Gemelli

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

Managing breakthrough Invasive Aspergillosis

Livio Pagano

Istituto di Ematologia-Polo di Onco-Ematologia
Fondazione Policlinico Agostino Gemelli
Università Cattolica S. Cuore
Roma

Sorveglianza Epidemiologica Infezioni Fungine nelle Emopatie Maligne

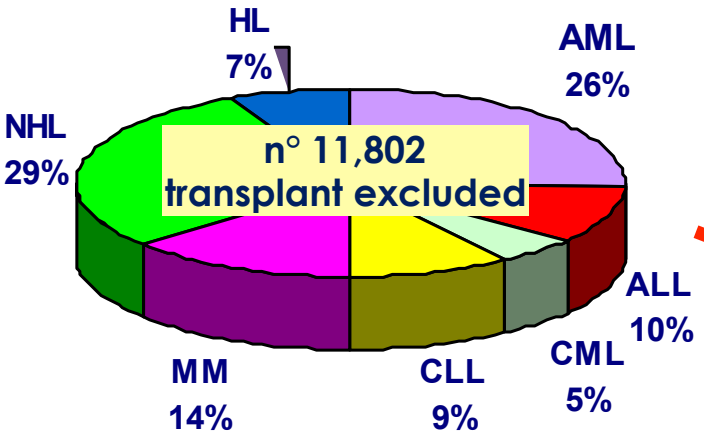
EORTC
The future of cancer therapy

Questions

- Who are the patients at greatest risk for invasive aspergillosis?
- Which are the most incriminated drugs for a breakthrough fungal infections?
- or, better, which is the most incriminated procedure for a breakthrough fungal infections?
- What does breakthrough fungal infections mean?
- How can we reduce the risk of breakthrough aspergillosis?

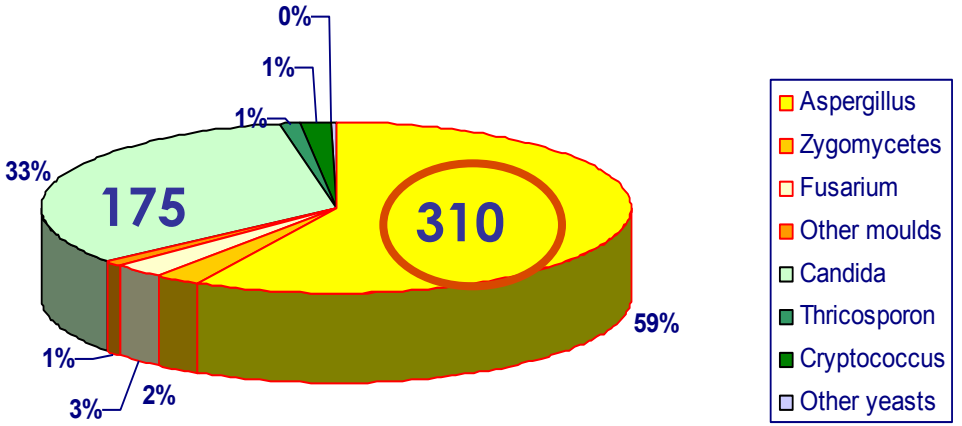
The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study

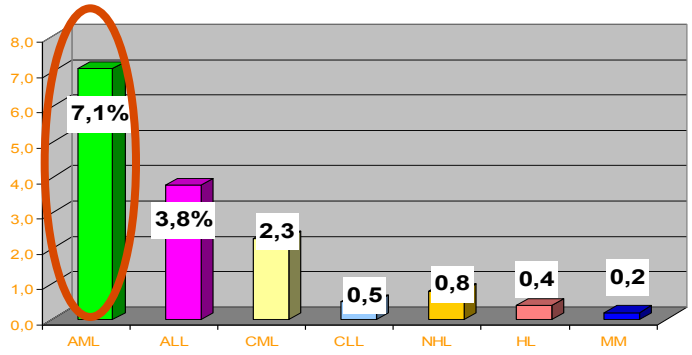
Pagano et al, Haematologica 2006



Overall Incidence: 4.6%

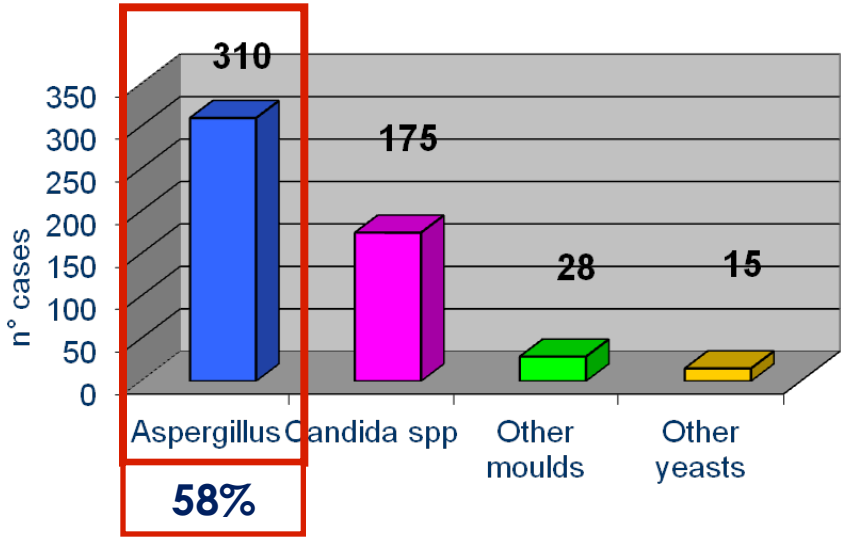
Yeasts/Moulds 1:3





AML:

EPISODES 213/310 INCIDENCE 7,1%



Epidemiology of IFI in AML

SEIFEM

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)
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)

Why these wide ranges?

It was due to:

