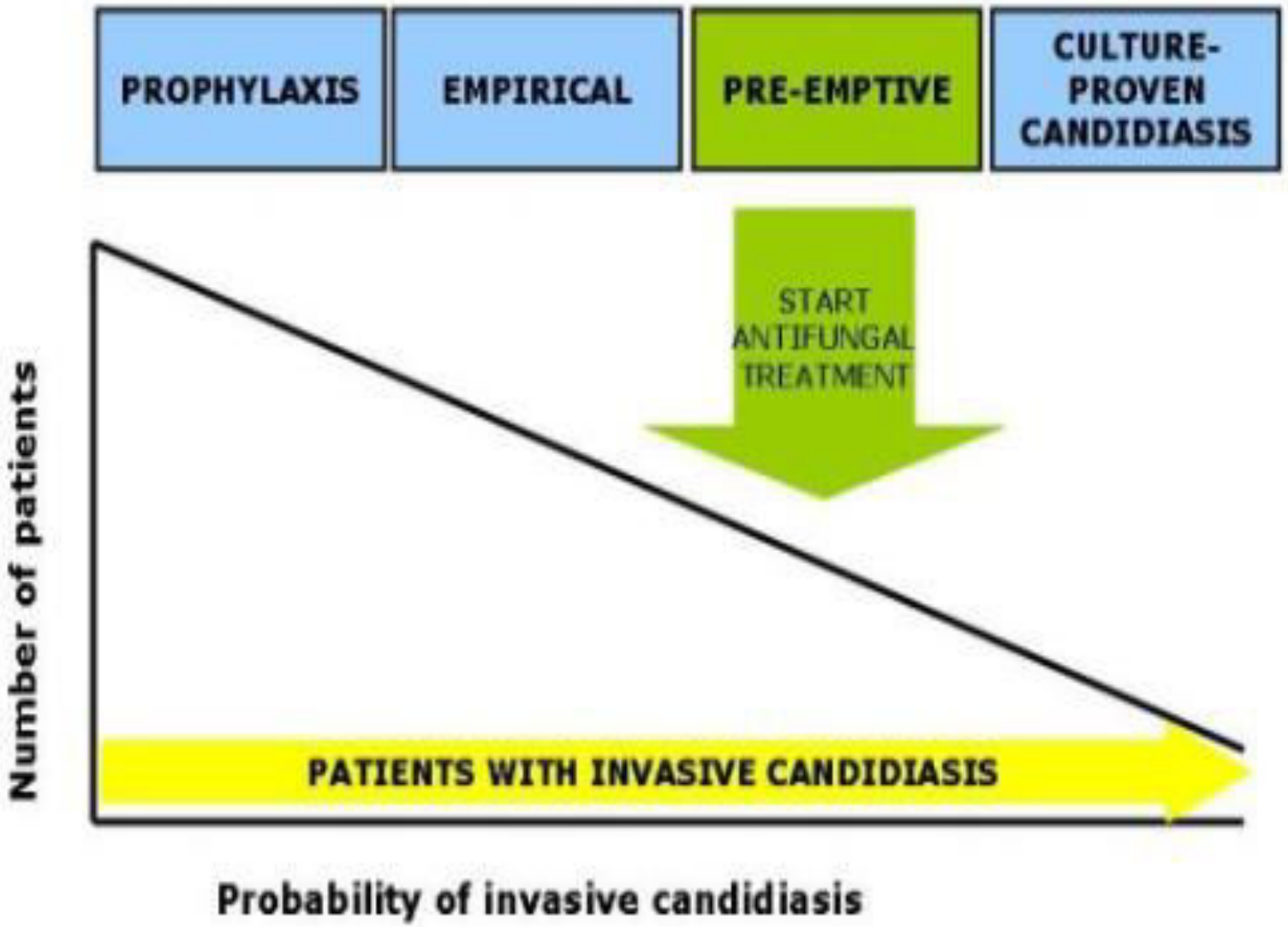
Candida infection in non-neutropenic ICU patients: Therapeutic strategies

Dr. Subhash Todi



Relationship between different antifungal strategies, probability of invasive candidiasis and number of patients potentially treated.

- A 40 yr old road traffic accident victim was admitted with head injury , requiring intubation. He has lung contusion , but no free fluid in the abdomen and CT abdomen normal

- ?Should he be started on antifungal prophylaxis

- A 60 yr old diabetic lady with urosepsis was admitted with septic shock , requiring high dose vasopressor , and on ventilator. She has grown e.coli in blood culture. She is three days in ICU and on broad spectrum antibiotics .

- Should she be started on antifungal prophylaxis ?

- A 40 yr old man admitted with enteric fever. He developed severe abdominal pain with guarding. An urgent laparotomy revealed ileal perforation with pus in abdominal cavity. Perf was sutured and omental patch was applied.

- Should this patient be started on antifungal prophylaxis ?

- A 60 yr old diabetic was admitted with COPD exacerbation. He had a prolonged ICU stay requiring multiple antibiotics and cortiocosteroid therapy. He is vent dependent but hemodynamically stable ,afebrile and tolerating enteral feed. His ET suction and urine have grown candida species.
- Should he be given preemptive or empirical antifungal therapy

- A 50 yr old diabetic patient admitted with pancreatititis. He has received imipenem for two weeks. He is spiking fever , abdominal CT shows some peripancreatic collection, His urine is growing candida.
- Should he be started empirically on antifungal?
- Which drug,dose , duration

- A 60 yr old COPD admitted with urosepsis with multiple organ failure , gradually stabilising . He has spiked a fever , but hemodynamically stable, started on broad spectrum antibiotics after sending cultures. 48 hours later culture is growing candida
- Which Antifungal will you choose , what dose , how long
- If he was in shock will your choice would have been different

Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David Andes,[4] Daniel K. Benjamin, Jr.,[5] Thierry F. Calandra,[11] John E. Edwards, Jr.,[6] Scott G. Filler,[6] John F. Fisher,[7] Bart-Jan Kullberg,[12] Luis Ostrosky-Zeichner,[8] Annette C. Reboli,[9] John H. Rex,[13] Thomas J. Walsh,[10] and Jack D. Sobel[3]

Antifungal prophylaxis

Intensive Care Med (2002) 28:1708–1717
DOI 10.1007/s00134-002-1540-y

ORIGINAL

Jorge Garbino
Daniel P. Lew
Jacques-A. Romand
Stéphane Hugonnet
Raymond Auckenthaler
Didier Pittet

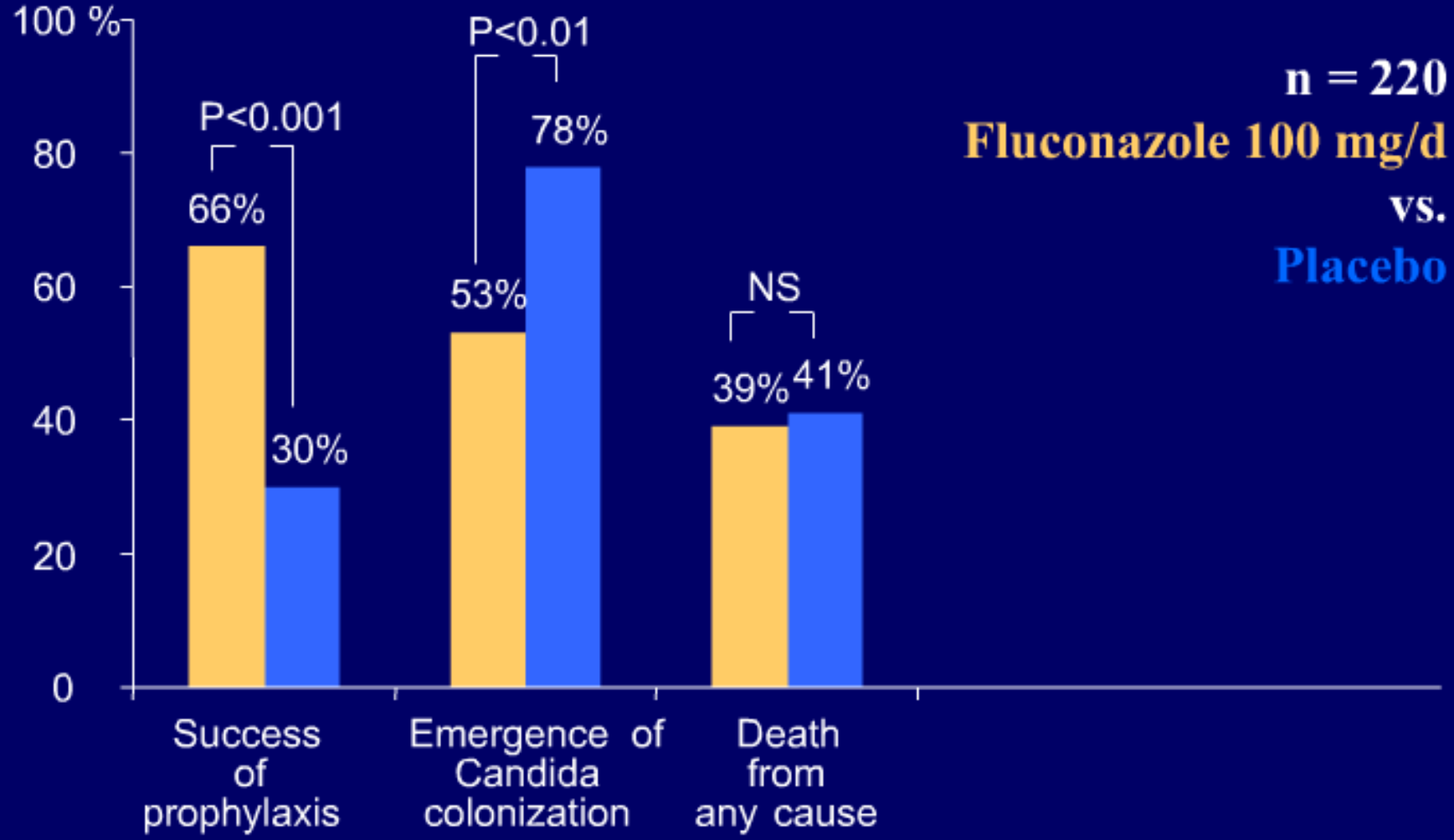
Prevention of severe *Candida* infections in nonneutropenic, high-risk, critically ill patients: a randomized, double-blind, placebo-controlled trial in patients treated by selective digestive decontamination

