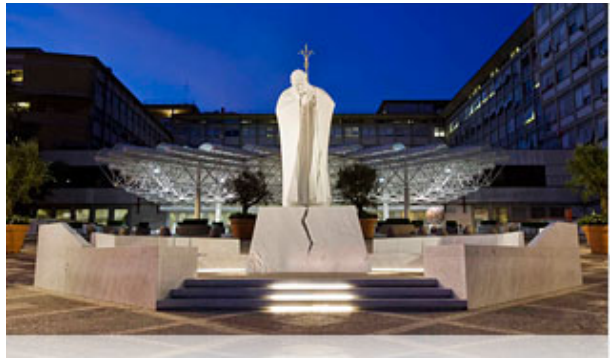
FIFTH
INTERNATIONAL SYMPOSIUM ON
SECONDARY LEUKEMIA
AND LEUKEMOGENESIS

ROMA, SEPTEMBER 22-24, 2016

Treatment of Invasive Fungal Infections in Therapy-related AML



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Questions

- Secondary leukemias have the same risk for fungal infection like other leukemias?
- Secondary leukemia should be treated like the others?
- What is the prognosis of IFI in secondary leukemia?

SEIFEM

Epidemiology of IFI in AML (1)

Reference	Study Type	Phase of Leukemia	Patient's characteristics	Type of Infection	IFI-Incidence
Glasmacher 2006	randomized, prospective, multicentric	Induction and consolidation	248 (ALL 13,7%, AML 69,0%, CML BC 4,4%, Lymphoma 10,1%, MM 0%, other 2,8%)	Invasive Aspergillosis (IA), proven IFI, suspected IFI (not available EORTC criteria)	proven 1,6% (IA 0,8%, candidiasis 0,4%, other 0,4%), suspected 8,9%
			246 (ALL 10,6%, AML 76,9%, CML BC 2,8%, Lymphoma 5,7%, MM 0,8%, other 3,3%)		proven 2,0% (IA 1,2%, candidiasis 0,4%, other 0,4%), suspected 11,4%
Cornely 2007	randomized, prospective, multicentric	induction	304 (AML 84%, MDS 16%)	possible/proven/probable (EORTC 2002)	proven/probable 2% (1% moulds, 1% yeast)
			298 (AML 87%, MDS 13%)	proven/probable	8% (7% moulds, <1% yeast)
			240 (AML 88%, MDS 12%)	proven/probable	8% (7% moulds, <1% yeast)
			58 (AML 83%, MDS 17%)	proven/probable	10% (moulds)
Pagano 2007	prospective, multicentric	NA	237 AML	proven/probable IA	12,7%
Pagano 2012	prospective, multicentric	induction	576 AML	possible/proven/probable	22,3%
Caira 2015	prospective multicentric		881 AML	possible/proven/probable	24,2%
Mattiuzzi 2009	prospective monocentric	Induction and reinduction	71 (77% AML, 23% MDS)	proven/probable (EORTC 2002)	0%
Vehreschild 2010	prospective monocentric	induction	77 AML	possible/proven/probable (EORTC 2002)	3,9% (2,6% IA; 1,3% candidiasi)
Tang 2015	prospective monocentric	induction	298 AML	possible/proven/probable	5,7% proven; 5% probable; 23,9% possible

SEIFEM

Epidemiology of IFI in AML (2)

Reference	Study Type	Phase of leukemia	Patient's characteristics	Type of Infection	IFI -Incidence
Bohm 2005	retrospective monocentric	induction and consolidation	82 AML (induction)	proven/probable	19,5% (13,4% IA; 6,1% candidiasis)
			44 AML (consolidation)	proven/probable	0%
Pagano 2006	retrospective multicentric	Induction,reinduction, consolidation	3012 AML	proven/probable	12,3% (7,9% molds; 4,4% yeast)
Nihtinen 2008	retrospective monocentric	induction and consolidation	847 AML	acute or chronic candida infections	8,7%
Barreto 2013	retrospective monocentric	Induction and consolidation	165 AML (12% MDS)	possible/proven/probable	14,5%
Heng 2013	retrospective monocentric	consolidation	106 AML	proven probable	2%
Neofytos 2013	retrospective monocentric	induction	254 AML	possible/proven/probable	48,4%
Gomes 2014	retrospective monocentric	induction	125 AML	proven/probable	16,8%
Kung 2014	retrospective monocentric	induction and reinduction	130 AML	possible/proven/probable	10,8%
Girmenia 2014	retrospective	induction	198 AML	proven/probable	17,2%

Proven/probable/possible = median 25% (4-48)

Proven/probable only = median 8% (2-17)

AML-Risk factors of IFI

Nucci et al, Blood 2014
Caira et al, Haemat 2015

SEIFEM

AML-Risk factors for IFI

-FACTORS- t-AML

Leukemia Related	Host Related	Treatment Related	Fungal Exposure
Lower Probability of CR (Adverse Cytogenetic/gene mutation profiles; WBC > 50.000/µL; Secondary AML).	Age > 65 yrs	Expected treatment related severe and prolonged neutropenia (ANC < 100/µL for > 10 d)	Rooms without HEPA filtration Building construtions or renovations
Baseline Neutropenia with ANC <500/µL for > 7 d, MDS-related phagocytic dysfunction.	Organ dysfunction with High comorbidity index or PS ≥ 2	Highly mucotoxic regimen	Airway Colonization By Aspergillus species
Leukemia Status: Relapse-Refractory > First Induction > Consolidation	Chronic Obstructive Pulmonary Disease Smoking, High exposure Job	Mucositis grade ≥ 3 for > 7 days, especially if involving lower gut.	Prior Aspergillosis
Day 15 BM Blasts > 5%	Immunity polymorphism	Esophagitis grade >2 WHO	Multisite colonization by Candida species.
No CR by end of Induction	Pharmacogenomics of antineoplastic drugs		

Pagano et al, Blood Reviews 2016

SEIFEM

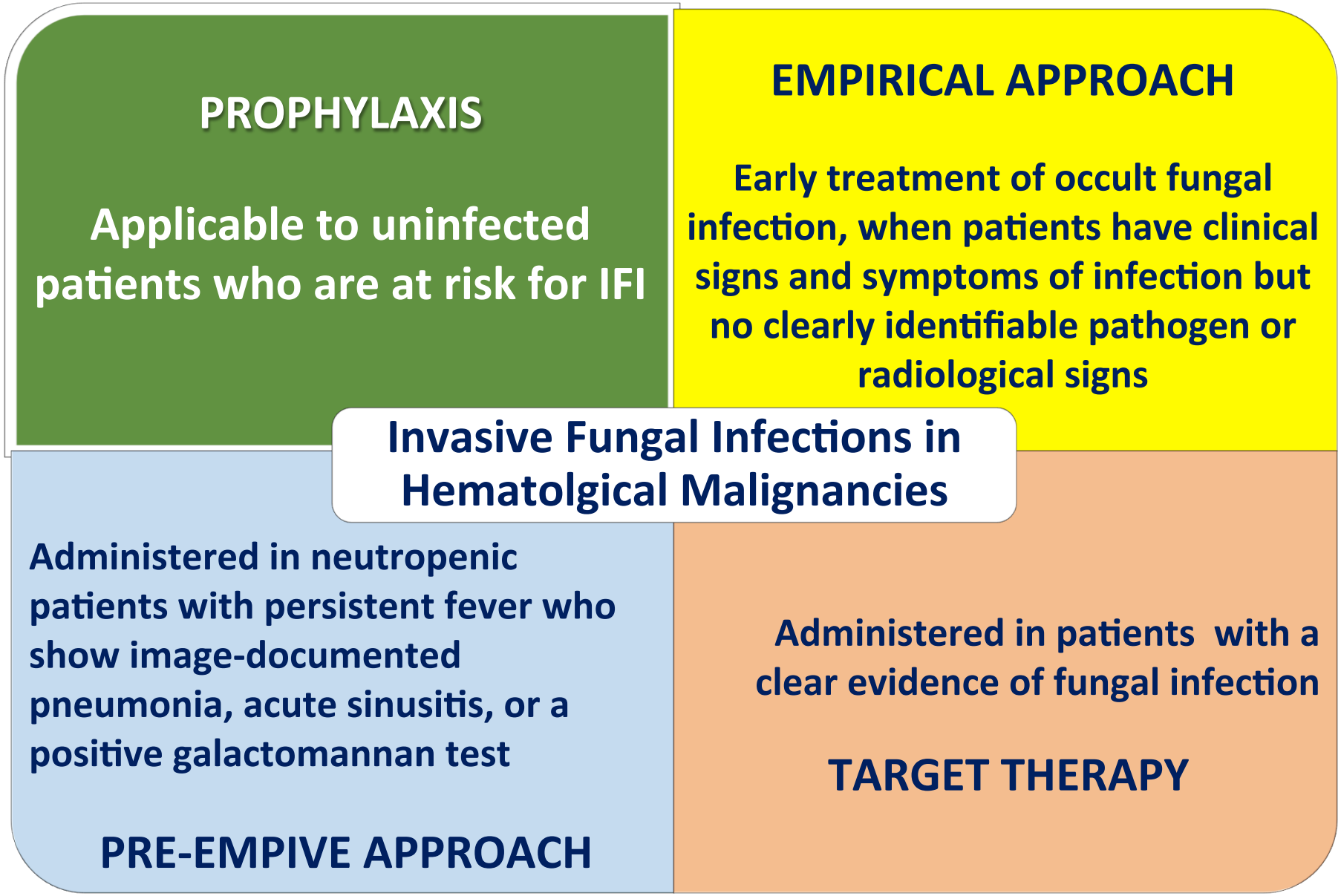
AML- IFI risk categories

HIGH Risk	INTERMEDIATE Risk	LOW Risk
AML-pts undergoing Induction CHT with any of the following Risk Factors: •Neutropenia at baseline, •low CR probability (Adverse K, secondary AML), •age > 65 yrs, •Significant pulmonary disfunction, •high e-TRM score.	AML-pts not meeting criteria for High or Low Risk groups.	AML-pts <45 yrs Undergoing first remission-induction or consolidation CHT and without Risk Factors for IFD APL treated with ATRA and/or ATO
AML-pts with Prior IA		
AML-pts undergoing salvage regimens for Relapsed/Refractory disease.		
t-AML		

