Post-HSCT Complications:

Fungal Infections

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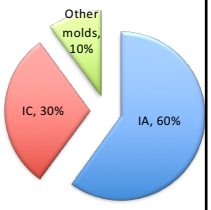
Incidence IFD in HO

- AML remission induction phase ≈12%
- ALL remission induction phase ≈6%
- HSCT, matched unrelated or mismatched ≈8%
- HSCT, matched related ≈6%
- Consolidation chemotherapy <5%
- Autologous HSCT <2%



Garcia-Vidal, et al Clin Infect Dis 2008;47:1041–50.
Pagano, et al. Haematologica 2006;91:1068– 75.
Kontoyiannis, et al. Clin Infect Dis 2010;50:1091–100.
Rogers et al. Br J Haem 2011;153:681–97

Strategies for Antifungal Therapy in HO

Strategy	Prophylaxis	Empiric (fever-driven)	Pre-emptive (diagnostic-driven)	Definitive
Probability of IFD	very low	low	higher	highest
Trigger for AFT	Risk factors	Clinical syndrome Persistent febrile neutropenia	Diagnostics HRCT GM PCR	Histology

Morrissey et al. Internal Med J 2014; 44:1298-1314
Maertens et al. haematologica 2012; 97: 325-327

Mold-active vs. FLU Prophylaxis in Chemotherapy or HSCT

20 RCTs, 5725 patients - hematological malignancy or HSCT

	Relative Risk	95% CI	P value
Proven/probable IFI	0.71	0.52 to 0.98	0.03
IA	0.53	0.37–0.75	0.0004
IFI-related mortality	0.67	0.47–0.96	0.03
Discontinuation due to SE	1.95	1.24–3.07	0.004
Overall mortality	1.0	0.88–1.13	0.96

Ethier et al. Br J Cancer 2012; 106:1626–1637

ECIL-3 (2009 update)

Setting	Options	
Leukemia, induction chemotherapy	Posaconazole (A1) Itraconazole (C1)	Fluconazole (C1) Inhaled L-AmB + fluconazole (B1)
Allogeneic HSCT recipients, initial neutropenic phase	Fluconazole (A1) Voriconazole (A1) Itraconazole (B1)	Inhaled L-AmB + fluconazole (B2) Micafungin (C1) L-AmB (C1)
Allogeneic HSCT recipients, GVHD phase	Posaconazole (A1) Voriconazole (A1)	Itraconazole (B1)

Maertens J, et al. Bone Marrow Transplant. 2011;46(5):709-18.

Empiric AFT for PFN

Randomization Group	N	Clinically Documented	Bacterial	Fungal	Viral-Protozoan	Shock
1. Discontinue KGC	16	2	3	1	0	6
2. Continue KGC alone	16	0	1	5	0	0
3. KGC + Amphotericin B	18	0	0	1	1	0

Table II. *Infectious complications which occurred in each of the randomized groups following randomization.*

Pizzo et al. Am J Med 1982; 72:101-11

Empiric AFT for PFN

ANC <500/mm³ | Fever (>38°C x3 or ≥38.5°C x1) | ≥ 4d Abx

Randomization

Abx only (n = 64)		Abx + AmB (n = 68)
IFI (6/64, 9.4%)	P = 0.1	IFI (1/68, 1.5%)
Death (4/64, 6.3%)	P = 0.05	Death (0/68, 0%)

EORTC IATCG. Am J Med 1989; 86:668-72

RCTs of empiric AFT for PFN

Composite end-point:

1. successful treatment of any base-line fungal infection
2. absence of any breakthrough fungal infection
3. survival for ≥7 days after the completion of therapy
4. no premature discontinuation of study therapy
5. resolution of fever during neutropenia

Empiric AFT for PFN

	Overall response	Resolution of fever	Reference
AmB	49.4%	58.1%	Walsh et al. NEJM 1999
AmBisome	50.1%	58.0%	
Voriconazole	26.0%	32.5%	Walsh et al. NEJM 2002
AmBisome	30.6%	36.5%	
Caspofungin	33.9%	41.2%	Walsh et al. NEJM 2004
AmBisome	33.7%	41.4%	

Walsh et al. N Engl J Med 1999;340:764-71
Walsh et al. N Engl J Med 2004;351:1391-402

Walsh et al. N Engl J Med 2002;346:225-34

FLU 400mg vs. AmB-d 0.5 mg/kg for Cancer Patients with PFN for ≥4 days

Satisfactory response = afebrile + no evidence of fungal infection + no termination due to lack of efficacy, drug toxicity, or death.