Fungal Prophylaxis Study

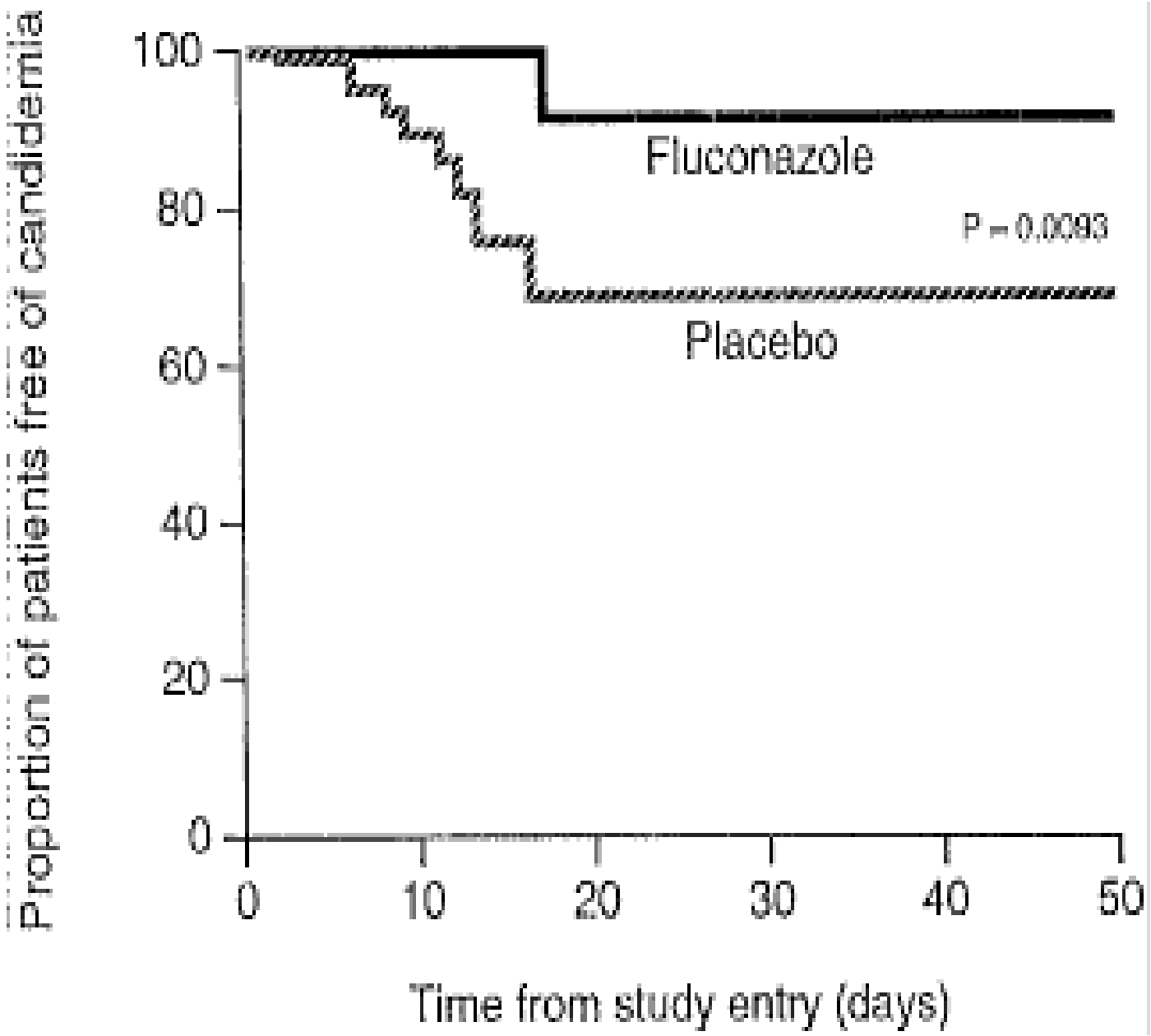
- PRDBPCT, medical and surgical ICU patients
- Large University hospital, Geneva, Switzerland
- Entry criteria
  - Anticipated ICU stay > 72 hours
  - Adult patients requiring mechanical ventilation for at least 48 hrs
  - All patients received SDD
- Fluconazole 100mg daily or placebo

Garbino J, Lew DP, Romand JA, et al: Intensive Care Med 2002; 28:1708-17

Endpoints of Fluconazole 100 mg/d vs. Placebo for ICU Prophylaxis



Garbino J, Lew DP, Romand JA, et al: *Intensive Care Med* 2002; 28:1708-17


Proportion of patients free of candidemia
100
80
60
40
20
0
Fluconazole
P = 0.0093
Placebo
0
10
20
30
40
50
Time from study entry (days)

- Prophylactic use of fluconazole in a selected group of mechanically ventilated patients at high risk for infection reduces the incidence of Candida infections, in particular candidemia

ANNALS OF SURGERY
Vol. 233, No. 4, 542–548

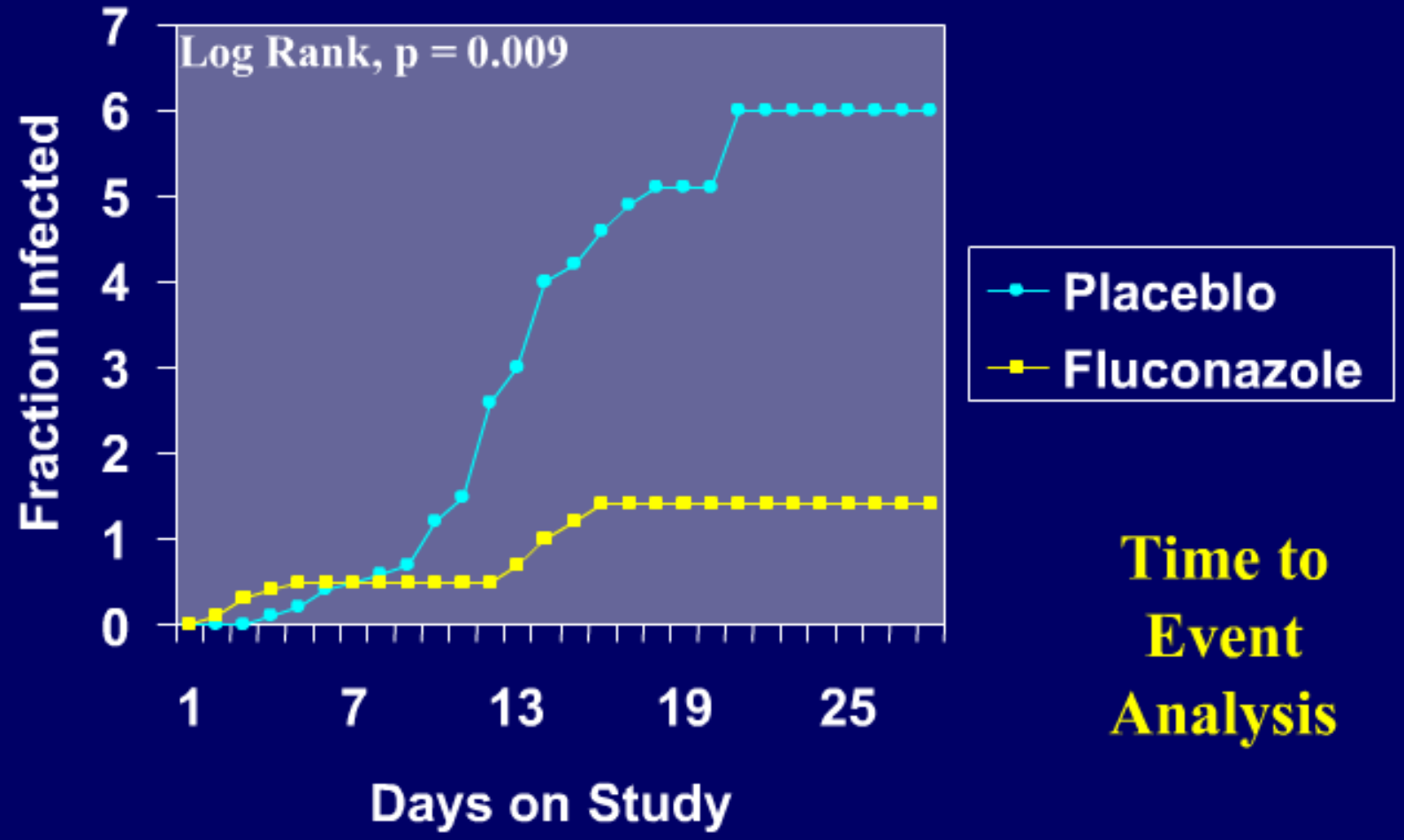
Double-Blind Placebo-Controlled Trial of Fluconazole to Prevent Candidal Infections in Critically Ill Surgical Patients

