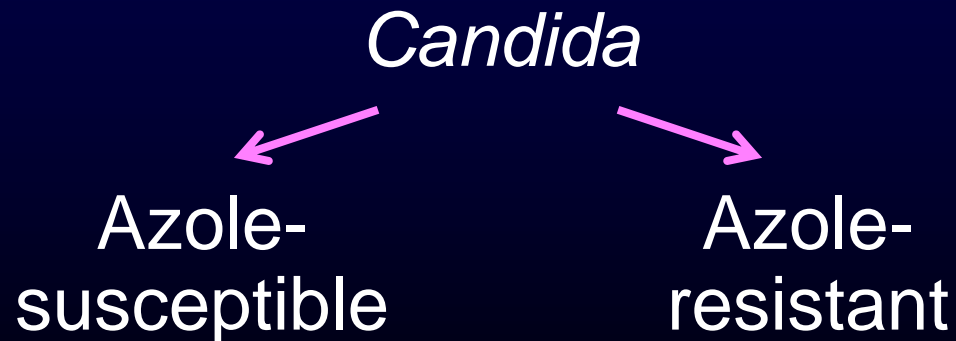
Target doses

- 6 mg/kg (3 mg/kg if CrCl <50 mL/min) for *C. albicans*, *C. parapsilosis*, and *C. tropicalis*
- 12 mg/kg (6 mg/kg if CrCl <50 mL/min) for *C. glabrata*

Concept Maps Related to Considerations of Therapy for *Candida*



- “For infections due to *C. parapsilosis*, fluconazole or LFAmB is preferred as initial therapy (B-III).”*



*Pappas PG et al. *Clin Infect Dis* 2009;48:503-535

Prediction of Azole-Resistant *Candida*

Shorr AF et al. *Crit Care Med* 2007;35:1077-1083

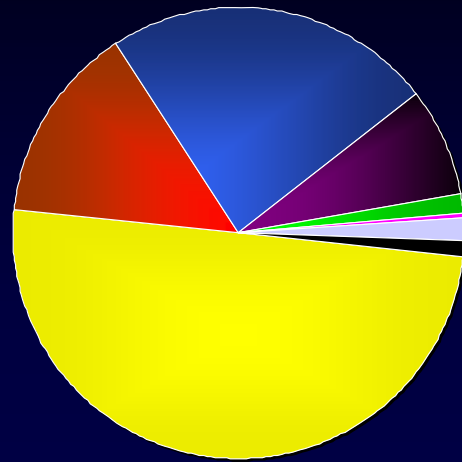
- Retrospective case series of 245 patients (60% in the ICU) in 2 academic, tertiary care centers
- *C. albicans* in 52% of infections and *C. glabrata* in 20%
- No variable, including both previous fluconazole exposure and severity of illness, correlated with the fungemia due to a non-*albicans* species

Chow JK et al. *Clin Infect Dis* 2008;46:1206-1213

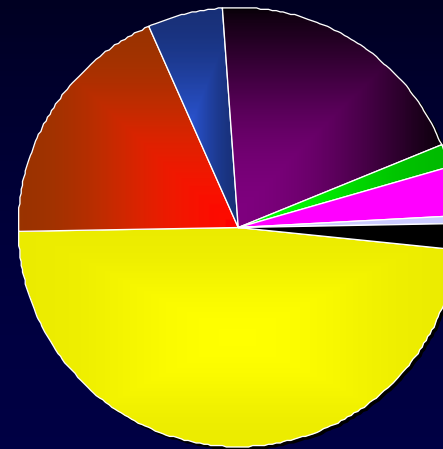
- Risk factors for non-*albicans Candida*
- Receipt of fluconazole
- Central venous catheter exposure