Pagano et al, Blood Reviews 2016

Current therapeutic approaches to fungal infections in immunocompromised hematological patients

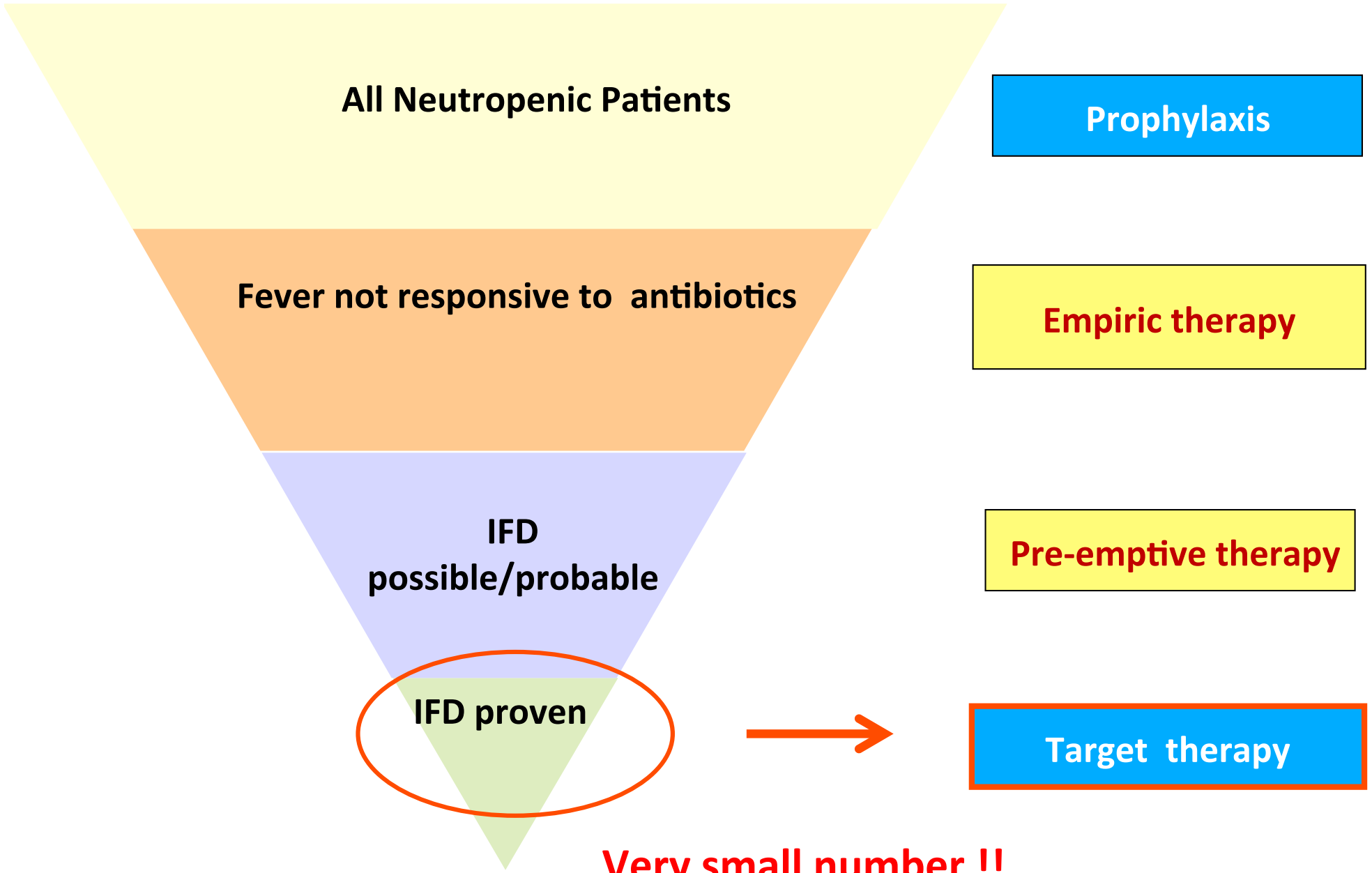
L. Pagano et al./Blood Reviews 24 (2010) 51–61



ECIL-6 recommendations for first-line treatment of invasive aspergillosis.

(Tissot et al, Haematologica 2016)

	Grade	Comments
Voriconazole	A I	Daily dose: 2x6 mg/kg on day 1 then 2x4 mg/kg (Initiation with oral therapy: C III)
Isavuconazole	A I	As effective as voriconazole and better tolerated
Liposomal amphotericin B	B I	Daily dose: 3 mg/kg
Amphotericin B lipid complex	B II	Daily dose: 5 mg/kg
Amphotericin B colloidal dispersion	C I	Not more effective than d-AmB but less nephrotoxic
Caspofungin	C II	
Itraconazole	C III	
Combination voriconazole + anidulafungin	C I	
Other combinations	C III	
d-AmB	A I – against	Less effective and more toxic



L. Pagano et al./Blood Reviews 24 (2010) 51–61

Antifungal Therapies

EMPIRIC THERAPY:

Only host factors plus fever

Now better defined
FEVER-DRIVEN

PRE-EMPTIVE THERAPY:

IFI diagnosis from any microbiological factor or any clinical factor (unless found in sterile fluids or positive blood culture for *Candida*)

Now better defined
DIAGNOSTIC-DRIVEN

TARGETED THERAPY:

IFI diagnosis from sterile fluids or blood culture positive for *Candida* or any invasive exam

Why Empirical Antifungal Therapy was introduced?

- High incidence and fatality rates for invasive fungal infections
- Insensitivity of cultures
- Many invasive fungal infections are diagnosed too late or only at autopsy
- Late treatment greatly reduces success rates

Based on observation or experiment, not on theory

It has been suggested to substitute with pre-emptive antifungal approach

- Many causes of non- infectious fever
- Probable overtreatment of many patients = ↑ toxicity
- Availability of new biomarkers (GM, PCR, β-D glucan, mannanes etc..), and imaging
- Excessive cost

On the basis of CMV infection in HSCTs, where it is shown that treating the asymptomatic infection defined by a biological marker reduces the risk of CMV disease