Robert K. Pelz, MD,*‖ Craig W. Hendrix, MD*‡‖ Sandra M. Swoboda, RN, MS,† Marie Diener-West, PhD,‡ William G. Merz, PhD,§ Janet Hammond, MD,* and Pamela A. Lipsett, MD,†¶

*From the Departments of *Medicine, †Surgery, ‡Epidemiology and Biostatistics, §Microbiology, ‖Clinical Pharmacology, and ¶Anesthesiology and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland*

- Single-center, tertiary care SICU
- 260 ICU pts, ICU LOS $\geq$ 3 days
- Enteral fluconazole 400mg qD vs. placebo

A Double-Blind Placebo-controlled Trial of Prophylactic Fluconazole to Prevent Candida Infections in Critically Ill Surgical Patients



Time to Event Analysis

Pelz RK, Hendrix CW, Swoboda SM et al: *Ann Surg* 2001; 233:542-8

Outcome - Candida Infection
Fluconazole 400 mg/day vs. Placebo

	Fluconazole (n=130)	Placebo (n=130)	P value
Candida infection	**11 (8.5%)**	**20 (15%) ***	**0.01**
Peritonitis	3	8	
Candidemia	1	3	
Catheter	1	6	
C. albicans	5 (45%)	12 (60%)	NS
C. glabrata	3 (27%)	5 (25%)	NS
Mortality	14 (11%)	16 (12%)	NS

*** But… 15% rate of Candida infection in placebo group high, similar to BMT!**

Multivariate Analysis of Predictors of Failure

	Risk Ratio	95% Confidence Interval
Fungal colonization	***10.64***	***1.43-78.74***
Randomization to fluconazole	0.45	0.21-0.98
APACHE III	1.02	1.01-1.04
Days to first dose of study drug	1.34	1.00-1.79

Pelz RK, Hendrix CW, Swoboda SM et al: *Ann Surg* 2001; 233:542-8

A Double-Blind Placebo-controlled Trial of Prophylactic Fluconazole to Prevent Candida Infections in Critically Ill Surgical Patients

- After adjusting for APACHE III score, days to first dose, and fungal colonization at enrollment, risk of fungal infection was reduced by 55% in the fluconazole group.

Conclusion:

Enteral fluconazole safely and effectively decreased the incidence of fungal infections in high risk, critically ill surgical patients.

Pelz RK, Hendrix CW, Swoboda SM et al: *Ann Surg* 2001; 233:542-8

[Intervention Review]
Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

PDF
- Summary (59 K)
- Standard (451 K)
- Full (535 K)

- Abstract

[Intervention Review]

Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients

Elliott Geoffrey Playford[1], Angela C Webster[2], Tania C Sorrell[3], Jonathan C Craig[4]

[1]Infection Management Services, Princess Alexandra Hospital, Woolloongabba, Australia. [2]School of Public Health, University of Sydney, Sydney, Australia. [3]Centre for Infectious Diseas
Hospital, Westmead, Australia. [4]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, Australia

Contact address: Elliott Geoffrey Playford, Infection Management Services, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Queensland, 4102, Australia. geoffrey_playford@

Editorial group: Cochrane Anaesthesia Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.
Review content assessed as up-to-date: 7 November 2005.

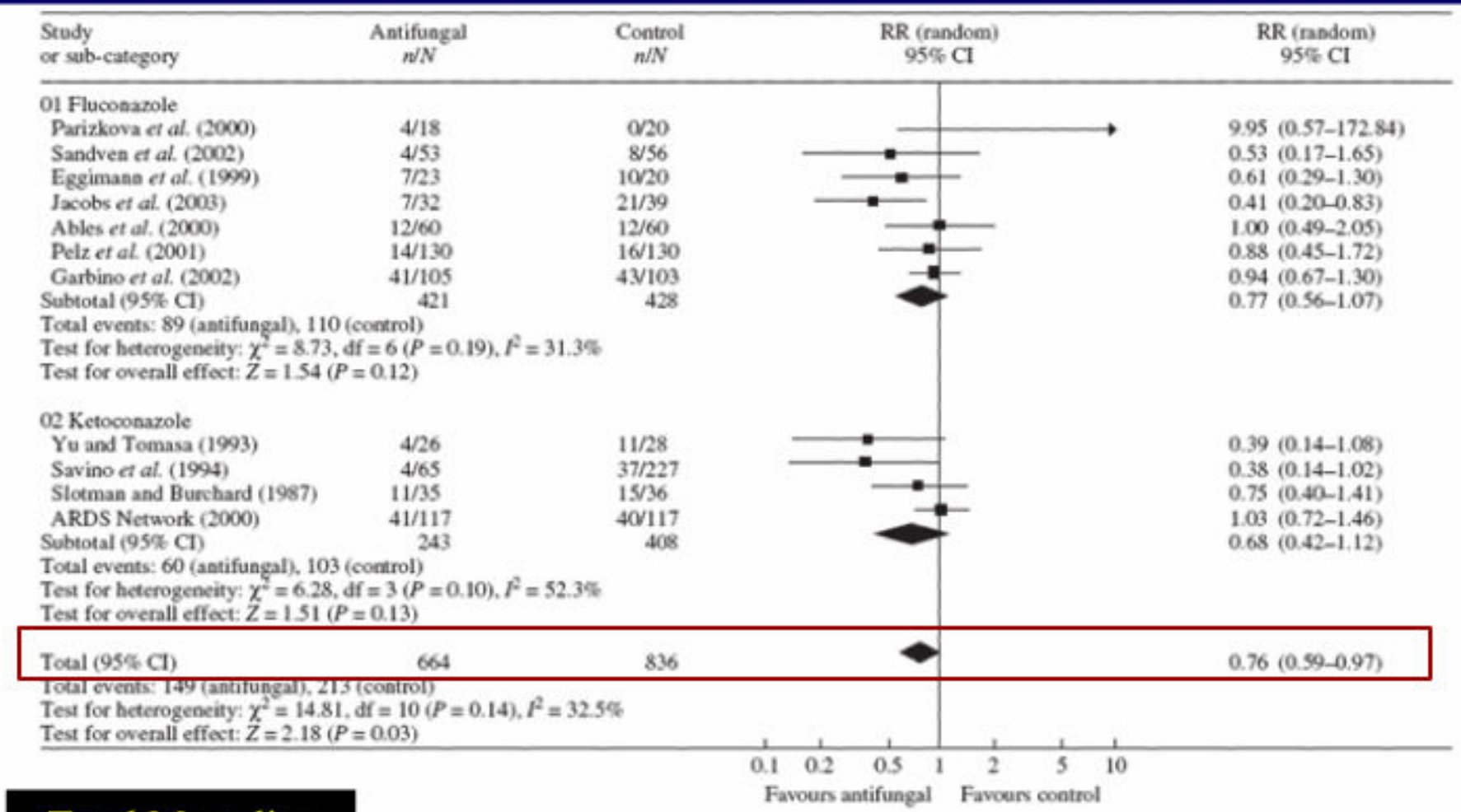
Antifungal agents for preventing fungal infections in non-neutropenic critically ill and surgical patients: systematic review and meta-analysis of randomized clinical trials

- Evaluate the effects of antifungal prophylaxis in non-neutropenic critically ill adult patients on all-cause mortality and the incidence of invasive fungal infections.
- 12 unique trials, n=1606 randomized pts
- Antifungal agents:
  - Fluconazole
  - Ketoconazole

Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004920.

Playford EG et al. Journal of Antimicrobial Chemotherapy 2006 Apr;57(4):628-38. Epub 2006 Feb 3.

