3rd European Conference on Infections in Leukemia

Antifungal prophylaxis in leukemia patients 2009 update of the ECIL-1 and 2 guidelines

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September 25 - 26 2009, Juan-les-Pins - France

ELN European LeukemiaNet

Excellence in science EBMT European Group for Blood and Marrow Transplantation

EORTC European Organisation for Research and Treatment of Cancer AISBL International Non-Profit Association under Belgian law IVZW

ICHS International Alliance for Immunocompromised Host Society

Background

- Prophylactic use of antifungals (primary prevention of invasive yeast/mould infections) has more or less become standard practice of care in neutropenic cancer patients and HSCT recipients (IDSA, CDC, ASBM).

- Almost 80 clinical trials and > 9000 patients randomized: no solid scientific conclusions available: power, design, patient selection, end point and end point definitions, new diagnostic tools and improved medical techniques …

- Primary antifungal chemoprophylaxis (PAC) results in overuse; the choice of the appropriate drug should be guided by efficacy, safety, and drug-related 'cost', including acquisition cost, toxicity, interactions, and resistance.

Background

- New antifungal agents have become available : voriconazole, posaconazole.
- Evidence-based European guidelines are needed.

Objectives

1. What is (are) the patient population(s) likely to benefit from *primary* antifungal chemoprophylaxis (PAC)?
2. Does PAC (~ compound) has an impact on
    1. The incidence of invasive fungal infections: yeast vs moulds?
    2. Overall mortality?
    3. Fungal-infection related mortality?
    4. Use of empirical antifungal therapy?
    5. Toxicity?
3. Is PAC associated with increased resistance or selection
4. How long should prophylaxis be given?
5. Should serum levels be monitored? Optimal level?

Methods

- Questionnaire on European practices.
- Literature review
  - Search
    - Medline
    - Cochrane
    - Pubmed
    - Manual search bibliography of referenced publications
    - ICAAC, ECCMID, ASH, ASCO, and EBMT 2002-2007
- CDC grading

1. Questionnaire

Summer 2005

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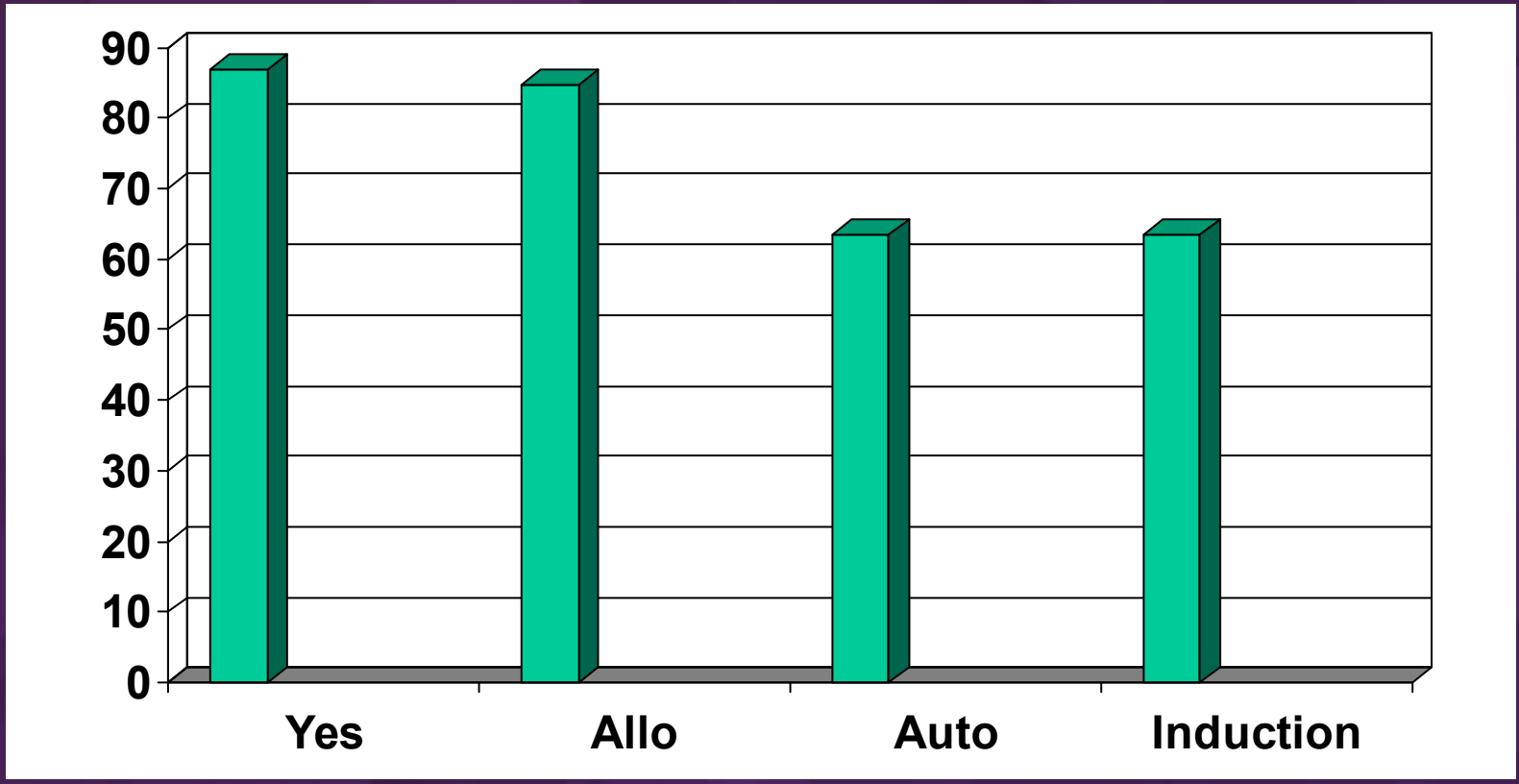
Do you Use Antifungal Prophylaxis?

