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2nd European Conference on Infections in Leukemia

2007 update of the ECIL-1 guidelines for Antifungal prophylaxis in leukemia patients, including allogeneic HSCT recipients

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ELN European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

ICHS International Conference on Hospital Safety

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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 or will 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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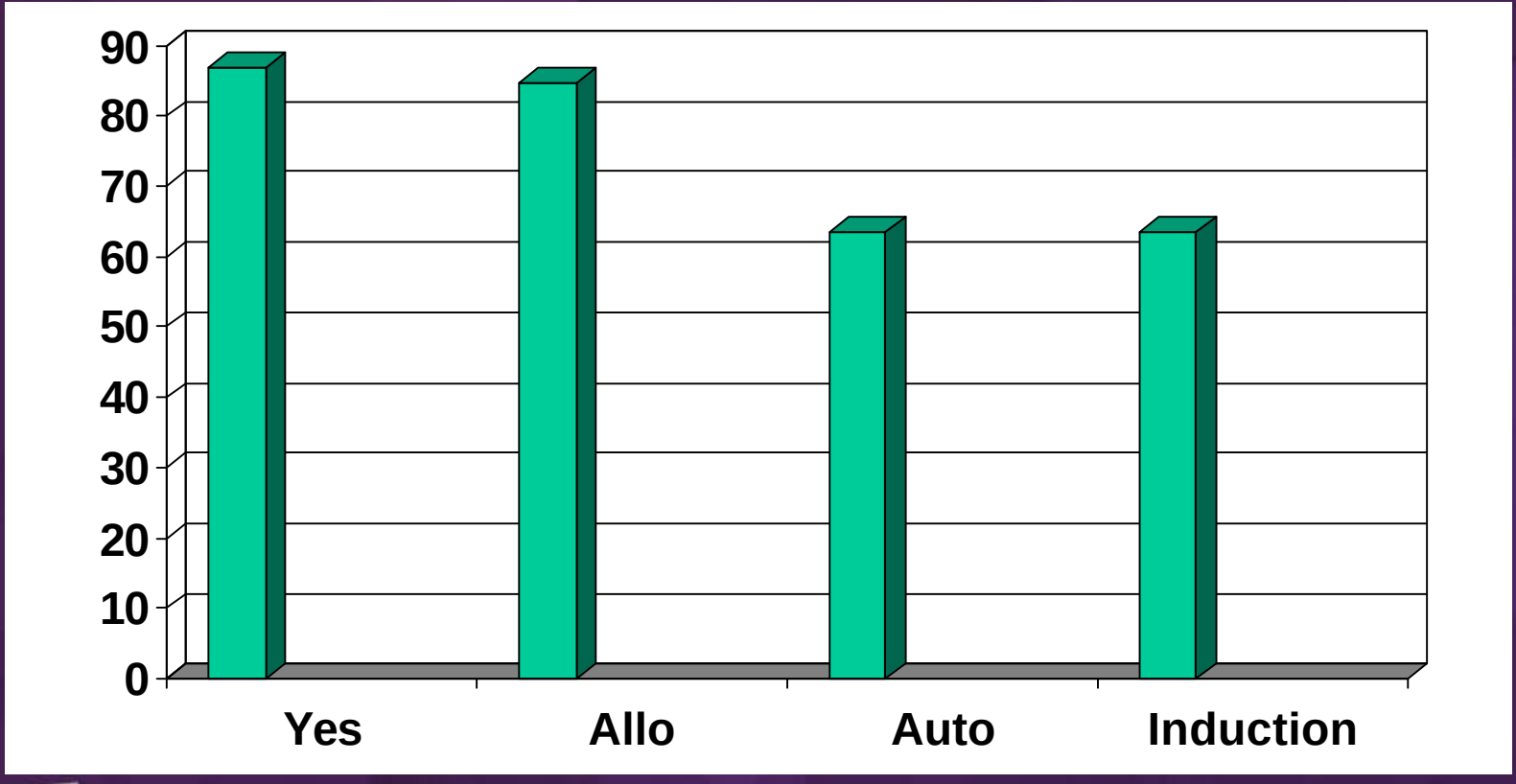
Do you Use Antifungal Prophylaxis?

