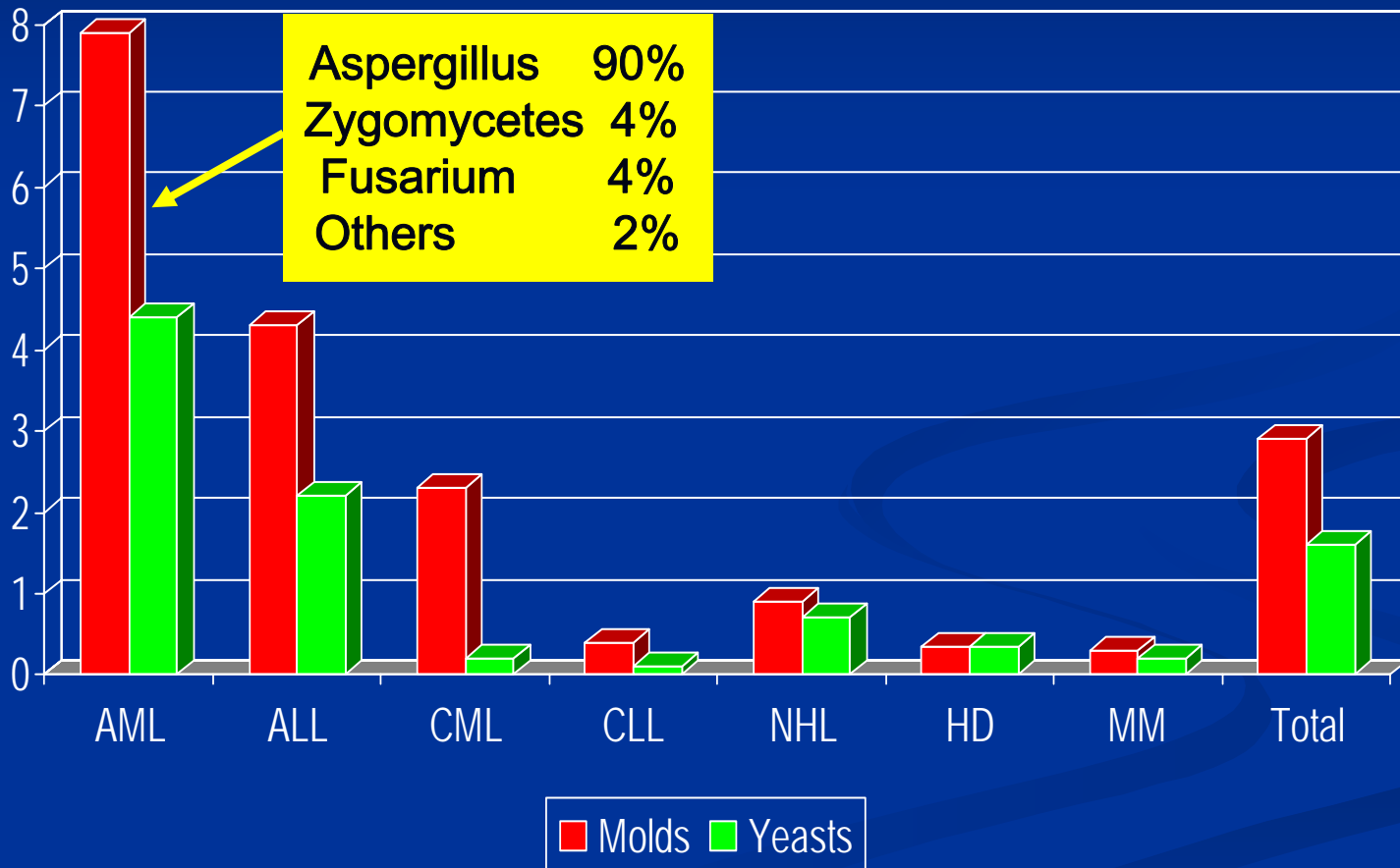# Aspergillosis
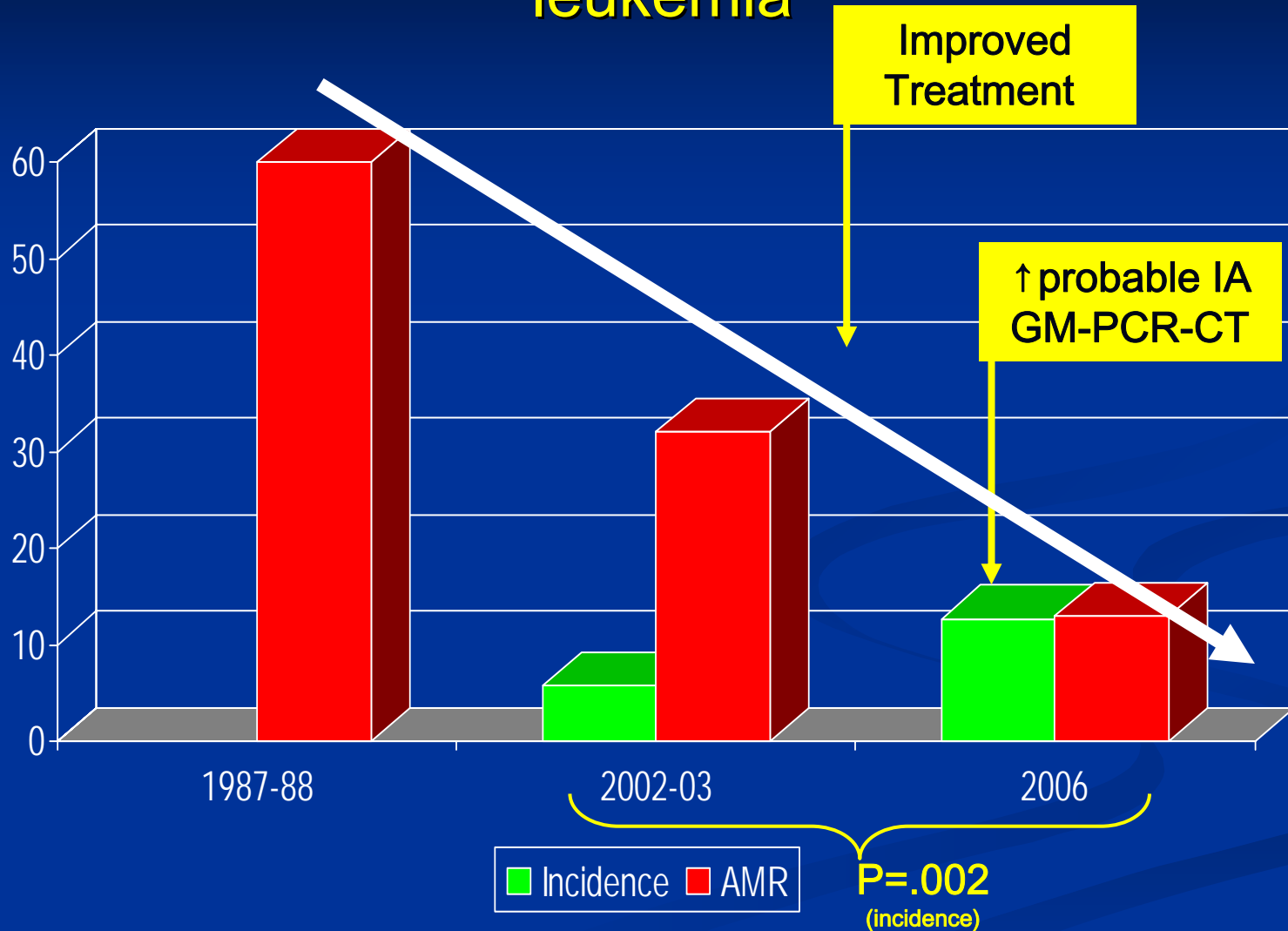## *Invasive disease in patients with leukemia*