- **Kind of prophylaxis**
- **Phase of underlying AML**
- **Number of cases**

SEIFEM

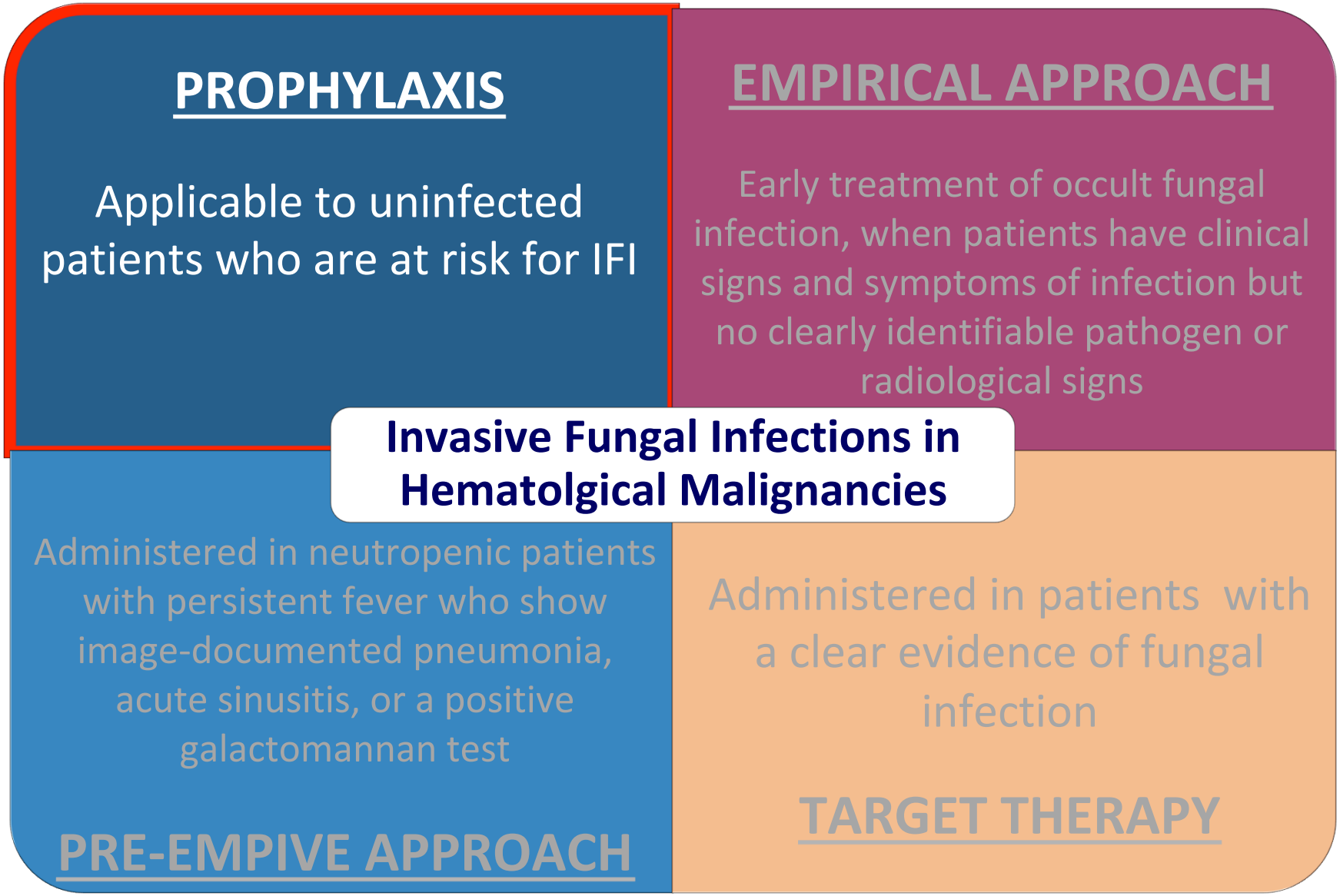
IFI risk statification in HM

HIGH Risk	INTERMEDIATE Risk	LOW Risk
AML 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 with Prior IA AML undergoing salvage regimens for Relapsed/Refractory disease.	AML not meeting criteria for High or Low Risk groups.	AML <45 yrs; Undergoing first remission-induction or consolidation CHT and without ANY Risk Factors for IFI APL treated with ATRA/ATO
Allogeneic Stem Cell transplantation (from donors other than a matched sibling donor, patients active HM, GVHD requiring high-dose steroids and history of previ	Allogeneic Stem Cell transplantation (from matched sibling donors, patients in complete remission with no evidence of GVHD and no previous IFI)	
MDS/AML receiving azacitidine as sal therapy after intensive regimens		
Acute Lymphoblastic Leukemia: patients (≥55y); Intensive pediatric r (induction); High Doses dexame Previously treated (relapsed/refractor		ia: inance on); TKI
		emia,
Pagano et al, Blood Reviews		MM, al

AML undergoing Induction CHT with any of the following Risk Factors: Neutropenia at baseline, low CR probability (Adverse kariotype, secondary AML), age > 65 yrs, Significant pulmonary disfunction, high e-TRM score
AML with Prior IA
AML undergoing salvage regimens for Relapsed/Refractory disease

Current therapeutic approaches to fungal infections in immunocompromised hematological patients

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



High Incidences of Invasive Fungal Infections in Acute Myeloid Leukemia Patients Receiving Induction Chemotherapy without Systemic Antifungal Prophylaxis: A Prospective Observational Study in Taiwan

Jih-Luh Tang et al

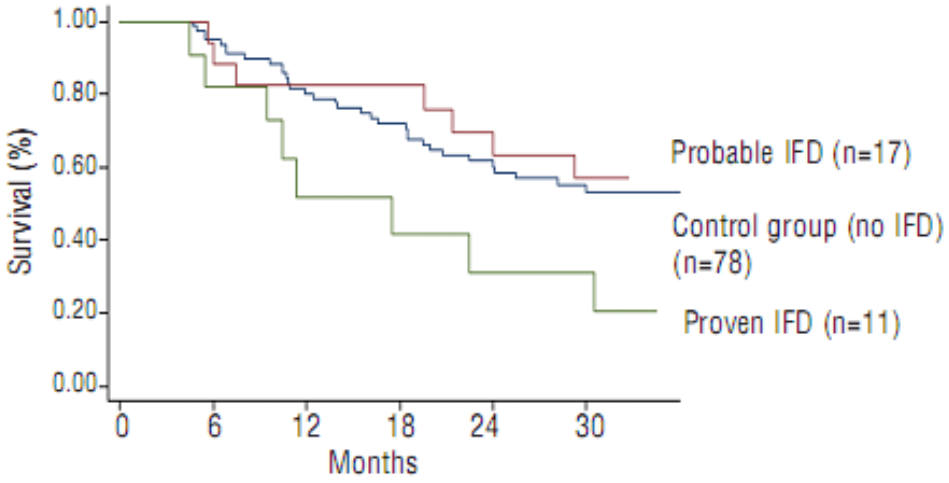
PLOS ONE June 10, 2015

- **From Jan 2004 to Dec 2009**
- **298 non-M3 adult AMLs in induction chemotherapy**
- **No systemic anti-fungal prophylaxis**
- **The median age 51 years**
- **The incidence of all-category IFIs was 34.6% (5.7% proven IFIs, 5.0% probable IFIs and 23.8% possible IFIs)**
- **29 (9.7%) patients died. 20 deaths due to IFIs (68.9%)**
- **The overall IFI-attributed mortality during induction chemotherapy was 6.7% (20/298)**

Impact of invasive fungal disease on the chemotherapy schedule and event-free survival in acute leukemia patients who survived fungal disease: a case-control study

Caroline Even,[1] Sylvie Bastuji-Garin,[2,3] Yosr Hicheri,[1,4] Cécile Pautas,[1] Francoise Botterel,[4,5,6] Sébastien Maury,[1,4] Ludovic Cabanne,[1] Stéphane Bretagne,[4,5,6] and Catherine Cordonnier[1,4,5]

haematologica | 2011; 96(2)

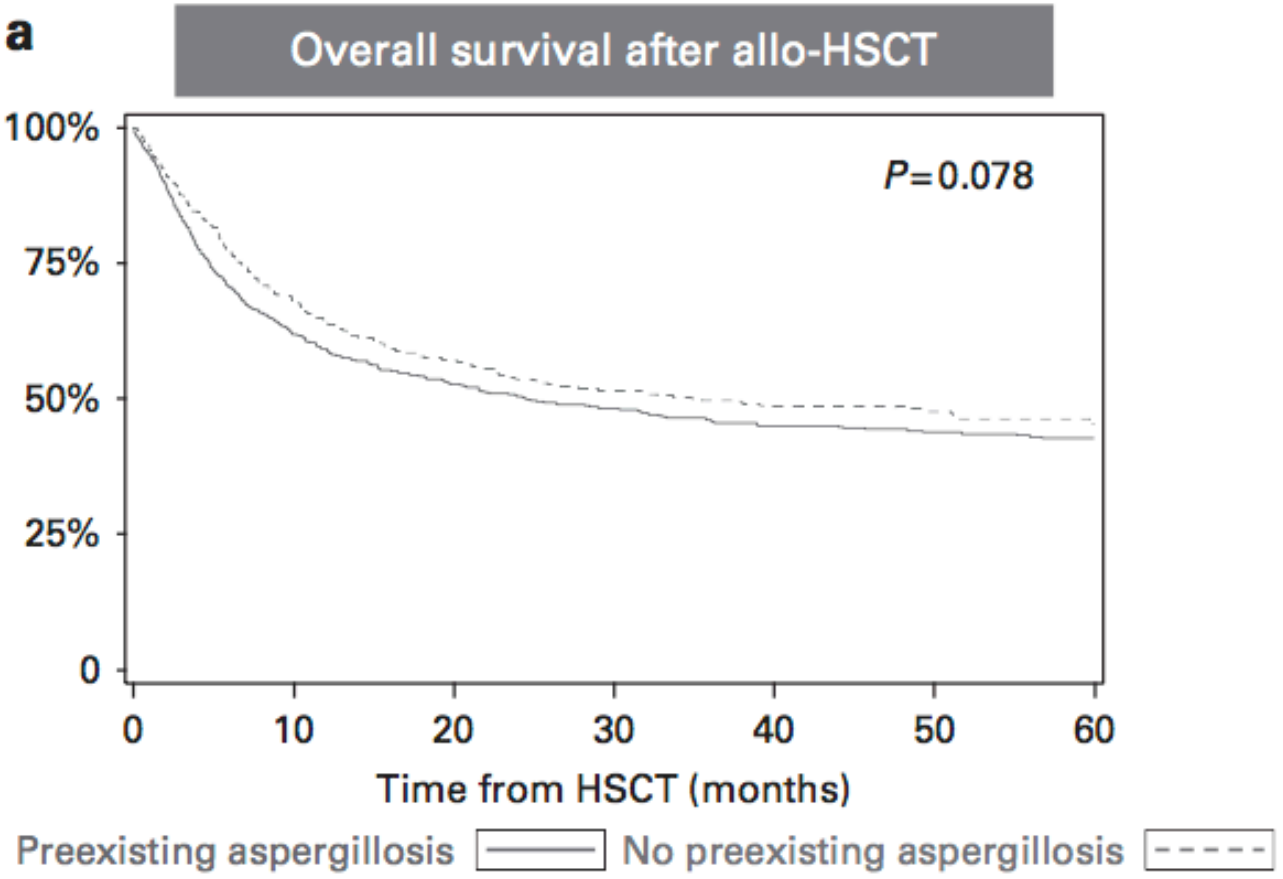


	Cases	Controls	P value
Delay in chemotherapy	57%	20,5%	0,001
Median (range) delay in days	11 (1-38)	4,5 (1-45)	0,0058
Changes in chemotherapy	28,6%	7,7%	0,009
Changes in schedule	68%	24,4%	<0,001