Regional Variability of *Candida* Infections

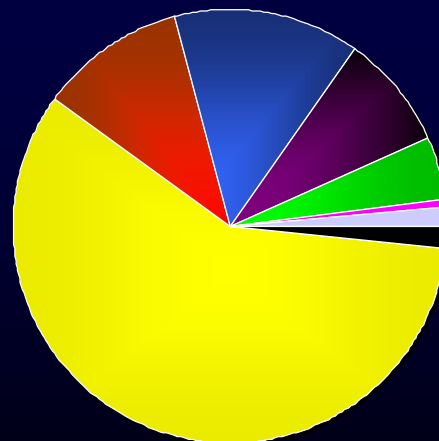
North America



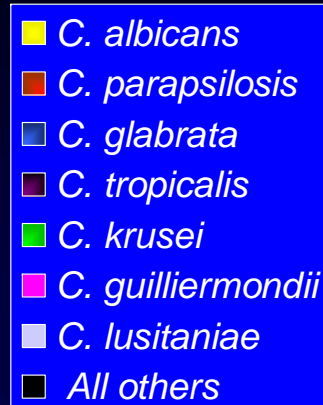
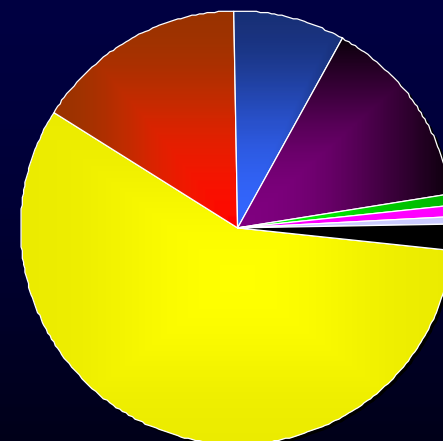
Latin America