Johan Maertens, MD
Dept of Hematology
University Hospital Gasthuisberg
Catholic University Leuven
Belgium

Invasive fungal infections in patients with hematological malignancies
excluding allogeneic transplantation

Aspergillus 90%
Zygomycetes 4%
Fusarium 4%
Others 2%

Pagano L et al. Haematologica 2006; 91: 1068-1075

Invasive aspergillosis in patients with acute leukemia

Pagano L et al. Clin Infect Dis 2007; 44: 1524-1525

Risk factors for IA in neutropenic patients with hematologic malignancies

- AML, MDS, ALL
  - Duration of neutropenia
  - Remission-induction chemotherapy
  - Short interval between cycles

- *Age*
- Gender
- *Co-morbidity score*
- *Relapsed malignancy*
- *High dose Ara-C (± fludara)*

MASCC II
Risk factors IFI in febrile neutropenic patients

Mühlemann et al. Leukemia 2005; 19: 545-550

Pathogenesis of invasive aspergillosis
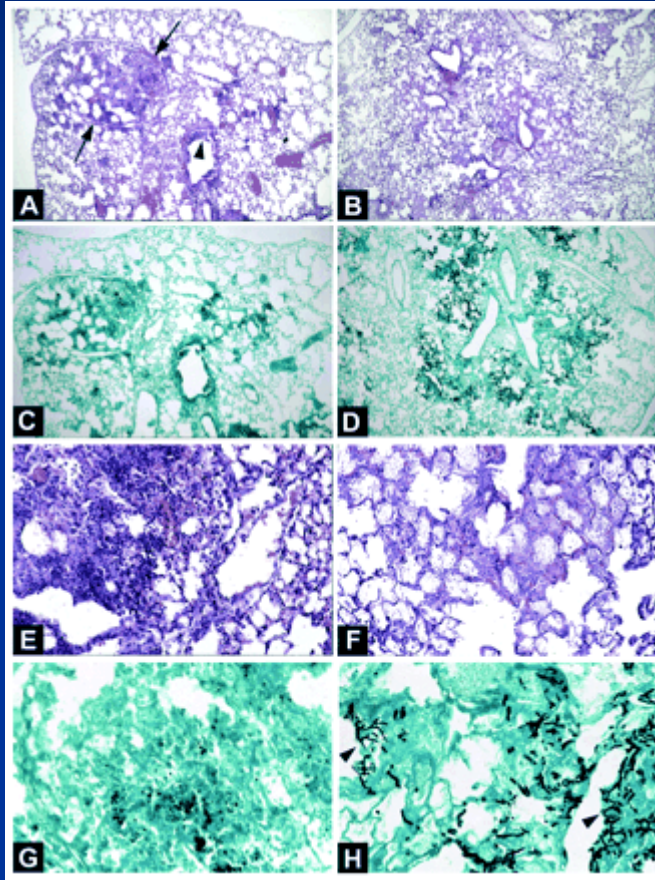
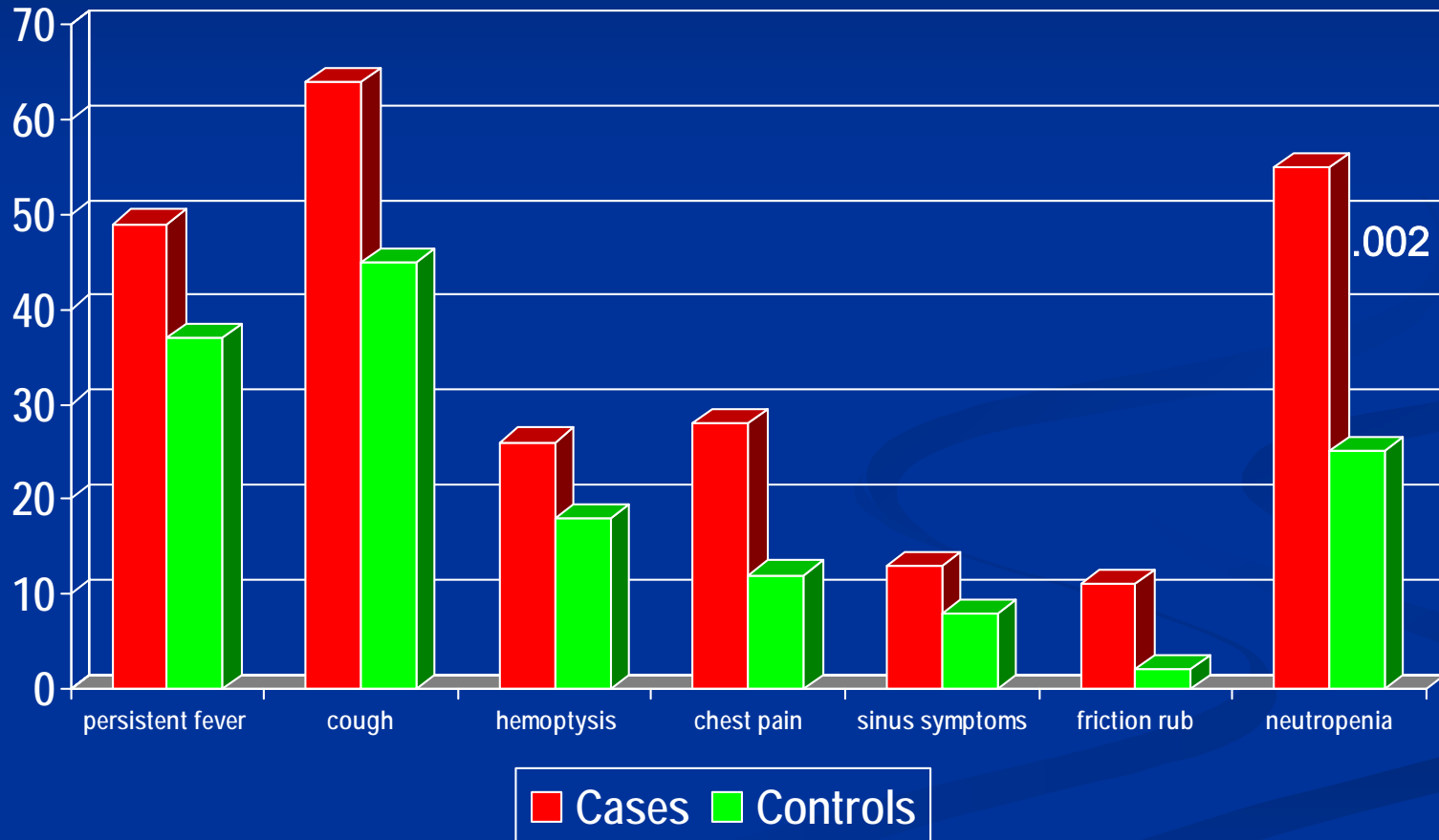|	Neutropenia
Cellular trafficking BAL fluid	No influx of PMN
Pathology	Diffuse pneumonia Few bronchiolitis No neutrophil infiltration
Fungal development	Invasion by large numbers of hyphae
Chitin	High in all organs
Galactomannan	High