Influence of pre-existing invasive aspergillosis on allo-HSCT outcome: a retrospective EBMT analysis by the Infectious Diseases and Acute Leukemia Working Parties

Penack et al BMT 2016

2005 -2010
1150 Acute Leukemia



A trend toward lower overall survival (P = 0.078, hazard ratio (HR) (95%CI): 1.16 (0.98, 1.36)) and higher non-relapse mortality (P = 0.150, HR (95% CI): 1.19 (0.94, 1.50)) in allo-HSCT recipients with pre-existing IA

blood 1995 86: 2063-2072

Antifungal prophylaxis in patients with hematologic malignancies: a reappraisal [see comments]

O Uzun and EJ Anaissie

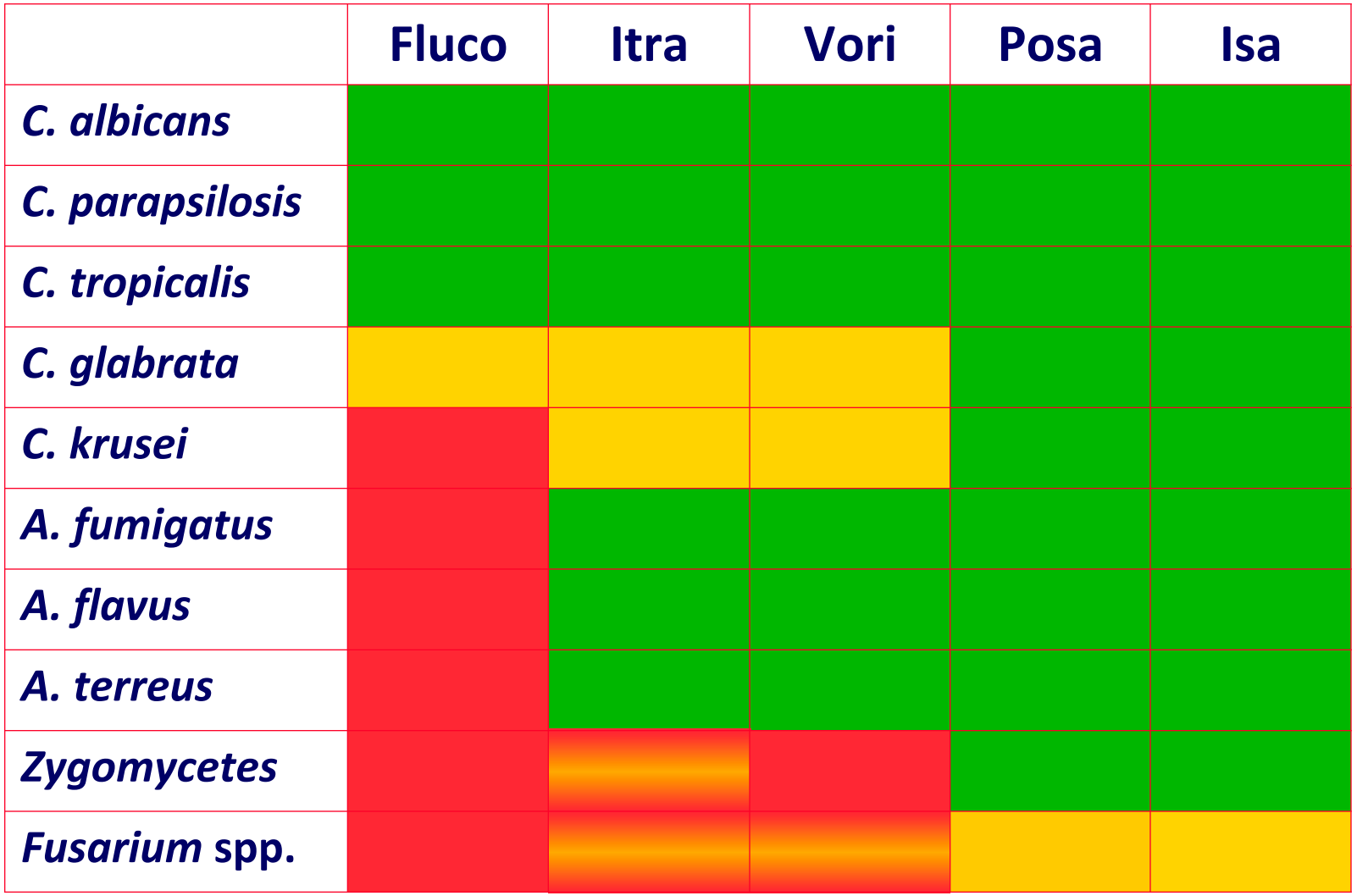
The IDEAL prophylactic agent:

- ***Safe***
- ***Effec***
- ***Fung***
  path
- ***Inexpensive***
- **Available in both oral and intravenous *formulation***
- **Associated with a low incidence of *resistance***

The better choice are azoles

Antifungal Activity of Azoles

> 75% sensible ≤ 50% < 5% not effective



Voriconazole Prophylaxis in allo-HSCTs

		N PATIENT	IFDs	P-VALUE
Wingard et al, Blood 2010 (allo-HSCTs)	Voriconazole	305	16 aspergillosis 3 candidemia 2 zygomycosis	
Marks et al, Br J Haemat 2011 (allo-HSCTs)	Voriconazole	234	0 candidemia 0 zygomycosis	No differences in IFD incidence
	Itraconazole	255	1 aspergillosis 2 candidemia 0 zygomicosis	Increased use of AF in Itra arm p<0.01

ONLY FOR ALLO-HSCTs

Posaconazole Prophylaxis

		N° PATIENT	IFIs	P-VALUE
Cornely et al, NEJM 2007 (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 (allo-HSCTs with GVHD)	Posaconazole	301	7 aspergillosis 16 IFIs	0.07 for IFIs 0.006 for IA
	Itraconazole	299	21 aspergillosis 27 IFIs	

Mould-active compared with fluconazole prophylaxis to prevent invasive fungal diseases in cancer patients receiving chemotherapy or haematopoietic stem-cell transplantation: a systematic review and meta-analysis of randomised controlled trials

Outcome (pro mould active)	Trials (patients)	RR	(95% CI)	p-value
Proven/Probable IFI	18 (4802)	0.71	(0.52-0.98)	0.03
Invasive Aspergillosis	15 (4503)	0.53	(0.37-0.75)	0.0004
Adverse events requiring antifungal discontinuation	16 (4493)	1.95	(1.24-3.07)	0.004
IFI- related mortality	15 (4272)	0.67	0.47-0.96)	0.03
IA-related mortality	9 (2614)	0.62	0.23-1.71)	0.36
Overall Mortality	16 (4870)	1.00	(0.88-1.13)	0.96

Eithier et al BJC 2012

ECIL 5 update/ IDSA 2017/ECCMID 2017

Antifungal drugs for Prophylaxis in AML

Antifungal	ECIL	IDSA 2017	ECCMID 2017
Posaconazole	A I	Strong recommendation; high-quality evidence	AI
Itraconazole	B I	Strong recommendation; moderate-quality evidence	D II
Fluconazole	B I	Not recommended	/
Voriconazole	B II	Strong recommendation; moderate-quality evidence	C II
L-AmB	C II	Not recommended	C II (all doses)
ABCD	C II	Not recommended	C III
Echinocandins	C II	Weak recommendation; low-quality evidence	C II (only Micafungin)
Aerosol L-AmB	B I	Not recommended	/
Aerosol AmB	A I against	Not recommended	B I (associated to Fluconazole)
AmB deoxycholate	A II against	Not recommended	/

Maertens et al, ECIL 5; Patterson et al, CID 2016; Cornely et al, CMI 2017

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

Pagano et al, Clin Infect Dis 2012

	ITRACONAZOLE 93 patients		POSACONAZOLE 260 patients
Probable/ Proven IFIs	13 (14%)	p <0.001	10 (3.8%)
Probable/ Proven IA	10 (10.7%)	p 0.02	7 (2.7%)

	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

Are these cases all Breakthrough Infections?