Europe



Asia-Pacific

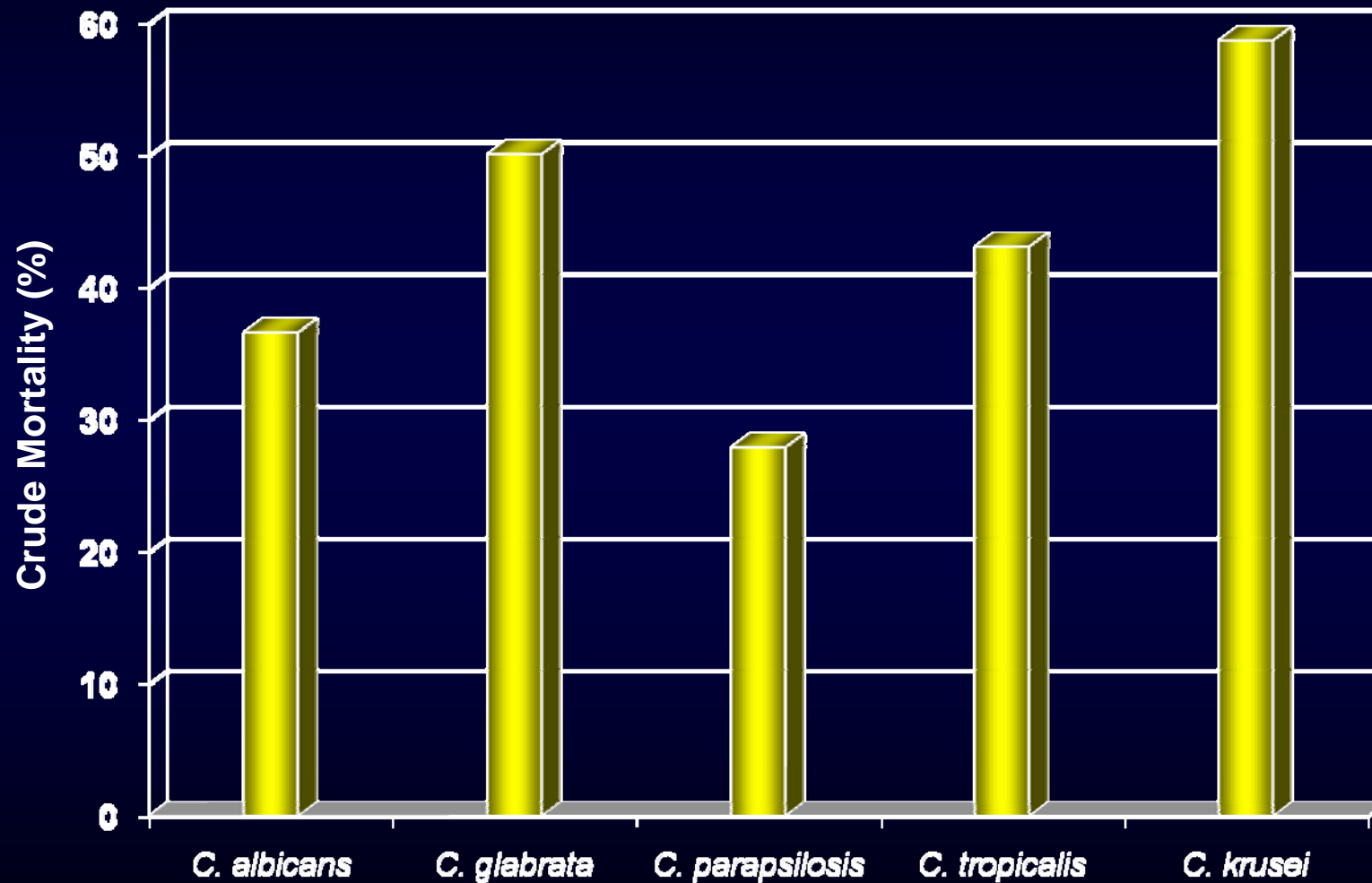


Epidemiology and Outcomes in Candidemia

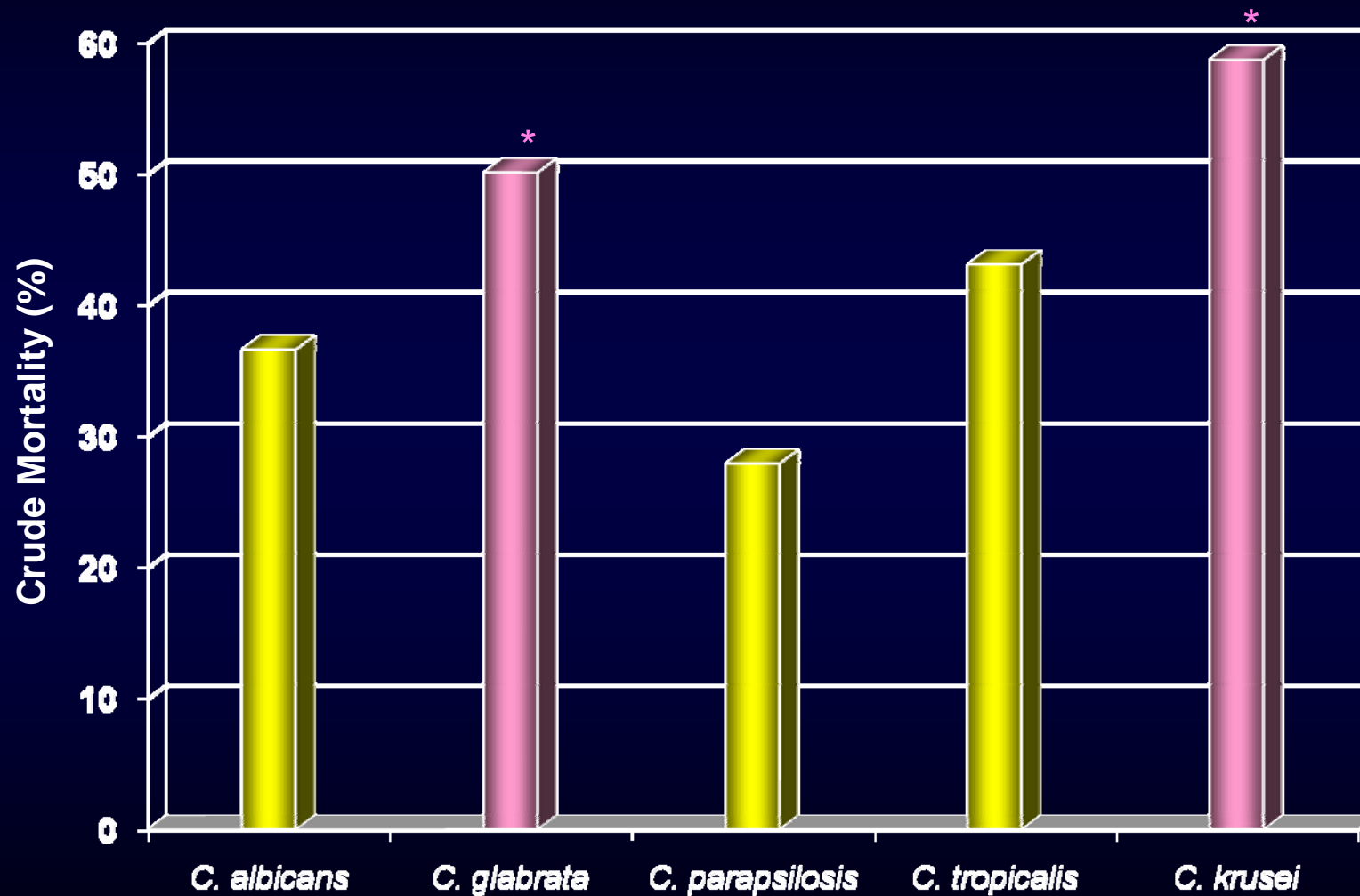
Data from the Prospective Antifungal Therapy Alliance Registry