	AmB-d (n = 159)	FLU (n = 158)	*P* value
Satisfactory response	106 (67%)	107 (68%)	-
New fungal lesions	10 (6%) [5 IC, 3 IA, 2 other]	13 (8%) [8 IC, 5 IA]	-
Toxicity	128 (81%)	20 (13%)	0.001
Early termination	11 (7%)	1 (1%)	P = 0.005
Overall mortality	34 (21%)	27 (17%)	-
Fungus-related mortality	5 (3%)	7 (4%)	-

Winston et al. Am J Med 2000; 108(4):282-9

Problems with empiric AFT

- Excessive AFT
- Increased adverse effects
- Increased costs
- Poor response
- Uncertainty
- ***Potentially miss afebrile patients with IFD***

"Empirical antifungal therapy is instituted for the treatment of "occult" fungal infection presenting as persistent neutropenic fever despite 4–7 days of empirical antibiotic therapy.

Approximately 22- 34% of neutropenic patients with cancer will receive an AF drug by these criteria, yet only ≈4% have a demonstrated IFI"

Freifeld AG, et al. Clin Infect Dis 2011;52:e56-93

Weekly GM & PCR screening in high risk populations

Test	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	DOR (95% CI)	AUROC (95% CI)	PPV, % (95% CI)[a]	NPV, % (95% CI)[a]
PCR	84 (71–92)	76 (64–85)	3.5 (2.3–5.4)	0.21 (.11–.39)	17 (7–38)	0.87 (.84–.90)	38	96
2 PCRs	57 (40–72)	93 (87–97)	8.4 (4.2–17.1)	0.46 (.32–.67)	18 (7–45)	0.87 (.84–.90)	59	92
GM	92 (83–96)	90 (81–95)	9.3 (4.6–18.7)	0.09 (.04–.19)	104 (37–295)	0.96 (.94–.98)	61	98
2 GMs	62 (48–74)	95 (91–97)	12.1 (6.3–23.3)	0.40 (.29–.57)	30 (13–70)	0.94 (.92–.96)	67	93
GM or PCR	99 (96–100)	64 (49–77)	2.8 (1.9–4.1)	0.02 (.01–.06)	128 (37–442)	0.99 (.97–.99)	33	10
GM and PCR	68 (54–80)	98 (94–100)	43.2 (12.6–149)	0.32 (.21–.49)	135 (38–475)	0.93 (.91–.95)	88	95

Arvanitis et al. Clin Infect Dis 2015;61(8):1263–72

Guidelines

Bone Marrow Transplantation (2012) 47, 846–854
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www.nature.com/bmt

ORIGINAL ARTICLE

ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients

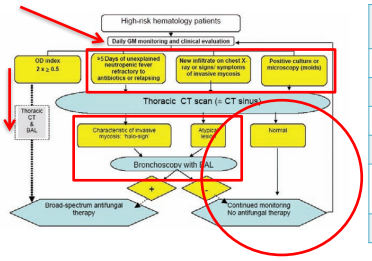
O Marchetti[1,6], F Lamoth[1,6], M Mikulska[2], C Viscoli[2], P Verweij[3] and S Bretagne[4,5] and the European Conference on Infections in Leukemia (ECIL) Laboratory Working Groups[7]

British Society for Medical Mycology best practice recommendations for the diagnosis of serious fungal diseases

Silke Schelenz, Rosemary A Barnes, Richard C Barton, Joanne R Cleveley, Sebastian R Lucas, Christopher C Kibbler, David W Denning, on behalf of the British Society for Medical Mycology

Lancet Infect Dis 2015; 15: 461–74

GM and CT - feasibility study



Total	88pt/ 136 episodes
Median age (R)	44 (16–75)
AML	37 (42%)
ALL	17 (19.3%)
Relapsed AL/MDS	23 (26.1%)
Remission induction	43 (31.6%)
Allo-HSCT	32 (23.5%)