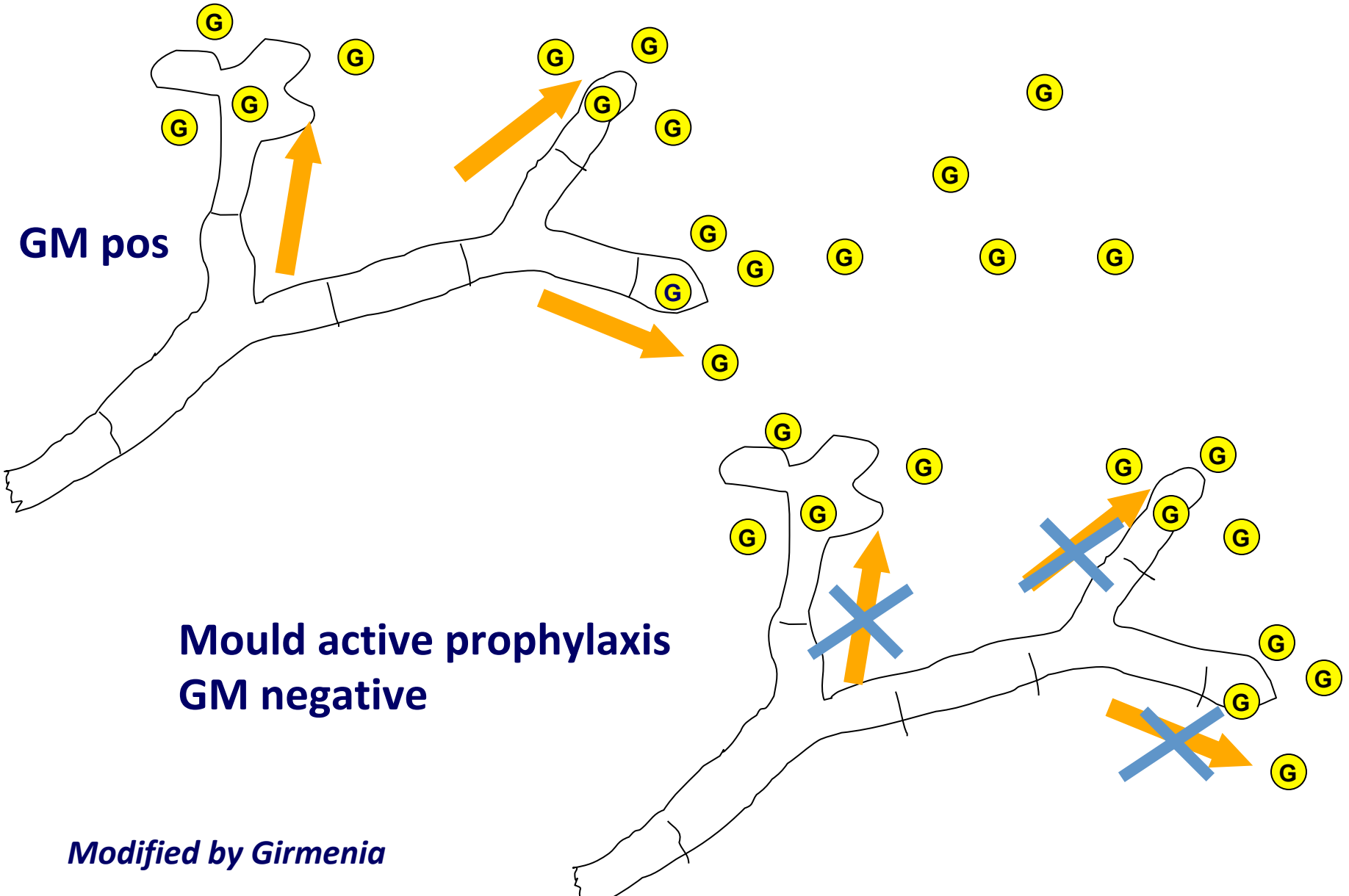
	Prophylaxis	Cases	Proven/ Probable IFD	IA	Systemic Antifungal Therapy	Overall Mortality
Cornely et al NEJM 2017	Posa	240	2%	1%	27%	16%
	Itra/Fluco	58	8%	7%	38%	22%
Ullman et al, NEJM 2017	Posa	301	5%	1%	nr	13%
	Itra	299	9%	6%	nr	12%
Wingards et al, Blood 2010	Vori	305	7%	5%	24%	19%
	Fluco	295	4%	2%	30%	20%
Marks et al, Br J Haem	Vori	234	2%	2%	30%	27%
	Itra	255	1%	0.4%	42%	33%

What does breakthrough fungal infections mean?

There are no standardized definitions !

An IFD could be considered to be a breakthrough IFD if the causative organism was different from that originally detected before the commencement of an antifungal therapy (including prophylaxis), occurrence was detected ≥3 days after the initiation of antifungal therapy, or subsequent infection occurred within 14 days after the discontinuation of any antifungal therapy

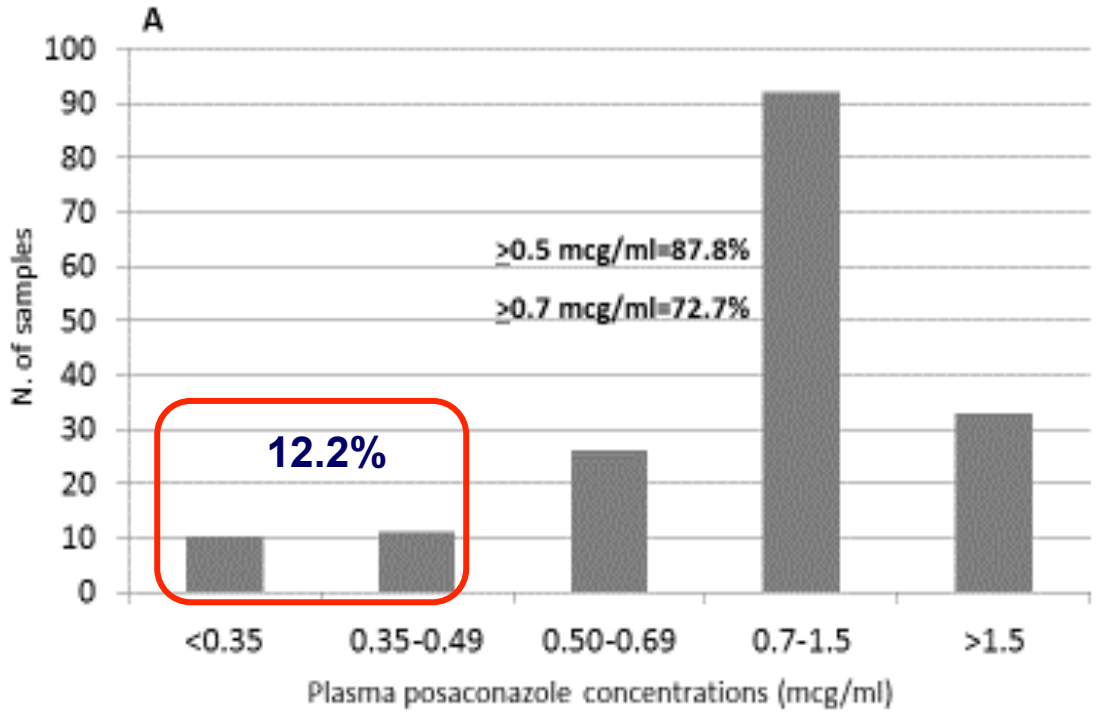
Mould active prophylaxis may decrease sensitivity of serum galactomannan assay?



Modified by Girmenia

Posaconazole oral suspension primary prophylaxis in acute leukemia and allogeneic stem cell transplant patients: can it be used without measurement of plasma concentration?