Balloy et al. Infect Immun 2005; 73: 494
*Chamilos et al. Haematologica 2006; 91: 986-9*

Issues "specific" to leukemia (→neutropenic) patients

- Hospitalized patients→ screening
- Improvements in rapid and accurate diagnosis of IA
- Paradigm of host immunity→ pIRIS
- Fewer drug interactions
- Co-morbidities
- Surgical intervention
- Prevention or early-diagnosis of IA
- First line therapy

Clinical and radiological predictors of IA in 96 cancer patients

Hachem R et al. Cancer 2006; 106: 1581-1586

Clinical and radiological predictors of IA in 96 cancer patients
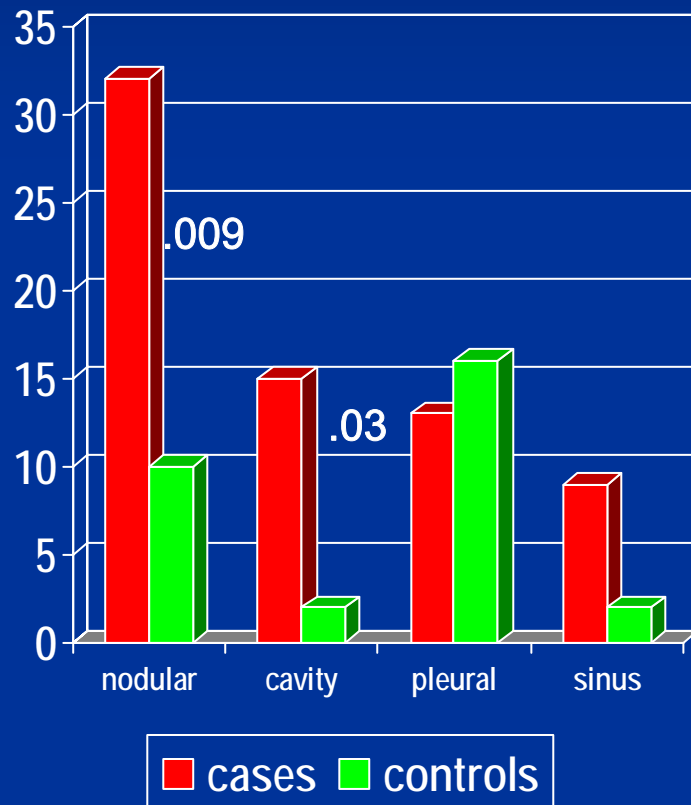
Odds ratio for risk of IPA
Multiple Regression Model

Leukemia	3.00
Neutropenia	4.30
Cavitary lesions	10.96
Nodular lesions	4.83

Hachem R et al. Cancer 2006; 106: 1581-1586

Sensitivity of conventional diagnostic procedures

Site of infection	Procedure	% performed	% sensitivity
Pulmonary	Chest X-ray	98	77
	BAL culture	38	62
	Sputum	72	58
	Nasal swab	56	32
	Surgical specimen	18	87
Cerebral	Cerebral CT	65	88
	Surgical specimen	8	66
Sino-nasal	Cranial CT	50	86
	Nasal swab	71	85
	Surgical specimen	19	100

CT imaging in IA
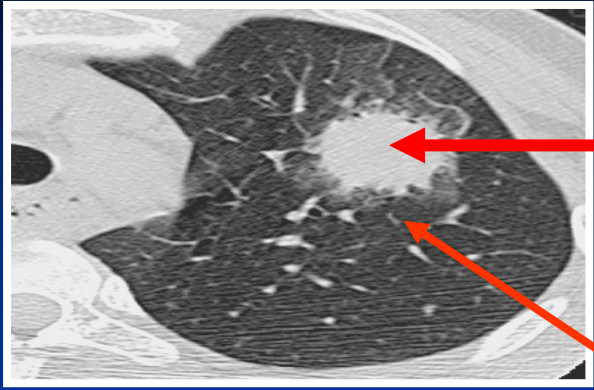
Macro-nodule

Perimeter of ground glass opacity

Nodules in IA	Nodule	Nodule with Halo
Neutrop	97 %	82 %
Non neutrop Hemato	96 %	49 %
Non-hemato	82 %	24 %