(N= 38)



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Do you Use Antifungal Prophylaxis?

(N= 38)

	Allo	Auto	Induction
Fluco	57.1	57.1	55
Itra caps	7.1	9.5	5
Itra sol	21.4	14.3	20
Itra iv	3.6	4.8	5
Vorico	3.6	4.8	5
Ambisome	3.6	-	-
Nystatin	10.7	14.3	15
Non-abs amphoB	17.9	19.0	25
AmphoB aerosol	7.1	-	-

2. Literature Review

Does Fluconazole Prophylaxis Reduce the Incidence of IFI ?

Population	Dose	Effect	Ref
Allogeneic	400 mg qd	Proven 18 → 7%	Slavin 1995, Marr 2000
Autologous	400 mg qd	Unknown	Goodman 1992 (52% auto)
AML w/o SCT	400 mg qd	None	Schaffner 1995
	400 mg qd	Proven/probable 24 → 7%	Rotstein 1999

In allogeneic SCT fluconazole 400 mg qd to reduce the incidence of IFI	AI
In autologous SCT fluconazole 400 mg qd to reduce the incidence of IFI	CIII
In AML w/o SCT fluconazole 400 mg qd to reduce the incidence od IFI	AI

Does Fluconazole Prophylaxis Reduce Attributable Mortality ?

Population	Dose	Effect	Ref
Allogenic	400 mg qd	21% → 13%	Slavin 1995, Marr 2000
Autologous	400 mg qd	5.6% → 0.6%	Goodman 1992 (52% auto)
AML w/o SCT	400 mg qd	None	Schaffner 1995
	400 mg qd	4.5% → 0.7%	Rotstein 1999

In allogeneic SCT fluconazole 400 mg qd to reduce attributable mortality	AI
In autologous SCT fluconazole 400 mg qd to reduce attributable mortality	AI
In AML w/o SCT fluconazole 400 mg qd to reduce attributable mortality	CIII

Does Fluconazole Prophylaxis Reduce Overall Mortality ?

Population	Dose	Effect	Ref
Allogeneic	400 mg qd	55% → 28%	Slavin 1995, Marr 2000
Autologous	400 mg qd	None	Goodman 1992 (52% auto)
AML w/o SCT	400 mg qd	None	Schaffner 1995
	400 mg qd	None	Rotstein 1999

In allogeneic SCT fluconazole 400 mg qd to reduce overall mortality	AI
In autologous SCT fluconazole 400 mg qd to reduce overall mortality	CIII
In AML w/o SCT fluconazole 400 mg qd to reduce overall mortality	CIII

Does Fluconazole Prophylaxis Reduce the Use of Empirical Antifungal Therapy ?

Population	Dose	Effect	Ref
Allogeneic	400 mg qd	Days until empiric antifungals 18 → 21	Slavin 1995, Marr 2000
Autologous	400 mg qd	Unknown	Goodman 1992 (52% auto)
AML w/o SCT	400 mg qd	Empiric antifungals 33% → 48%	Schaffner 1995
	400 mg qd	Empiric antifungals 50% → 57%	Rotstein 1999

In allogeneic SCT fluconazole 400 mg qd to reduce empiric antifungals	AI (?)
In autologous SCT fluconazole 400 mg qd to reduce empiric antifungals	CIII
In AML w/o SCT fluconazole 400 mg qd to reduce empiric antifungals	EI

Does Secondary Prophylaxis Reduce the Incidence of Breakthrough IFI ?

Population	Dose	Result	Ref
Allogeneic	Various	Relapse rate 33% univariate risk factor analysis	Offner 1998
Autologous	?	?	?
AML w/o SCT	Various	Relapse rate 16% multivariate risk factor analysis	Cornely 2003

In allogeneic SCT secondary prophylaxis to reduce BT-IFI	C III
In autologous SCT secondary prophylaxis to reduce BT-IFI	C III
In AML w/o SCT secondary prophylaxis to reduce BT-IFI	C III

Itraconazole: meta-analysis

	N	Os/IV	IFI	IAI	FI-Mor
Gotzsche & Johansen	3	1	0.51 0.27-0.96	-	-
Bow	5	3	0.61 0.38-0.89	0.91 0.44-1.18	0.78 0.38-1.60
Glasmacher	13	6/2	0.60 0.43-0.89	0.67 0.41-1.10	0.65 0.43-0.98

Efficacy of itraconazole correlates closely with the dose: oral solution at 400 mg/day or iv formulation at 200 mg/day (supported by *in vitro* studies and animal models)

Menichetti	Os vs. placebo	Mixed ~75% AL	Double-blind	201/205
Morgenstern	Os vs. fluco	Mixed ~1/3 auto's	Open	218/227
Harousseau	Os vs. amphoB	Mixed ~70% AL	Double-blind	281/276
Lass-Flörl	Os vs. amphoB	Mixed	Open	52/54
Marr	Itra* vs. fluco	Allogeneic Tx	Open	151/148
Winston	Itra vs. fluco	Allogeneic Tx	Open	71/67