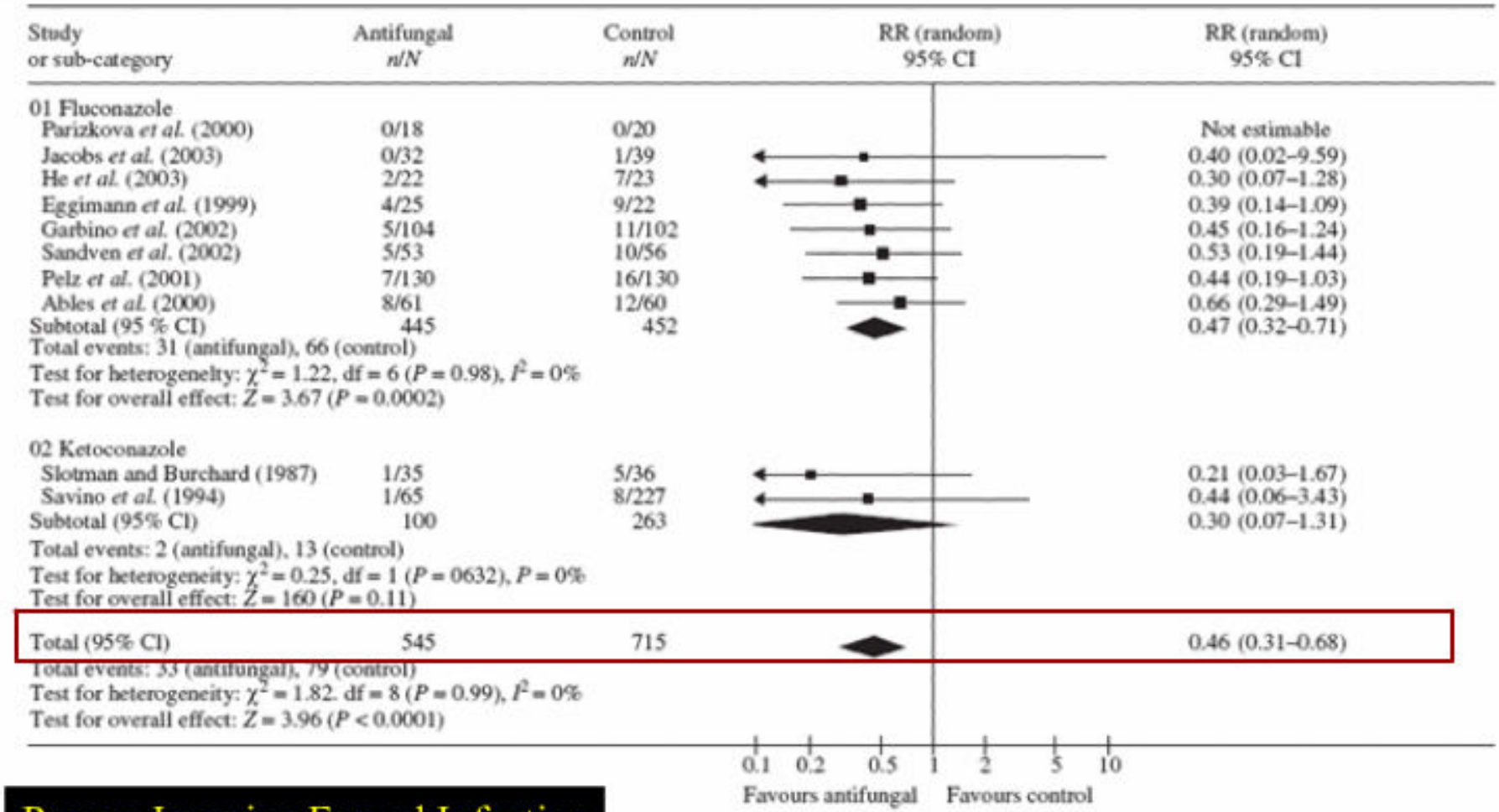
Antifungal agents for preventing fungal infections in non-neutropenic critically ill and surgical patients: systematic review and meta-analysis of randomized clinical trials



Total Mortality

Playford EG et al. Journal of Antimicrobial Chemotherapy 2006 Apr;57(4):628-38. Epub 2006 Feb 3.

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



Proven Invasive Fungal Infection

Playford EG et al. Journal of Antimicrobial Chemotherapy 2006 Apr;57(4):628-38. Epub 2006 Feb 3.

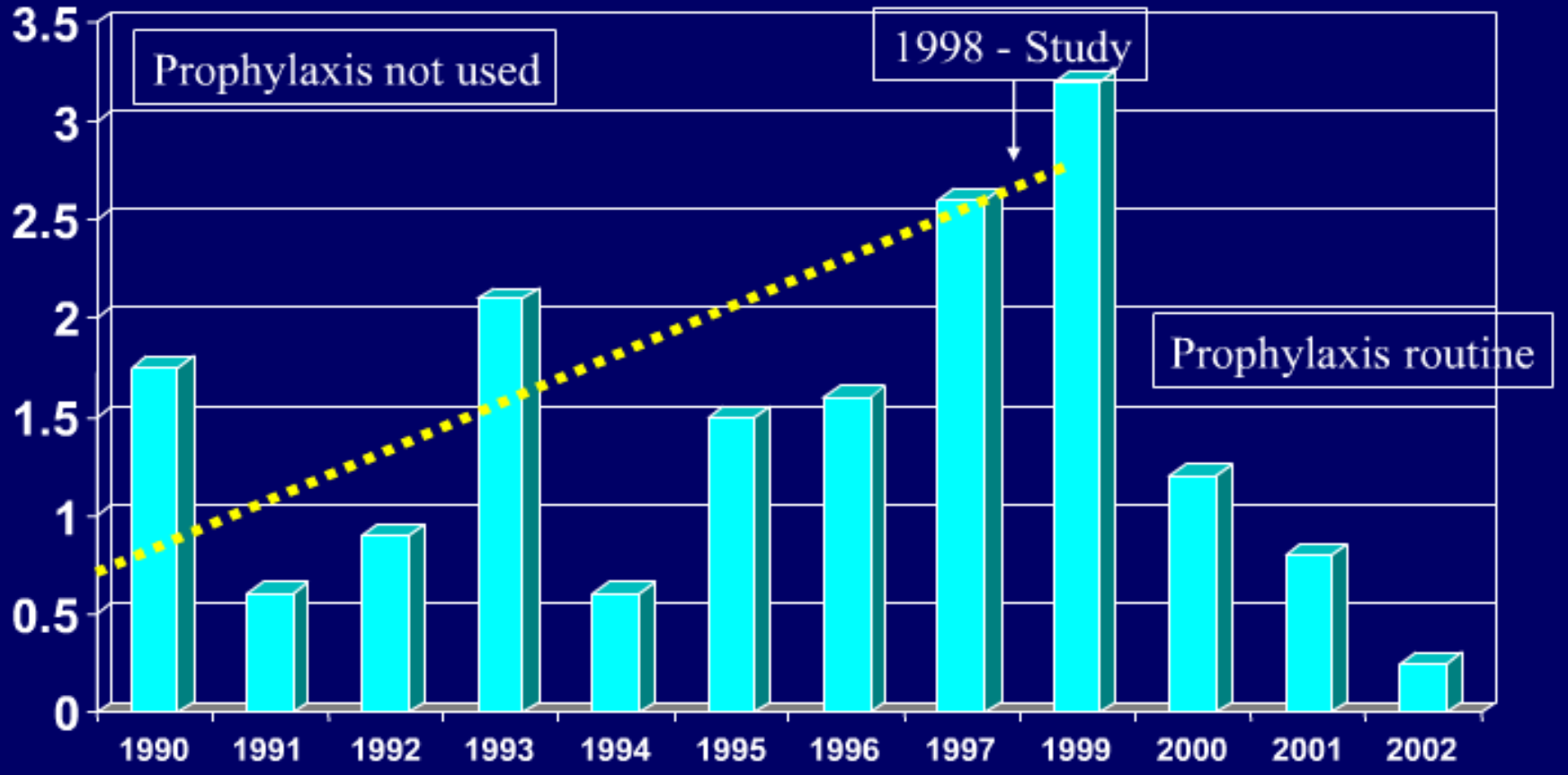
- Prophylaxis with fluconazole or ketoconazole in critically ill patients reduces invasive fungal infections by one half and total mortality by one quarter. Although no significant increase in azole-resistant *Candida* species associated with prophylaxis was demonstrated, trials were not powered to exclude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

Candidemia: Impact of Antifungal Prophylaxis in a SICU

- Retrospective review of Candidemia
- SICU, Large tertiary care hospital
- 1990 to 2002
- Antifungal prophylaxis began in 2000 for high-risk patients
- PRE-prophylaxis: 1990-2000
- POST-prophylaxis: 2000-2002