Hazard ratio: 0.571
Log-rank P < .01

Halo sign:	143	135	124	119	113	109	108	105	101	100
No halo sign:	79	73	66	58	55	49	48	45	45	42
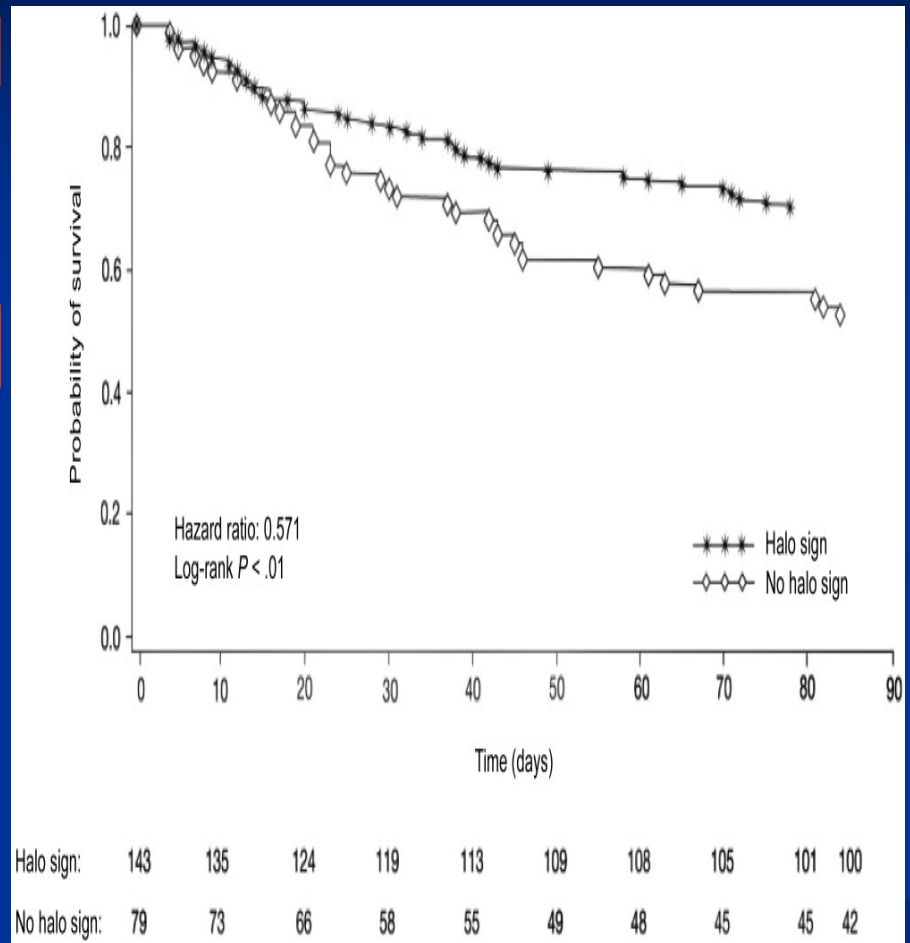
Greene et al.
Clin Infect Dis 2007; 44: 373-9

Non-culture based microbiological assays

	GM	PCR	Glucan
Early detection	+	+	+
Broad range of pathogens	-	+/-	+
Identification to species level	-	+	-
Good performance	+	+	+
Quantitative results	+	+/-	+
Rapid available	+	+	+
Low cost	+/-	-	-

Excellent negative predictive values

Per-test sensitivity & specificity for different cutoffs
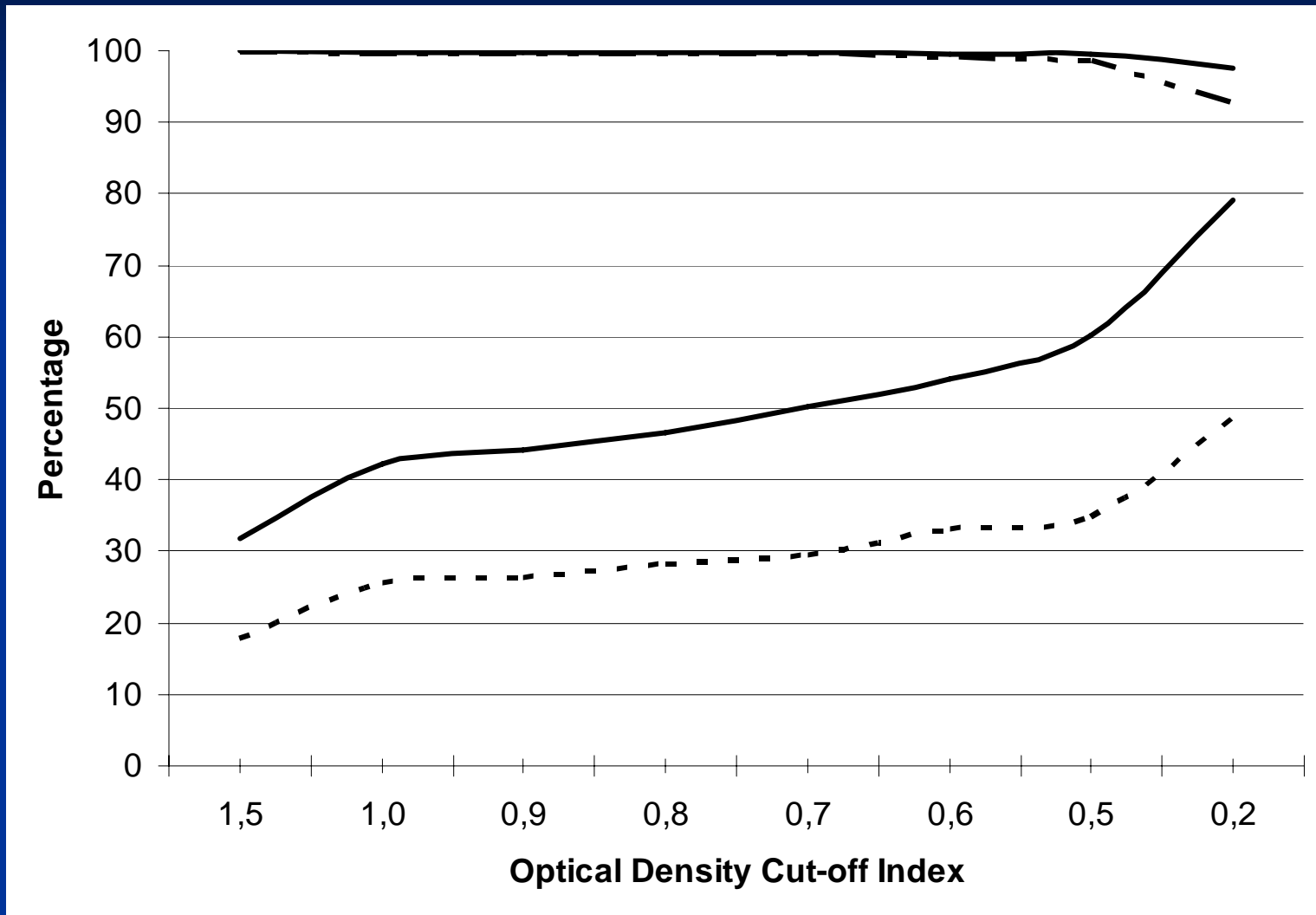
Maertens et al. CID 2007; 44: 1329

Blood samples-2x/week-OD index ≥0.5 (caveats!)
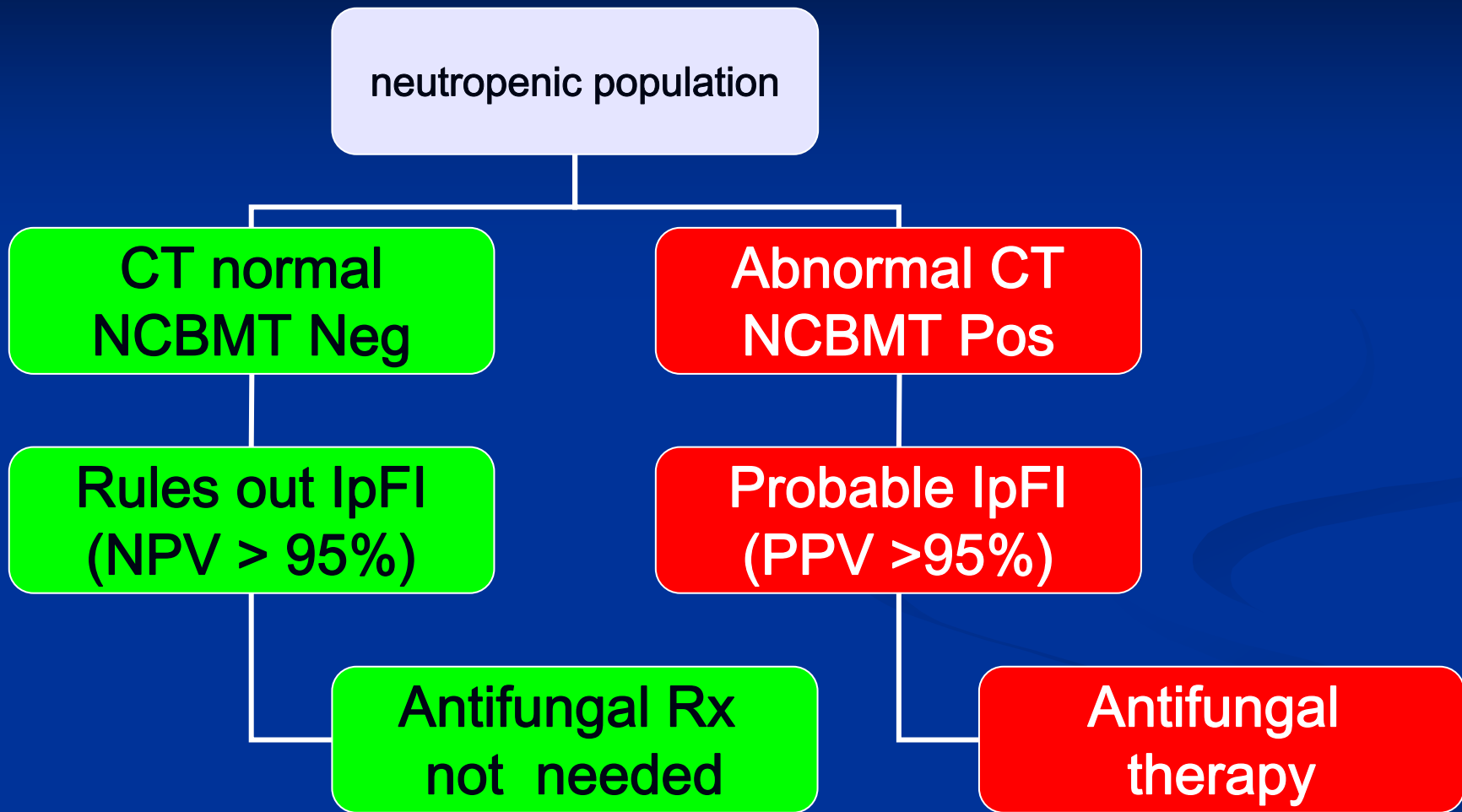
Outcome and Prognosis? ... BAL?

SCREENING

Neutropenic patients and HSCT recipients

Solid organ transplant recipients and ICU patients

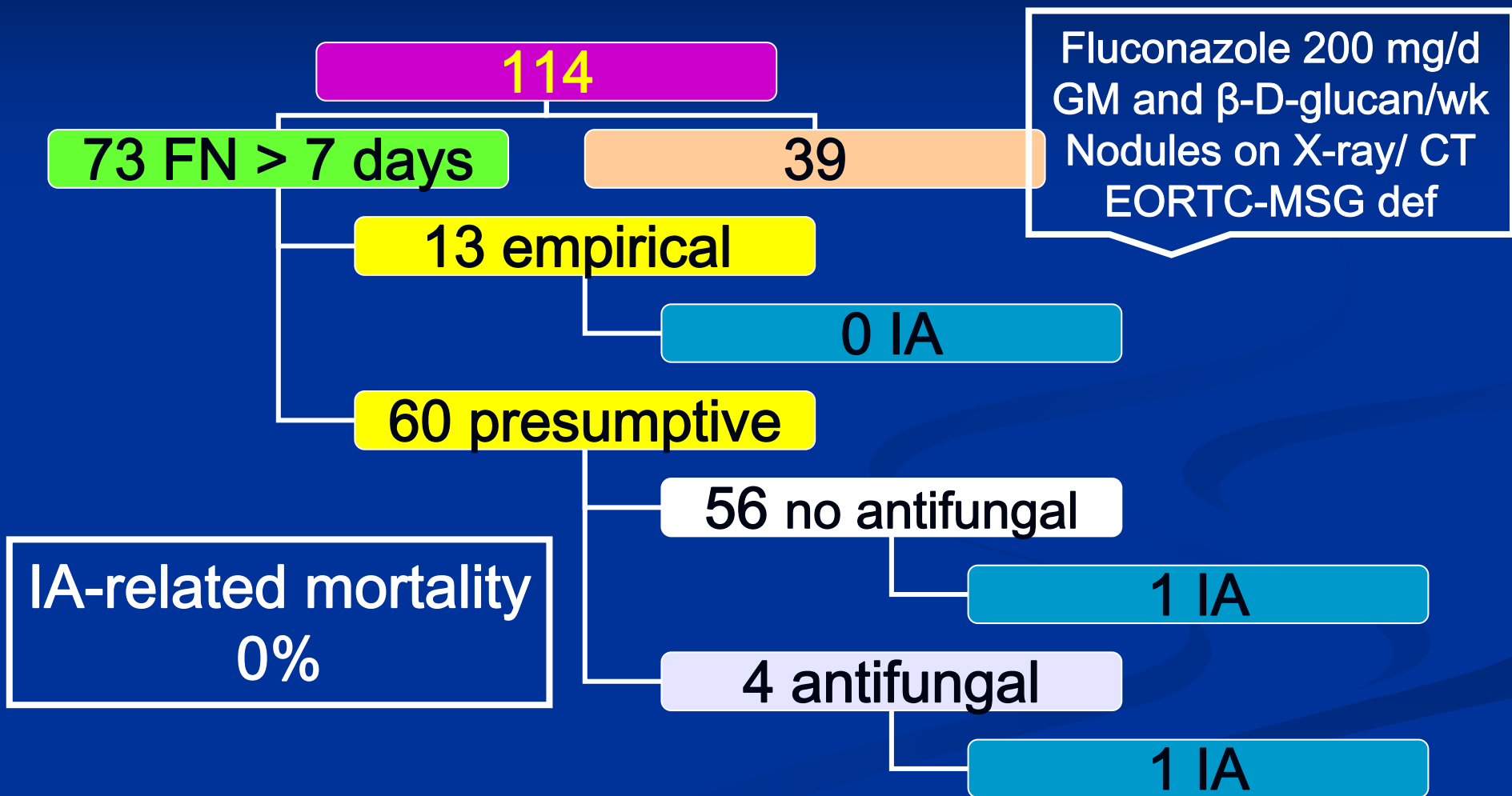Outcome ... Prognosis? ... erum?