Invasive fungal infections Proven deep fungal	Overall mortality	Attributable mortality	Empiric therapy	Toxicity
24 % vs 33 % (0.035) 2.5 vs 4.4 % (ns)	7% vs 9% (ns)	1 vs 5 (ns)	ns (for AL)	ns
10 vs 13 (ns) 6 vs 1 (0.06)	-	7 vs 0 (0.024)*	34 vs 52	Itra > fluco
IA: 1.8 % vs 3.3 % (ns) 2.8 % vs 4.7 % (ns)	6 % vs 8 % (ns)	1 vs 5	ns	ns
1 vs 4	5.7 % vs 5.5 % (ns)	-	-	ns
7 % vs 15 % (0.03) Mold: 5 % vs 12 % (0.03)	(ns)	-	ns	Itra > fluco
9 % vs 25 % (0.01) **IA: 4 % vs 12 % (ns)**	45 % vs 42 % (ns)	9 % vs 18 % (ns)	-	Itra > fluco

Itraconazole for allo BMT

- (+) PAC continued during GvHD period
- (W,M-) Open label, non-inferiority studies
- (W-) not matched for crucial risk factors
- (W-) high incidence of *proven* IFI in fluco-arm: 25%
- (M-) unexpected drug interaction resulting in increased toxicity and differences in fungal-free survival

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Posaconazole prophylaxis studies:
Design and Treatment

	Allo-GvHD/Ullmann	AML-MDS/Cornely
Design	Double blind, double dummy	Prospective, randomized, evaluator blinded
Populations	HSCT recipients with acute or chronic GVHD treated with intensive immunosuppressive therapy	Newly diagnosed or 1st relapse AML or MDS patients receiving intensive chemotherapy who are neutropenic (ANC ≤500 cells/mm^3) for ≥7 days
Treatment regimen	POS 200 mg oral suspension 3x/day or FLU 400 mg capsule 1x/day	POS 200 mg oral suspension 3x/day or standard azole (FLU 400 mg oral suspension 1x/day or ITZ 200 mg oral solution 2x/day)
Duration of treatment	Up to 112 days	Initiated with each cycle of chemotherapy for up to 84 days
Follow up	2 months after end of treatment	100 days post-randomisation

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

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

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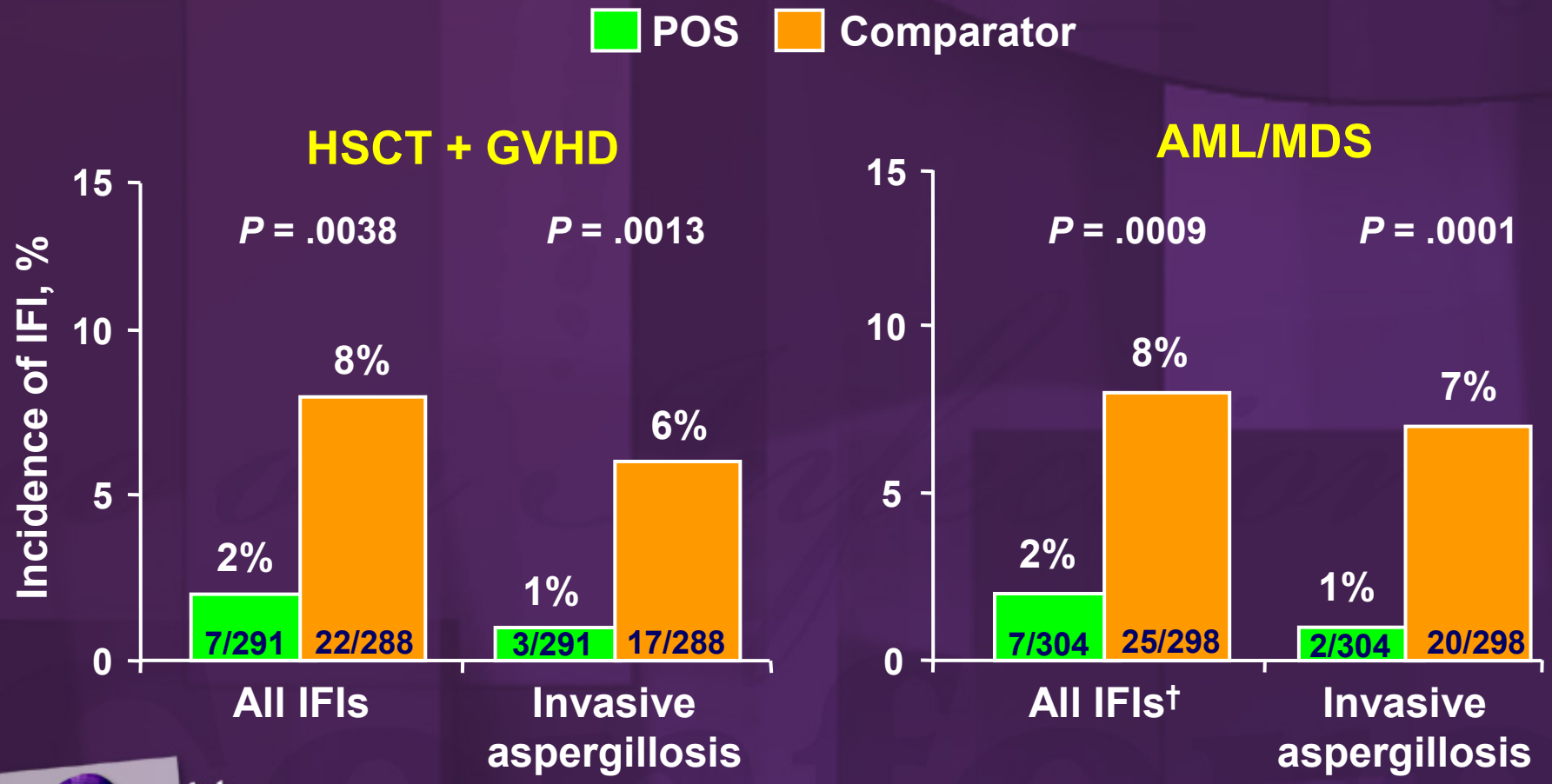
Incidence of Proven/Probable IFIs While on Treatment*



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*Populations are all-treated (ITT subset who received ≥1 dose of study drug) in HSCT + GVHD study and ITT population in AML/MDS study.
†Primary end point.