The NEWS in diagnosis

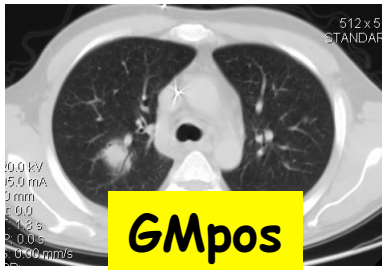
The DIAGNOSTIC DRIVEN approach

PRE-EMPTIVE

SURVEY

TC

TC



TC

Risk Period

GM GM GM GM GM GM GM GM GM GM GM

Maertens et al, CID (2005) 41:1242–50

4gg

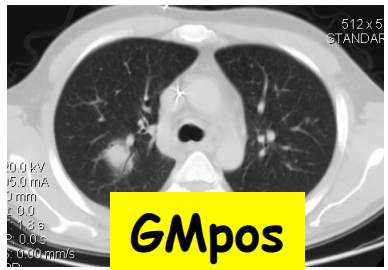
Fever

GM GM GM

Girmenia et al. JCO (2009) 28:667-674

DIAGNOSTIC-DRIVEN

TC



SYMPTOMATIC APPROACH

TC: thoracic computed tomography scanning
GM: Galactomannan♪

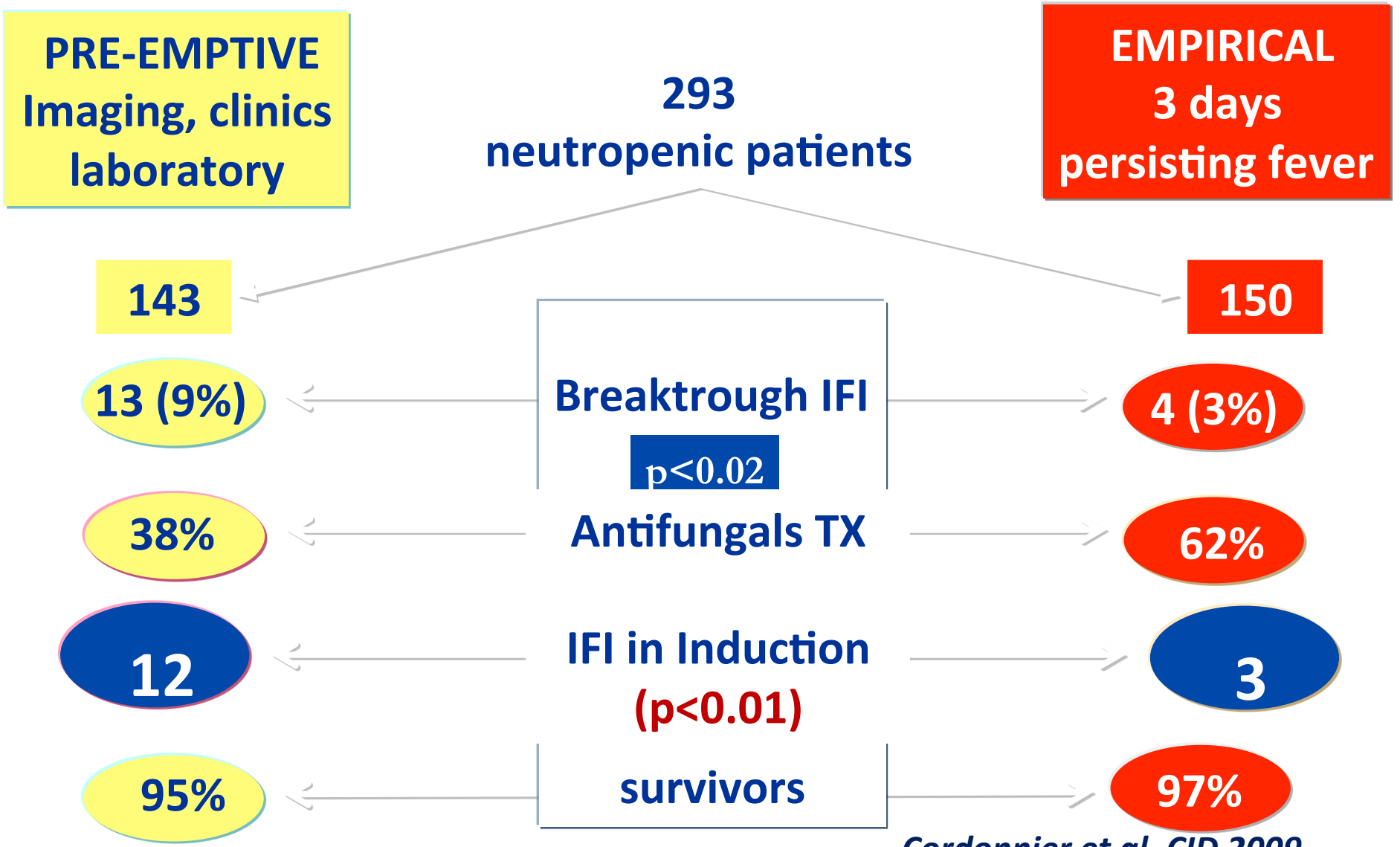
Courtesy of C. Girmenia

Pre-emptive strategy criteria

Data from literature

Reference	Intensive work-up	Criteria to start pre-emptive
Maertens *et al*, Clin Infect Dis. 2005 Nov 1;41(9):1242-50	- Cultures of blood, sputum and infected sites - Chest CT - Bronchoscopy with BAL	- GM ≥ 0.5 x 2; or - Pos for both TAC and BAL
Oshima *et al*, J Antimicrob Chemother. 2007 ;60(2):350-5	Not specified	- Fever ≥ 7 days + GM ≥ 0.6 x 2; or - Pos Rx +/- TAC
Cordonnier *et al*, Clin Infect Dis. 2009 15;48(8)	- Blood cultures x 2, urine culture - X-ray	- Fever ≥ 4 days + GM ≥ 1.5 x 1; or - Clinical suspicion of IFD
Dignan *et al*, Bone Marrow Transplant. 2009;44(1):51-6	- Blood cultures x 2, X-ray - Chest CT	- Fever ≥ 3 days + pos TAC; or - Clinical suspicion of IFD
Aguilar-Guisado *et al*, Bone Marrow Transplant. 2010 ;45 (1):159-64	- Blood cultures, X-ray - Chest CT	- Fever ≥ 5 days + sever sepsis, septic shock, infection of lung, skin CNS, sinus, abdomen
Girmenia *et al*, J Clin Oncol. 2010;28(4):667-74.	- Blood cultures x 3, GM x 3, CT	Fever ≥ 4 days + proven/probable/ possible IFD
Tan *et al*, Int J Infect Dis. 2011 May;15(5):e350-6	- GM x 2	-fever + GM ≥ 0.5 x 2; or -fever + GM ≥ 0.5 + pos CT

Empirical versus Preemptive Antifungal Therapy for High-Risk, Febrile, Neutropenic Patients: A Randomized, Controlled Trial



Cordonnier et al. CID 2009

Prevert study – Induction vs Consolidation

	Induction		Conso/autologous SCT	
	Empirical n=78	Preemptive n=73	Empirical n=72	Preemptive n=70
Median duration of neutropenia	26 d (21-31)	26 d (18-32)	11 d (9-16)	12 d (10-16)
Survival %	94.9%*	93.2%*	100%	97.1%
IFD (%)	3 (3.8%)**	12 (16.4%)**	1 (1.4%)	1 (1.4%)
- *Candida*	0	5	0	0
- *Asperg*	3	7	1	1

* Non-inferiority not ruled out

** p < .01

Cordonnier et al, Clinical Infectious Diseases (2009) 48:1042–51

The use and efficacy of empirical *versus* pre-emptive therapy in the management of fungal infections: the HEMA e-Chart Project

Livio Pagano,[1] Morena Caira,[1] Annamaria Nosari,[2] Chiara Cattaneo,[3] Rosa Fanci,[4] Alessandro Bonini,[5] Nicola Vianelli,[6] Maria Grazia Garzia,[7] Mario Mancinelli,[1] Maria Elena Tosti,[8] Mario Tumbarello,[9] Pierluigi Viale,[10] Franco Aversa,[11] and Giuseppe Rossi[3] on behalf of the HEMA e-Chart Group, Italy

Haematologica. 2011 Sep; 96(9):1366-70

Descriptive, not randomized, not interventional study

EMPIRICAL THERAPY

- Administration of an antifungal agent to a neutropenic patients with **persistent fever** without a known source of infection and unresponsive to appropriate antibacterial agents
- 190 patients

PRE-EMPTIVE THERAPY

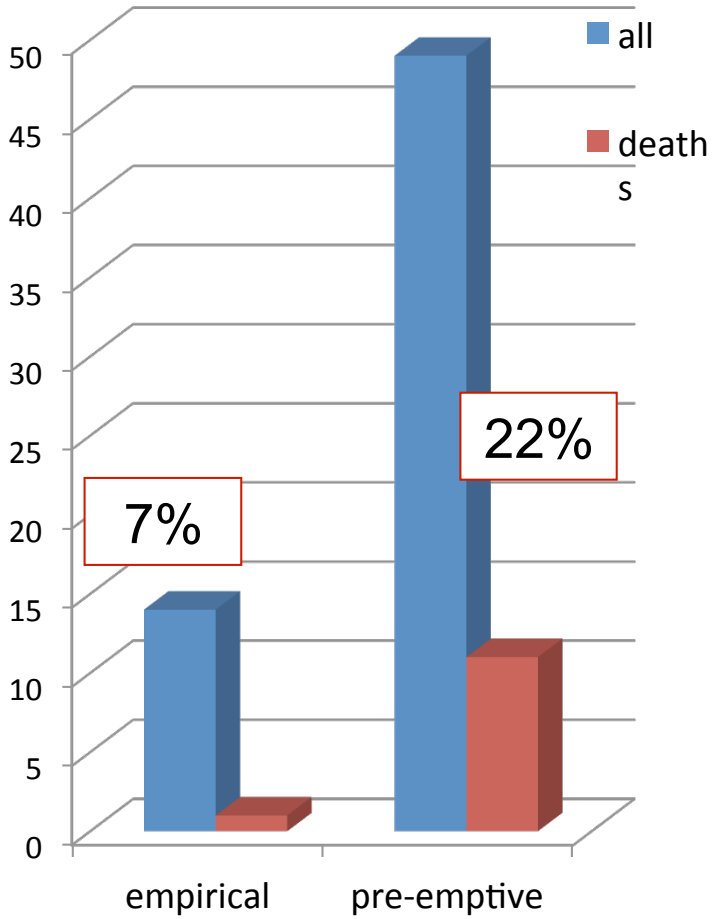
- Administration of an antifungal agent to patients **with laboratory tests or radiographic signs indicative of invasive fungal disease**, without definitive proof from histopathology or cultures in an appropriate clinical subset.*
- 207 patients

* According to *Maertens et al, Clinical Infectious Diseases (2005) 41:1242–50*

Empirical *vs* Pre-Emptive

IFDs incidence

	Proven/probable IFDs
Empirical n°190	14 (7.4%)
	p-value 0.001
Pre-emptive n°207	49 (23.7%)



IFD-attributable mortality rate

p-value 0.002

Haematologica. 2011 Sep; 96(9):1366-70

ESCMID Aspergillosis Guideline 2014

PRELIMINARY

Haematology and Oncology, Haematopoietic Cell Transplantation

Andrew J. Ullmann, Murat Akova, Rosemary Barnes, Nicolay Klimko, Olivier Lortholary, Johan Maertens, Livio Pagano, Patricia Ribaud, Anna Skiada, Janos Sinko, Claudio Viscoli, Oliver A. Cornely

Fever-driven strategy: In which patients to perform?