DIAGNOSIS

BAL but OD index unknown

Negative and positive predictive value in neutropenia

neutropenic population

CT normal NCBMT Neg

Abnormal CT NCBMT Pos

Rules out IpFI (NPV > 95%)

Probable IpFI (PPV >95%)

Antifungal Rx not needed

Antifungal therapy

Martino et al. Br J Haematol 2005; 132: 138 (modified)
Maertens et al. Curr Opinion infect Dis 2006; 19: 551-6

Presumptive treatment for IA in allogeneic HSCT recipients (before engraftment)

114

73 FN > 7 days

39

Fluconazole 200 mg/d
GM and β-D-glucan/wk
Nodules on X-ray/ CT
EORTC-MSG def

13 empirical

0 IA

60 presumptive

56 no antifungal

1 IA

4 antifungal

1 IA

IA-related mortality 0%

Oshima K et al. J Antimicrobial Chemother 2007

Fluconazole prophylaxis

Persistent neutropenic FUO ≥ 4 day while receiving appropriate AB therapy

GAPS IN KNOWLEDGE
Safe and effective to continue fluconazole prophylaxis with negative chest CT findings and laboratory markers??
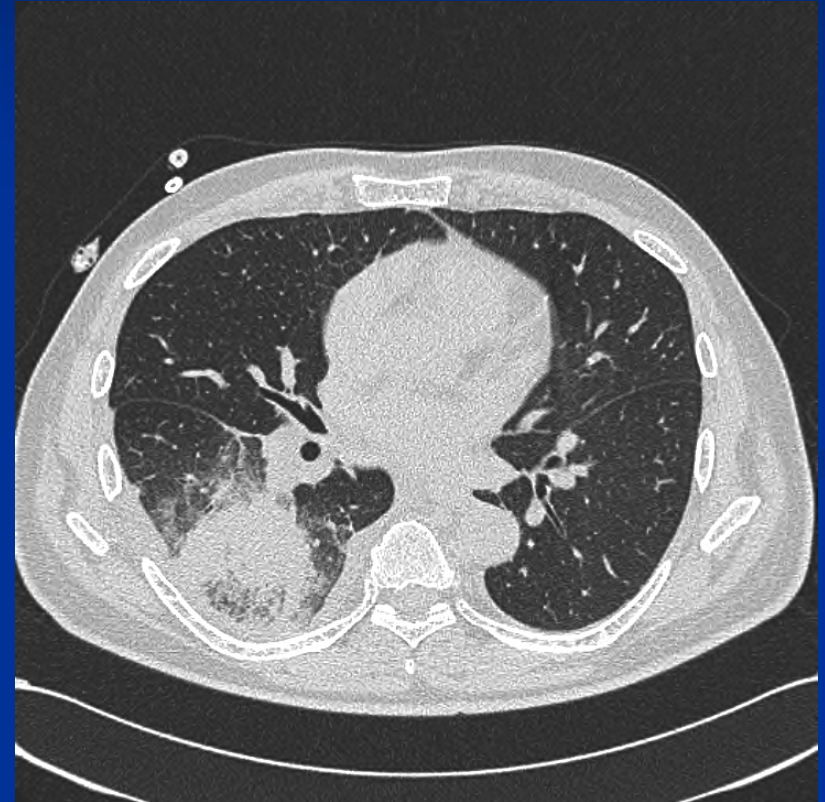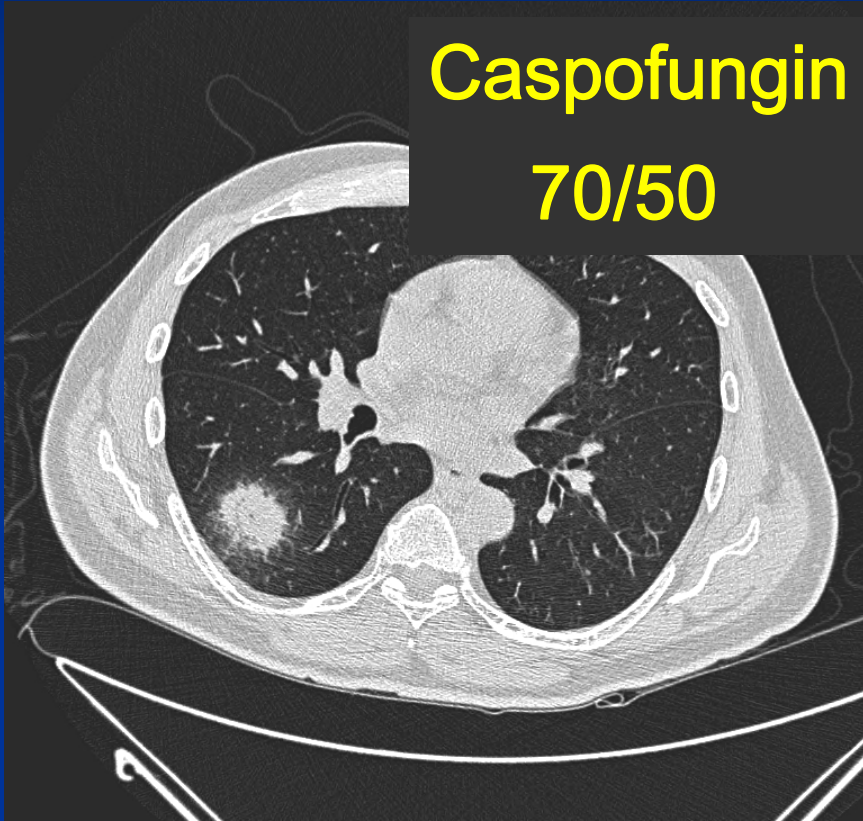
STANDARD OF CARE
Empirical modification of antifungal regimen to a mold-active agent

Segal et al. Clin Infect Dis, 2007; 44: 402-409

'PIRIS'
Pulmonary Immune Reconstitution Inflammatory Syndrome

Caspofungin
70/50

- Neutrophils: 0/µL   GM serum: 3.2   GM BAL: 8.6
- Neutrophils: 12.360 /µL   GM serum: 0.8   GM BAL: 1.2

'PIRIS'
Pulmonary Immune Reconstitution Inflammatory Syndrome

- New onset of or worsening clinical and radiological pulmonary findings consistent with an infectious/ inflammatory pulmonary condition
- Temporal relationship with neutrophil recovery
- Absence of new extrapulmonary lesions
- ≥ 50% decrease in serum GMI titers without treatment modifications
- Subsequent resolution without treatment modification