- Prospective data from 2019 candidemic patients from 23 North American medical centers
- Incidence of candidemia
 - *C. albicans* in 45.6%
 - non-*albicans* in 54.4%
- Patients with *C. glabrata* and *C. krusei* candidemia most likely to have received prior azole therapy

Distribution of *Candida* species in 1890 Cases of *Candida* Bloodstream Infections and Associated Crude Mortality



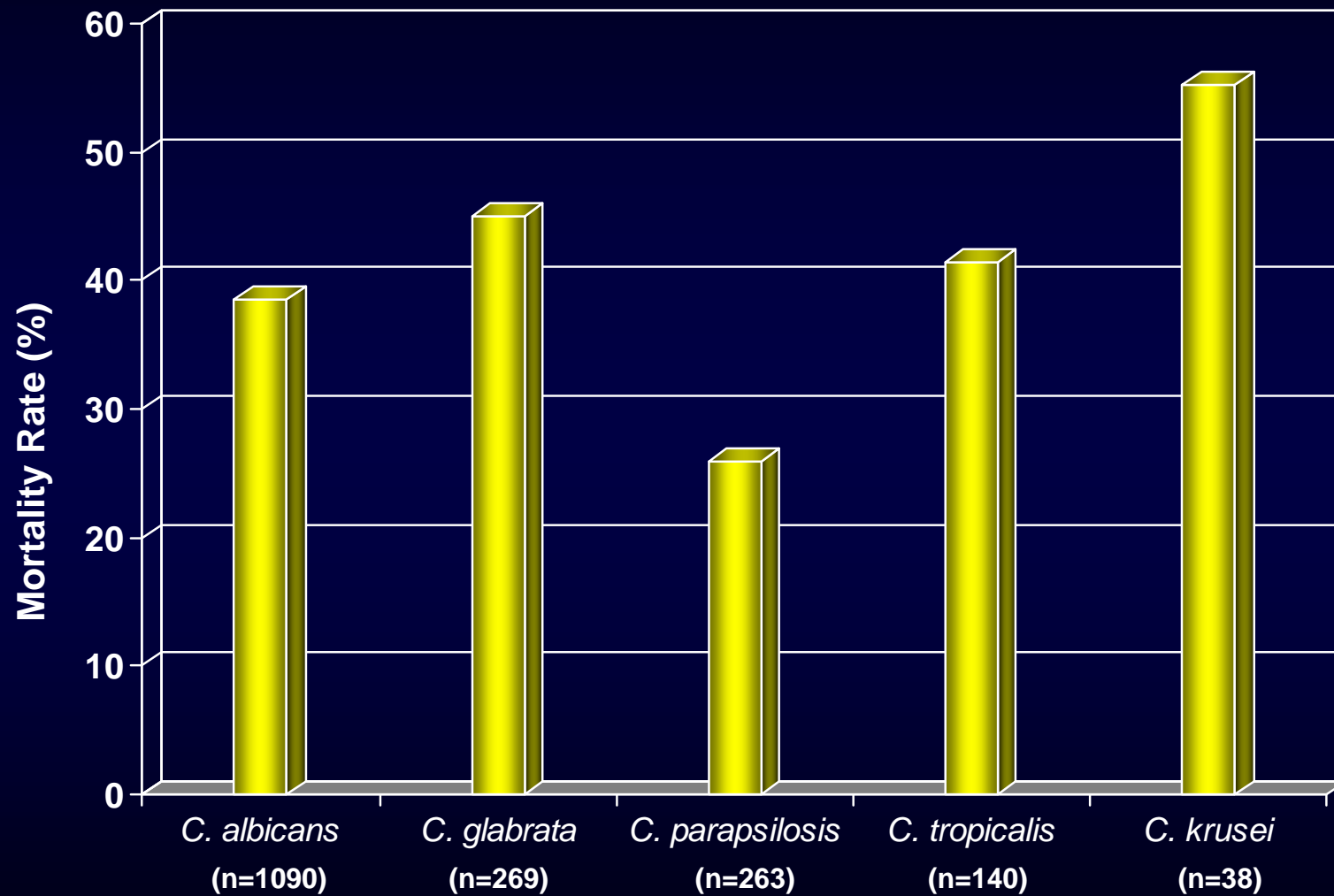
Distribution of *Candida* species in 1890 Cases of *Candida* Bloodstream Infections and Associated Crude Mortality