(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

Fluconazole (Oliver)

Itraconazole (Johan)

Other (Pascale & Werner)

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
Allogenic	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
Allogenic	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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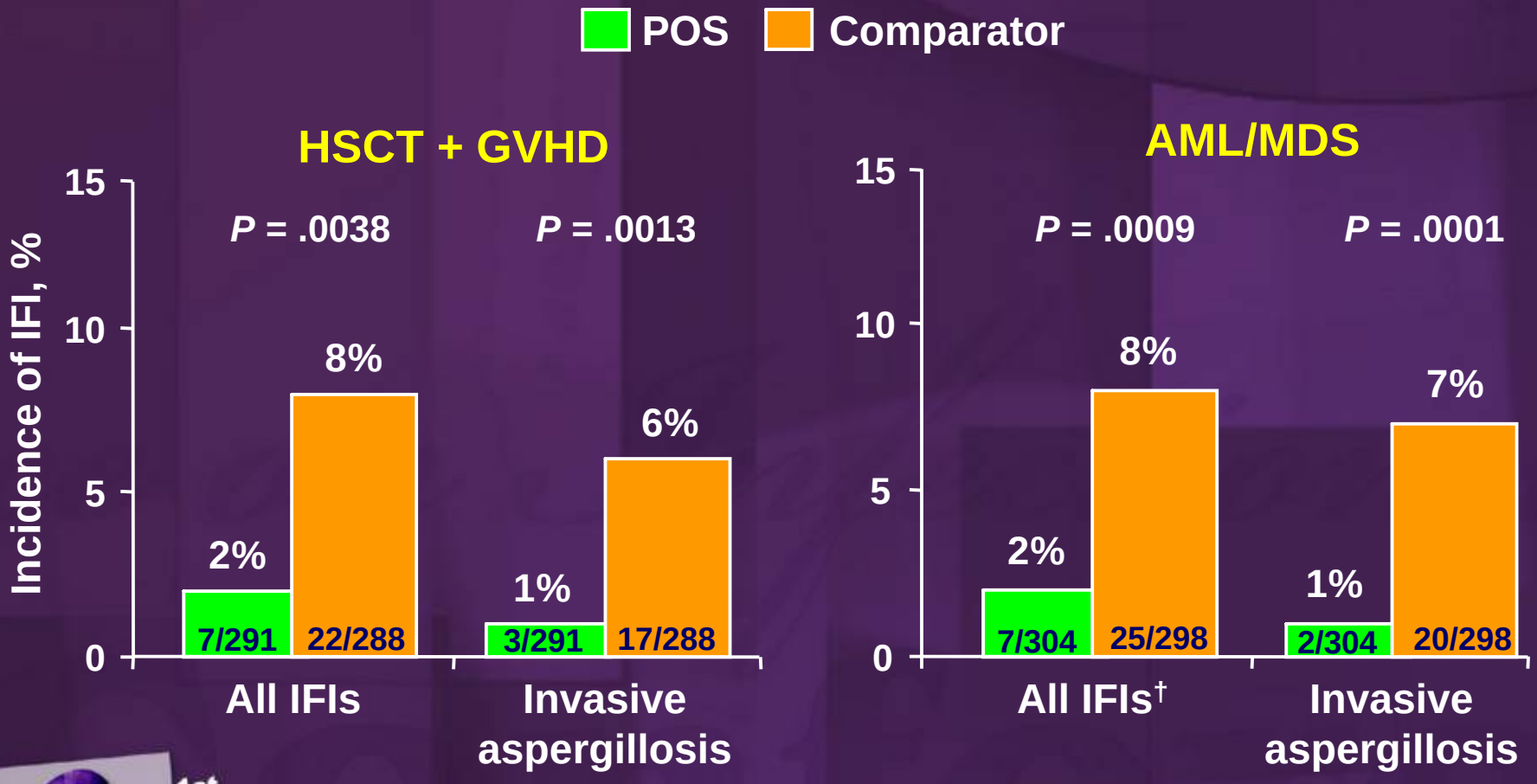
Incidence of Proven/Probable IFIs While on Treatment*