Micelli et al. Cancer 2007; 110: 112-120

# GM index as a surrogate endpoint for outcome of invasive aspergillosis

- 43 patients with IA (89% myeloma)
- Correlation between clinical outcome (survival or death) and GMI-based outcome (kappa correlation)

Endpoint	Assessment		
	6 weeks	9 weeks	12 weeks
From start of anti-mold therapy	0.74	0.94	1.0
From first (+) GMI	0.79	0.94	1.0

"good" excellent perfect

Woods et al. Cancer 2007; 110: 830-834; Buvé et al. Submitted

Primary treatment of invasive aspergillosis in 'leukemia'

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

% response

|	
Ampho B	38%
Voriconazole	63%
AmBisome	49%
Caspofungin	33%
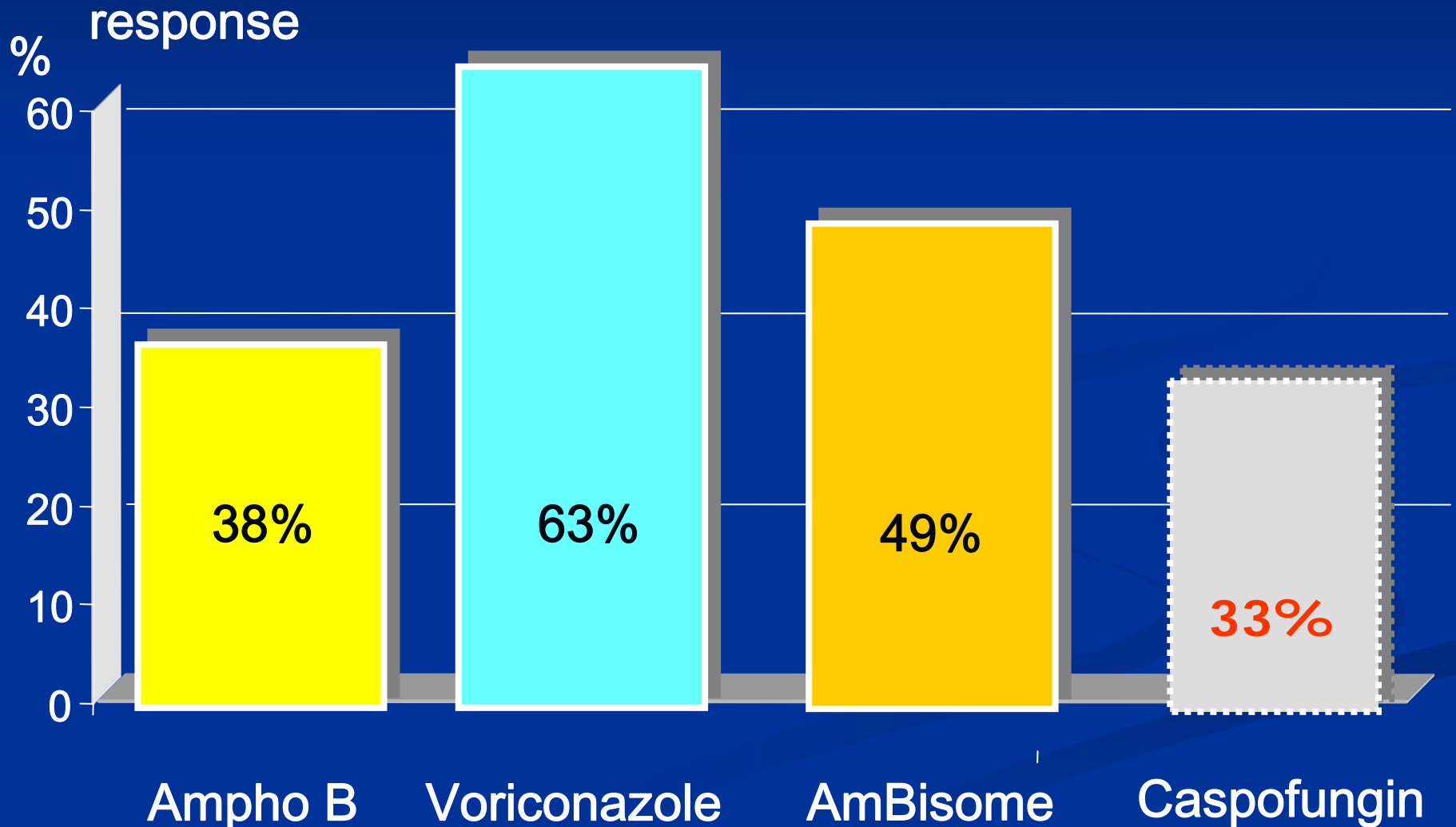
Primary treatment of invasive aspergillosis in 'leukemia'

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

Study	Vorico	L-AmB 3	Caspo
Haematological malignancy	52.1%	93%	100%
Microbiologically confirmed	68.1%	38%	100%
Antigen only	-	25%	75%
Survival @ w12	70.8%	72%	54%
Success @ end of therapy	53.5%	50%	33%
Neutropenia @ baseline	45%*	71%	85%
Success in neutropenia @ baseline	50.8%	43%	29%