Swoboda SM, Merz WG, Lipsett PA: *Surgical Infections* 2003;4(4):345-354

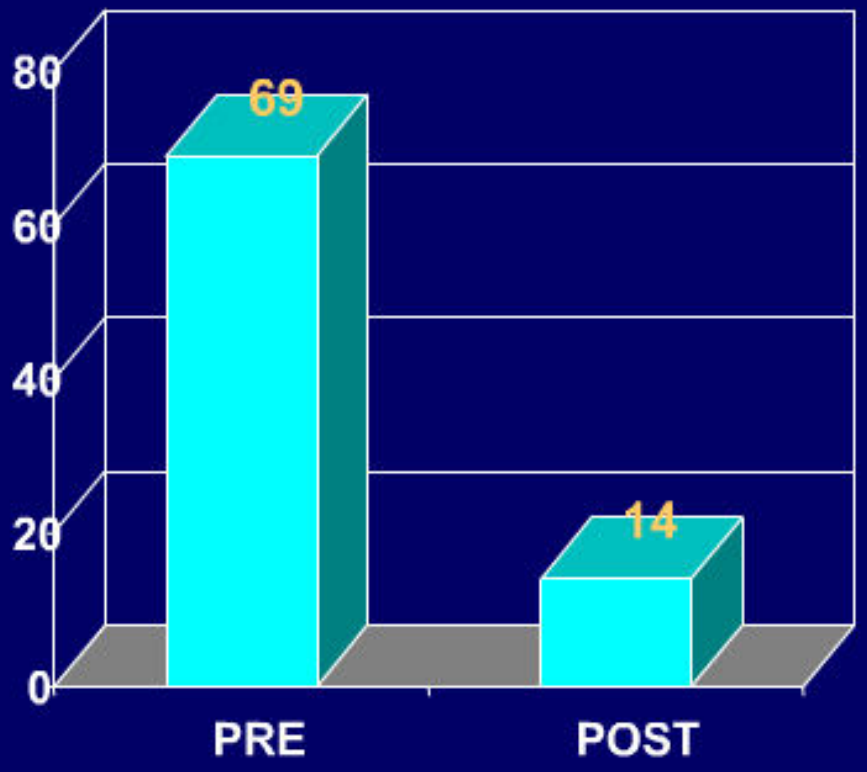
Annual Incidence of Candidemia per 1000 pt days



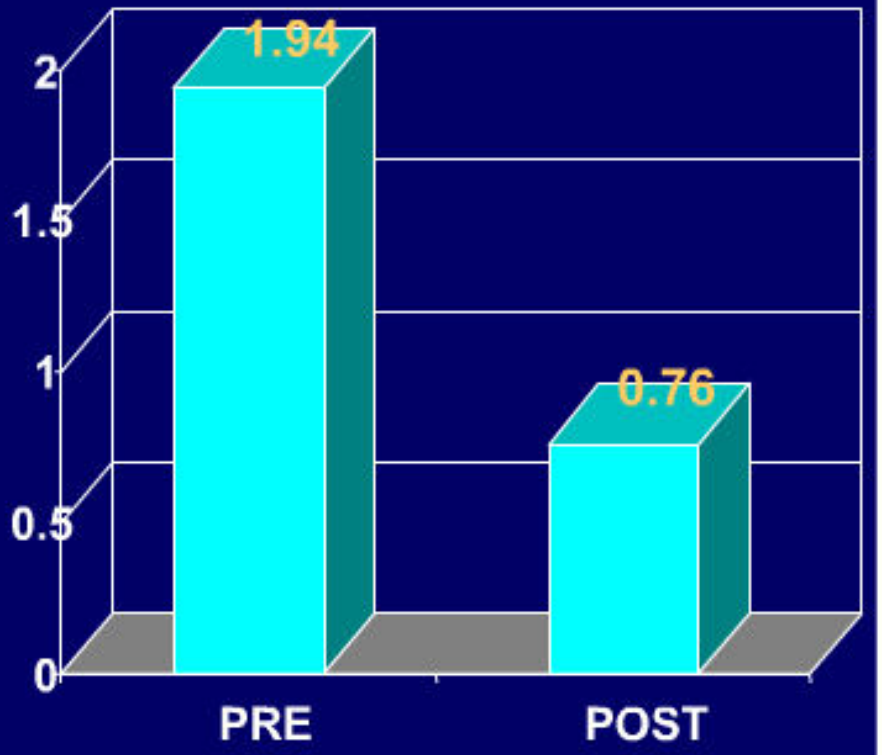
Dashed line: Linear regression with annual increase of 0.20 per yr from 1990-99

Swoboda SM, Merz WG, Lipsett PA: *Surgical Infections* 2003;4(4):345-354

Candidemia: Impact of Antifungal Prophylaxis in a SICU



Number of patients



Number / 1000 patient days

OR 0.44; CI 0.25-0.78, p=0.004 – Mortality 52% both PRE and POST

Swoboda SM, Merz WG, Lipsett PA: *Surgical Infections* 2003;4(4):345-354

Candidemia: Impact of Antifungal Prophylaxis in a SICU

	PRE (n=69)	POST (n=14)	P value
Colonization	62 (90%)	9 (64%)	0.05
C. albicans	45%	21%	0.11
C. glabrata	30%	64%	0.01
Other	25%	15%	
Non-albicans sp.	38/69 55%	11/14 79%	0.10

Swoboda SM, Merz WG, Lipsett PA: *Surgical Infections* 2003;4(4):345-354

Recommendation

- For ICUs that show very high rates of invasive candidiasis, compared with the normal rates of 1%–2%, antifungal prophylaxis may be warranted , and selected ICU patients who are at highest risk of invasive candidiasis may benefit from antifungal prophylaxis .

Crit Care Med. 2013 Feb;41(2):565-72. doi: 10.1097/CCM.0b013e31826a409c.

Evaluation of efficacy of probiotics in prevention of candida colonization in a PICU-a randomized controlled trial.

Kumar S, Bansal A, Chakrabarti A, Singhi S.

Department of Pediatrics, Advanced Pediatric Centre, Chandigarh, India.

Abstract

OBJECTIVE: To evaluate the efficacy of probiotics in prevention of Candida colonization in a PICU.

DESIGN: Prospective double blinded, randomized controlled trial.

SETTING: PICU of a tertiary care teaching hospital in north India.

SUBJECTS: One hundred fifty children (106 boys, 44 girls), 3 months to 12 yrs old, on broad spectrum antibiotics for at least 48 hrs were randomized using computer-generated random numbers to receive probiotic mix (EUGI) (n = 75) or placebo (n = 75).

INTERVENTION: Patients received one sachet twice a day of either probiotics or placebo for 7 days. Probiotics contained Lactobacillus acidophillus, Lactobacillus rhamnosum, Bifidobacterium longum, Bifidobacterium bifidum, Saccharomyces boulardi, Saccharomyces thermophilus, fructo-oligosaccharides; and placebo-contained lactose packed in similar-looking sachets. Rectal swabs for fungal culture were taken at day 0, 7, and 14 of enrollment. Primary outcome measure was prevalence of rectal colonization with Candida on day 14 postenrollment; secondary outcomes were growth of Candida in urine (candiduria) and blood (candidemia). Patients were followed until completion of 14 days study period or death of patient.

RESULTS: Demographic and clinical variables were comparable in two groups. Prevalence of Candida colonization on day 0 was similar (15 of 75) in both the groups. On day 7, 27.9% (19 of 68) patients in the probiotic group and 42.6% (29 of 68) patients in the placebo group were colonized (relative risk 0.65; 95% confidence interval 0.41-1.05; p = 0.07), whereas, on day 14, colonization was observed in 31.3% (21 of 67) patients in the probiotic group and 50% (34 of 68) in the placebo group (relative risk 0.63; 95% confidence interval 0.41-0.96; p = 0.02). Thus, the relative reduction in prevalence of Candida colonization on day 7 and 14 in the probiotic group was 34.5% and 37.2%, respectively. The increase in number of colonized patients from day 0 to 7 and day 0 to 14 was significant in the placebo group (p = 0.004 and 0.001, respectively) but not in the probiotic group (p = 0.30 and 0.19, respectively; McNemar test). Candiduria was significantly less common in the probiotic group than in the placebo group (17.3% vs. 37.3%; relative risk 0.46; 95% confidence interval 0.26-0.82; p = 0.006). However, prevalence of candidemia did not differ significantly in two groups (1.6% in the probiotic group vs. 6.35% in placebo group; relative risk 0.46; 95% confidence interval 0.08-2.74; p = 0.39).

CONCLUSIONS: Supplementation with probiotics could be a potential strategy to reduce gastrointestinal Candida colonization and candiduria in critically ill children receiving broad spectrum antibiotics.

Comment in

Preventing invasive candidiasis in high-risk critically ill patients: avoid antibiotics or give probiotics? [Crit Care Med. 2013]

- A 40 yr old road traffic accident victim was admitted with head injury , requiring intubation. He has lung contusion , but no free fluid in the abdomen and CT abdomen normal

- ?Should he be started on antifungal prophylaxis

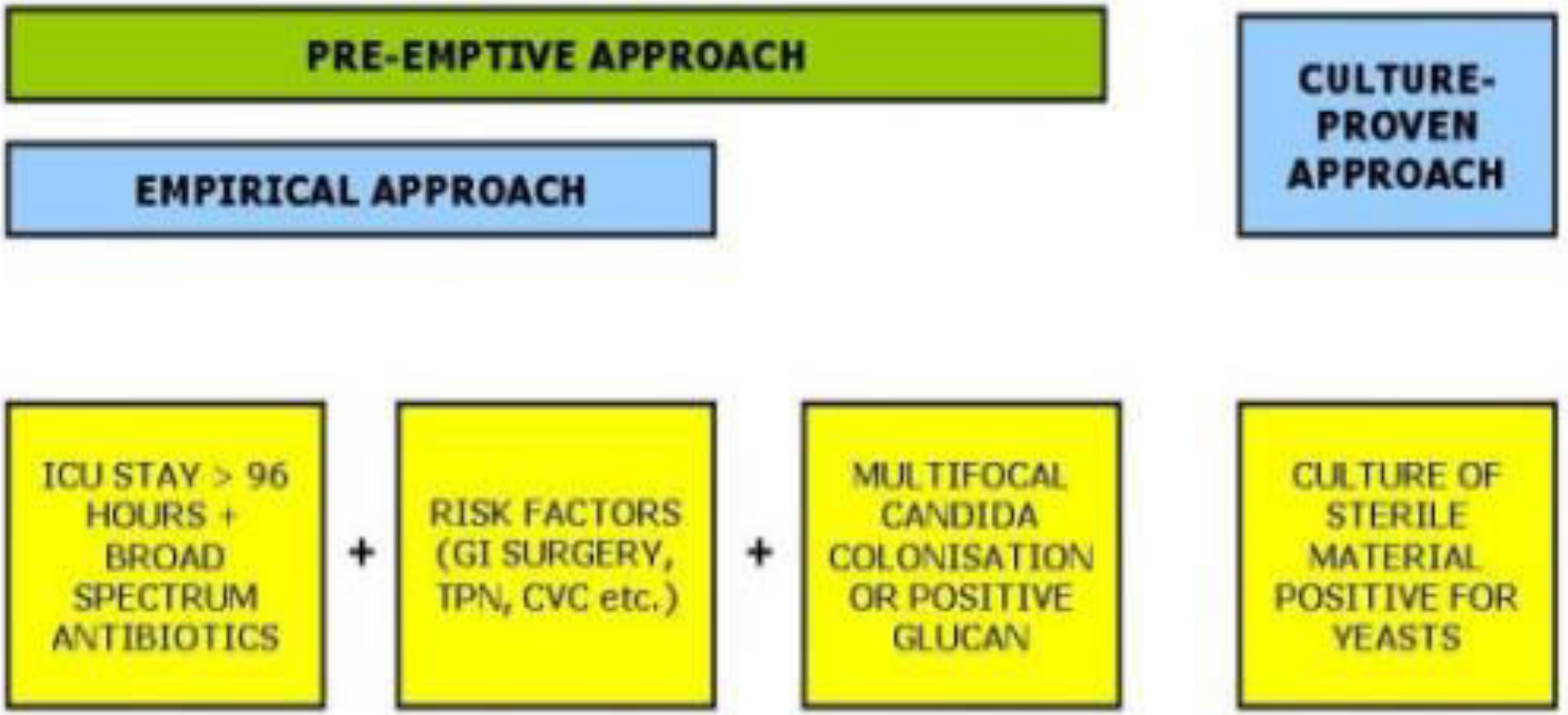
- A 60 yr old diabetic lady with urosepsis was admitted with septic shock , requiring high dose vasopressor , and on ventilator. She has grown e.coli in blood culture. She is three days in ICU and on broad spectrum antibiotics .

- Should she be started on antifungal prophylaxis ?

- A 40 yr old man admitted with enteric fever. He developed severe abdominal pain with guarding. An urgent laparotomy revealed ileal perforation with pus in abdominal cavity. Perf was sutured and omental patch was applied.

- Should this patient be started on antifungal prophylaxis ?

Empirical /Pre emptive therapy


PRE-EMPTIVE APPROACH
EMPIRICAL APPROACH
CULTURE-PROVEN APPROACH
ICU STAY > 96 HOURS + BROAD SPECTRUM ANTIBIOTICS
+
RISK FACTORS (GI SURGERY, TPN, CVC etc.)
+
MULTIFOCAL CANDIDA COLONISATION OR POSITIVE GLUCAN
CULTURE OF STERILE MATERIAL POSITIVE FOR YEASTS

Empirical

- Fever
- Not responding to broad spectrum antibiotic
- Risk factor for candida present
- Multifocal candida colonisation

Preemptive

- Afebrile
- Risk factor for candida present
- Multifocal candida colonisation
- Positive B-d Glucan

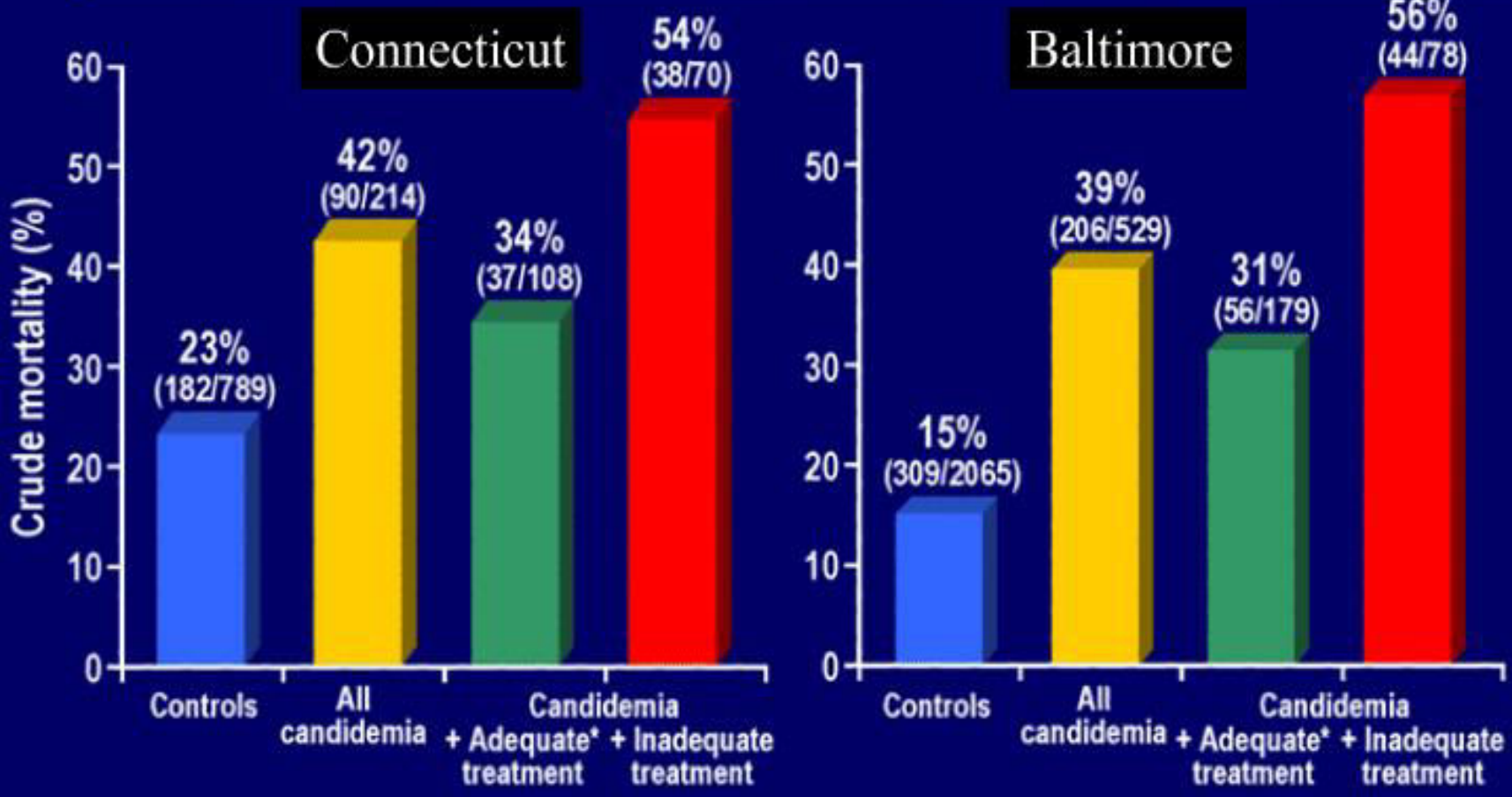
Empirical

- Fever
- Not responding to broad spectrum antibiotic
- Risk factor for candida present
- Multifocal candida colonisation

Preemptive

- Fever
- Not responding to broad spectrum antibiotic
- Risk factor for candida present
- Multifocal candida colonisation
- Positive B-d Glucan

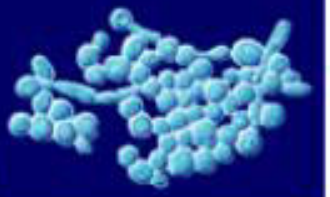
Impact of Inadequate Antifungal Therapy on Crude Mortality in Candidemia



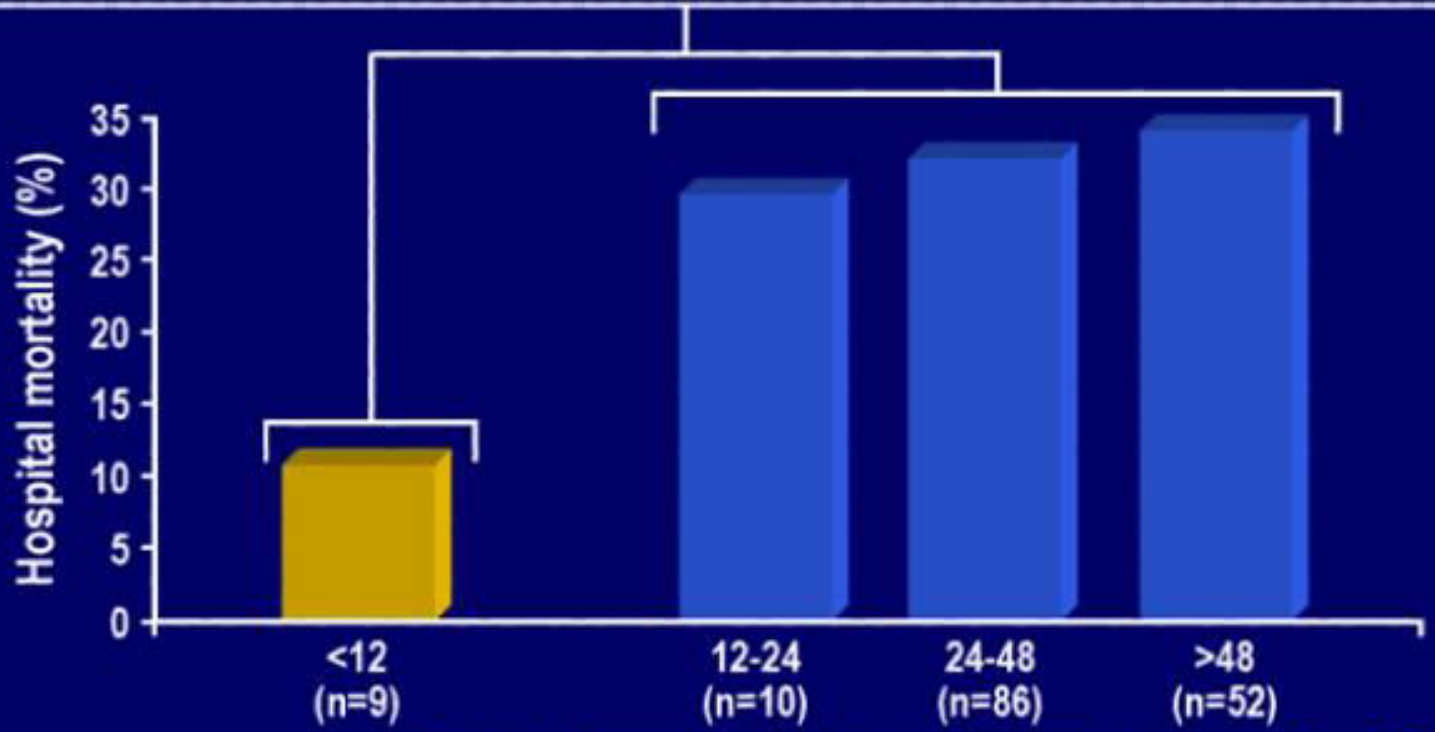
*Adequate treatment was defined as any systemic antifungal medication administered for a minimum of 7 days after the first *Candida*-positive blood culture.

Adapted from Morgan J et al. *Infect Control Hosp Epidemiol*. 2005;26:540-547.

Significantly Increased Risk of Hospital Mortality With Delayed Antifungal Therapy



Adjusted odds ratio for difference: 2.09 (95% CI: 1.53-2.84; P=.018)*



N = 157
Candida BSI
31.8% mortality at 30-days

*By multiple logistic regression analysis.

Morrell M et al. *Antimicrob Agents Chemother*. 2005;49:3640-3645.

Impact on mortality of early antifungal therapy

158 candidemic patients
In-hospital mortality: 31.8%

Variable	Adjusted odds ratio	95% Confidence interval	*P* value
APACHE II score (one-point increments)	1.24	1.18–1.31	<0.001
Prior antibiotic treatment	4.05	2.14–7.65	0.028
Delay in antifungal treatment	2.09	1.53–2.84	0.018

Antimicrob Agents Chemother 2005; 49: 3640-3645

- Risk factors
- Multifocal colonisation

Table 1. Particular risk factors associated with candidemia due to different *Candida* species

Candida species	Risk factor
Candida tropicalis	Neutropenia and bone marrow transplantation
Candida krusei	Fluconazole use
	Neutropenia and bone marrow transplantation
Candida glabrata	Fluconazole use
	Surgery
	Vascular catheters
	Cancer
	Older age
Candida parapsilosis	Parenteral nutrition and hyperalimentation
	Vascular catheters
	Being neonate[a]
Candida lusitaniae and *Candida guilliermondii*	Previous polyene use
Candida rugosa	Burns

http://ccforum.com/content/14/6/244

Table 2. Common susceptibility of various *Candida* species

Species	Amphotericin B	Echinocandins[a]	Fluconazole	Itraconazole	Voriconazole[b]
Candida albicans	S	S	S to R[c]	S	S
Candida glabrata	S	S	S-DD to R	S-DD to R	S to R[d]
Candida krusei	S	S	R	S-DD to R	S
Candida lusitaniae	S to R[e]	S	S	S	S
Candida parapsilosis	S	S to R[f]	S	S	S
Candida tropicalis	S	S	S	S	S

Recommendations

- Criteria for starting empirical antifungal therapy in nonneutropenic patients remain poorly defined.
- Early initiation of antifungal therapy may reduce morbidity, mortality, and length of stay in critically ill patients, but the widespread use of these agents must be balanced against the risk of toxicity, costs, and the emergence of resistance.

Recommendations

- Empirical therapy for suspected candidiasis in nonneutropenic patients is similar to that for proven candidiasis

- A 50 yr old diabetic patient admitted with pancreatititis. He has received imipenem for two weeks. He is spiking fever , abdominal CT shows some peripancreatic collection, His urine is growing candida.
- Should he be started empirically on antifungal?

- **WHAT IS THE TREATMENT OF CANDIDEMIA IN NONNEUTROPENIC PATIENTS?**

Recommendations

- Selection of antifungal agent for candida
  - history of recent azole exposure
  - a history of intolerance to an antifungal agent
  - the dominant *Candida species and current susceptibility* data in a particular clinical unit or location
  - severity of illness
  - relevant comorbidities
  - evidence of involvement of the CNS, cardiac valves, and/or visceral organs

- Fluconazole should be considered first-line therapy for patients
  - who have mild to moderate illness (i.e., are hemodynamically stable)
  - who have no previous exposure to azoles
  - who do not belong in a group at high risk of *C. glabrata (infection e.g., elderly patients, patients with* cancer, and patients with diabetes).

- Patients with candidemia and suspected concomitant endocardial or CNS involvement should probably not receive fluconazole as initial therapy
- They should receive an agent that is fungicidal, such as AmB (for endocardial or CNS candidiasis) or an echinocandin (for endocardial candidiasis)

- Step-down therapy to fluconazole is reasonable for patients who have improved clinically after initial therapy with an echinocandin or AmB and who are infected with an organism that is likely to be susceptible to fluconazole (e.g., *C. albicans, C. parapsilosis, and Candida tropicalis)*

- The echinocandins demonstrate significant fungicidal activity against all *Candida species, and each has demonstrated success* in ~75% of patients in randomized clinical trials

- Because of their efficacy, favorable safety profile, and very few drug interactions, the echinocandins are favored for initial therapy for patients
    - who have a recent history of exposure to an azole
    - moderately severe to severe illness (i.e., are hemodynamically unstable)
    - allergy or intolerance to azoles or AmB,
    - high risk of infection with *C. krusei or C. glabrata*

- The Expert Panel favors fluconazole over the 3 available echinocandins for treatment of candidemia due to *C. parapsilosis on the basis of the decreased in vitro* activity of echinocandins against *C. parapsilosis*

- Most experts agree that the echinocandins are sufficiently similar to be considered interchangeable

- Voriconazole possesses activity against most *Candida species, including C. krusei ,*
  - need for more-frequent administration
  - less predictable pharmacokinetics
  - more drug interactions
  - and poor tolerance to the drug

- Voriconazole does not provide predictable activity against fluconazole-resistant *C. glabrata*

- AmB-d is recommended as initial therapy
  - when alternative therapy is unavailable or unaffordable
  - when there is a history of intolerance to echinocandins or azoles
  - when the infection is refractory to other therapy
  - when the organism is resistant to other agents
  - when there is a suspicion of infection due to non-*Candida yeast, such as Cryptococcus neoformans*.

Table 4. Choice of antifungals for treatment of candidemia in critically ill patients

Treatment	First choice	Alternative
Pre-emptive or empirical	Echinocandin	Lipid formulation of amphotericin B
Culture-proven candidemia		
Candida albicans	Echinocandin	Fluconazole or lipid formulation of amphotericin B
Candida glabrata	Echinocandin	Lipid formulation of amphotericin B
Candida krusei	Echinocandin	Lipid formulation of amphotericin B
Candida parapsilosis	Lipid formulation of amphotericin B	Echinocandin or fluconazole

Table 6. Dosing of currently available antifungals for treating candidemia

Drug	Loading dose (first 24 hours)	Daily dose
Fluconazole	800 mg (12 mg/kg)	400 mg (6 mg/kg)
Itraconazole	–	200 mg/day*
Voriconazole	6 mg/kg every 12 hours for first two doses	3 mg/kg every 12 hours
Posaconazole	–	200 mg x 3*
Amphotericin B deoxycholate	–	0.5 to 1 mg/kg
Liposomal amphotericin B	–	3 mg/kg
Lipid complex amphotericin B	–	5 mg/kg
Anidulafungin	200 mg	100 mg
Caspofungin	70 mg	50 mg
Micafungin	–	100 mg

*After a full meal.

Table 7. Main differences between the three echinocandins available

Variable	Anidulafungin	Caspofungin	Micafungin
Loading dose	200 mg 100 mg for EC	70 mg No loading dose for EC	None
Daily dose for different indications	100 mg/day 50 mg/day for EC	50 mg/day	100 mg/day for candidemia 150 mg/day for EC 50 mg/day in prophylaxis
Age of patients according to FDA indication	Adults	>3 months	Neonates Children Adults
Metabolism	Slow chemical degradation at physiologic temperature and pH	Hepatic metabolism + spontaneous chemical degradation	Hepatic metabolism + enzymatic biotransformation
Indication for *Aspergillus* infection	None	Yes, in patients who are refractory to or intolerant of other therapies	None
Indications in neutropenic patients	None	Empirical therapy for presumed fungal infections in febrile, neutropenic patients	Prophylaxis of *Candida* infections in HSCT recipients
Dose adjustment in moderate hepatic impairment	None	Dose reduced (see Table 9)	None
Dose adjustment in severe hepatic impairment	None	Unknown	Unknown

Table 8. Dose adjustment required in case of renal and hepatic impairment

Drug	Dose adjustment	Comments
Renal impairment		
All echinocandins	None	–
Fluconazole	Yes	50% of the dose if CrCl <50
Itraconazole oral solution	None	Do not use intravenous formulation due to carrier accumulation (cyclodextrin) if CrCl <30
Posaconazole	None	If CrCl <20, monitor closely for breakthrough infections due to the variability in exposure
Voriconazole, oral formulation only	None	Do not use intravenous formulation due to carrier accumulation (cyclodextrin) if CrCl <50
Amphotericin B deoxycholate	Do not use	Switch to less nephrotoxic formulation
Amphotericin B lipid formulations	Unknown	–
Hepatic impairment		
Anidulafungin	None	
Caspofungin	Yes	Moderate hepatic impairment (Child–Pugh score 7 to 9) 35 mg daily, with 70 mg loading dose
Micafungin	None	No data in severe hepatic impairment
Fluconazole	None	
Itraconazole oral solution	Unknown	Patients with impaired hepatic function should be carefully monitored when taking itraconazole
Posaconazole	None	
Voriconazole	Yes	50% of maintenance dose in mild to moderate hepatic impairment (Child–Pugh class A and B); no data in Child–Pugh class C; patients with hepatic insufficiency must be carefully monitored for drug toxicity
Amphotericin B	Unknown	

- The Expert Panel favors an echinocandin for patients with
    - moderately severe to severe illness
    - patients who have had recent azole exposure
    - Species resistant to azoles

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

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

- For infection due to *C. parapsilosis, fluconazole is recommended*

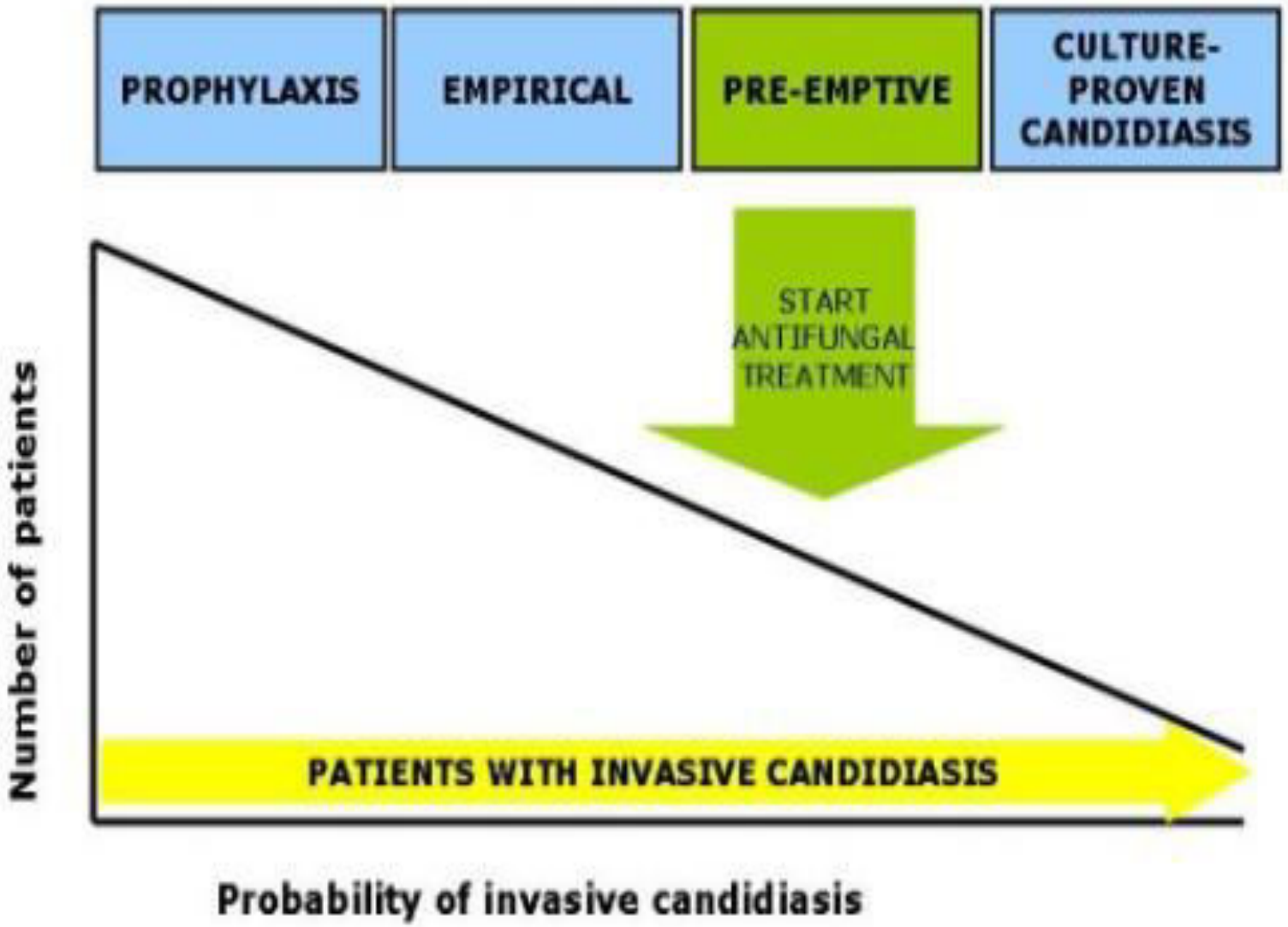
- Voriconazole is recommended as step-down oral therapy for selected cases of candidiasis due to *C. krusei or voriconazole-susceptible C. glabrata*

- Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida species from the bloodstream* and resolution of symptoms attributable to candidemia

- For all patients with candidemia, a dilated funduscopic examination sometime within the first week after initiation of therapy.

- Intravenous catheter removal is strongly recommended for nonneutropenic patients with candidemia

- A 60 yr old COPD admitted with urosepsis with multiple organ failure , gradually stabilising . He has spiked a fever , but hemodynamically stable, started on broad spectrum antibiotics after sending cultures. 48 hours later culture is growing candida
- Which Antifungal will you choose , what dose , how long
- If he was in shock will your choice would have been different



Relationship between different antifungal strategies, probability of invasive candidiasis and number of patients potentially treated.

Thank You