*potentially azole-resistant

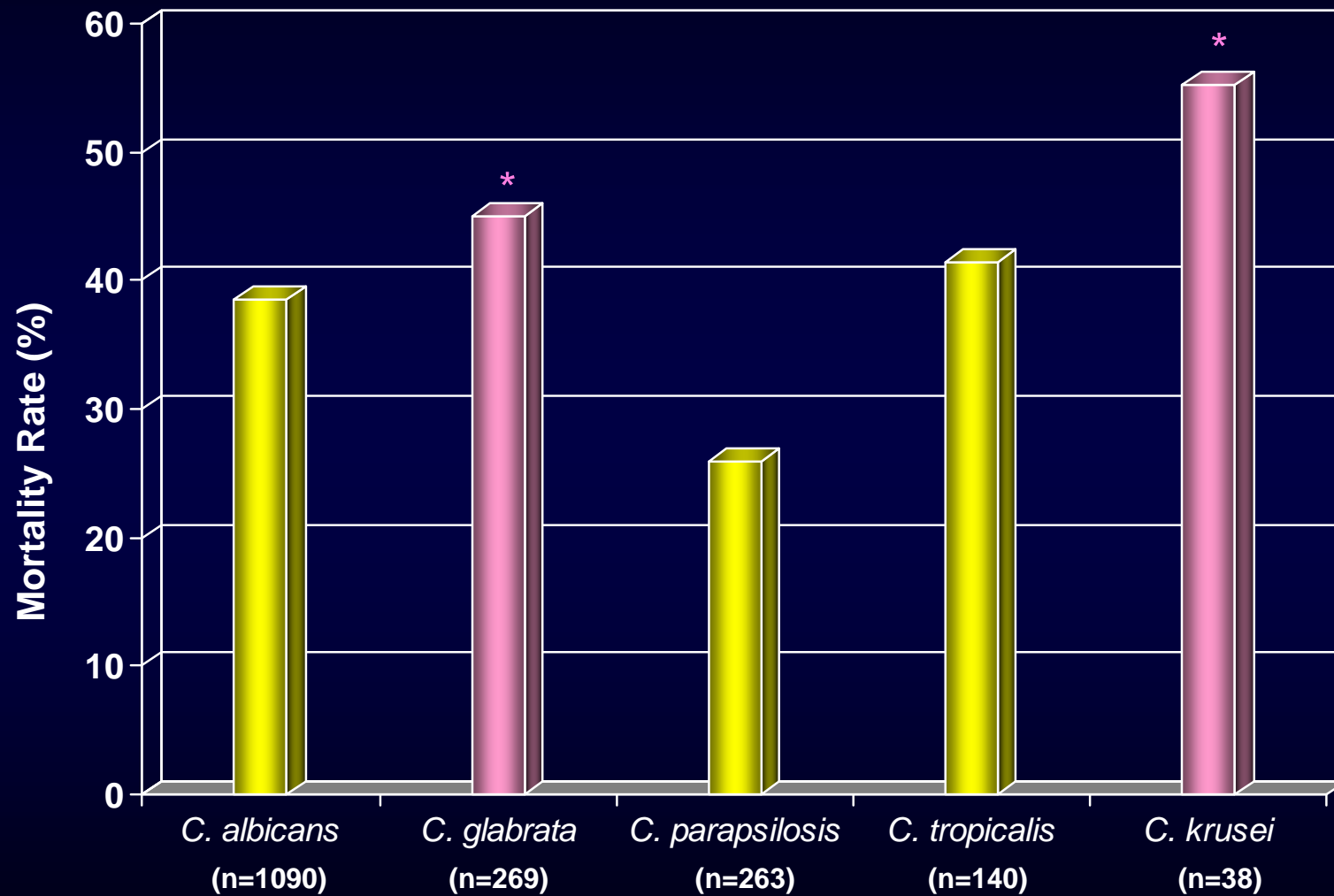
Mortality at 30 Days from *Candida* Bloodstream Infections in Europe