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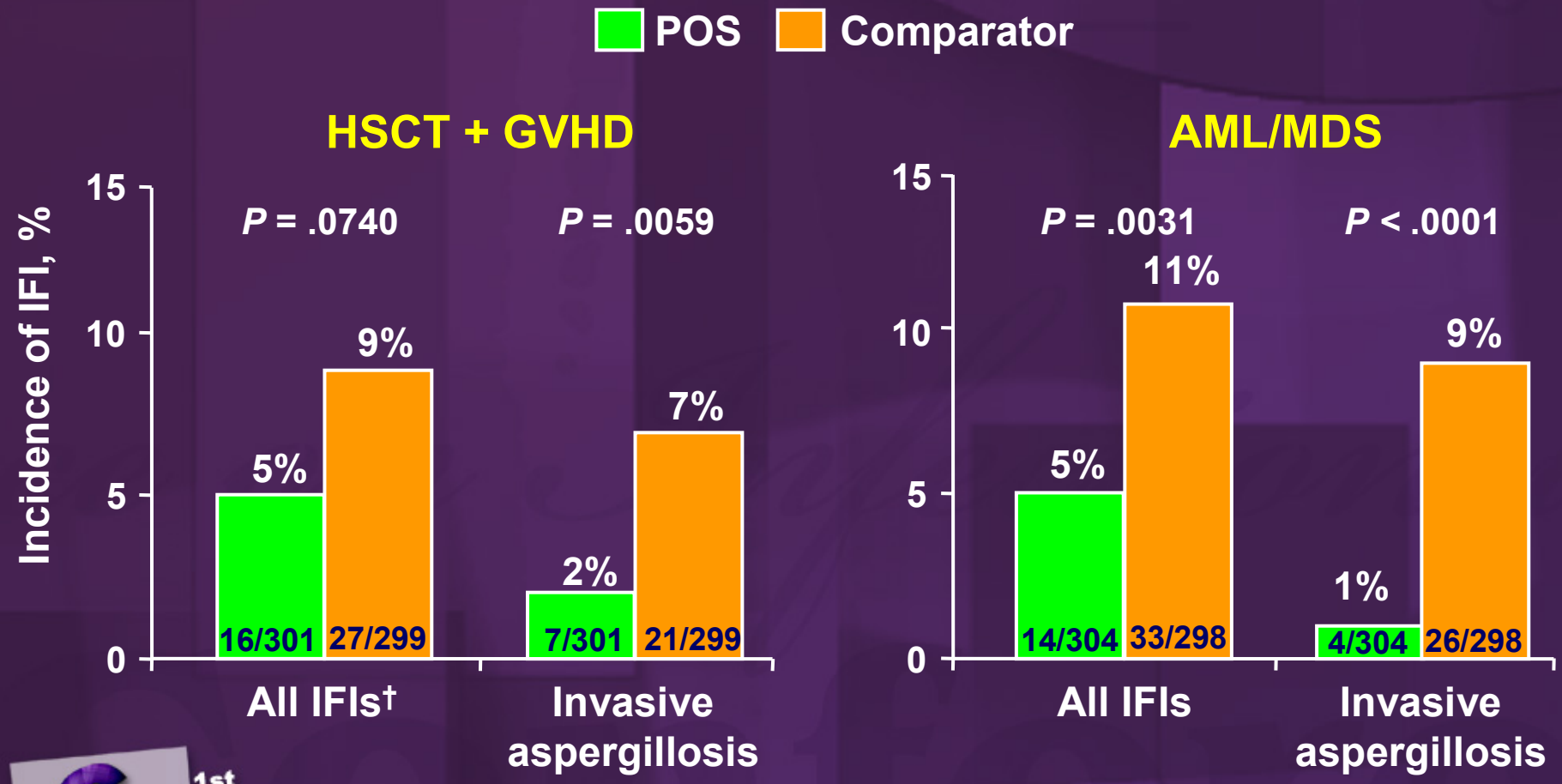
Incidence of Proven/Probable IFIs During Fixed Time Period*



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*Within 112 days and 100 days postrandomisation for the HSCT + GVHD and AML/MDS studies, respectively.

†Primary end point.

Fluconazole (AI) vs. posaconazole (AI) in Allogeneic HSCT

Proposals within the group

- 1. To separate the neutropenic from the non-neutropenic (GvHD) phase
- 2. To add a footnote
  - Fluconazole AI only
    - during the neutropenic phase of allogeneic HSCT and
    - when combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of invasive mould infections

Primary prophylaxis with voriconazole in allogeneic hematopoietic stem cell transplant recipients : *Two trials analyzed*

1- Wingard J et al. ASH 2007 Oral Session
Results of a Randomized, Double-Blind Trial of Fluconazole (FLU) vs. Voriconazole (VORI) for the Prevention of Invasive Fungal Infections (IFI) in 600 Allogeneic Blood and Marrow Transplant (BMT) Patients

2 – Marks D et al. ICAAC 2009, San Francisco, M-1249a
Voriconazole (VOR) versus itraconazole (ITR) for primary prophylaxis of invasive fungal infections in allogeneic HSCT recipients