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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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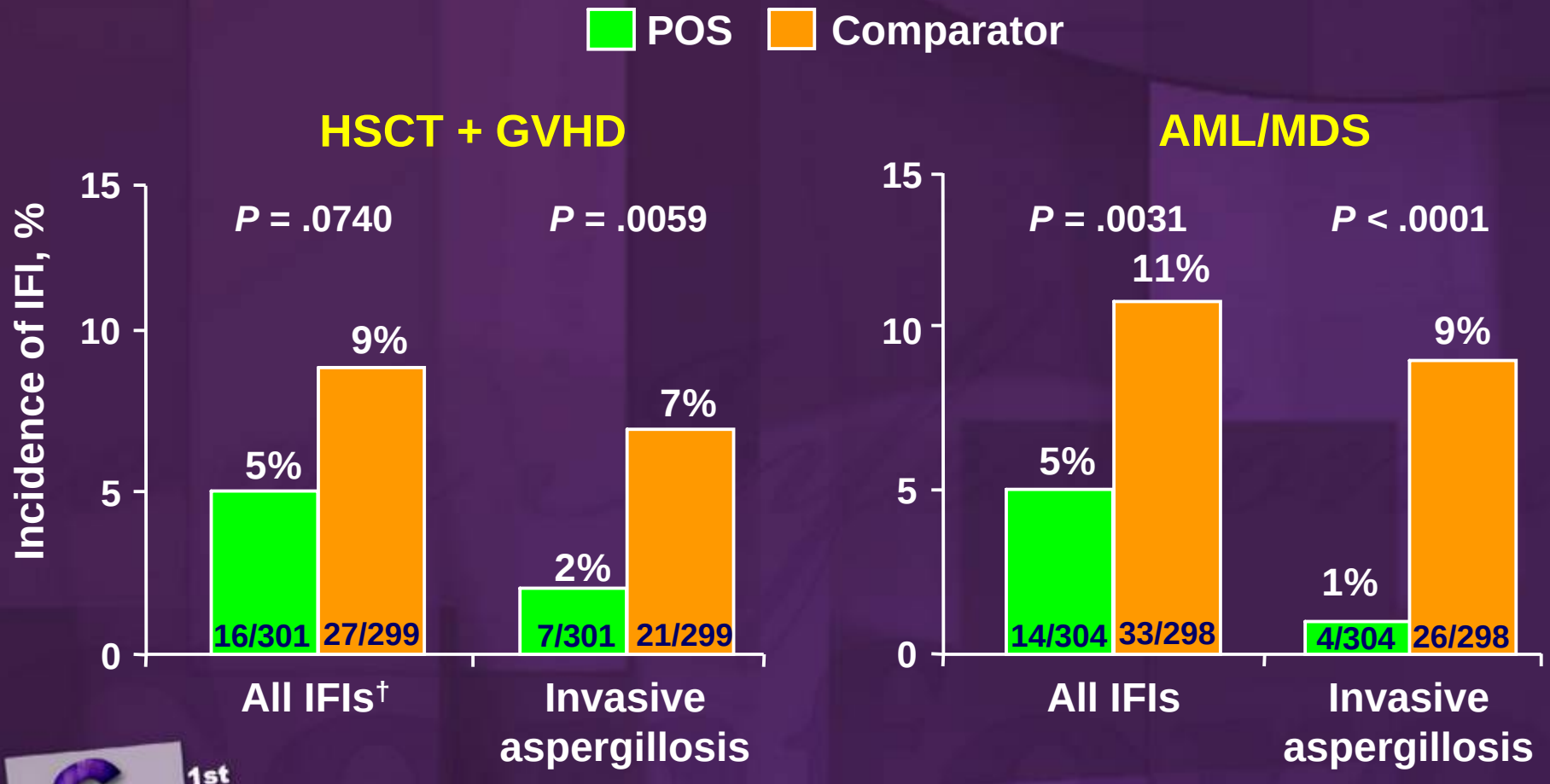
Incidence of Proven/Probable IFIs During Fixed Time Period*



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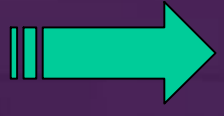
*Within 112 days and 100 days postrandomisation for the HSCT + GVHD and AML/MDS studies, respectively.

†Primary end point.

Echinocandins

- Van Burik : - 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

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 RCT
  - 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!

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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	4	9
Death related to IFI	2	8
Toxicity (ns d)	Discontinuation 2.8%	

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CI

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 (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	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

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Antifungal prophylaxis in leukemia patients

- Allogeneic hematopoietic stem cell transplantation
  - Fluconazole 400 mg qd iv/oral: AI[2]
  - Itraconazole 200 mg IV followed by oral solution 200 mg bid: BI[1,2,3]
  - Posaconazole 200 mg tid oral: AI[2,3]
  - Micafungin 50 mg qd iv: CI
  - Polyene[4] iv: CI
- Induction chemotherapy of acute leukemia
  - Fluconazole 50-400 mg qd iv/oral: CI[2]
  - 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

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. The ECIL recommendation for aerosolized amphotericin B is DI

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Unsolved Questions and New Areas of Research

Secondary antifungal prophylaxis has not been studied in a well-designed prospective, randomized clinical trial.

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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Data presented by O. Cornely
Secondary prophylaxis registry