Distribution of plasma concentrations at steady state in 168 samples (115 prophylaxis courses) in AL pts



Girmenia et Al. Med Mycol. 2016

Posaconazole TDM (83 courses)

Reasons for discontinuation in AL patients with two or more measurements

Reason for PCZ-OS discontinuation	Inadequate PPC pattern, 18 courses	Sufficient PPC pattern, 12 courses	Adequate PPC pattern, 53 courses
Shift to another antifunfgal drug (11)*	6 (33.3%)	2 (16.7%)	3 (5.7%)
Proven-probable or possible IFD (6)	3 (16.7%)	1 (8.3%)	2 (3.8%)
Empiric antifungal therapy (5)	3 (11.1%)	1 (8.3%)	1 (1.9%)

() n. of cases

*The rate of shift to another antifungal drug was significantly higher in courses with an inadequate PPC pattern as compared to courses with sufficient or adequate PPC pattern, P=0.007

Not always failure in prophylaxis means inadequate dosage, but more frequently yes..

Girmenia et Al. Med Mycol. 2016

Posaconazole TDM

(83 courses)
in AL patients with two or more measurements

Variable	Inadequate PPC pattern, (18)	Sufficient PPC pattern, (12)	Adequate PPC pattern, (53)	P*
Oral mucositis, n. (%)				
No	11 (61.1)	7 (58.3)	36 (67.9)	0.78
Yes	7 (38.9)	5 (41.7)	17 (32.1)	
Diarrhea, n. (%)				
No	8 (44.5)	10 (83.3)	49 (92.4)	0.0001
Yes	10 (55.5)	2 (16.7)	4 (7.6)	
Use of PPI, n. (%)				
No	13 (72.2)	10 (83.3)	46 (86.8)	0.17
Yes	5 (27.8)	2 (16.7)	7 (13.2)	
Feeding, n. (%)				
Adequate	15 (83.3)	10 (83.3)	48 (90.6)	0.45
Poor	3 (16.7)	2 (16.7)	5 (9.4)	
Compliance, n. (%)				
Good	16 (88.9)	12 (100)	51 (92.2)	0.20
Poor	2 (11.1)	0 (0)	2 (7.8)	

PPC = plasma posaconazole concentration; PPI = proton pump inhibitor
* Courses with inadequate PPC pattern were compared to courses with sufficient/adequate PPC pattern

Girmenia et Al. Med Mycol. 2016

Interactions of mold-active azoles (voriconazole and posaconazole) with coadministered chemotherapic agents and target therapies

COADMINISTERED AGENT	INTERACTION MECHANISM	EFFECT	RECOMMENDATIONS AND ACTIONS
Vinca Alkaloids Vincristine	Inhibition CYP3A4	Increased neurotoxicity	Avoid coadministration
Alkylating agents Cyclophosphamide (CTX)	Inhibition CYP3A4/2C9	↑ hepatotoxicity ↓ activation to hydroxy-CTX	Monitor Avoid coadministration
Bruton's tyrosine kinase inhibitors Ibrutinib	Inhibition CYP3A4/2C9	↑ Ibrutinib exposure	420 mg standard dose 280 mg if Fluco; 140 mg if Posa/vori
PI3K inhibitors Idelalisib	Inhibition CYP3A4/Pgp	↑ AUC	Monitor for side effect
JAK2 inhibitors Ruxolitinib	Inhibition CYP3A4/2C9	↑ Ruxolitinib exposure	↓ dose 50%; monitor cytopenias
TKI			
Imatinib	Inhibition CYP3A4	↑ Imatinib exposure	Avoid coadministration
Dasatinib	Inhibition CYP3A4	↑ D. exposure,↑ QT interval	Avoid coadministration, monitor ECG
Nilotinib	Inhibition CYP3A4	↑ N. exposure, ↑ QT interval	Avoid coadministration, monitor ECG
ponatinib	Substrate CYP3A4	↓ TKI dosage	Avoid coadministration
sorafenib	Inhibition CYP3A4	No effect	Monitor QTc
Midostaurin	Inhibition CYP3A4	↑ adverse reaction	Avoid coadministration, monitor QTc
Quirzatinib	Inhibition CYP3A4	↑ Quirzatinib exposure	↓ dose (induc 40 mg ->20 mg)

Azole resistance in *Aspergillus fumigatus*: a side-effect of environmental fungicide use?

- The presence of a single resistance mechanism (denoted by TR/L98H) was found in over 90% of itraconazole-resistant Dutch *A. fumigatus* isolates, which also showed reduced susceptibility to voriconazole and posaconazole
- This is in contrast with a different pattern of resistance observed in British *A. fumigatus* isolates, where a wide variety of *cyp51A* mutations (substitutions at codons G54, G138, P216, F219, M220, and G448), have been found
- TR_{34}/L98H isolates were recovered primarily from azole-naïve patients and were also recovered from the environment. These observations suggest that azole-resistant *Aspergillus* is acquired by patients from an environmental source rather than arising through azole therapy

Verweij et al. Lancet Infect Dis 2009; Camps SM, et al. J Clin Microbiol 2012; Snelders E, et al. PLoS One 2012

Azole Resistance in *Aspergillus fumigatus*: Can We Retain the Clinical Use of Mold-Active Antifungal Azoles?

Table 3. Reported Mortality Rates in Patients With Invasive Aspergillosis in Different Time Periods

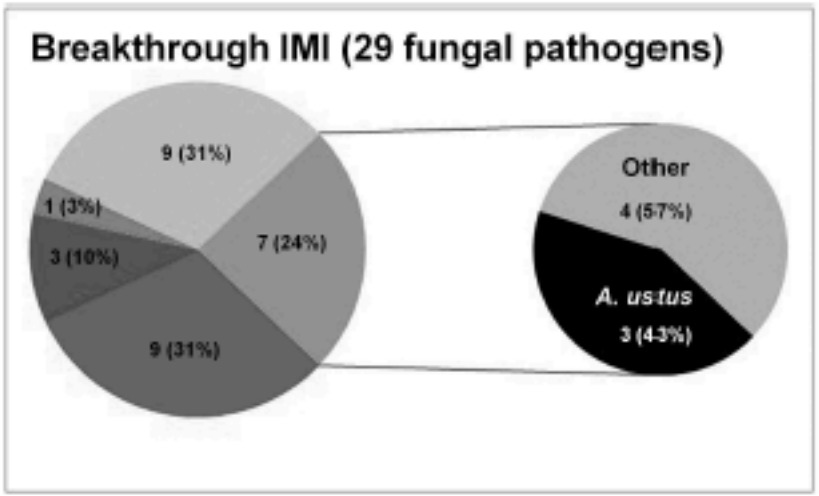
	Aspergillus Disease			
Era	IA	Comment	CNS IA	Comment
c-AmB era	65% [2]	122 of 187 patients receiving c-AmB died.	95%–100% [3]	Literature review
	71.6% [55]	187 of 261 patients with IA died.	99% [56]	Review of 141 cases of CNS IA in immunocompromised patients, of whom 140 died.
Azole era	27.5% [57]	9-wk mortality: 39 of 142 patients receiving voriconazole monotherapy.	45.6% [7]	Retrospective analysis of 81 patients with CNS IA treated with voriconazole
	28.5% [58]	Population-based study analyzing 8563 aspergillosis cases in France.	35.4% [59]	Literature review: 4 of 11 patients with CNS IA who received voriconazole monotherapy.
Azole resistant	100% [44]	Culture-positive patients with proven and probable IPA treated with voriconazole (5/5)	86% [24, 44, 60]	7 cases of azole-resistant CNS IA have been reported, of which 6 were fatal.
	88% [45]	8 HSCT patients with culture-positive, azole-resistant IA, of whom 7 died.		
	100% [54]	ICU patients with culture-positive azole-resistant IA died (10/10), compared with 21 of 28 (75%) with azole-susceptible IA.		

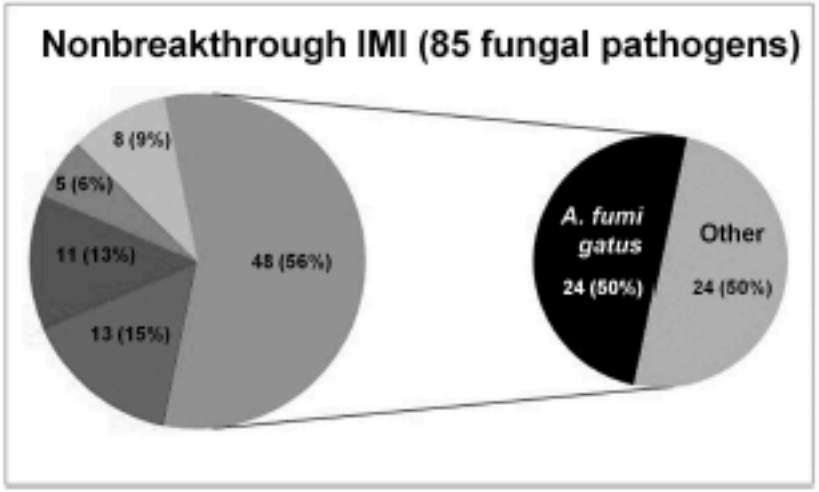
Abbreviations: c-AmB, conventional amphotericin B; CNS, central nervous system; HSCT, hematopoietic stem cell transplant; IA, invasive aspergillosis; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis.