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Patients w AL or MDS and neutropenia with induction and/or with allo SCT	Reduce IA incidence	**Empirical antifungal therapy (e.g. caspofungin, liposomal AmB)**	**A**	**I**	Pizzo AJM 1982 EORTC AJM 1989 Goldberg EJC 2008 Cordonnier CID 2009 Girmenia JCO 2010	
	Reduce fungal-related mortality		**B**	**II**	Pagano Haematologica 2011	vs. diagnostic driven therapy

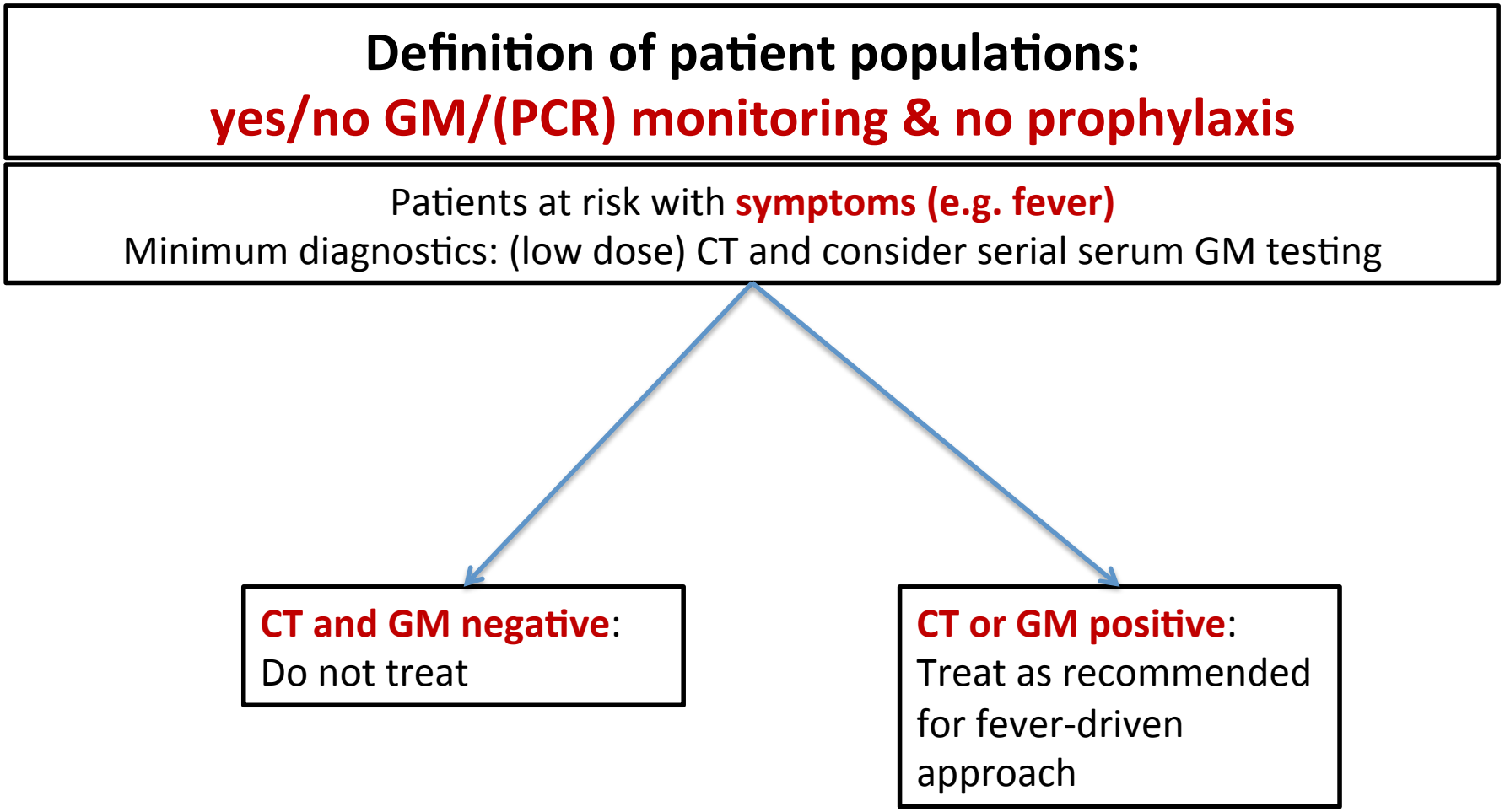
Consensus statement for treatment duration (SoR: B):
if no infiltrates, then discontinuation after WBC recovery

Fever-driven strategy: Diagnostic procedures for persistence or relapse of fever/diagnostic procedures for suspected breakthrough IA

Population	Intention	Intervention	SoR	QoE	Ref	Comment
Monitoring patients receiving mould-active prophylaxis / therapy	To diagnose IA	**GM (serum)**	**A**	**II**	Hoenigl Mycoses 2013	77% sensitivity in patients with mould-active regimens
		GM + PCR (serum)	**C**	**II**	Morrissey Lancet ID 2013	Reduce empirical antifungal treatment Missing standard for PCR (=> downgrading)
		(1-3)- *ß*-D-glucan (serum); not *Aspergillus* specific	**B**	**II**	Obayashi CID 2008 Ellis J Med Microbiol 2008	Either GM or BDG for testing, both are not yet considered standard (Consensus statement)
	To rule out infiltrates that are suggestive for IPA	**HR CT**	**A**	**II**	Heussel JCO 1999 Ho Mycoses 2011	

ESCMID Aspergillus Guidelines

Diagnostic-Driven Consensus: Algorithm I



Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America

Patterson et al, Clinical Infectious Diseases® 2016;63(4):433–42

What Strategies Are Recommended for Empiric and Preemptive Strategies in Allo-HSCTs and Patients Treated for AML?

Empiric antifungal therapy is recommended for high-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy. Antifungal options include a lipid formulation of AmB (strong recommendation; high-quality evidence), an echinocandin (caspofungin or micafungin) (strong recommendation; high-quality evidence), or voriconazole (strong recommendation; moderate quality evidence)

Early initiation of antifungal therapy in patients with strongly suspected IPA is warranted while a diagnostic evaluation is conducted (strong recommendation; moderate-quality evidence)

Other evaluations must be done in order to understand which is the most correct approach

Empiric **Pre-Emptive**

- Patients to treat
- Efficacy of the approach
- Toxicity of drugs
- Outcome
- Cost
- The role of prophylaxis

A prospective survey of febrile events in hematological malignancies

L. Pagano · M. Caira · G. Rossi · M. Tumbarello · R. Fanci · M. G. Garzia · N. Vianelli · N. Filardi · P. De Fabritiis · A. Beltrame · M. Musso · A. Piccin · A. Cuneo · C. Cattaneo · T. Aloisi · M. Riva · G. Rossi U. Salvadori · M. Brugiatelli · S. Sannicolò · M. Morselli · A. Bonini · P. Viale · A. Nosari · F. Aversa · for the Hema e-Chart Group*, Italy

Ann Hematol (2012) 91:767–774

- 19 EVALUABLE CENTERS for Epidemiological Analysis
- 3197 NEWLY DIAGNOSED PATIENTS

	EVT	%
Bacterial	301	34.6
Fungal	95	10.9
Viral	7	0.8
DTRF	48	5.5
FUO	386	44.4
Mixed infections	32	3.6
Fungi/Bacteria	23	
Bacteria/Virus	6	
Fungi/Virus	2	
Bacteria/Fungi/Virus	1	
TOTAL	869	

	EVT	%
ALL	5	4%
AML	93	82%
CML	0	0%
CLL	2	2%
NHL	7	6%
HD	0	0%
MDS	3	3%
MM	3	3%
MPD	0	0%

FEVER may frequently be the earliest and only warning sign in HEMATOLOGICAL patients

869 FEBRILE EVENTS = 27.1%

Toxicity of antifungal agents used in empirical and pre-emptive approach

	D-AmB	L-AmB	Itra	Caspo	Vorico
Liver	20%	6-17%	3%	8%	8%
Renal	14%	5-11%	5%	2%	11%
Infusion-related	70%	30-50%	20%	35%	30%
Discontinuation	20%	7-15%	20%	5%	10%
OVERALL TOXICITY	High	Moderate	Low	Low	Low

Bogaert et al, Ann Int Med 2001; Walsh et al, N Eng J Med 1999, 2002, 2004

Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study

Mark S Pearce, Jane A Salotti, Mark P Little, Kieran McHugh, Choonsik Lee, Kwang Pyo Kim, Nicola L Howe, Cecile M Ronckers, Preetha Rajaraman, Sir Alan W Craft, Louise Parker, Amy Berrington de González