Maertens et al. Clin Infect Dis 2005; 41:1242–50

GM and CT - feasibility study

- 117 episodes of neutropenic fever
- 41 episodes (35%) satisfied existing criteria for EAT
- AFT used for in only 7.7% (78% reduction)
- **Early initiation of AFT 10 episodes (7.3%) that were clinically not suspected of being IFI**
- No undetected cases of IA
- 12-week survival rate for patients with IFI was 63.6%

Maertens et al. Clin Infect Dis 2005; 41:1242–50

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

Catherine Cordonnier,[1] Cécile Pautas,[1] Sébastien Maury,[1] Anne Vekhoff,[4] Hassan Farhat,[11] Felipe Suarez,[5] Nathalie Dhédin,[6] Francoise Isnard,[7] Lionel Ades,[12] Frédérique Kuhnowski,[8] Françoise Foulet,[2] Mathieu Kuentz,[1] Patrick Maison,[3] Stéphane Bretagne,[2] and Michaël Schwarzinger[9,10]

Clinical Infectious Diseases 2009; 48:1042–51

DD-AFT vs. EAFT

- ≥ 18y
- Chemotherapy for hematological cancer or autologous HSCT
- Expected ANC<500/mm³ for ≥10d
- **Excluded** allo-HSCT, suspected IFI, previous AmB toxicity, Karnofsky score <30% and HIV

Cordonnier C et al. Clin Infect Dis 2009;48:1042-1051

Baseline Characteristics

	Empiric AFT (n = 150)	DD-AFT (n = 143)
Age (mean ± SD)	52.0 13.5 y	52.1 14.1 y
AML	**99 (66%)**	**98 (68.5%)**
ALL	8 (5.3%)	
Lymphoma	39 (26.0%)	36 (25.2%)
Induction	70 (46.7%)	67 (46.9%)
Any prophylaxis	**63 (42.0%)**	**69 (48.3%)**
AmB prophylaxis	47 (31.3%)	51 (35.7%)
Neutropenic ≥10d	**127/146 (87%)**	**124/141 (87.9%)**

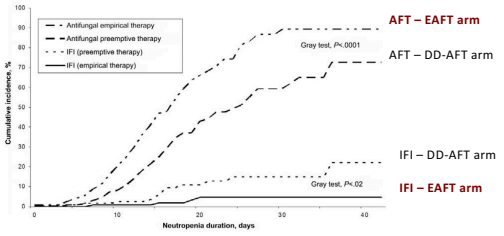
Cordonnier C et al. Clin Infect Dis 2009;48:1042-1051

Efficacy End Points in the ITT Population (n 293)

Efficacy end point	Empirical treatment arm (*n* = 150)	Preemptive treatment arm (*n* = 143)	Difference (95% CI)	*P*[a]
Primary				
Alive at study completion	146 (97.3)	136 (95.1)	−2.2 (−5.9 to 1.4)	.31
Secondary				
IFI	4 (2.7)	13 (9.1)	−6.4 (−10.9 to −1.9)	<.02
Baseline IFI due to				
Aspergillus species	2	6	…	
Candida species	0	3	…	
Breakthrough IFI due to				
Aspergillus species	2	2	…	
Candida species	0	2	…	
IFI-related mortality	0 (0)	3 (2.1)	−2.1 (−4.1 to 0.0)	.11
Duration of temperature ≥38°C,[b] days				
Median (IQR)	13 (5–21)	12 (5–20)	…	NS
Range	1–42	1–59	…	

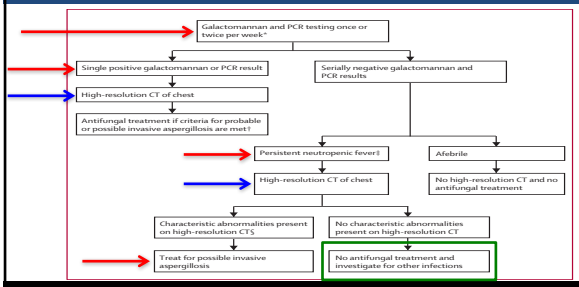
Cordonnier C et al. Clin Infect Dis 2009;48:1042-1051