Data from the European Confederation of Medical Mycology



Mortality at 30 Days from *Candida* Bloodstream Infections in Europe

Data from the European Confederation of Medical Mycology



*potentially azole-resistant

Additional Consideration in the Selection of Antifungal Therapy for Invasive Candidiasis

- “All of the azole antifungals inhibit cytochrome P₄₅₀ enzymes to some degree. Thus, clinicians must carefully consider the influence on a patient’s drug regimen when adding or removing an azole.”

Potential Drug-Drug Interactions (PDDI) with Azoles

	France ¹	USA ²
Risk of PDDI	27%	70%
Potential interactions	Rifampicin (45%) Cyclosporine (40%) Glimepiride (10%) Glibenclamide (5%)	Prednisone (25%) Midazolam (18%) Warfarin (15%) Methylprednisolone (14%) Cyclosporine (11%) Nifedipine (10%)

¹Depont F et al. *Pharmacoepidemiol Drug Saf* 2007;16:1227-1233

²Yu DT et al. *Pharmacoepidemiol Drug Saf* 2005;14:755-767

Concepts in the Treatment of Candidemia

- In an attempt to prevent complications of metastatic *Candida* infection, every patient with candidemia should
 1. be treated with a course of antifungal therapy.*
 2. have intravascular lines removed (Some clinical judgment allowed in IDSA guidelines [*Clin Infect Dis* 2004;38:161-189].)

*American College of Physicians'
Medical Knowledge Self-Assessment Program IX
(*MKSAP IX*), Infectious Disease Medicine, 1991; page 311

Candida Bloodstream Infection in 245 Patients at BJH Who Received Antifungal Therapy 2004–2006

Occurrence of persistent fungemia ($P < .001$)

- In 3 (1.7%) patients who had their CVCs removed
- In 9 (22%) who did not have CVCs removed

Quality Improvement Measures in the IDSA Guidelines

1. Fundoscopic exam on all patients with proven invasive candidiasis
2. Starting antifungals within 24 hours of positive culture
3. Confirmatory negative blood cultures start of therapy

Recommendations for Antifungal Prophylaxis

- ICU patients - for high-risk patients in adult units with a high incidence of invasive candidiasis (B-I)
 - Fluconazole 400 mg (6 mg/kg) daily
- Solid-organ transplant recipients - for high-risk liver (A-I), pancreas (B-II), and small bowel (B-III) transplant recipients
 - Fluconazole 200–400 mg (3–6 mg/kg) daily for at least 7-14 days
 - LAmB 1–2 mg/kg daily, each for at least 7–14 days

De-Escalation Therapy*

Stage 1

Administering broad-spectrum antibiotic therapy to improve outcomes (decrease mortality, prevent organ dysfunction, and decrease length of stay)

Stage 2

Focusing on de-escalating as a means to minimize resistance and improve cost-effectiveness‡

*With invasive candidiasis, referred to as *transition* or *stepdown* therapy in the 2009 IDSA guidelines for invasive candidiasis (*Clin Infect Dis* 2009;48:504-535)

‡In some patients, redirection of therapy needed to cover resistant pathogens not covered with the initial regimen, to provide source control, or to treat fungal pathogens

Summary of Important Considerations Influencing the Selection of Antifungal Therapy in the ICU

- Data support the fact that delays in appropriate antifungal therapy are associated with increased mortality.
- Factors influencing antifungal selection in patients with invasive candidiasis include (1) severity of illness, (2) history of prior azole therapy, and (3) risk of infection with azole-resistant strains of *Candida*.
- Pharmacokinetic and toxicity issues may influence the therapeutic agent chosen.
- Modifications such as stepdown or transition therapy have been emphasized in recent guidelines.