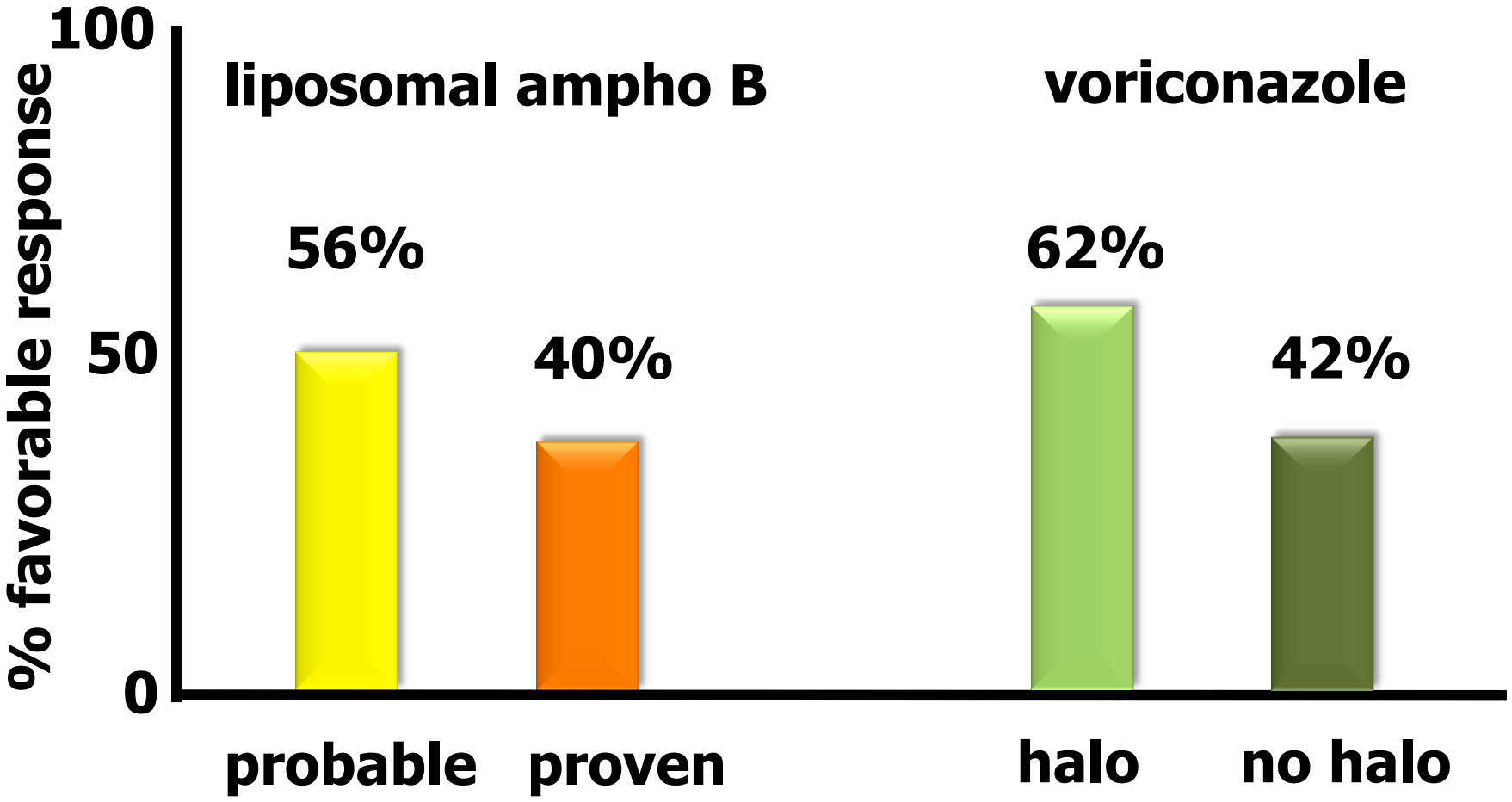
Lancet 2012; 380: 499–505

CT-scan	Dose Efficacy (mSv)	Equal to standard thorax X-ray
Skull	1.7	85
Cervical spine	1.7	85
Dorsal spine	7.7	385
Thorax	7.8	390
Abdomen	5.1	255
Lumbar spine	8.8	440

Warning: toxicity of exams ??!!??

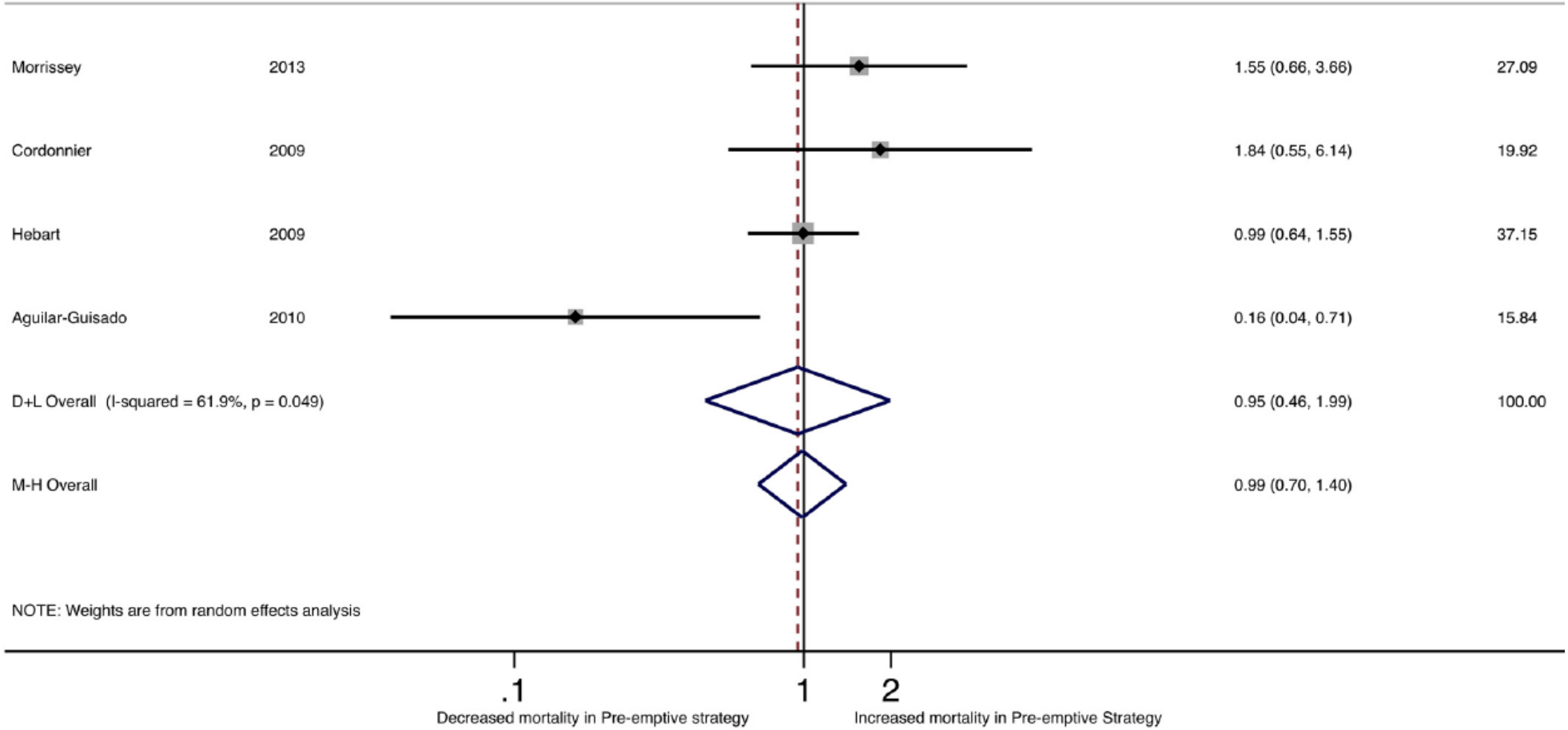
Impact of Early vs. Late Intervention

Greene et al. Clin Infect Dis 2007; 44:373-379
Cornely et al. J Antimicrob Chemother 2010; 65:114-117



Meta-Analysis and Cost Comparison of Empirical versus Pre-Emptive Antifungal Strategies in Hematologic Malignancy Patients with High-Risk Febrile Neutropenia

Fung M et al, PlosOne 2015



Strategy	Pre-IFD Diagnosis Antifungals[b]	Incident IFD Treatment Antifungals[c]	Total Cost[d] ($)
Empirical Therapy	858	574	2378
Pre-emptive Therapy	263	844	2053

Posaconazole Prophylaxis

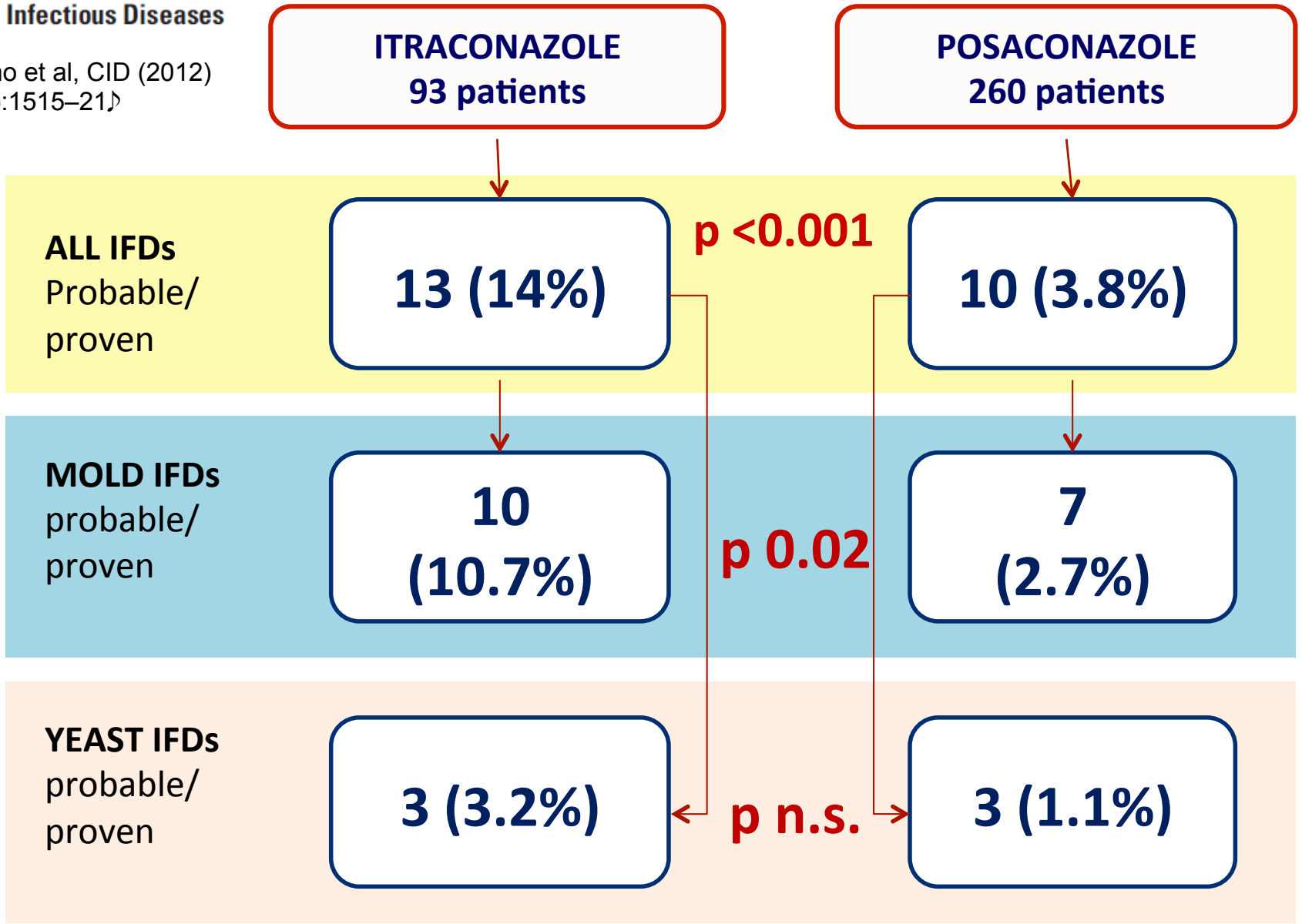
		N patients	IFIs	p-value
Cornely et al, NEJM (2007) 356:348-359 (AML/MDS in Induction)	Posaconazole	304	2 aspergillosis 7 IFIs	<0.001
	Fluconazole Itraconazole	240 58	20 aspergillosis 25 IFIs	
Ullman et al, NEJM 2007 356:348-359 (allo-HSCTs with GVHD)	Posaconazole	301	7 aspergillosis 16 IFIs	0.07 for IFIs 0.006 for IA
	Itraconazole	299	21 aspergillosis 27 IFIs	