Verweij et al. Clin Infect Dis 2016

Changing Epidemiology of Invasive Mold Infections in Patients Receiving Azole Prophylaxis

Lamoth et al CID 2017

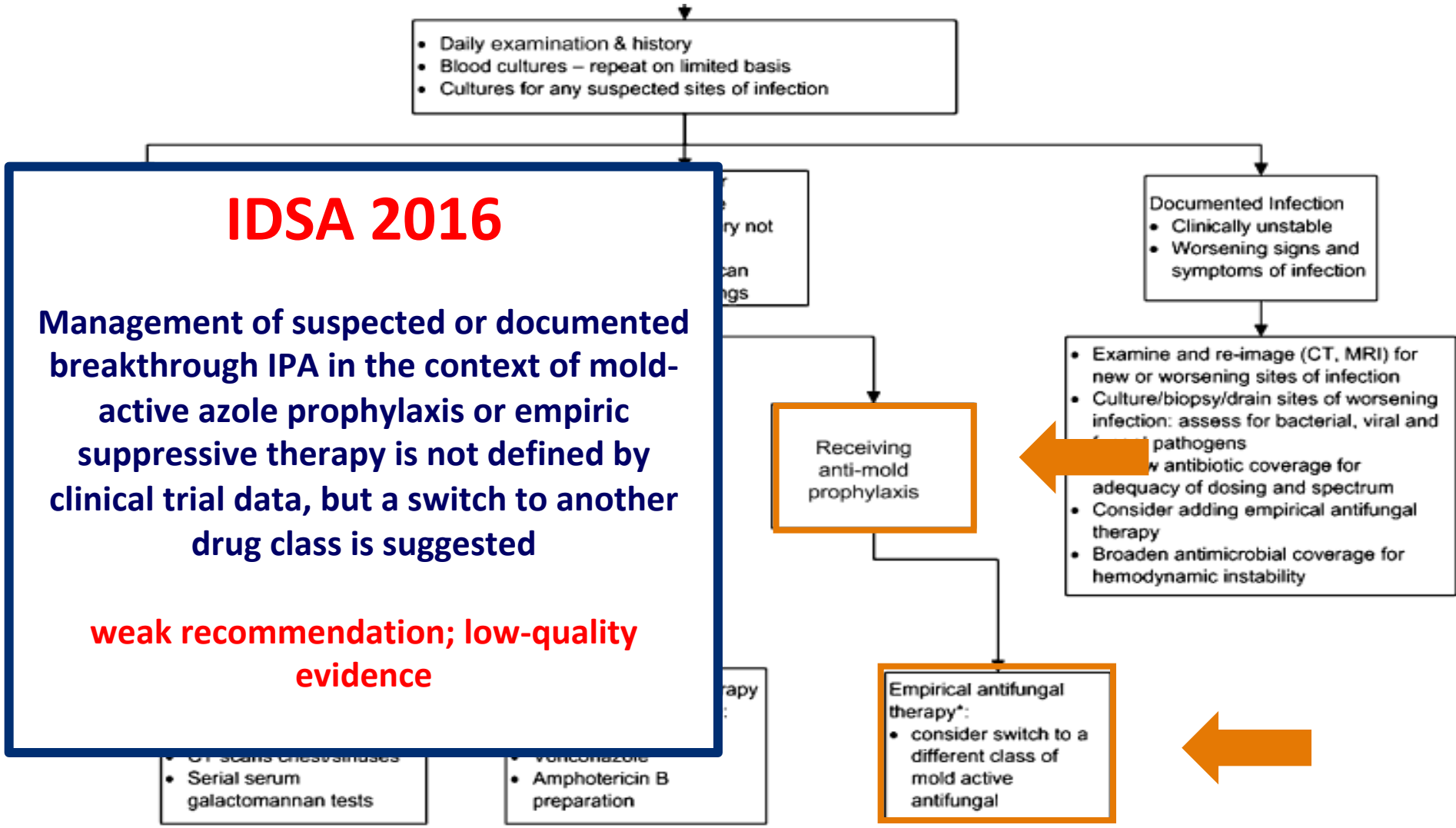




Both during posaconazole or voriconazole prophylaxis.
Results:

- **More non-*Aspergillus* infections**
- **Among *Aspergillus* higher percentuage of *A. ustus***

IDSA guidelines 2010



IDSA 2016

Management of suspected or documented breakthrough IPA in the context of mold-active azole prophylaxis or empiric suppressive therapy is not defined by clinical trial data, but a switch to another drug class is suggested

weak recommendation; low-quality evidence

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

Diagnosis and Management of Aspergillus Diseases: Executive Summary of the 2017 ESCMID-ECMM-ERS Guideline

Definition of patient populations:
GM (and PCR) monitoring OR mould-active prophylaxis

Symptoms (e.g. persistent fever)

Positive GM or PCR

Minimum diagnostic procedures: CT and microbiological work-up (cytology, culture & biomarkers)

CT negative / biomarker negative:
If prophylaxis: Continue prophylaxis, consider TDM, and actively exclude alternative foci (e.g. sinusitis)
If no prophylaxis: No antifungals and actively exclude alternative foci (e.g. sinusitis)

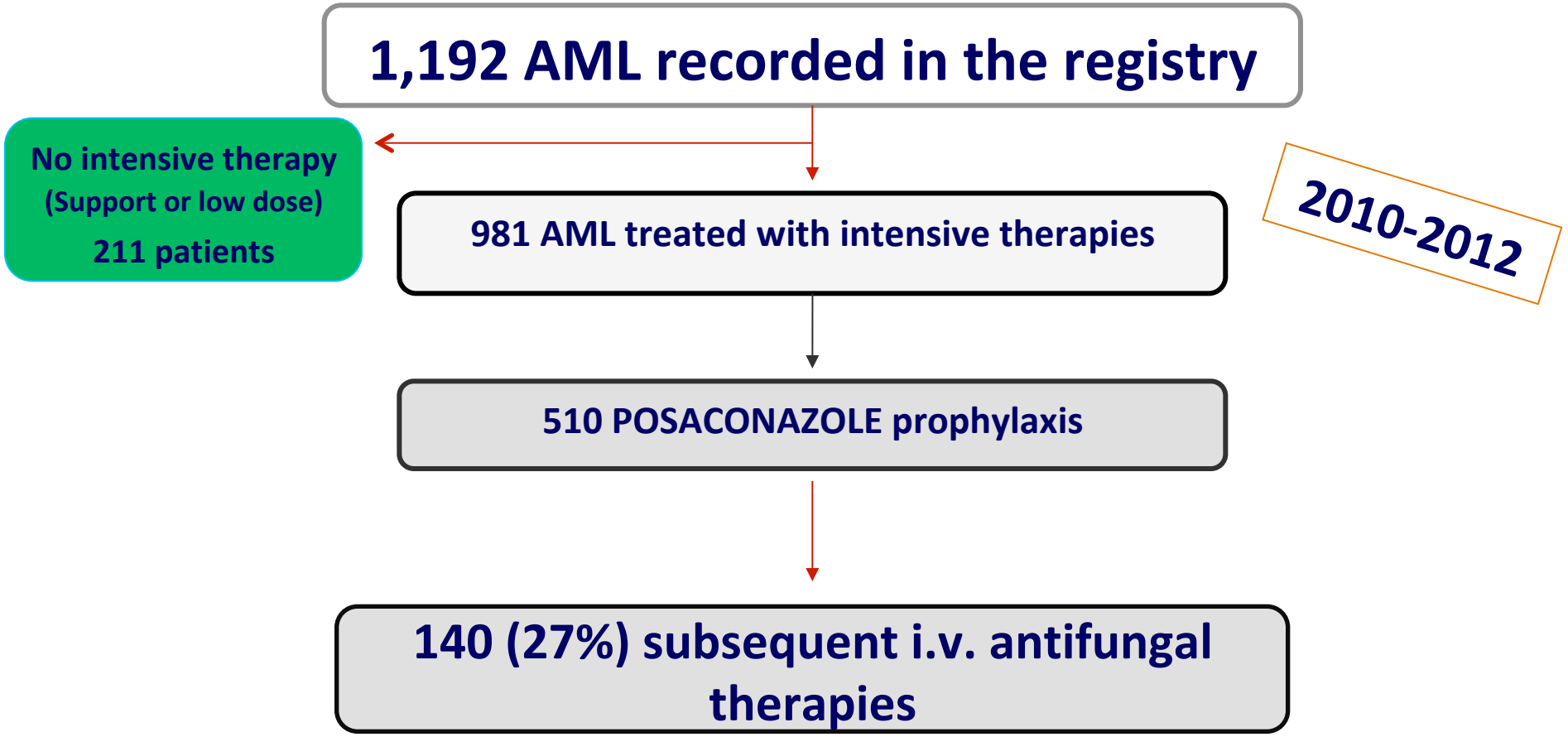
CT positive / biomarker negative:
If prophylaxis: Discontinue prophylaxis or consider TDM. Treat as recommended for targeted treatment, but change antifungal class
If no prophylaxis: Start antifungal therapy for fever-driven strategy