Patients with uncontrolled malignancy have a lower survival at 12 weeks

OA Cornely, et al. 2nd Advances Against Aspergillosis, Athens, Greece, 2006
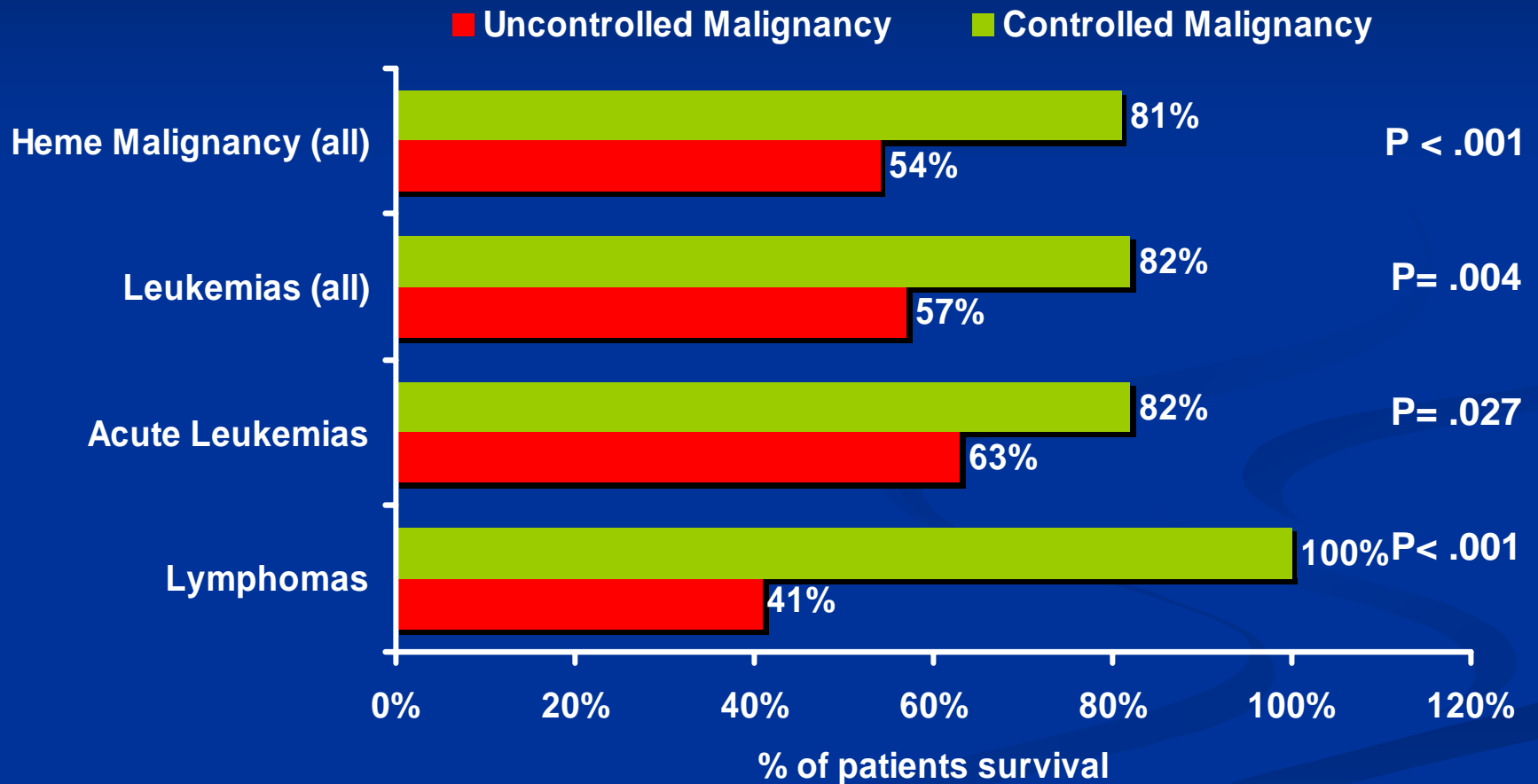
Antifungal Prophylaxis in Cancer Patients:
Fluco v. Drug with Antimold Activity: Meta-analysis

Outcome	Fluco	Anti-mold	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 *Candida*	23/1668	20/1700	1.20
Documented *Aspergillus*	83/1913	43/1947	2.13

* Relative risk > 1 favors the anti-mold group

Robenshtok et al. J Clin Oncol 2007; 25 (34)
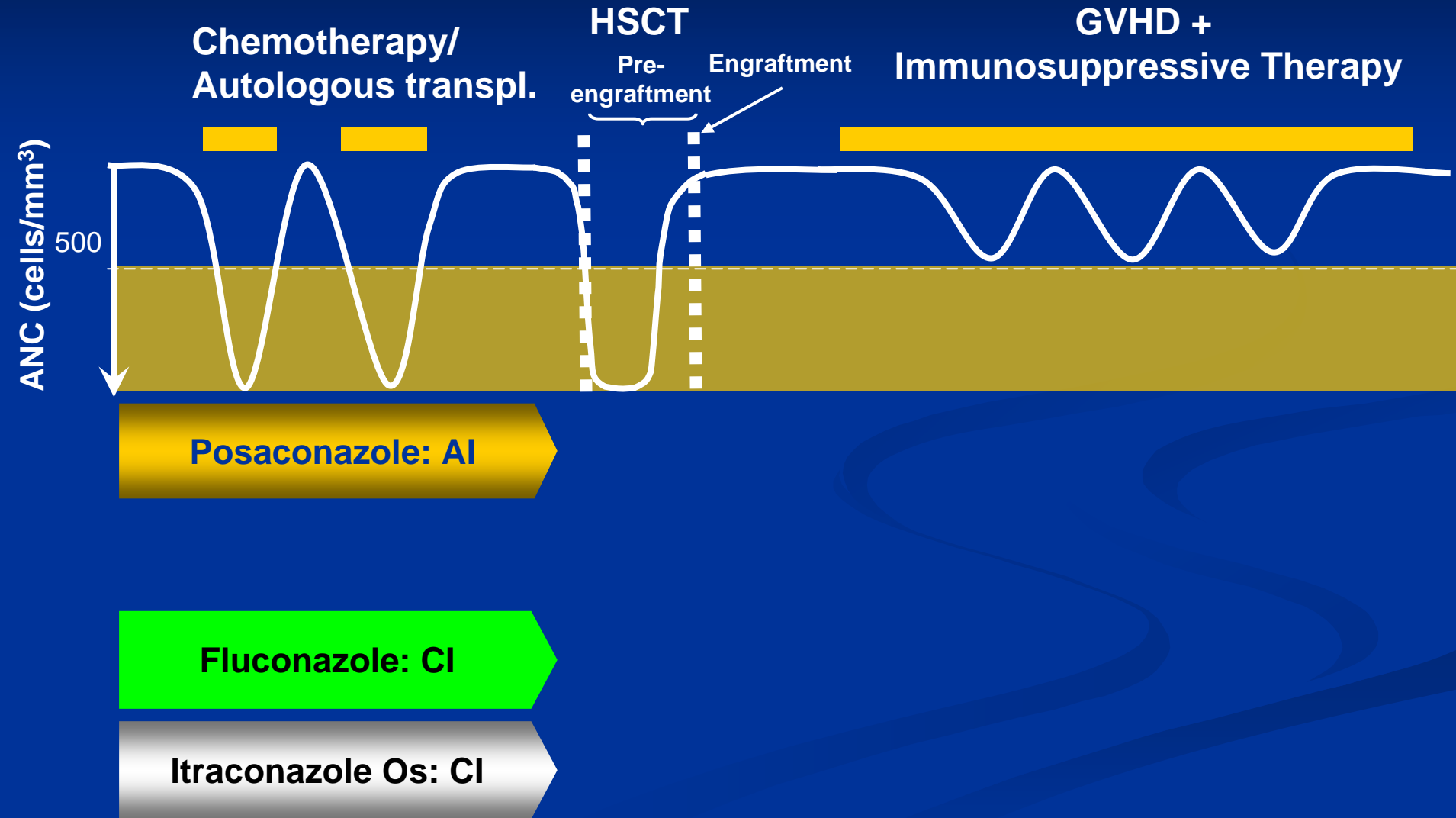
Conclusions

- IA: an emerging fungal infection in leukemia patients
- IA: improved outcome
- Better diagnostic tools ~ new treatment strategies
- Immune reconstitution
- GM can serve as a surrogate marker
- First line treatment: voriconazole but more data (all agents) would be welcome