SEIFEM 2010

Evaluation of the Practice of Antifungal Prophylaxis Use in Patients With Newly Diagnosed Acute Myeloid Leukemia: Results From the SEIFEM 2010-B Registry

Clinical Infectious Diseases

Pagano et al, CID (2012) 55(11):1515–21♪



SEIFEM 2010

Secondary endpoints

Posaconazole prophylaxis was also able to reduce:

- possible IFDs
- short term overall mortality
- the need of subsequent i.v. antifungal therapies

	ITRA N°93	POSA N°260	p-value
Frontline antifungal approach	41 (45.1%)	69 (26.6%)	0.001
• Empirical	21 (22.6%)	53 (20.3%)	0.49
• Pre-emptive	13 (14%)	12 (4.6%)	0.003
• Target	7 (7%)	4 (1.5%)	0.004

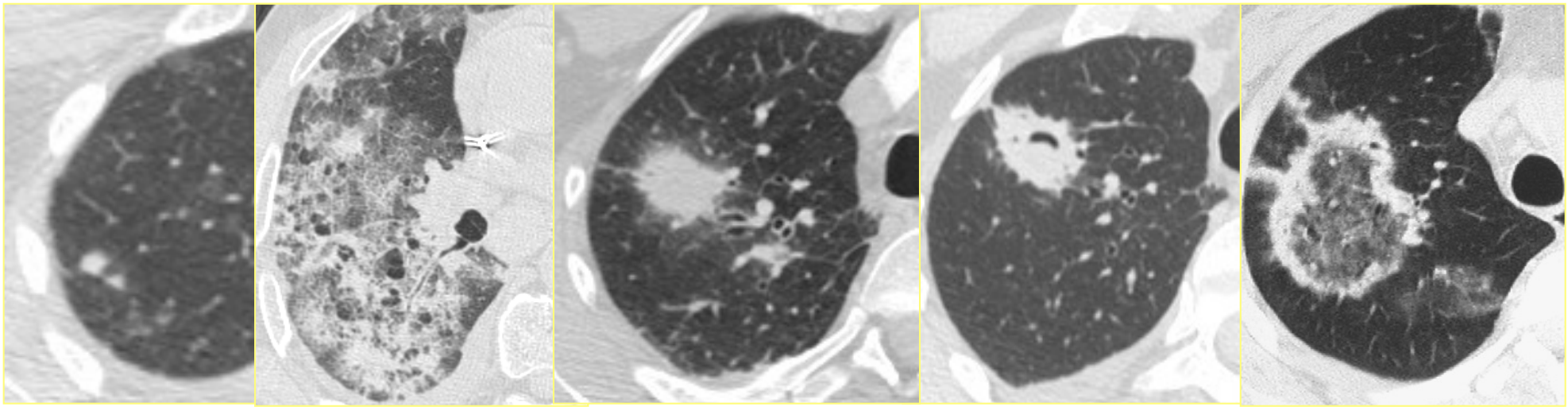
No CHANGES in the EMPIRICAL USE

Pagano et al, CID (2012) 55(11):1515–21♪

HRCT – findings for IFI

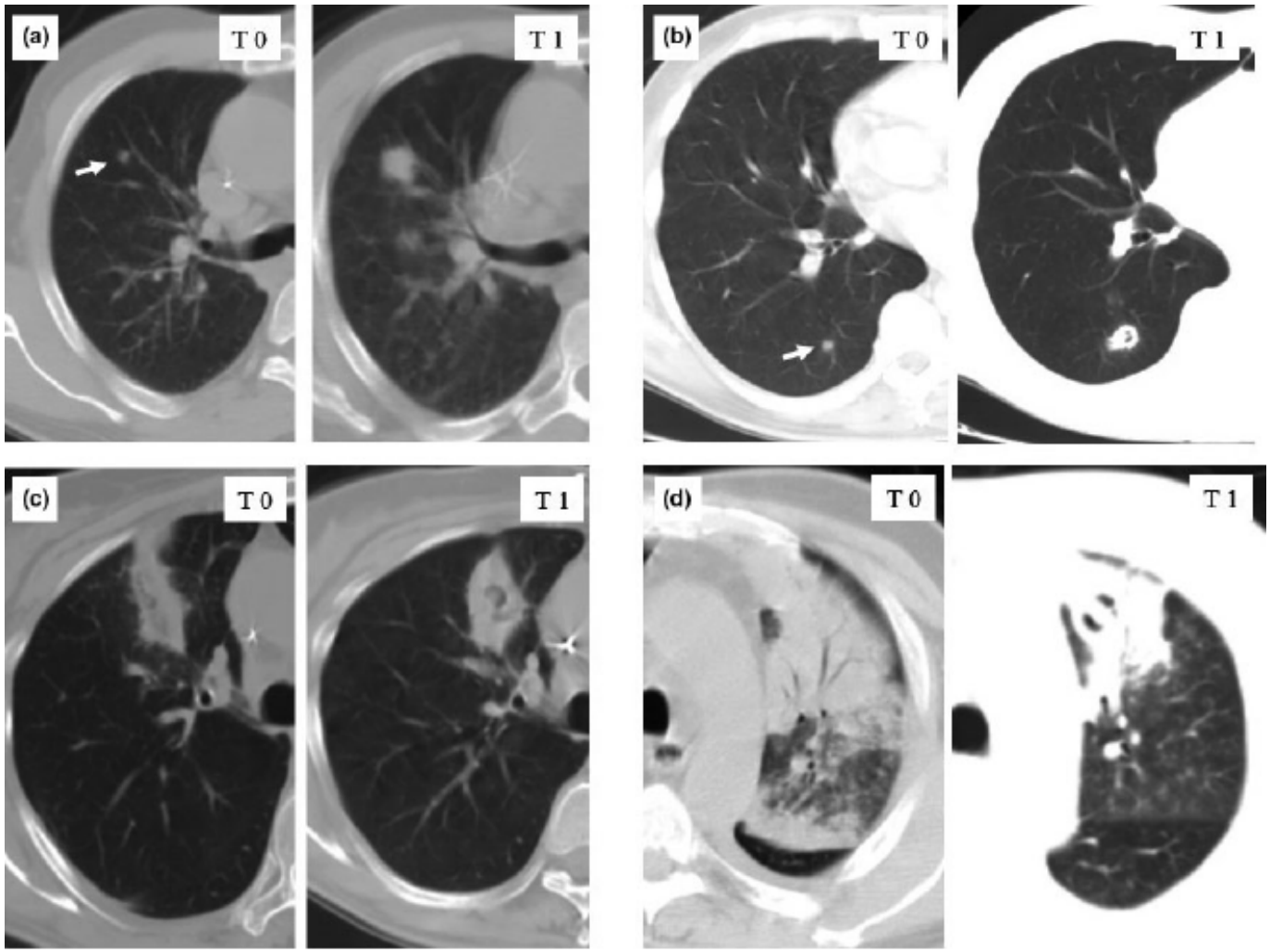
nodule
mass/ consolidation/ GGO
“halo sign”
“air crescent sign”
“reversed halo sign”