Study Overview

- Double-blind controlled trial comparing
  - Fluconazole 400 mg QD po or iv

    Vs.
  - Voriconazole 200 mg BID po or iv
  - Multicenter trial of BMT Clinical Trials Network
  - Study drug to be given for 100 days (or 180 days if on corticosteroids or CD4<200/µL if graft T-cell depleted)
  - Galactomannan screening twice weekly for 60 days (then once weekly until day 100 if no GVHD or twice weekly if GVHD)
  - Standardized empirical antifungal therapy permitted for suspected IFI limited to <14 days

Wingard J et al. 2007

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Study Endpoints

- IFIs were scored using EORTC/MSG criteria, modified:
  - All subjects were considered to have host criteria
  - "Presumptive" IFI were cases that met host and clinical criteria PLUS had a bronchoscopy that failed to show other infectious pathogens
- Blinded assessment by protocol committee formed the basis of analysis
- Primary endpoint: fungal-free survival (FFS) at 180 days
  - Alive and free of proven/probable/presumptive IFI
- Powered to detect 12% difference in FFS (600 patients)
  - Assumptions: Will detect increase of FFS from 0.50 to 0.62 with power of 80%, type 1 error of 5%

Wingard J et al. 2007

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Patient Characteristics

	FLU N=295	VORI N=305
Age (median)	43 years	43 years
% 18 years or above	92%	91%
Disease		
AML	101 (34%)	133 (44%)
ALL	64 (22%)	58 (19%)
CML	60 (20%)	43 (14%)
MDS	49 (17%)	49 (16%)
NHL	21 (7%)	22 (7%)
Disease risk status = good	263 (89%)	283 (93%)
Donor source = related	169 (57%)	168 (55%)

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Wingard J et al. 2007

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Safety

Toxicities (Grades 3-5)*	FLU N = 295	VORI N = 305
Liver	18%	15%
Confusion	5%	6%
Photopsia	0%	1%
Psychosis	4%	2%
Renal	11%	9%
Hypoxia	22%	18%

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*Maximal toxicity grade through day 180

Wingard J et al. 2007

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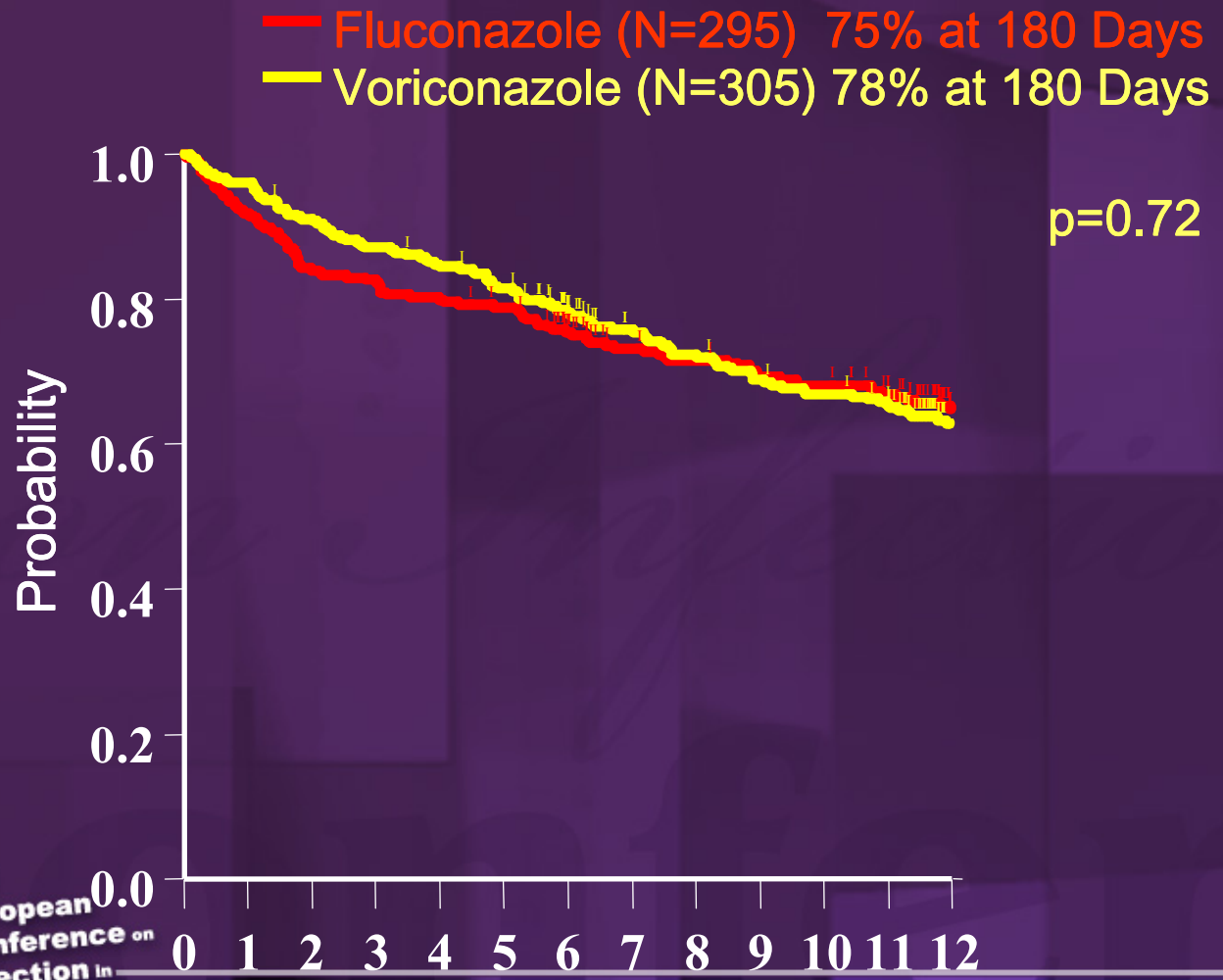
Fungal-free Survival