CT negative / biomarker positive:
Actively exclude alternative foci (e.g. sinusitis). Treat as recommended for targeted treatment, but change antifungal class if prophylaxis was given

CT positive / biomarker positive:
Treat as recommended for targeted treatment, but change antifungal class if prophylaxis was given

Cornelly et al, CMI 2018 in press

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



Pagano et al, JAC 2014

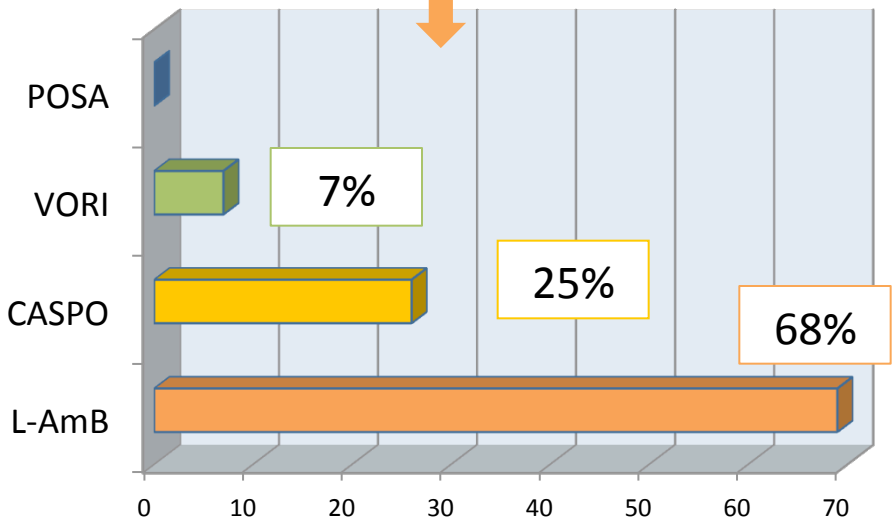
Data from the SEIFEM registry

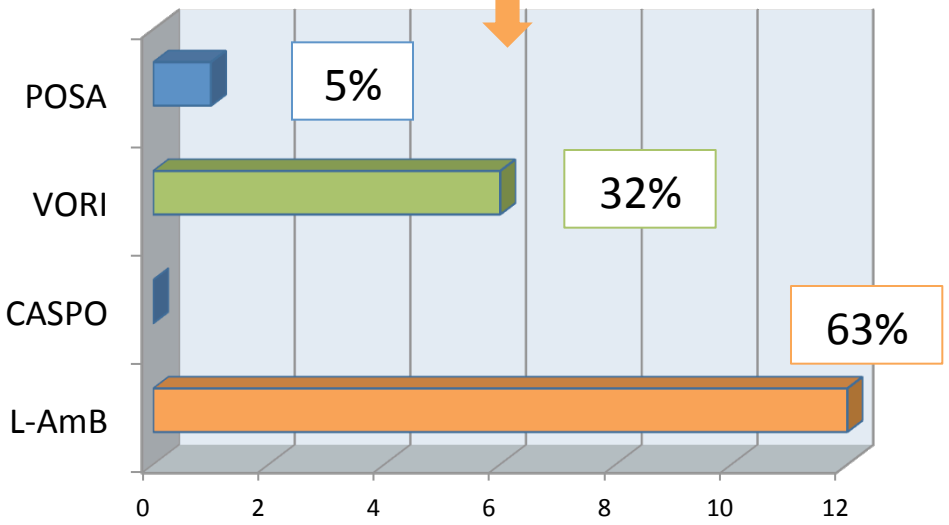
SEIFEM

127
antifungal therapies

102 (80%)
empirical

19 (15%)
pre-emptive





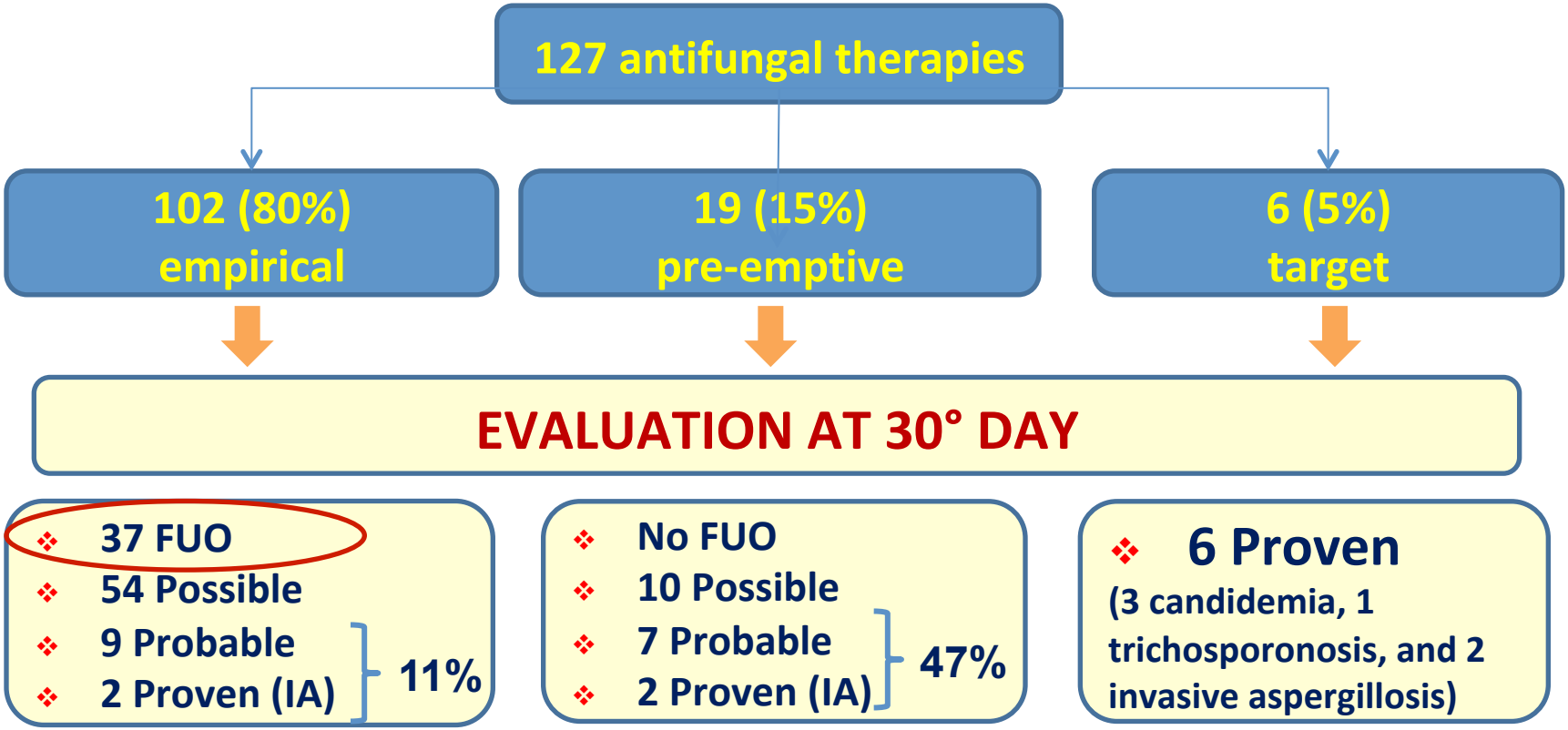
Pagano et al, JAC 2014

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			
❖ Posaconazole	1	Possible	22	/	1