imaging findings can overlapping from each other



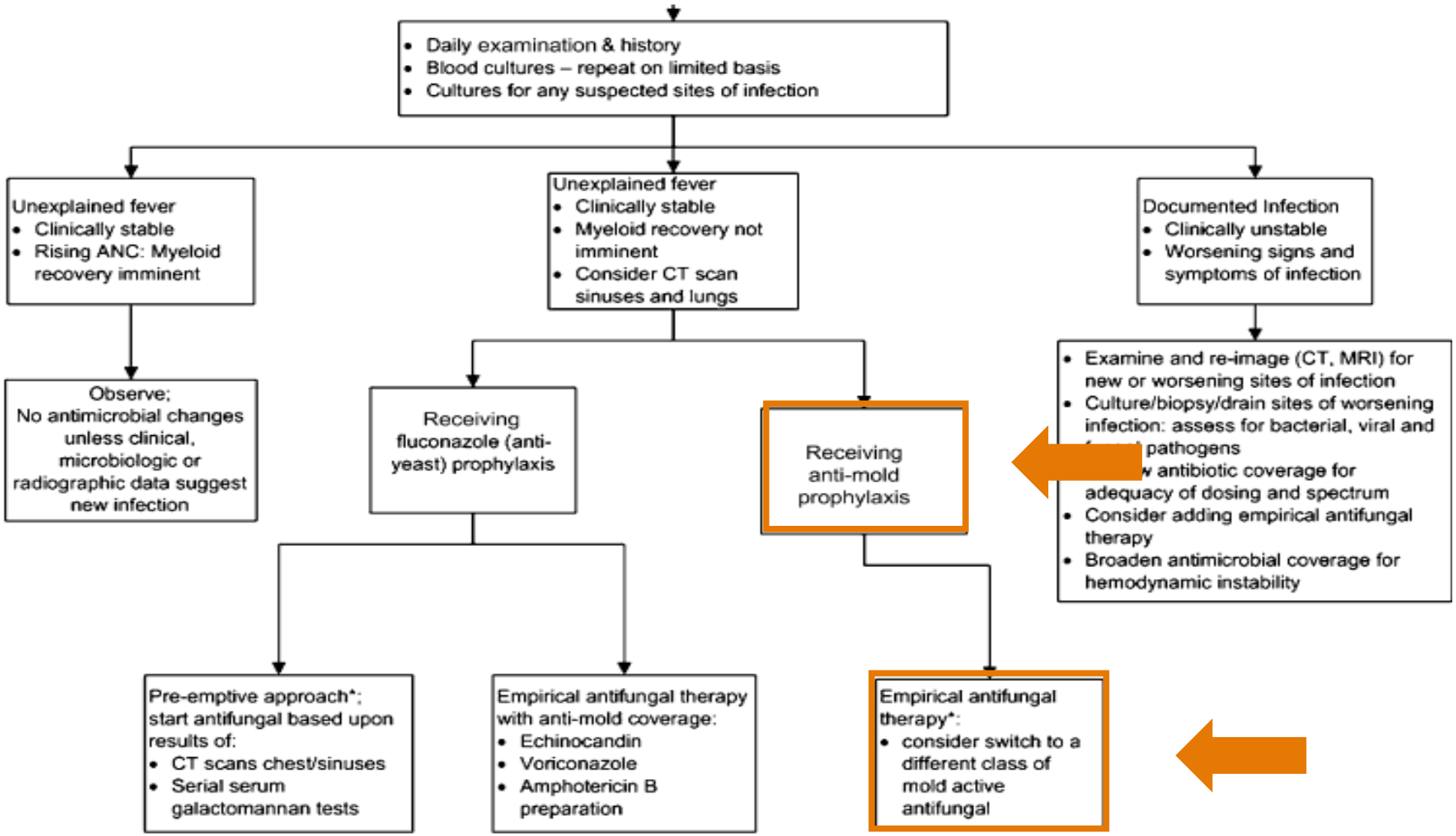
nodule | consolidation/ GG opacities | “halo sign” | “air crescent sign” | “reversed halo sign”

Pulmonary fungal infections in patients with acute myeloid leukaemia: is it the time to revise the radiological diagnostic criteria?



Maccioni et al, Mycoses 2016

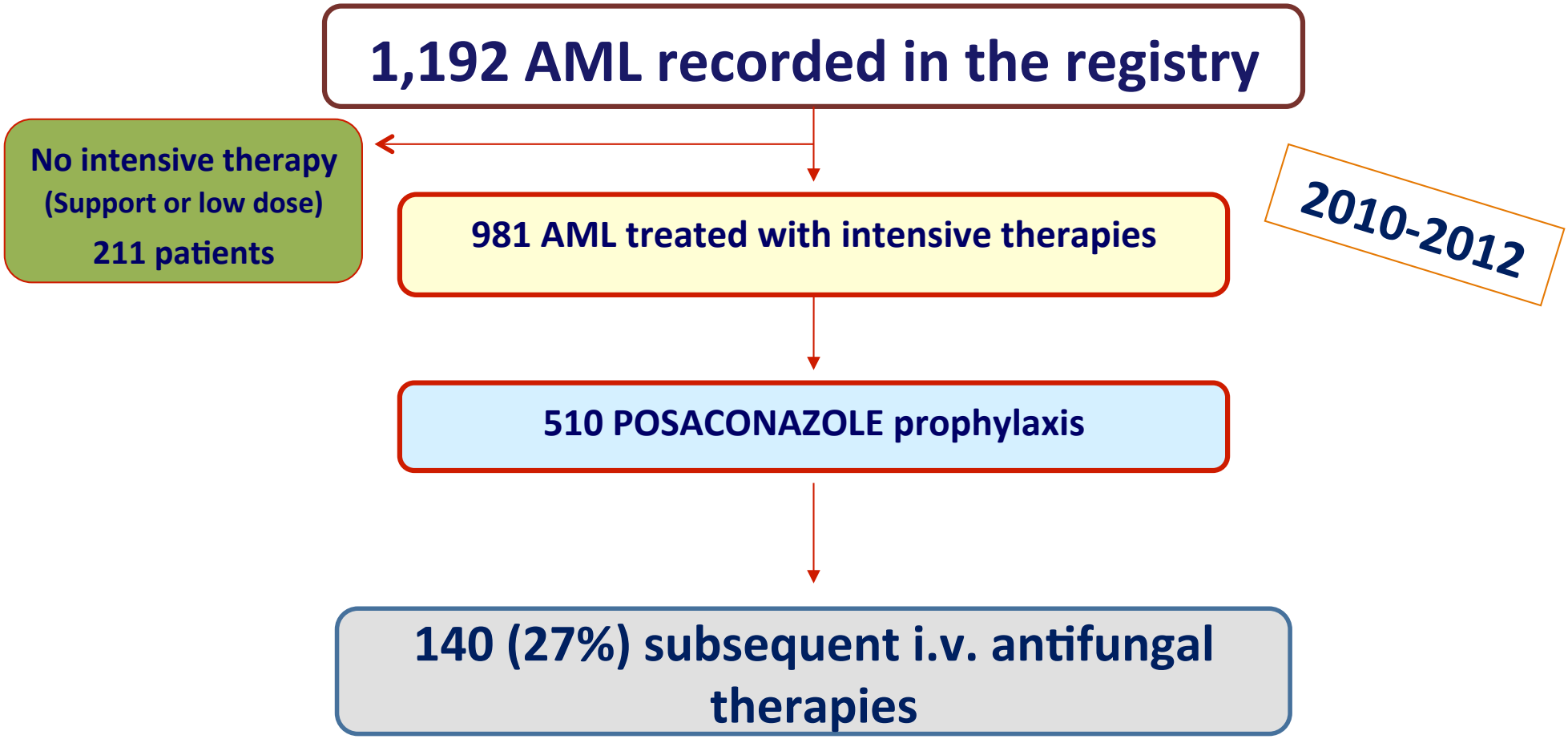
IDSA guidelines: 2010 update



Freifeld et al, Clin Infect dis (2011); 52(4):e56–e93

Systemic antifungal treatment after posaconazole prophylaxis: results from the SEIFEM 2010-C survey