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Wingard J et al. 2007

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Microbiologically Documented Proven/Probable Fungal Infections Through Day 180

Fungal Genus	FLU	VORI
• Aspergillus*	16*	7*
• Candida	3	3
• Zygomycetes	3	2
• Other	1	1
Totals**	23**	13**

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*p = 0.05 ** p = 0.11

Wingard J et al. 2007

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Voriconazole (VOR) versus itraconazole (ITR) for primary prophylaxis of invasive fungal infections in allogeneic HSCT recipients
Marks et al. ICAAC 2009, San Francisco, M-1249a

- **Prospective, open-label, multicenter study**
- **Patients ≥ 12 y of age; 234 VOR and 255 ITR**
- **From day 0 till at least day + 100 and up to day +180**
- **Primary composite endpoint: patient surviving without proven or probable IFI at day +180 or discontinuing prophylaxis for >14 days (= success of prophylaxis or SoP)**
- **SoP at day +100: VOR 55% vs. ITR 41% (p=0.0007)**
- **SoP at day +180: VOR 49% vs. ITR 35% (p=0.0004)**
- **IFI incidence: VOR 1.3% and ITR 2%**
- **Survival at day +180: 85% both arms**
- **Sufficient days of prophylaxis: VOR 54% vs. ITR 40% (p=0.0014)**
- **No patient developed IFI while on VOR vs. 3 patients while on ITR**

Marks D et al. 2009

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Antifungal prophylaxis in allogeneic SCT

Proposed changes only

Neutropenia w/o GvHD	
Fluconazole* 400 mg/d	AI
Posaconazole	No data
Voriconazole 200 mg bid	Provisional AI
GvHD > grade I	
Fluconazole 400 mg/d	CI
Posaconazole 200 mg tid	AI
Voriconazole 200 mg bid	Provisional AI

* combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections

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Echinocandins

Van Burik J et al. Clin Infect Dis 2004

- - 882 patients, randomized, double-blind
  - micafungin (50mg/d) vs fluconazole (400mg/d)
  - overall efficacy : 80% mica. vs 73% fluco.
  - colonisation, breakthrough infections, toxicity, mortality = identical in both arms.
- Data are sparse (Mattiuzzi, Cornely, Powles, Stute, Hiemenz, Ifran)

Few patients, not exclusively high-risk patients, few proven FI

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Caspofungin versus itraconazole in patients with hematologic malignancies

Mattiuzzi et al. AAC 2006; 50: 143

Number of episodes	Caspo 50 mg N= 106	Itraconazole 200 N = 86
Success	55 (52%)	44(51%)
Proven and probable IFI	7 (6%)	5 (6%)
Pneumonia/FUO And systemic antifungals	40 (37%)	29 (34%)
Death	7	7
Death related to IFI	4	2
Discontinuation	8 (9%)	4 (4%)

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Insufficient data to propose recommendation due to design and statistics

Oral and IV Polyenes

- Oral suspension (1.5-3 g/day): not indicated
- Aerosolized amphotericin B: not indicated
  - Prospective randomized trial by Schwartz et al, Blood 1999; 93: 3654
- IV conventional amphotericin B: not indicated
  - 0.1-0.2 mg/kg/day or 0.5 mg/kg 3 times weekly
  - Nephrotoxic
  - Studies not powered to detect significant differences
- Lipid-based formulations: not indicated
  - Cost
  - Toxicity (ABCD versus fluconazole)
  - Studies not powered to detect significant differences

Liposomal amphotericin B in BMT recipients

Falagas & Vardakas, Am J Hematol 2006

- 2 double-blind placebo controlled randomized controlled trials
  - Kelsey 1999 and Tollemar 1993
  - CI
- Meta-analysis:
  - Proven fungal infections: OR = 1.03 (0.03-37.55)
  - Suspected fungal infections: OR = 0.83 (0.47-1.45)
  - Mortality: OR = 1.33 (0.71-2.52)
- Lip AmB should be avoided in BMT recipients due to the lack of supporting evidence, its high cost, and common side effects….
  A large RCT is urgently needed

Low-dose liposomal amphotericin B in prolonged neutropenia

Penack et al. Ann Oncol 2006; 17: 1306

Number of episodes	L-AmB 50 mg/2d N= 110	No systemic prophylaxis N = 109
Proven and probable IFI	5 (4.6%)	22 (20.2%)
Proven and probable IFI 1st neutrop. episode	5/75 (6.7%)	20/57 (35%)
Pneumonia	6	28
Systemic antifungals	24	64
FUO	30	37
Superficial FI	2	10
Death (related to IFI)	4 (2)	9 (8)
Toxicity (ns δ)	Discontinuation 2.8%	

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CI

Aerosolized amphotericin B

- Aerosolized conventional amphotericin B: DI

  Schwartz et al. Blood 1999; 93: 3654-3661

- Aerosolized liposomal amphotericin B

  Rijnders et al. Clin Infect Dis 2008; 46: 1401-8

  – *Single center, double-blind, placebo-controlled*
  – *L-AmB 10 mg twice weekly + fluconazole (dose?)*
  – *Protocol-specified diagnostic algorithm*
  – *PE: proven & probable IA (EORTC-MSG and modified)*
  – *2 blinded investigators*