No statistical difference between L-AmB and Caspo

No statistical difference between L-AmB and Vori

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



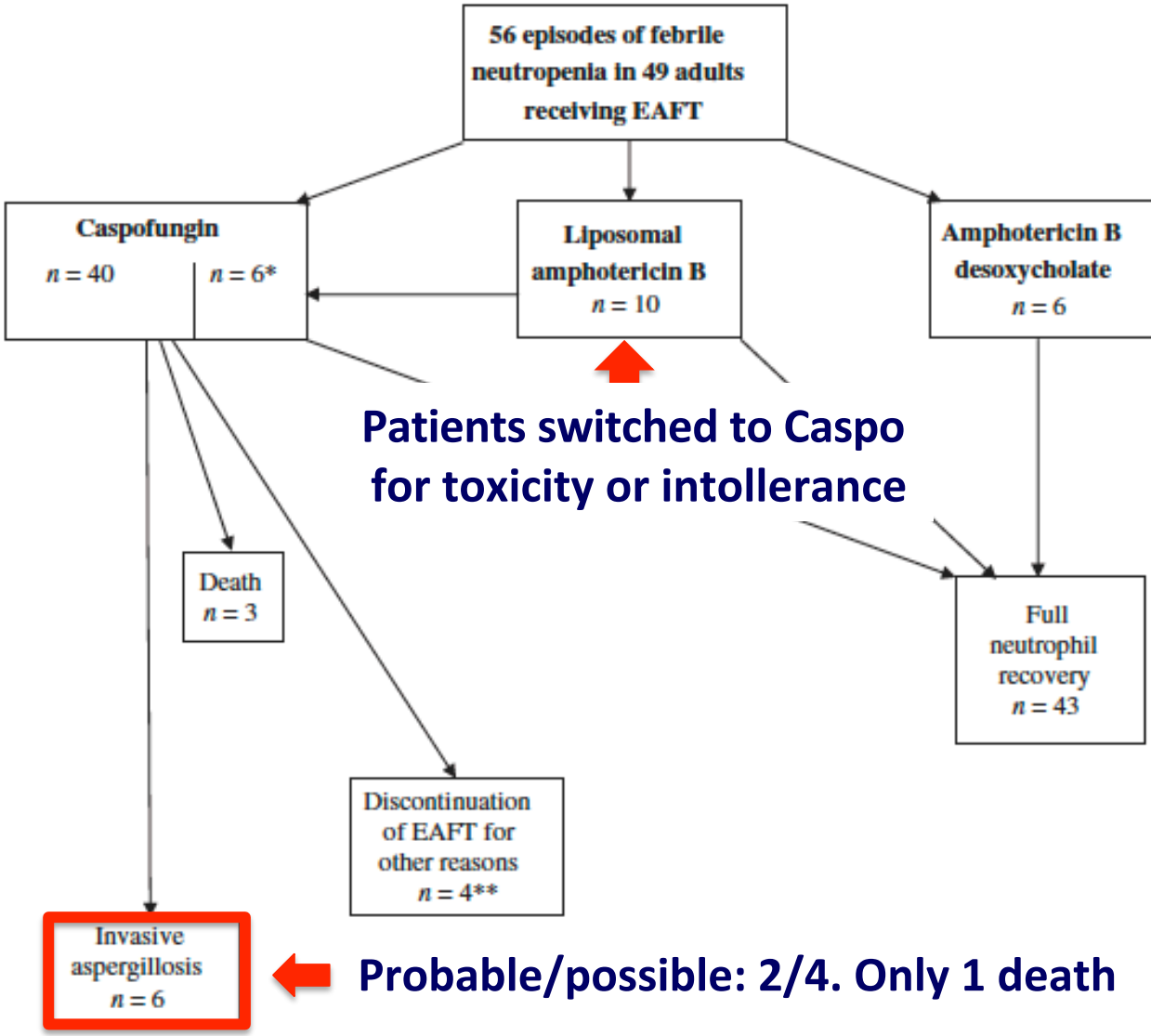
Pagano et al, JAC 2014

High rate of breakthrough invasive aspergillosis among patients receiving caspofungin for persistent fever and neutropenia

Lafaurie et al, CMI 2010

All patients with an hematological malignancy treated with high doses of chemotherapy or with HSCT procedures

All patients previously received antifungal prophylaxis with Fluconazole



Breakthrough invasive mould infections in patients treated with caspofungin

Pang et al, J Infect 2014

N°	Age (year), sex	Underlying condition	Neutropenia at onset of breakthrough IMD	Reason for caspofungin therapy	Exposure to caspofungin (days)	Pathogen	Site of IMD (degree of certainty)	Mycological findings	Therapy of breakthrough IMD	Response	Survival (days)	Death from IMD
1	68, M	NHL, diabetes	No	Candidemia	31	*Aspergillus* sp.	Lung (probable)	GM (serum)	Vori, ABLC + caspo	Failure	19	Yes
2	67, M	HCL, neutropenia, diabetes	No	Candidemia	7	*Aspergillus* sp.	Lung (probable)	GM (serum)	ABLC, L-AmB, Vori	Failure	30	Yes
3	56, M	ALL, neutropenia, diabetes, T-cell suppressor	No	Candidemia	21	*Aspergillus* sp.	Lung (proven)	Histopath (lung biopsy), GM (serum)	Vori	Failure	84+	NA
4	67, F	AML, neutropenia	No	Candidemia	15	*Aspergillus* sp.	Lung (probable)	GM (BAL)	Vori	CR	84+	NA
5	62, M	AML, neutropenia	Yes	Candidemia	9	*IMD*	Lung (possible)	None	Vori	CR	55	No
6	74, M	AML, neutropenia	Yes	Aspergillosis	16	*Fusarium moniliforme*	Blood (proven)	Culture (blood)	Vori + terbinafine	Failure	23	Yes
7	70, M	CLL, neutropenia, T-cell suppressor	Yes	Aspergillosis	7	*Mucor* sp.	(probable)	Culture (tracheal aspiration)	None	Failure	1	Yes
8	38, M	HSCT, myeloma, GvHD, neutropenia, diabetes, steroids, T-cell suppressor	No	Prophylaxis	56	*A. fumigatus*	Lung (probable)	Culture (BAL)	Vori	Failure	69	Yes
9	52, M	HSCT, CLL, neutropenia, steroids, T-cell suppressor	No	Prophylaxis	55	*A. fumigatus*	Lung (probable)	Culture (sputum), GM (serum)	L-AmB + caspo, L-AmB + vori	Failure	33	Yes
10	40, M	HSCT, ALL, GvHD, neutropenia, T-cell suppressor	No	Prophylaxis	20	*Aspergillus* sp.	Lung (probable)	GM (serum)	None	Failure	11	Yes
11	40, M	NHL, HIV+, neutropenia	No	Empirical	28	*A. fumigatus*	Lung (proven)	Culture (lung biopsy)	Vori, L-AmB	CR	45	No
12	51, M	AML, neutropenia	Yes	Empirical	9	*Aspergillus* sp.	Lung (proven)	Histopath (lung biopsy), GM (serum)	L-AmB + caspo, Vori	CR	84+	NA
13	49, M	AML, neutropenia	Yes	Empirical	8	*Mucor* sp.	Lung (proven)	Culture (lung biopsy)	L-AmB, Posa	CR	84+	NA
14	67, M	AML, neutropenia	Yes	Empirical	11	*Aspergillus* sp.	Lung (probable)	GM (serum)	Vori	CR	84+	NA
15	65, M	AML, neutropenia	Yes	Empirical	9	*IMD*	Lung (possible)	None	L-AmB, Vori	CR	84+	NA
16	60, M	AML, neutropenia	Yes	Empirical	8	*Aspergillus* sp.	Lung (probable)	GM (serum)	Vori, Vori + L-AmB	CR	84+	NA
17	25, F	ALL, neutropenia	Yes	Empirical	21	*Hormographiella aspergillata*	Lung (proven)	Culture (lung biopsy)	Vori, L-AmB	CR	84+	NA

How can we reduce the risk of breakthrough aspergillosis?