J Antimicrob Chemother
doi:10.1093/jac/dku227



Pagano et al, JAC 2014 ;69(11):3142-7

SEIFEM 2010

545 POSACONAZOLE prophylaxis

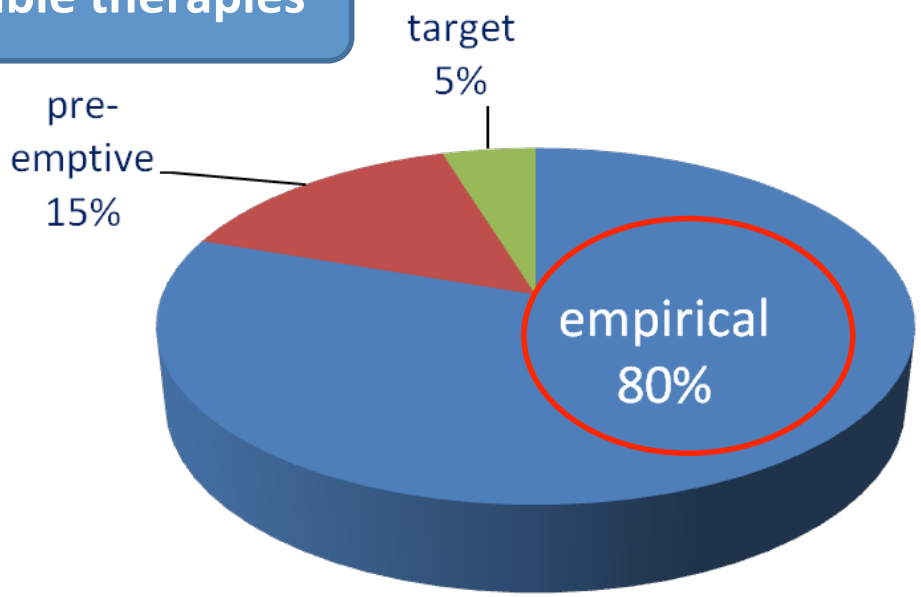
>5 days

140 (26%) subsequent i.v. antifungal therapies

≥7 days

127 evaluable therapies

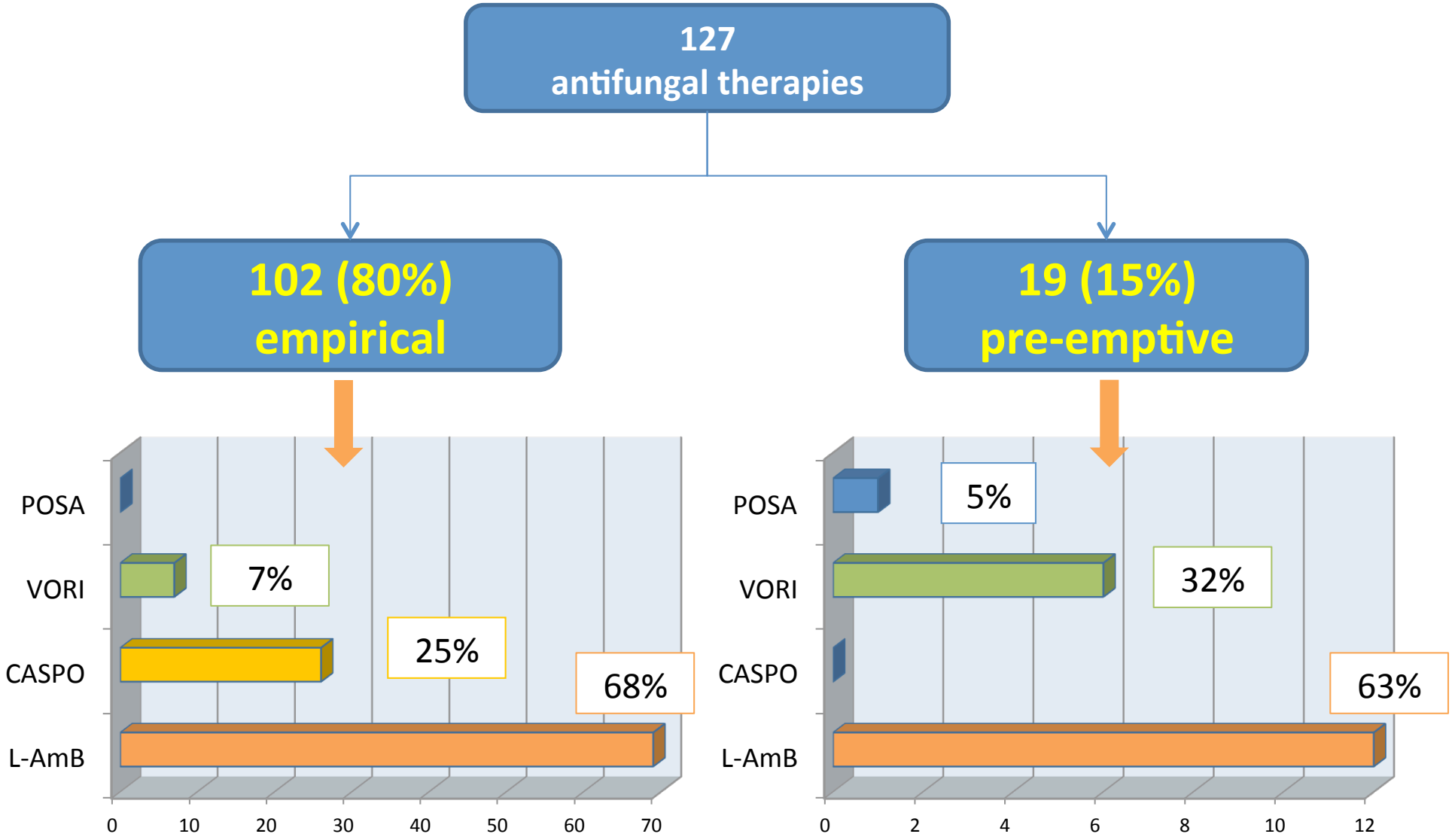
3 EARLY DEATHS due to IFDs:
- 2 aspergillosis
- 1 PJP



Pagano et al, JAC (2014) 65: 2013–2018

SEIFEM 2010

Data from the SEIFEM registry



Pagano et al, JAC (2014) 65: 2013–2018

Kind of Evidence	Cases	At 30 days	Duration Mean (range)	AMR	Overall mortality
Empirical	**102**		**14 d (6-90)**	**3 (3%)**	**26 (25%)**
❖ L-AmB	69	FUO 26 Possible 37 Probable 4 Proven 2	13 (6-40)	3	15
❖ Caspofungin	26	FUO 9 Possible 12 Probable 5	11 (14-58)	/	9
❖ Others (4 ABLC, 3 voriconazole)	7	FUO 2 Possible 5	11 (7-19)	/	2
Pre-Emptive	**19**		**18 d (8-42)**	**0**	**4 (21%)**
❖ L-AmB	12	Possible 5 Probable 7 Proven 1	15 (8-30)	/	2
❖ Voriconazole	6	Possible 4 Probable 2 Proven 1	23 (10-42)	/	1
❖ Posaconazole	1	Possible	22	/	1

Meta-Analysis and Cost Comparison of Empirical versus Pre-Emptive Antifungal Strategies in Hematologic Malignancy Patients with High-Risk Febrile Neutropenia

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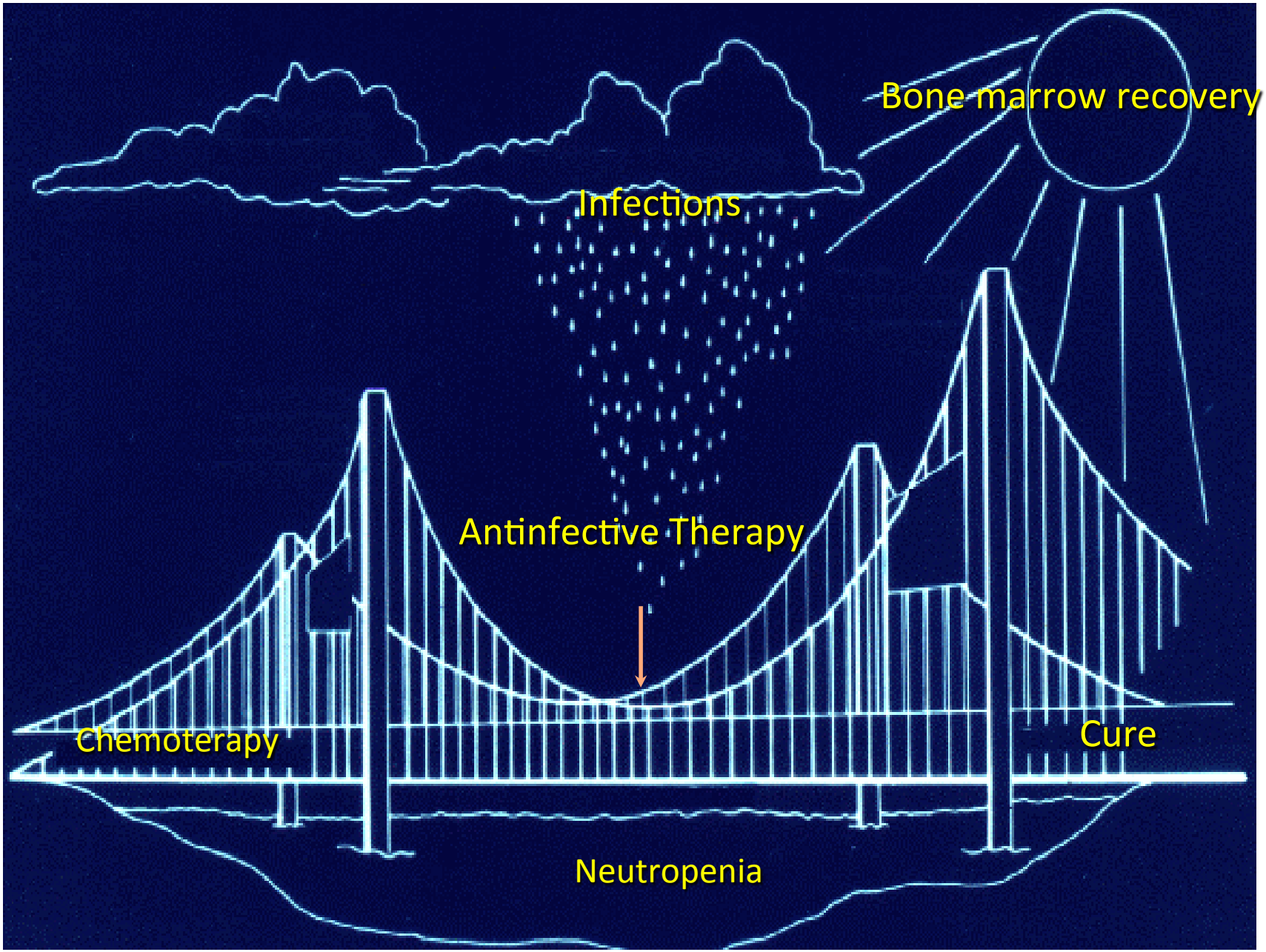
PLOS ONE | DOI:10.1371/journal.pone.0140930 November 10, 2015

Conclusions

Compared to empirical antifungal therapy, pre-emptive antifungal therapy in patients with high-risk FN may decrease antifungal use without increasing mortality. We demonstrate a state of economic equipoise between empirical and diagnostic-directed pre-emptive antifungal treatment strategies, influenced by small changes in cost of antifungal therapy and diagnostic testing, in the current literature. This work emphasizes the need for optimization of existing fungal diagnostic strategies, development of more efficient diagnostic strategies, and less toxic and more cost-effective antifungals.



Courtesy Pizzo