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Aerosolized liposomal amphotericin B plus fluconazole during prolonged neutropenia

	Randomized (n=271) Liposomal AmB n=139	Placebo n=132	
Age	49	50	>0.1
M/F	77/62	81/51	>0.1
HEPA yes	108	100	>0.1
Hematologic Disease			
AML-MDS	65	67	>0.1
Other	74	65	>0.1
Hematological treatment			
Chemotherapy	100	85	>0.1
Autologous HSCT	25	31	>0.1
Allogeneic HSCT	14	16	>0.1
Disease status			
Untreated	73	64	>0.1
Other (*)	66	68	>0.1

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Rijnders et al. Clin Infect Dis 2008; 46: 1401-8

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Results

	Liposomal AmB	Placebo	p=	OR
EORTC-MSG IPA Proven/Probable				
MITT	6 / 139	18 / 132	**0.005**	**0.26** (0.09-0.72)
OT	2 / 90	13 / 97	**0.007**	**0.14** (0.02-0.66)
***Modified* EORTC-MSG Proven/Probable IPA**				
MITT	11 / 139	23 / 132	**0.013**	**0.37** (0.16-0.83)
OT	3 / 90	17 / 97	**0.002**	**0.16** (0.03-0.56)

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Rijnders et al. Clin Infect Dis 2008; 46: 1401-8

Results

Fluconazole (dose?) was given to all patients

Discontinuation of inhalation therapy for at least one week

49 of 139 patients in the liposomal AmB group (35%)

35 of 132 patients in the placebo group (27%) (p=0.12)

Reasons for discontinuation

Feeling to weak/to sick to use the inhalation system

Technical problem with adaptive aerosol delivery system (Halolite>Prodose)

Intolerance (bad taste, coughing, nausea)

IC withdrawal at the start of a 2nd or 3rd course of chemotherapy

Rijnders et al. Clin Infect Dis 2008; 46: 1401-8

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Aerosolized liposomal amphotericin B plus fluconazole during prolonged neutropenia

- Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology: BII

  Cornely et al. Haematologica, 2009; 94: 113-122

- ECIL-3 recommendation

  – BI for acute leukemia-patients (during neutropenia)
  – BII for allogeneic HSCT recipients (few patients in the study)

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Primary antifungal Prophylaxis in Cancer Patients:
Fluco v. Drug with Anti-mold Activity: Meta-analysis

Outcome	Fluconazole	Anti-mould	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

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* Relative risk > 1 favors the anti-mould group

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

Issues in comparative studies on prophylaxis

- Insufficient sample size + many patients with a low risk of IFI + exclusion of critically ill patients: favors demonstration of equivalence !
- Underpowered to evaluate efficay in sub-groups
- Inclusion criteria should provide a high enough incidence of IFI (> 10%?) to warrant PAC
- *Acute leukemia and allogeneic stem cell transplantation*
  - Not all allogeneic transplant have the same risk (Anaissie)
  - AML > ALL
  - Relapsed or refractory disease > de novo
  - Mucositis
  - ↓ cell-mediated immunity: fludarabine, steroids, GvHD
    - Colonization status: high negative predictive value (Candida)
    - Aspergillus more problematic (building, season, HEPA, ..)

Issues in comparative studies on prophylaxis

- Open design
- 'Suspected' or 'possible' FI (empirical therapy) is not a valid end point
- No prespecified diagnostic protocol or minimun duration of antibacterial therapy
- Double-blind
- Study end points
  - Incidence of proven and probable invasive yeast and mould infections (EORTC/MSG criteria): requires adherence to diagnostic protocol
  - Overall mortality and fungus-attributable mortality
  - (superficial and mucosal infections)
  - Toxicity
  - Colonization and resistance

Many (not all) of these problems have been addressed in recently completed trials with posaconazole

Increase of microbial shift and induction of resistance during antifungal prophylaxis!

- The use of FLU prophylaxis influenced the occurrence of more non-*C albicans* infections and was accompanied by difficult to treat and more virulent colonisations and infections (Hamza 2004, Marr 2002; 2000, Uzun 1995, Pfaller 2004).
- Antifungal prophylaxis was associated with microbial shifts, as an 8+fold increase was observed in *C. glabrata* colonisation in the FLU and in *C. albicans* in the MICAFUNGIN arm (van Burik 2004).
- A trend in fungal colonisation in patients receiving antifungal therapy is shown in another study: 27 out of 79 patients colonized with *Aspergillus* received AMB or ITRA therapy pre-emptively for more than two weeks (Marr 2002).
- Cancer patients with positive *Aspergillus* cultures who are pre-exposed to AMB or triazoles have high frequency of non – *A. fumigatus* and these isolates were found to be AMB-resistant (Lionakis 2005).

These findings may reflect, at least, partly, antifungal selection pressure caused by antifungals in high-risk patients

Azole resistant yeasts in patients receiving antifungal prophylaxis

Period	No patients	Main results	References
1994-1997	655	FLU increased colonisations with non *albicans* species (53%) mostly *C. glabrata* and *C krusei*, 5.3% of *C. albicans* were FLU resistant	Marr 2002
1988-1992	474	FLU-prophylaxis was directly associated with fungemia by *C. krusei* (OR=27.07) and *C. glabrata* (5.08)	Abi-Said 1997
1993	253	No increase in infections and colonisation in patients receiving FLU	Winston 1993
1994-1995	300	No significant increase in breakthrough infections	Slavin 1995
1989-1990	463	Significant increase in *C. krusei* infections and colonisation by *C. krusei* (41%)	Wingard 1991
1989-1996	234	*C. krusei* fungemia increased significantly (doubled from 5- to 10%) in patients with FLU	Abbas 2000
1994-1995	274	Colonisation by non *C. albicans* increased in both study arms, FLU and placebo	Laverdiere 2000
1991	365	No differences were found between the study groups	Goodman 1992
1996-1999	395	Increased infection with *C glabrata* and *C krusei* were observed	Martino 2002
1999-2001	304	No difference in the incidence of IFI during the study period (FLU 16%, vs ITRA 13%)	Martino 1994
1999- 2000	882	Breakthrough infections for MICA and FLU were 1.6% and 2.4%. *C. glabrata* colonisation in the FLU and *C. albicans* in the MICA-arm increased significantly	Van Burik 2004

Drug monitoring of itraconazole

- Relationship between dose, drug concentration and efficacy (Leather, Glasmacher, Buchkowsky)
- Effective prophylaxis probably needs serum concentration ≥ 500 ng/ml of itra (Poirier, Leather, Glasmacher, Buchkowsky)
- Wide inter and intra patients variations in the plasma level of itraconazole; drug interactions (Kageyama, Prentice, Cheymol)
- Itraconazole can be dosed reliably and fast

Conclusions : Drug monitoring recommended for oral formulation frequency not well defined, probably weekly

Duration of antifungal prophylaxis
Clinical practice in 31 centers in 2001

N (%)	Drug	Duration
15 (50)	Flu 400mg q.d.	Neutrophil count ≥ 500/µl
6 (19)	Flu 100-200mg q.d.	End of immunesuppression
4 (12)	Itra 200 mg b.i.d.	d 30 (1) end of immunesuppression (3)
4 (12)	Amph B conv. 0,5 mg/kg q.d. (1) lipid 1-3 mg/kg q.d. (3)	Neutrophil count ≥ 500/µl => Flu till end of immunesuppression
2 (6)	No prophylaxis	

Trifilio et al., 2001

3. Evidence-Based Recommendations

UPDATE ECIL-3 2009: Summary slide

Primary antifungal prophylaxis in leukemia patients

- Induction chemotherapy of acute leukemia
  - Fluconazole 50-400 mg qd iv/oral: CI[2,5]
  - Itraconazole oral solution 2.5 mg/kg bid: CI[1,2,3]
  - Posaconazole 200 mg tid oral: AI[2,3]
  - Candins iv: insufficient data
  - Polyene[4] iv: CI
  - Aerosolized liposomal amphotericin B in combination with oral fluconazole: BI

1. may be limited by drug interactions and/or patient tolerability
2. azoles should not be used empirically in case of prior azole prophylaxis
3. it is recommended to monitor serum drug concentrations
4. includes low doses of conventional amphotericin B and lipid formulations.
5. combined with a mould-directed diagnostic approach for centers not having HEPA-filtered rooms and/or having a high baseline incidence of mould infections

The ECIL recommendation for aerosolized amphotericin B deoxycholate is DI

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UPDATE ECIL-3 2009: Summary slide

Primary antifungal prophylaxis in leukemia patients

- Allogeneic hematopoietic stem cell transplantation: neutropenic phase
  - Fluconazole 400 mg qd iv/oral: AI[2,5]
  - Itraconazole 200 mg IV followed by oral solution 200 mg bid: BI[1,2,3]
  - Posaconazole 200 mg tid oral: no data
  - Micafungin 50 mg qd iv: CI
  - Polyene[4] iv: CI
  - Voriconazole 200 mg bid oral: provisional AI
  - Aerosolized liposomal amphotericin B plus fluconazole: BII
- Allogeneic hematopoietic stem cell transplantation: GvHD phase
  - Fluconazole 400 mg qd iv/oral: CI[2]
  - Itraconazole 200 mg IV followed by oral solution 200 mg bid: BI[1,2,3]
  - Posaconazole 200 mg tid oral: AI[2,3]
  - Candins iv: insufficient data
  - Polyene iv: CI
  - Voriconazole 200 mg bid oral: provisional AI
  - Aerosolized liposomal amphotericin B plus fluconazole: insufficient data

Secondary Antifungal Prophylaxis - Risk Factors for Breakthrough IFI in AML Patients with Prior IPA

Factors predisposing for BT-IFI	OR	CI
duration of neutropenia, per each day	1.043	1.008 – 1.078
high-dose cytosine arabinoside	3.920	1.120 – 12.706
number of antibiotics, per each antibiotic	1.504	1.089 – 2.086
partial response as outcome of prior IFI	4.037	1.301 – 12.524
newly diagnosed AML	3.823	0.953 – 15.340
high efficiency particulate air filter during prior IFI	0.198	0.036 – 1.089

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Cornely et al. J Antimicrob Chemotherapy 2008

UPDATE ECIL- 3 2009

Secondary antifungal prophylaxis

- Condition:
  - Previously documented and fully resolved IFI plus
  - A new episode of
    - prolonged neutropenia (usually chemotherapy-induced)
    - severe immunosuppression (usually transplantation)
- Recommandation: AII
  - Cordonnier C, et al. Bone Marrow Transplant. 2004;33(9):943-8 and VOSIFI study presented at ASH 2008, San Francisco
  - Vehreschild JJ, et al. Int J Antimicrob Agents. 2009; 34(5):446-50.
  - Cornely O, et al. J Antimicrob Chemother. 2008 ;61(4):939-46.
  - Stute N, et al. Bone Marrow Transplant. 2004; 33 Suppl 1: S735
- No drug-specific recommendations possible, but choice should be based on the causative fungal pathogen of the previous IFI and the response to antifungal agents during that episode