1st European Conference on Infection in Leukemia

Empirical Antifungal Therapy

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Sept. 30th / Oct. 1st 2005 Juan-les-Pins - France

ELN European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

ICHS International Conference on Infection in the Immunocompromised Host

Background

- Empirical antifungal therapy for suspected invasive fungal infections (IFI) is a standard of care in neutropenic cancer patients with persistent fever despite broad-spectrum antibiotics *(IDSA, CID, 2002)*
- New antifungal agents offer alternative treatment options
- Choice of the appropriate drug guided by efficacy, safety and economic issues represents a new challenge
- Evidence-based European guidelines are needed

Objectives

1. European experts' management strategies ?
2. Impact of empirical antifungal therapy :
   - Fever ?
   - Breakthrough IFI ?
   - Mortality due to IFI ?
   - Toxicity ?
   - In leukemia vs. allo- vs. auto-HSCT ?
   - In FUO vs. documented infections ?
   - Patients receiving vs. not receiving antifungal prophylaxis ?
3. Evidence-based European guidelines for empirical AF therapy

Methods

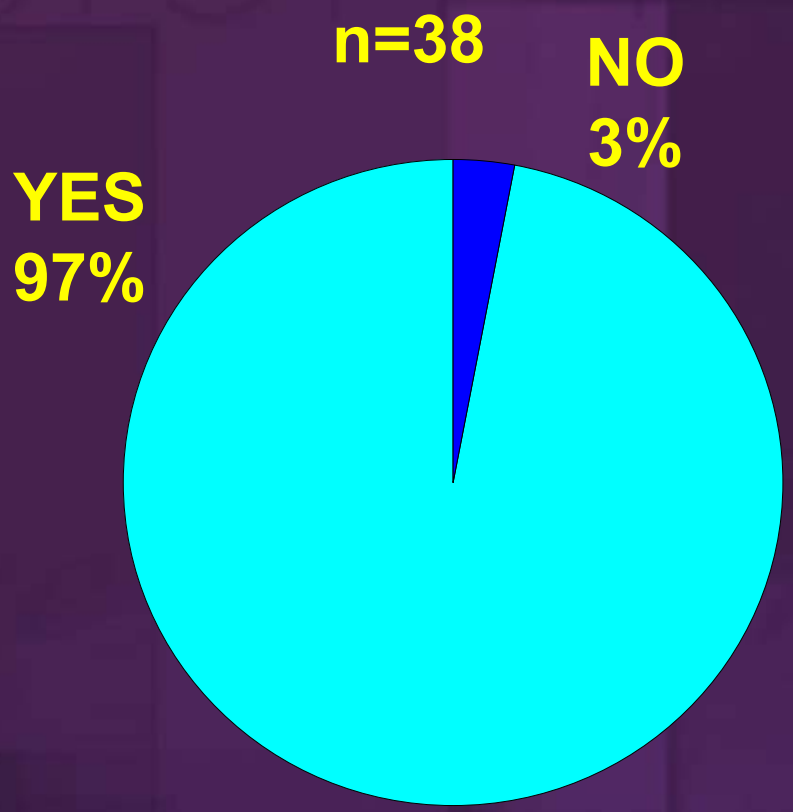
1. Questionnaire: European experts' practices
2. Literature review

   Search
   - MEDLINE (Medical Subject Heading terms)
   - COCHRANE
   - PUBMED
   - MANUAL SEARCH in bibliography of reference publications
   - ICAAC, ECCMID, ASH, ASCO, and EBMT 2002-2005

   Analysis of comparative clinical trials
3. CDC grading

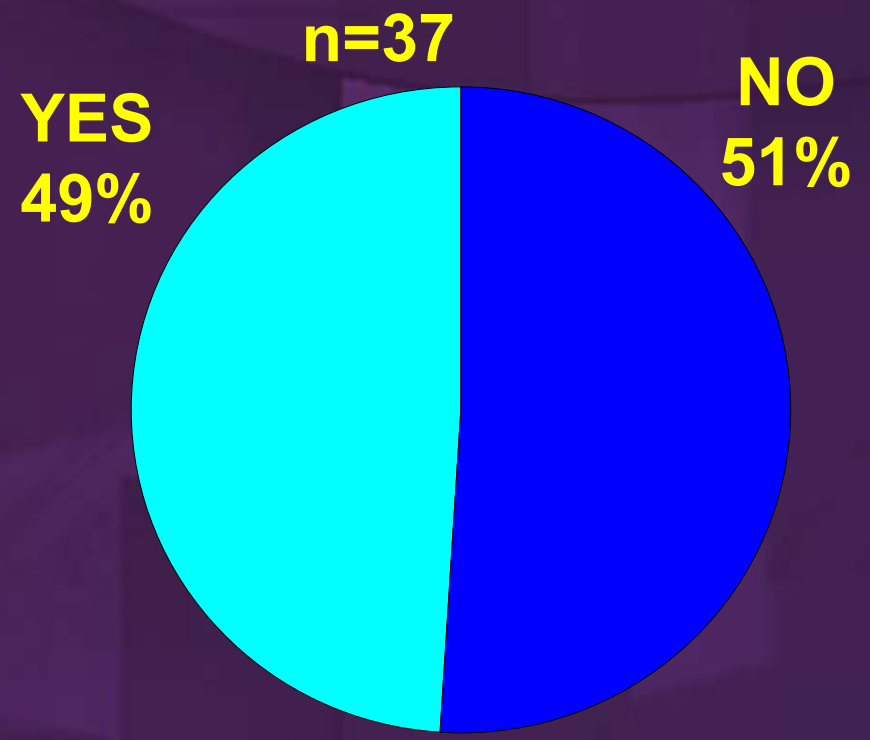
1. Questionnaire: Experts' Practices

Do You Use Empirical Antifungal Therapy ?



Time of initiation ?
First febrile episode 5 d (3 to 8.5) vs. Fever relapse 3 d (1 to 8.5)
p<0.001

Is Time of Initiation Different in Presence of Microbiologically Documented Bacterial Infection ?



Time of initiation ?
MDI 6.5 d (4 to 8) vs. CDI/FUO 4 d (3 to 6)
p<0.001

Antifungal Regimen and Clinical Setting

1. Type of cytotoxic chemotherapy
- Induction/Consolidation AL: Ampho B deoxycholate
- Allo-HSCT: Liposomal AmB
- Auto-HSCT: Ampho B deoxycholate

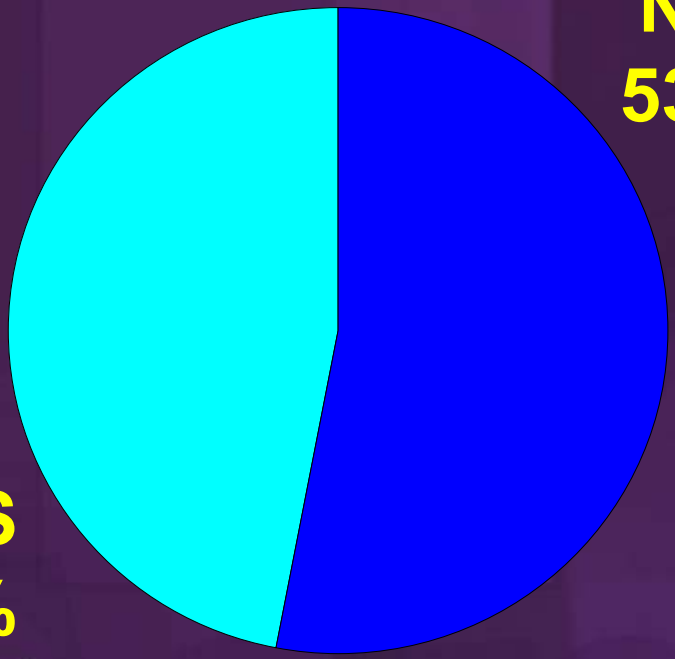
2. Clinical presentation
- FUO: Ampho B deoxycholate
- GI-tract colonization/Enterocolitis: Fluco / AmB-d / Caspo
- Pneumonia/Positive galacto-Mn: Voriconazole
- Clinical unstability: Liposomal AmB or Caspofungin

3. Antifungal prophylaxis influences choice of empirical regimen for 62% of experts

Questionnaire on European Experts' