

BVIKM-SBIMC

La Hulpe, 6 November 2008

Antifungals in Invasive Fungal Infections:

Antifungals in neutropenic patients

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Outline of this 20 min. talk

- Fungal epidemiology in neutropenic patients
- Which drugs should be on the hospital formulary?
- In which situation should these agents be used?
 - What are the major drawbacks?!

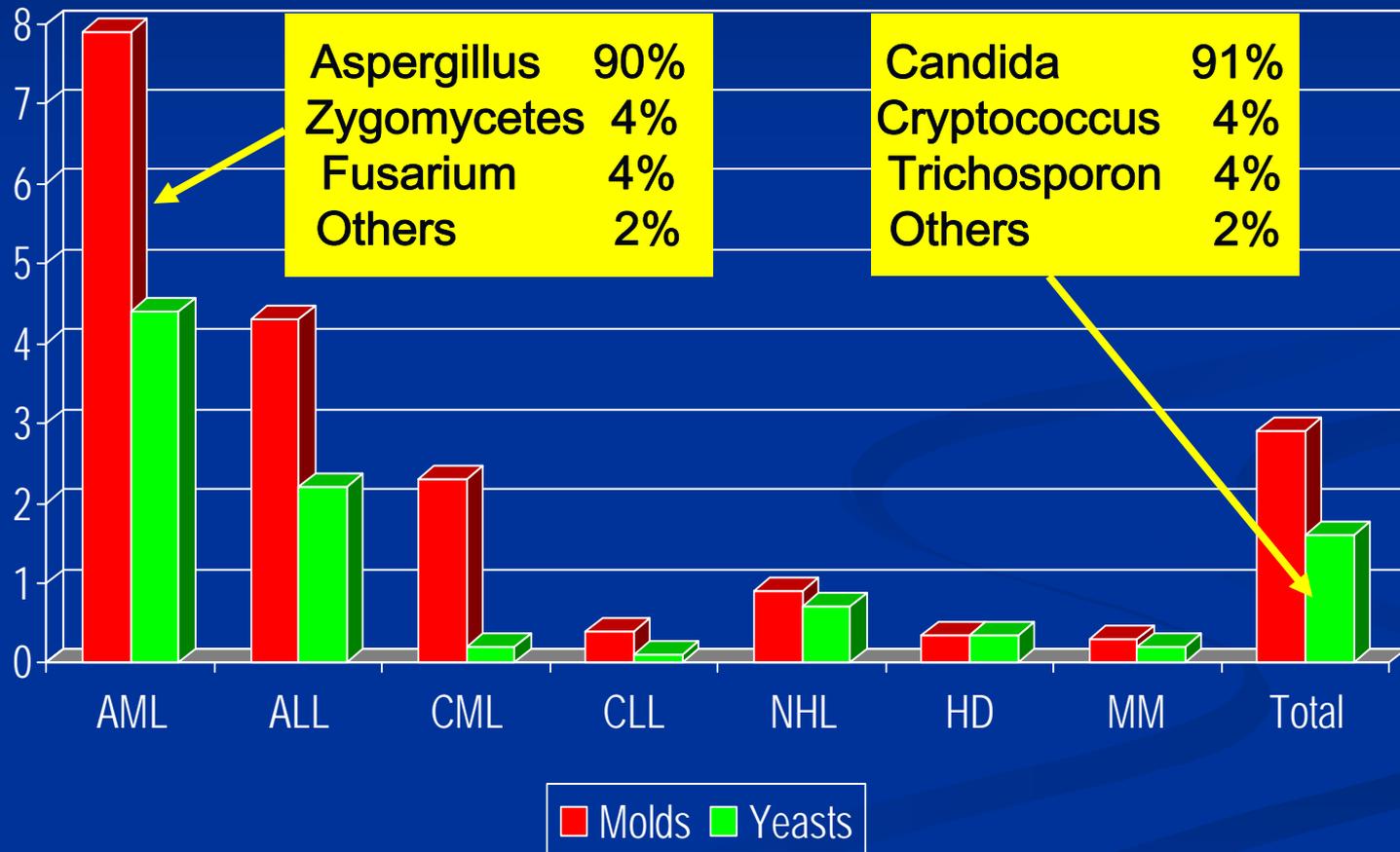
Invasive fungal infections in patients with hematological malignancies: *an autopsy series*

- MD Anderson Cancer Hospital: 1989-2003
 - 1017 autopsies; invasive mycoses 319 (31%)
 - Increasing frequency of molds: 19% to 25

Etiological agent	1989-1993, (%)	1999-2003, (%)
<i>Aspergillus</i>	16	19
<i>Zygomycetes</i>	0.9	3
<i>Candida</i>	13	8

Invasive fungal infections in patients with hematological malignancies*: *Italian data*

* *excluding allogeneic transplant*



Candidemia in cancer patients:

hemat

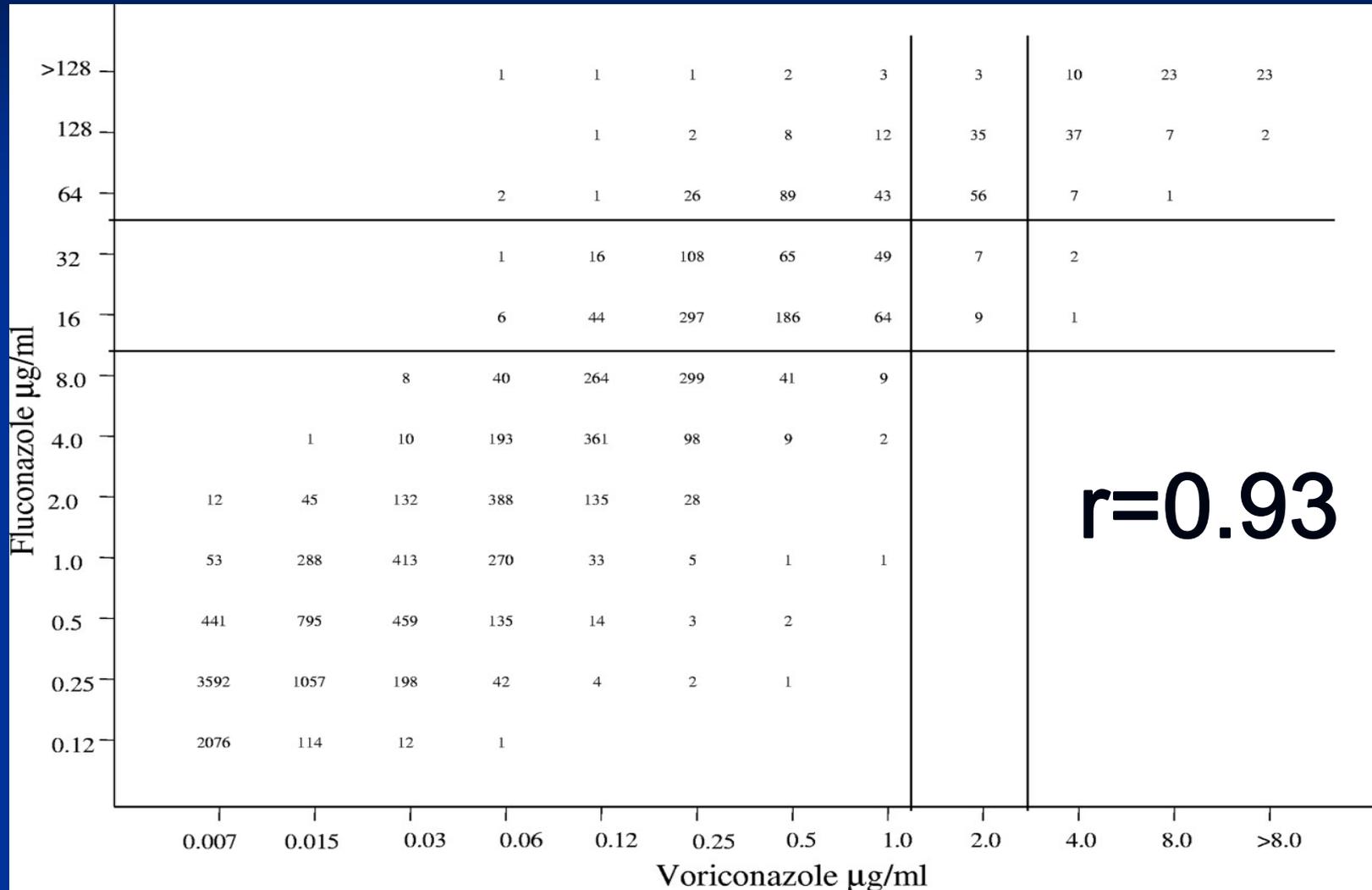
Breakthrough candidemia

De novo candidemia

tumor

	Hemato Malig (n =281)	Solid T (n=354)	P value
C. albicans	14%	45%	<0.001
C. glabrata	31%	18%	<0.001
C. parapsilosis	14%	20%	0.05
C. krusei	24%	2%	<0.001
C. tropicalis	10%	8%	ns
Fluco prophylaxis	> 50%	16%	<0.001
Response AF Rx	49%	73%	<0.001

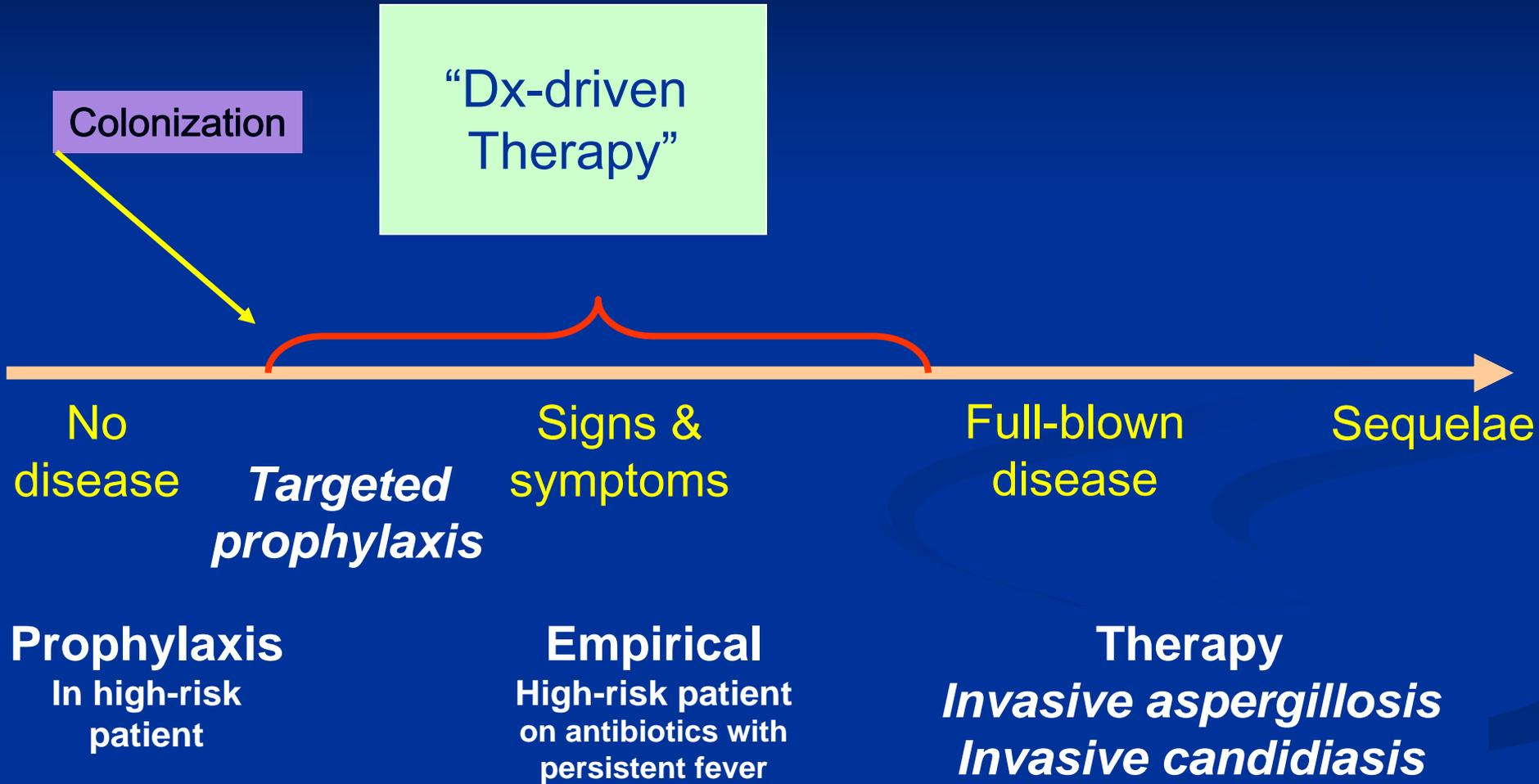
Use of Fluco as a Surrogate Marker To Predict Susceptibility and Resistance to Vorico (and Posaco) (CLSI)



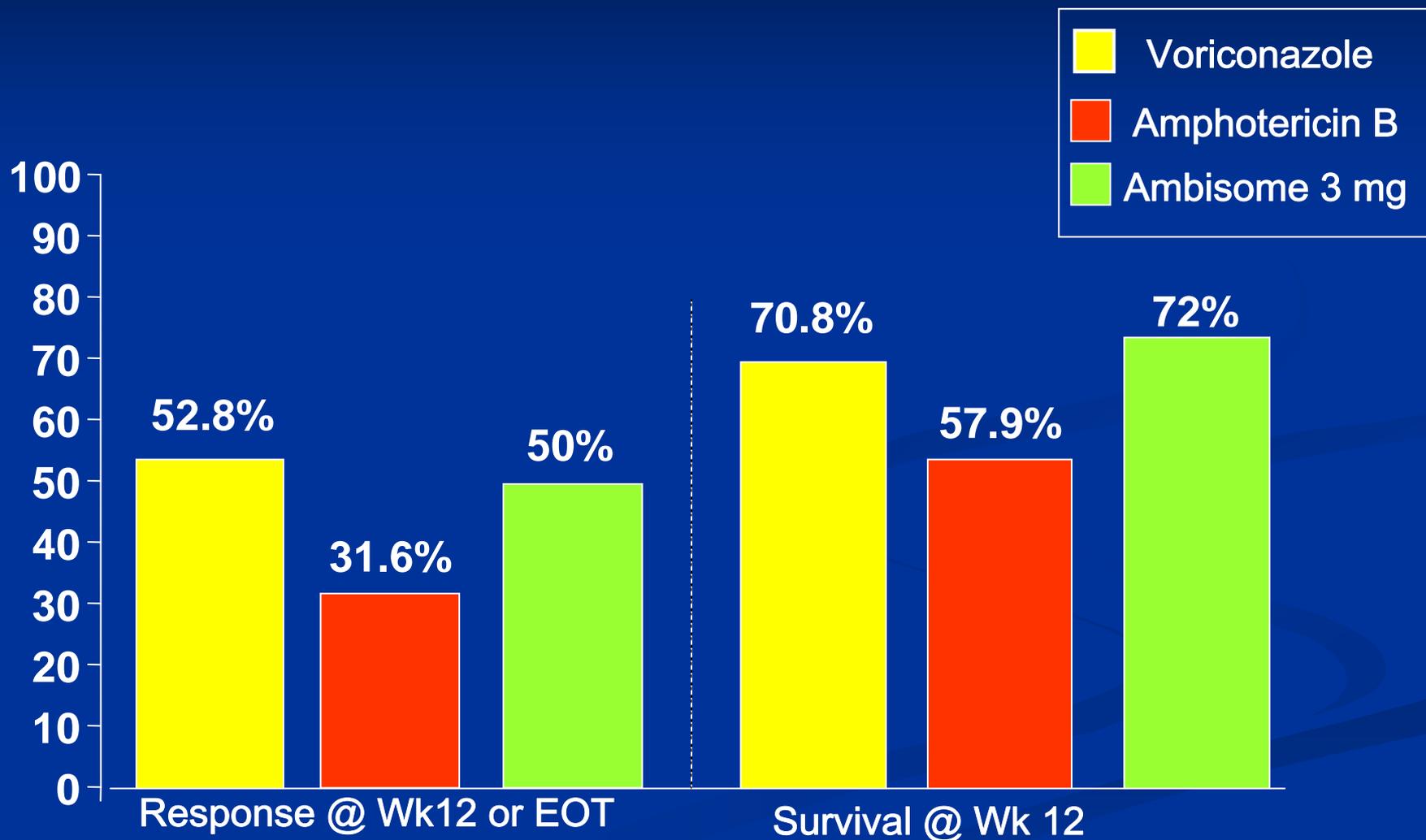
Pfaller et al. JCM 2007; 45: 70 and 2008; 46: 551

The continuum of invasive fungal infection

From colonization to disease



Primary treatment of invasive aspergillosis: *response rate vs. survival*



Herbrecht et al. N Engl J Med 2002; Cornely et al. Clin Infect Dis 2007

Voriconazole for proven/probable IA: AI (ECIL and IDSA)

A
M
B
I
S
O
M
E
3

Prior azole therapy
Voriconazole contraindicated
Potential for serious drug interactions
Hepatic impairment
Moderate to severe renal impairment and IV administration
Mixed mold possible
(Children < 2 years of age)
(Cardiac risk factors)

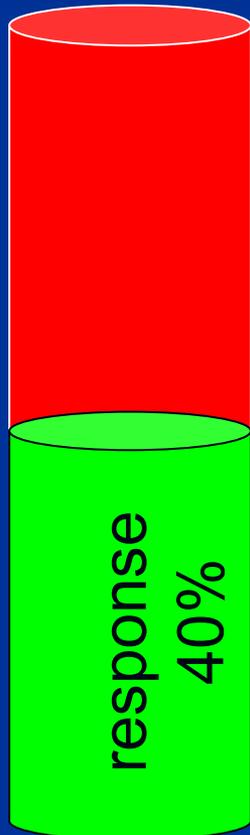
A
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Persistent/breakthrough infection
Hepatic impairment development
Treatment intolerance

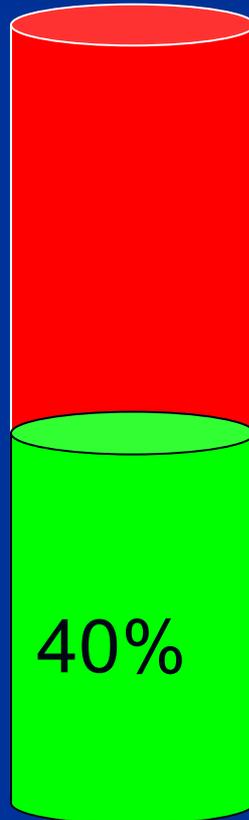
Salvage for Invasive Aspergillosis

Refractory / intolerant

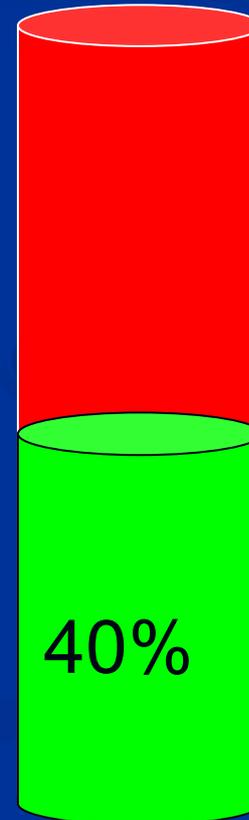
casprofungin
n=146



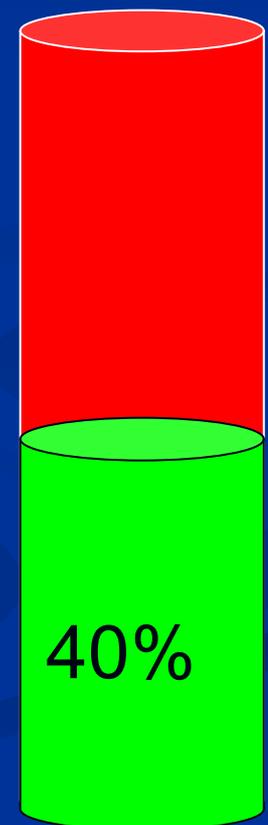
posaconazole
n=107



ampho B lipid
complex

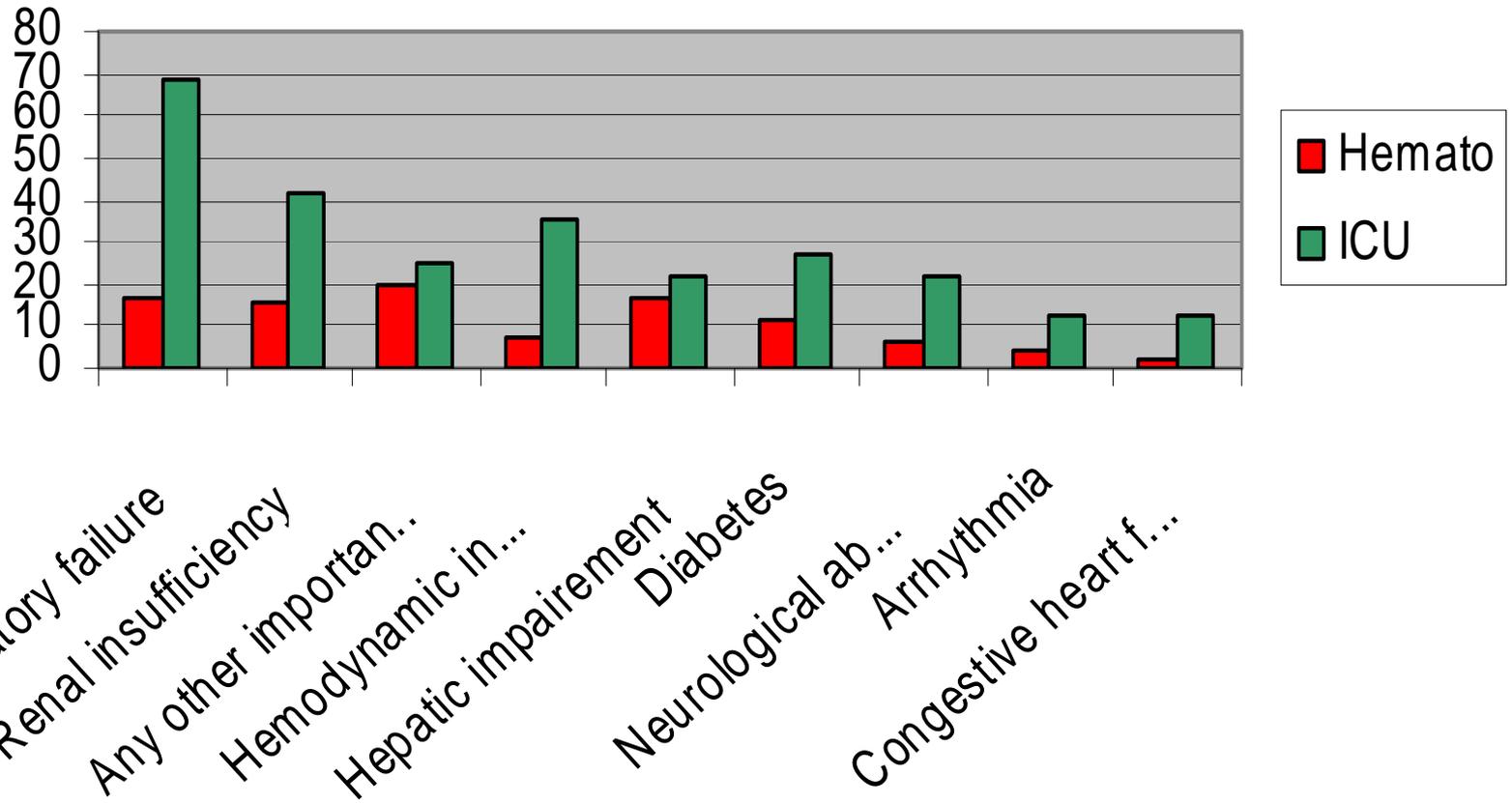


voriconazole
n=144



INVASIVE FUNGAL INFECTIONS

OBSERVATIONAL SURVEY



Why do patients with IA fail voriconazole therapy?

- Voriconazole therapeutic drug monitoring
 - Retrospective study of 28 patients
 - Drug monitoring because of progression (17) or toxicity (11)
 - 15 of 17 with progression has a transplant and IA

VCZ	> 2.05 µg/mL	< 2.05 µg/mL
No. of patients	10	18
Favorable res	10 (100%)	8 (44%)

P<0.025

Invasive Candida infection in leukemia: ECIL guidelines 2007

Agent	Overall population	Patients with hematological malignancies and neutropenia
Fluconazole	AI	CIII
		DIII if azole prophylaxis or colonisation with <i>C. glabrata</i>
		EIII if colonisation with <i>C. krusei</i>
Amphotericin B deoxycholate	AI	CIII
Lipid-amphotericin B	AI	BII
Caspofungin	AI	BII
Voriconazole	AI	BII

Empirical antifungal therapy.

Probably the best available antifungal approach in the absence of sophisticated diagnostic tools

Empirical antifungal therapy

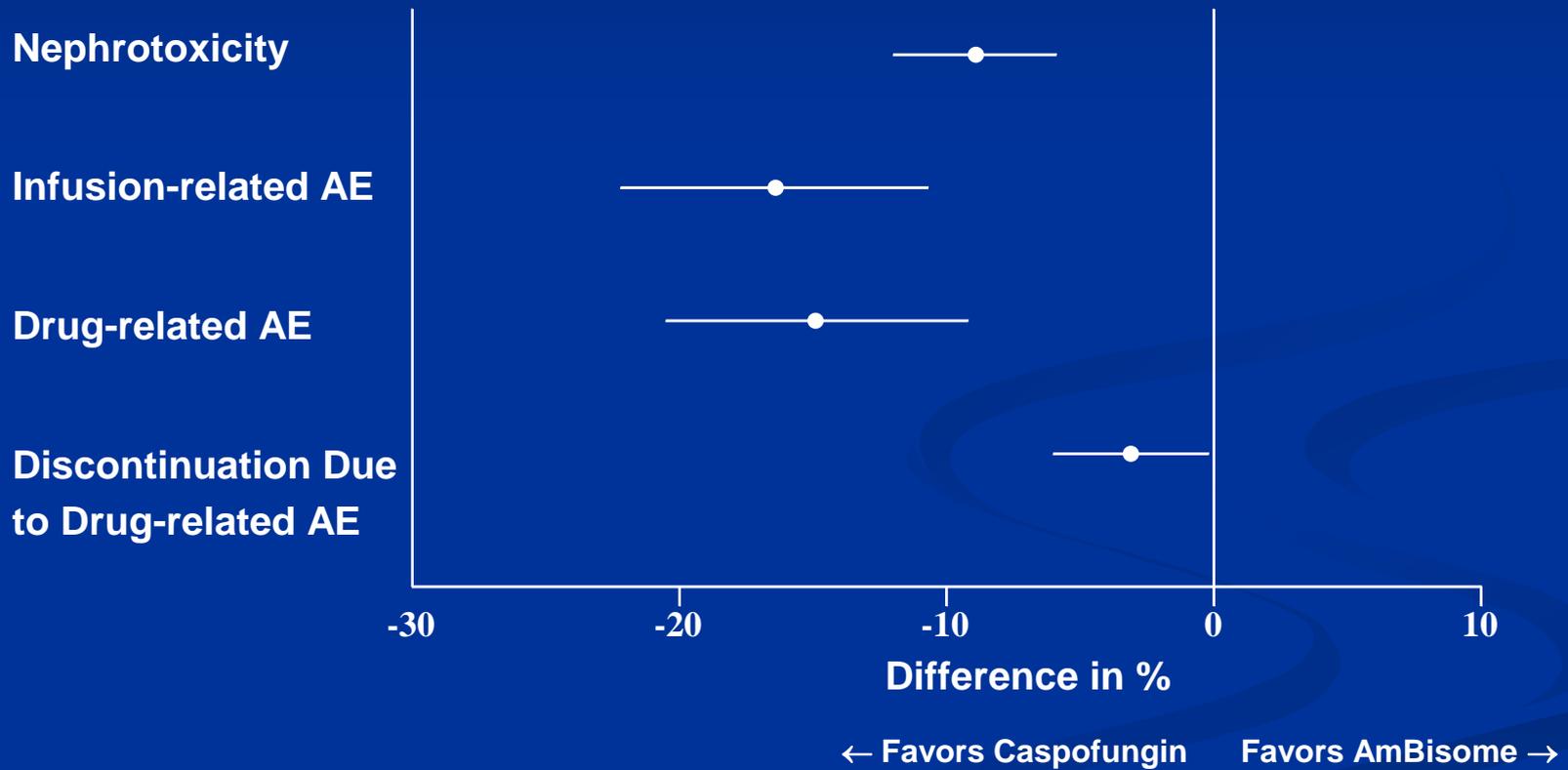
- Objective: treatment of occult fungal infections, not prevention
- Target population: prolonged neutropenic patients with
 - Persistent **fever** despite 4-7 days broad-spectrum antibiotics OR
 - Recurrent **fever** following initial resolution and persistent neutropenia
 - (allogeneic HSCT recipients with undifferentiated **fever**)
 - (prolonged **fever** on ICU)

Conclusions from the empirical studies

- There are several **reasonable choices** for the empirical antifungal therapy of febrile neutropenic patients: L-AmB, itraconazole, caspofungin, [voriconazole].
- None of these agents has demonstrated **superiority** over a comparator, thus none stands “above the crowd” with respect to efficacy.
- These large studies have provided enormous data with regard to **safety** and have advanced our understanding of this condition in general.
 - Double-blind studies are essential to minimize investigator bias, e.g. early withdrawal of pts.
 - Fever as an element of the composite outcome score must be reassessed

Caspofungin: My agent of choice, based on safety endpoints!

(Confidence Intervals for the difference)



Fluconazole prophylaxis in HSCCT recipients

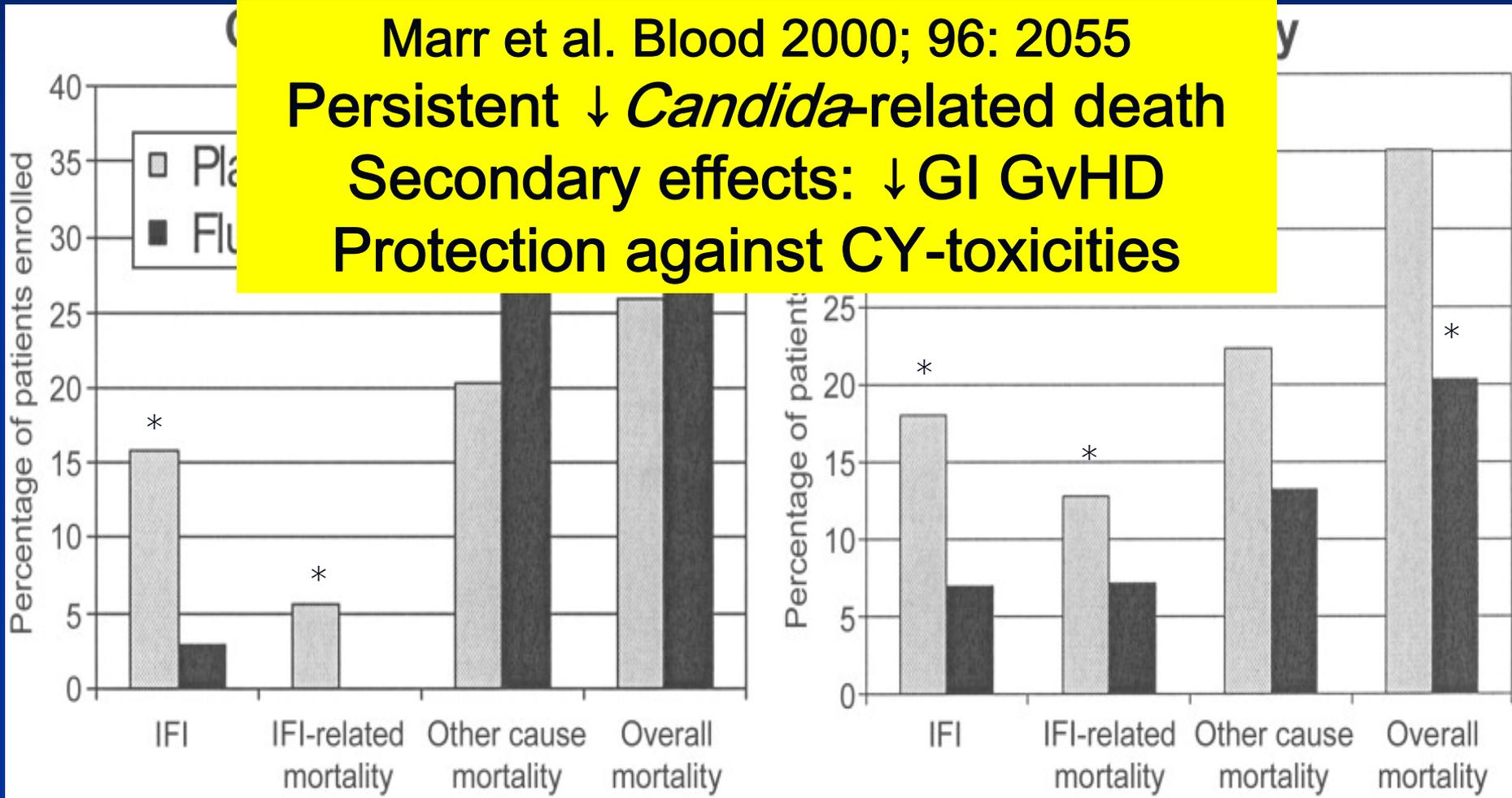
Auto (48%) + Allo (52%)

FLU (400 mg/d) vs. placebo → engraftment

Auto (12%) + Allo (88%)

FLU (400 mg/d) vs. placebo → day 75

Marr et al. Blood 2000; 96: 2055
 Persistent ↓ *Candida*-related death
 Secondary effects: ↓ GI GvHD
 Protection against CY-toxicities



Goodman JL et al. *N Engl J Med.* 1992;326:845-851.

Slavin MA et al. *J Infect Dis.* 1995;171:1545-1552.

Antifungal Prophylaxis in Cancer Patients:

Fluco v. Drug with Antimold Activity: Meta-analysis

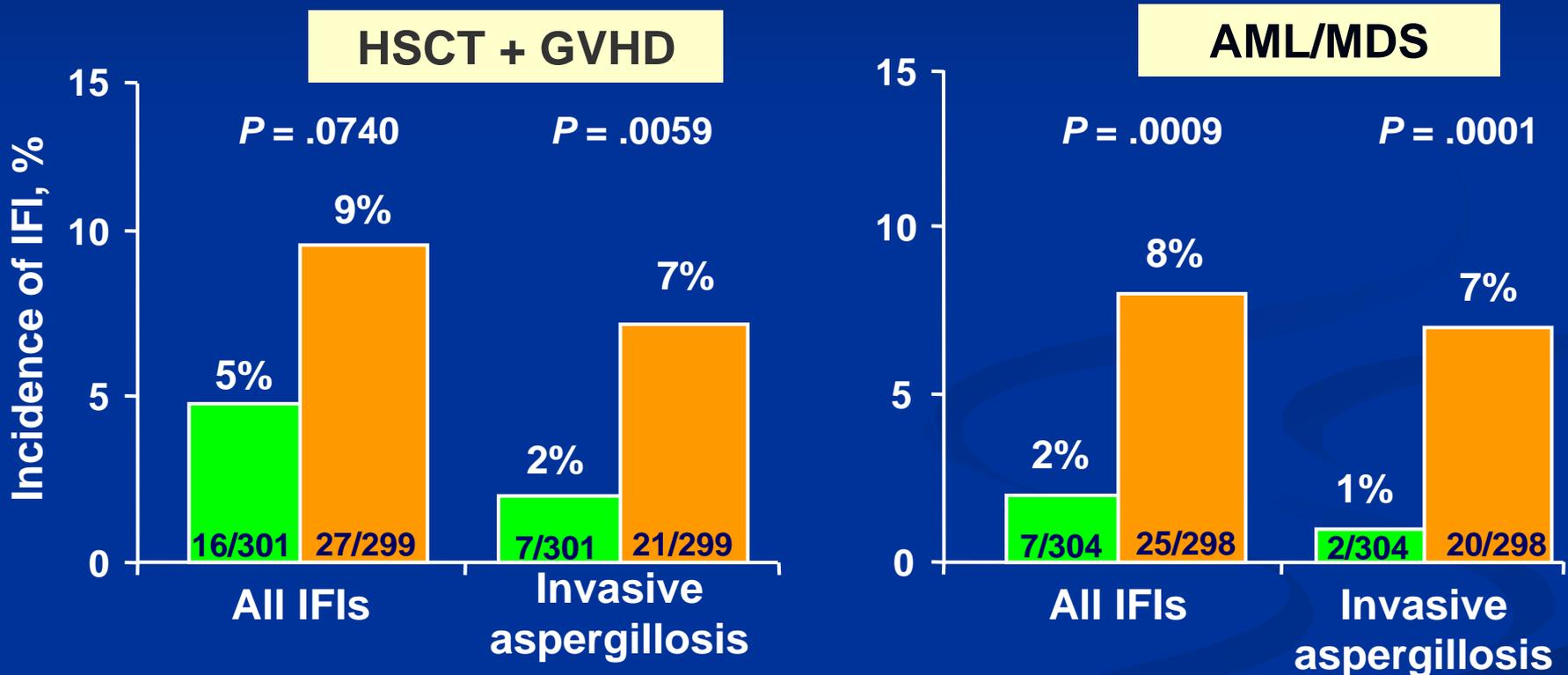
Posaconazole

Outcome	Fluco	Posaconazole	Relative risk*
All-cause mortality	248/1697	244/1717	1.14
Fungal-related mortality	49/1686	32/1656	1.58
Documented IFI	53/1141	41/1157	1.40
Any IFI	237/1870	175/1950	1.53
Documented non-albicans <i>Candida</i>	23/1668	20/1700	1.20
Documented <i>Aspergillus</i>	83/1913	43/1947	2.13

* Relative risk > 1 favors the anti-mold group

Incidence of proven & probable IFIs (primary time point)

POS Comparator

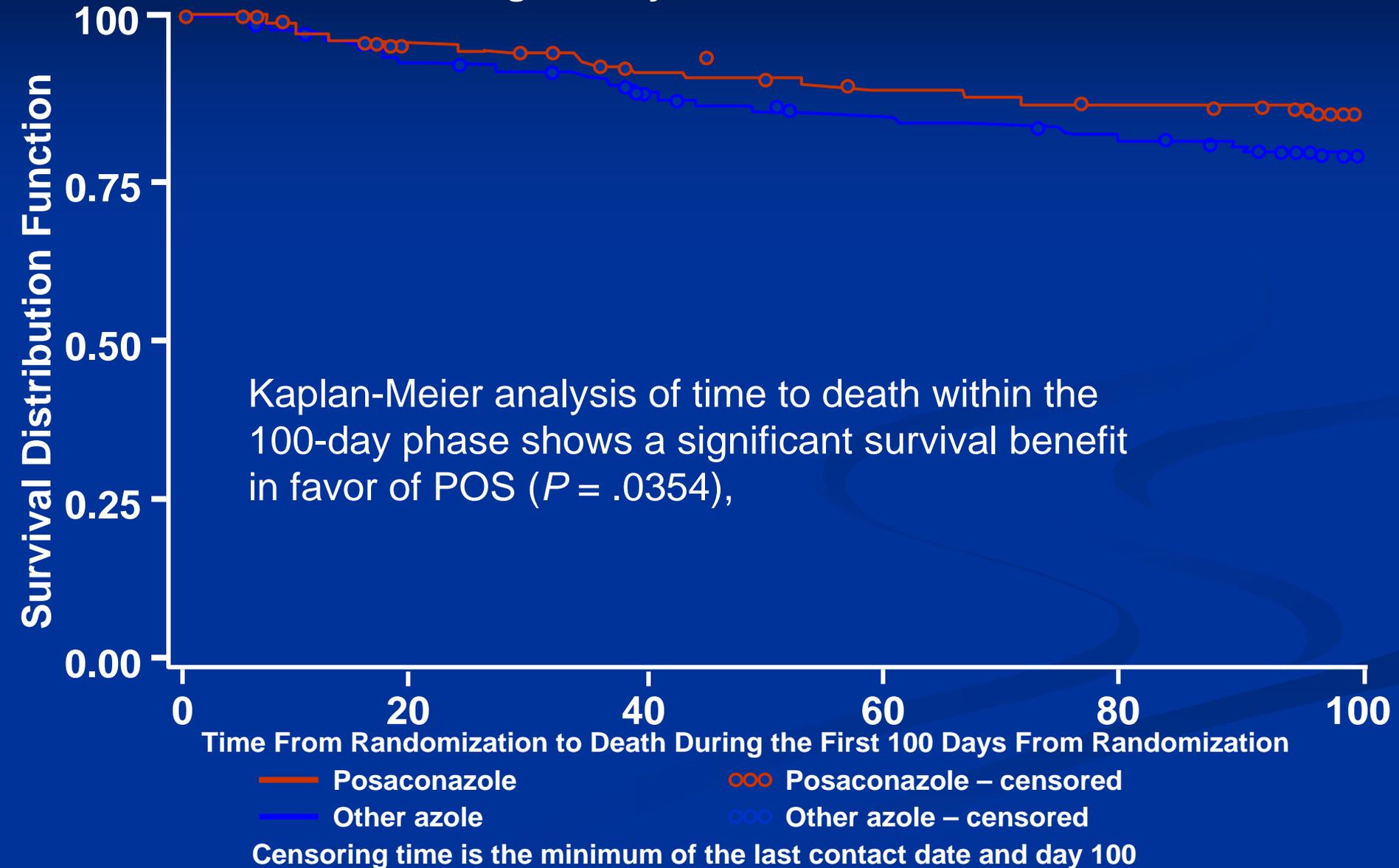


Ullmann et al. N Engl J Med 2007; 356: 335-347

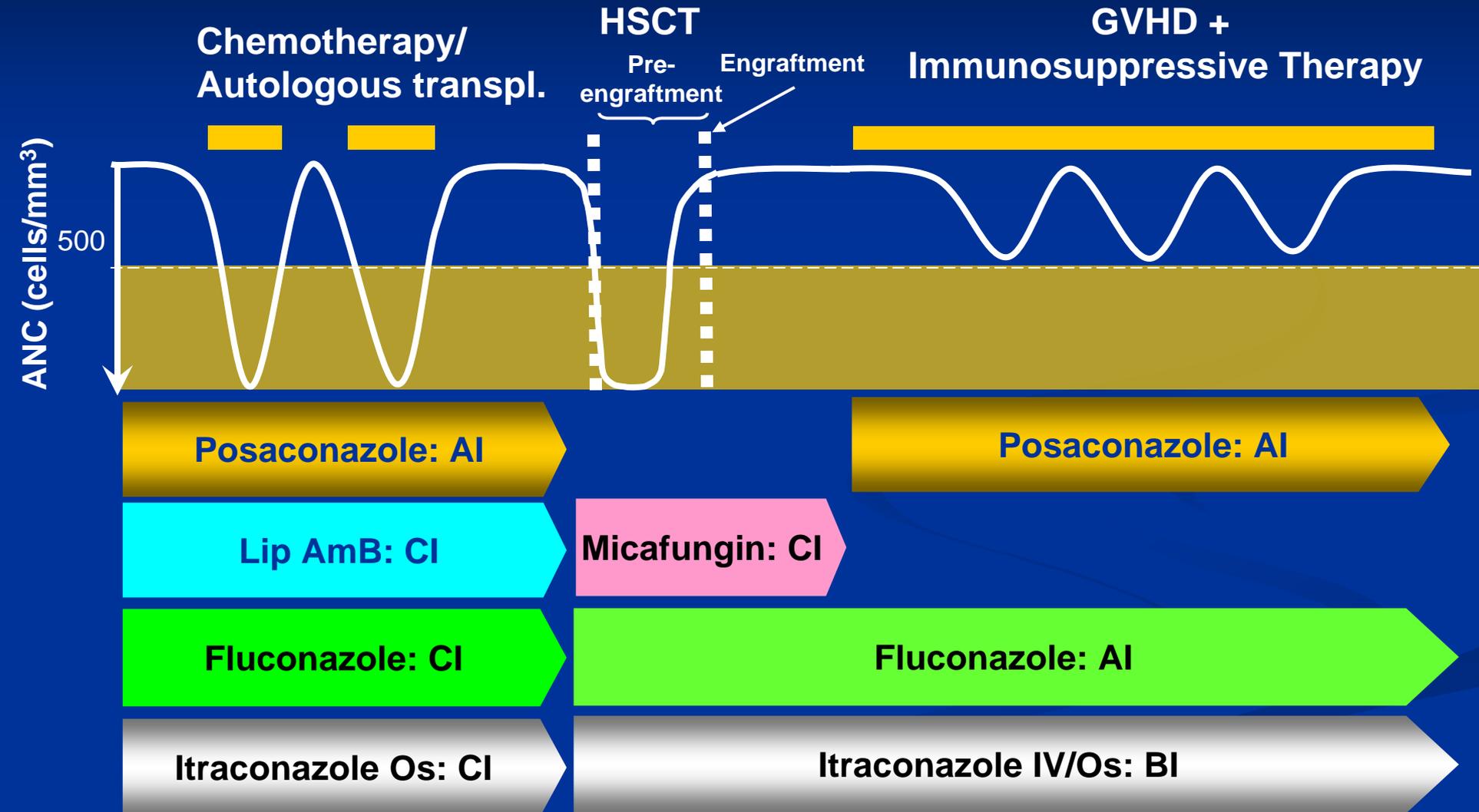
Cornely et al. N Engl J Med 2007; 356: 348-359

AML/MDS Time to Death (overall mortality)

During 100 days from randomization



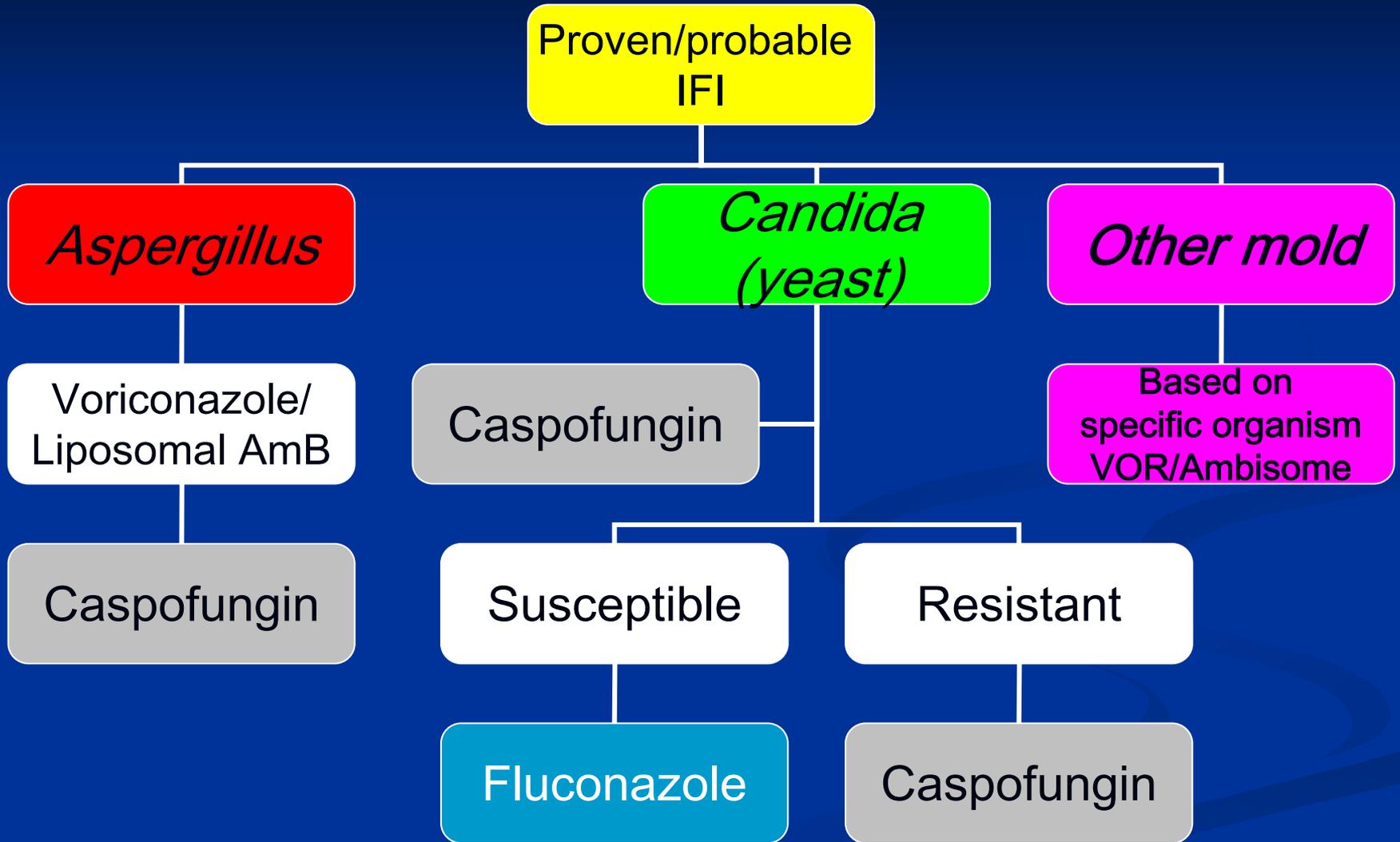
Antifungal Prophylaxis ECIL recommendations



Some words of caution...

- Unanticipated side effects
 - See itraconazole and cyclophosphamide
- Need for therapeutic drug monitoring
 - See itraconazole/voriconazole
 - Dose-response relation in salvage therapy
 - Effect of food intake: what about mucositis?
- Drug interactions
 - An azole class effect (although fewer than comparators)
- Changes in colonizing/infecting flora
 - See voriconazole
- How to handle breakthrough infections?
- Interference with diagnostic tools
 - False sense of security

My personal algorithm



the hematologist's formulary choice*

- **Fluco IV/or**: prophylaxis (+ Dx-driven approach) and step down therapy IC (susceptible isolates)
 - Ketoco/Itraco: endemic mycosis
- **Vorico IV/or**: 1st line IA and fusariosis and scedosporiosis
- **Posaco OS**: prophylaxis neutropenia AML-MDS
 - Isavuco: ??
- **Caspo IV**: empirical and 1st line Candida and 2nd line IA
 - Anidula and mica: -
- **C AmphoB**: -
- **Liposomal ampho B IV**: alternative of choice 1st line IA and 1st line zygomycosis
 - Aersolized liposomal ampho B: +
 - Other lipid formulations: -

* Not taking into account Belgian reimbursement criteria