Cumulative incidence of AFT and IFI during neutropenia



Cordonnier C et al. Clin Infect Dis 2009;48:1042-1051

GM + PCR DDT vs Empiric AFT



Morrissey et al. Lancet Infect Dis 2013; 13: 519–28

Baseline Characteristics

	Empiric AFT (n = 122)	DD-AFT (n = 118)
Age (median (IQR)	49 (36–57)	48 (35–54)
Allo-HSCT	92 (75%)	99 (84%)
AML	53 (43%)	46 (39%)
HLA-matched, unrelated	31 (25%)	26 (22%)
HLA-mismatch, related	4 (3%)	8 (7%)
Graft, Peripheral blood	82 (67%)	80 (68%)
ITR prophylaxis	41 (34%)	46 (39%)
VOR/POS Prophylaxis	13 (11%)	16 (13%)
FLU prophylaxis	33 (27%)	34 (29%)

Morrissey et al. Lancet Infect Dis 2013; 13: 519–28

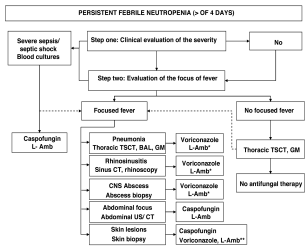
GM + PCR DDT vs FDT

	Standard diagnosis group (n=122)	Biomarker diagnosis group (n=118)	% difference between groups (95% CI)	p value
Received empirical treatment with antifungal drugs	39 (32%)	18 (15%)	17% (4 to 26)	0·002
Mortality				
All-cause	18 (15%)	12 (10%)	5% (−4 to 14)	0·31
Invasive aspergillosis-related	6 (5%)	3 (3%)	2% (−2·5 to 7·3)	0·5
Other invasive fungal disease-related*	0	2 (2%)	..	0·24
Incidence of invasive aspergillosis				
Proven	1 (1%)	1 (1%)	..	1·0
Probable	0	16 (14%)	−14% (−20 to −7)	<0·0001
Possible	0	6 (5%)	−5% (−9 to −1)	0·013

Fever was absent in 55% of probable and possible IA in the biomarker group

Morrissey et al. Lancet Infect Dis 2013; 13: 519–28

DD-AFT in Seville



PFN > 5 days

Total	72 patients
ANC <100	84 (98.8%)
AML	5 (34.7%)
ALL	4 (5.5%)
MDS	4 (5.5%)
Allo-HSCT	15 (17.6%)

Aguilar-Guisado M et al. Haematologica 2012;97(3):464-71

DD-AFT in Seville

Final diagnosis of PFN episodes	Antifungal therapy N. (%)	No antifungal therapy N. (%)
Infection	**43 (82.7)**	**25 (75.7)**
Invasive fungal infection	22 (42.3)	0
Proven IFI[1]	3 (5.8)	0
Probable IFI	9 (17.3)	0
Possible IFI	10 (19.2)	0
Non-fungal infection	21 (40.4)	25 (75.7)
Not infection	**9 (17.3)**	**7 (21.2)**
Tumor fever	5 (9.6)	5 (15.1)
Drug fever	2 (3.8)	2 (6.1)
Pulmonary thromboembolism	1 (1.9)	0
GVHD[2]	1 (1.9)	0
Unknown fever	**0**	**1[3] (3)**
TOTAL	**52 (100)**	**33 (100)**
IFI high-risk episodes[4]	**26 (50)**	**9 (27.3)**
Non IFI high-risk episodes	**26 (50)**	**24 (72.7)**

Aguilar-Guisado M et al. Haematologica 2012;97(3):464-71

PLOS ONE

RESEARCH ARTICLE

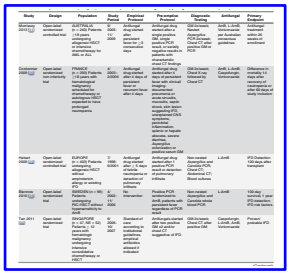
Meta-Analysis and Cost Comparison of Empirical versus Pre-Emptive Antifungal Strategies in Hematologic Malignancy Patients with High-Risk Febrile Neutropenia

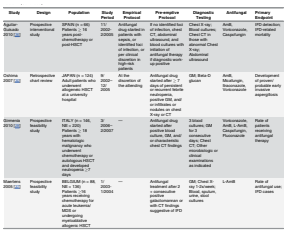
Monica Fung[1,2]*, Jane Kim[3], Francisco M. Marty[2,4,5], Michaël Schwarzinger[6,7,8], Sophia Koo[2,4,5]

1 Beth Israel Deaconess Medical Center, Department of Internal Medicine, Boston, Massachusetts, United States of America, **2** Harvard Medical School, Boston, Massachusetts, United States of America, **3** Harvard T.H. Chan School of Public Health, Department of Health Policy and Management, Boston, Massachusetts, United States of America, **4** Brigham and Women's Hospital, Division of Infectious Diseases, Boston, Massachusetts, United States of America, **5** Dana-Farber Cancer Institute, Boston, Massachusetts, United States of America, **6** Translational Health Economics Network, Paris, France, **7** Decision Sciences in Infectious Disease: Prevention, Control, and Care, INSERM, IAME, Paris, France, **8** Université Paris Diderot, IAME, Paris, France

Fung M, et al. PLoS ONE 2015; 10(11): e0140930

DD vs FD AFT studies in HO





Fung M, et al. PLoS ONE 2015; 10(11): e0140930

IFD-related outcomes in FD vs DD AFT in high-risk neutropenic patients

Study	IFD Detection RR (95%CI)	IFD Detection Empiric (%)	IFD Detection Pre-emptive (%)	IFD-related Mortality RR (95%CI)	IFD-related Mortality Empiric (%)	IFD-related Mortality Pre-emptive (%)	Overall Mortality RR (95% CI)	Overall Mortality Empiric (%)	Overall Mortality Pre-emptive (%)
Morrissey 2013 [31]	4.76 (1.87–12.10)	4.1 (5/122)	19.5 (23/118)	0.86 (0.27–2.75)	4.9 (6/122)	4.2 (5/118)	1.55 (0.66–3.66)	6.6 (8/122)	10.2 (12/118)
Cordonnier 2009 [26]	3.41 (1.14–10.21)	2.7 (4/150)	9.1 (13/143)	7.34 (0.38–140.86)	0.0 (0/150)	2.1 (3/143)	1.84 (0.55–6.14)	2.7 (4/150)	4.9 (7/143)
Hebart 2009 [29]	0.99 (0.52–1.91)	8.1 (17/207)	8.2 (16/196)	0.82 (0.36–1.87)	4.8 (10/207)	3.6 (7/196)	0.99 (0.64–1.55)	16.4 (34/207)	16.3 (32/196)
Blennow 2010 [34]	—	0.0 (0/8)	7.7 (1/13)	—	—	—	—	—	—
Tan 2011 [35]	0.62 (0.11–3.39)	12.0 (3/25)	7.4 (2/27)	—	—	—	—	—	—
Aguilar-Guisado 2010 [36]	0.09 (0.01–1.75)	11.5 (3/26)	0.0 (0/40)	0.13 (0.01–2.64)	8.0 (2/26)	0.0 (0/40)	0.16 (0.04–0.71)	30.7 (8/26)	5.0 (2/40)
Oshima 2007 [30]	—	0.0 (0/13)	3.3 (2/60)	—	0.0 (0/13)	0.0 (0/60)	—	—	—
Girmenia 2010 [28]	—	—	—	—	—	—	—	—	—
Maertens 2005 [37]	—	—	—	—	—	—	—	—	—
M-H RR (95%CI)		**1.70 (1.12–2.57)**			**0.85 (0.45–1.62)**			**0.99 (0.70–1.40)**	
D-L RR (95%CI)		1.47 (0.55–3.96)			0.82 (0.36–1.87)			0.95 (0.46–1.99)	
		Q = 13.90 (df = 4), p = 0.01			Q = 3.62 (df = 3), p = 0.31			Q = 7.88 (df = 3), p = 0.05	
Heterogeneity		I^2 = 71.3%			I^2 = 17.0%			I^2 = 61.9%	
		Between study τ^2 = 0.81			Between study τ^2 = 0.13			Between study τ^2 = 0.33	

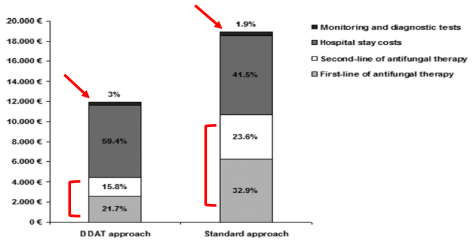
Fung M, et al. PLoS ONE 2015; 10(11): e0140930

FD-AFT vs. DD-AFT in high-risk neutropenic patients

Study	Antifungal Use RR (95%CI)	Antifungal Use Empiric (%)	Antifungal Use Pre-emptive (%)	Antifungal Duration (mean) Empiric (%)	Antifungal Duration (mean) Pre-emptive (%)	p
Morrissey 2013 [31]	0.48 (0.29–0.79)	30.3 (36/122)	23.7 (18/118)	—	—	—
Cordonnier 2009 [26]	0.64 (0.50–0.81)	61.3 (92/150)	39.2 (56/143)	7.0 days	4.5 days	**<0.01**
Hebart 2009 [29]	1.56 (1.25–1.93)	36.7 (76/207)	57.1 (112/196)	84.2% (64/76) <30 days	79.5% (89/112) <30 days	NS
Blennow 2010 [34]	—	—	—	—	—	—
Tan 2011 [35]	0.76 (0.38–1.51)	44.0 (11/25)	33.3 (9/27)	—	—	—
Aguilar-Guisado 2010 [36]	—	—	—	—	—	—
Oshima 2007 [30]	0.08 (0.03–0.19)	100.0 (13/13)	6.7(4/60)	—	—	—
Girmenia 2010 [28]	0.57 (0.42–0.77)	52.8 (84/220)	30.1 (48/220)	—	—	—
Maertens 2005 [37]	0.22 (0.11–0.43)	35.0 (41/117)	7.7 (9/117)	—	—	—
M-H RR (95%CI)		**0.72 (0.53–0.81)**		—		
D-L RR (95%CI)		**0.48 (0.27–0.85)**		—		
		Q = 91.01 (df = 6), p <0.01				
Heterogeneity		I^2 = 93.4%		—		
		Between study τ^2 = 0.503				

Fung M, et al. PLoS ONE 2015; 10(11): e0140930

Cost-effectiveness



Martin-Pena et al. AAC 2013; 57:4664-72

IDSA Guidelines 2010: Neutropenic Fever

- **AFT may be withheld in patients who remain febrile >4-7 days if:**
  - Clinically stable
  - No clinical or chest and sinus **CT** signs of fungal infection
  - Negative **serological assay** results for evidence of IFI, and
  - No positive cultures for fungi from any body site

Freifeld AG et al. Clin Infect Dis 2011;52(4):e56–e93

INTERNAL MEDICINE JOURNAL

Internal Medicine Journal **44** (2014)

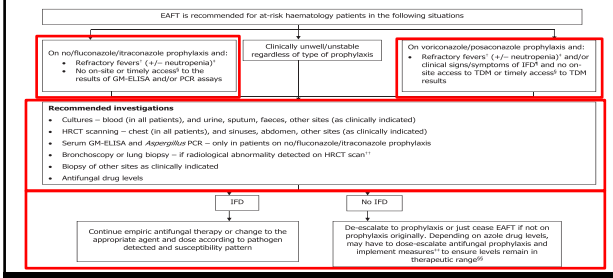
Consensus guidelines for the use of empiric and diagnostic-driven antifungal treatment strategies in haematological malignancy, 2014

C. O. Morrissey,[1,2] N. M. Gilroy,[3,4] N. Macesic,[5] P. Walker,[6,7] M. Ananda-Rajah,[1,8] M. May,[9] C. H. Heath,[10,11] A. Grigg,[12,13] P. G. Bardy,[14,15,16] J. Kwan,[17] S. W. Kirsa,[18] M. Slavin,[13,19,20] T. Gottlieb[21] and S. Chen[22,23,24]

Essentials

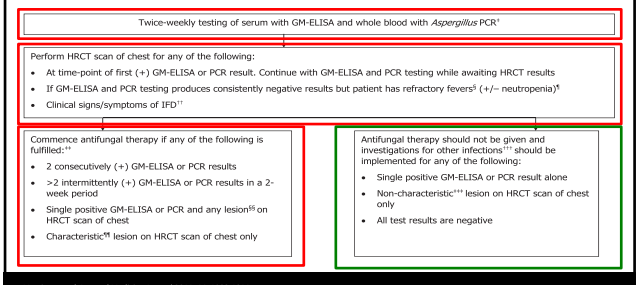
- Ready access to GM ± PCR testing.
- Ready access to HRCT + reports.
- The team
  - Interest
  - Expertise
  - Availability

Setting 1: No Access to GM/PCR



Morrissey et al. Internal Medicine Journal 2014; 44: 1298-1314

Setting 2: Access to GM/PCR



Morrissey et al. Internal Medicine Journal 2014; 44: 1298-1314

IDSA 2016 Guidelines: Candidemia in Neutropenic Patients

	SoR	QoE
Echinocandin as initial therapy	Strong	Moderate
L-AmB is is an effective but less attractive alternative because of the potential for toxicity	Strong	Moderate
Fluconazole is an alternative for non-critically ill patients and no prior azole exposure	Weak	Low
Voriconazole can be used in situations in which additional mold coverage is desired	Weak	Low

SoR, strength of recommendation; QoE, quality of evidence; L-AmB, liposomal amphotericin

Pappas et al. Clin Infect Dis 2016; 62(4):e1-e50

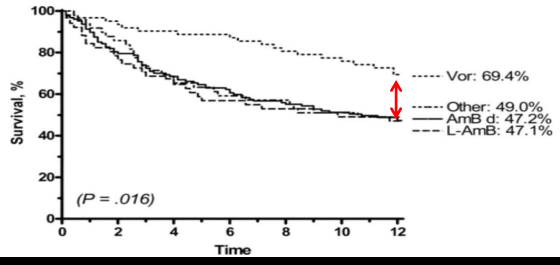
The New England Journal of Medicine

VORICONAZOLE VERSUS AMPHOTERICIN B FOR PRIMARY THERAPY OF INVASIVE ASPERGILLOSIS

Raoul Herbrecht, M.D., David W. Denning, F.R.C.P., Thomas F. Patterson, M.D., John E. Bennett, M.D., Reginald E. Greene, M.D., Jörg-W. Oestmann, M.D., Winfried V. Kern, M.D., Kieren A. Marr, M.D., Patricia Ribaud, M.D., Olivier Lortholary, M.D., Ph.D., Richard Sylvester, Sc.D., Robert H. Rubin, M.D., John R. Wingard, M.D., Paul Stark, M.D., Christine Durand, M.D., Denis Caillot, M.D., Eckhard Thiel, M.D., Pranatharthi H. Chandrasekar, M.D., Michael R. Hodges, M.D., Haran T. Schlamm, M.D., Peter F. Troke, Ph.D., and Ben de Pauw, M.D., for the Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group*

2002; 347:408-415

Overall survival according to 1st-line therapy
(289 cases over 9 years, France)



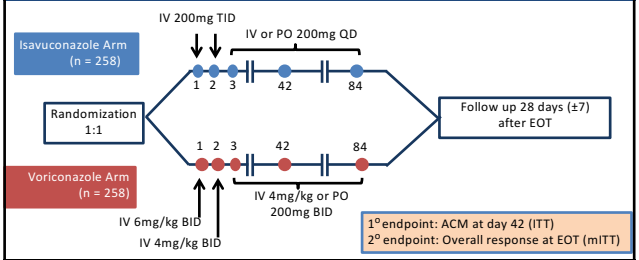
Nivoix Y et al. Clin Infect Dis 2008;47: 1176-84

IA salvage therapy

- Lipid formulations of Amphotericin B
- Caspofungin
- Posaconazole
- Micafungin
- Combinations

Limper et al. Am J Respir Crit Care Med 2011; 183:96-128

Isavuconazole vs. Voriconazole for Invasive Mold Infections
(SECURE)



Maertens et al. Lancet 2016;387:760–769

Conclusion

- Antifungal prophylaxis strategy should be tailored to risk of IFI in specific patient groups
- Empiric (fever-driven) AFT is associated with:
  - unnecessary AFT,
  - increased toxicity,
  - inflated costs, and
  - **risk of missing IFI**

Conclusion

- Diagnostic-driven strategies are associated with:
  - improved diagnosis of IA,
  - reduced unnecessary AFT, and
  - **NO increased mortality**.

Conclusion

- Voriconazole is the primary treatment of choice for IA
- Isavuconazole is a promising new azole for IMI
- Combination antifungal therapy only in carefully selected patients with IA

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Thank you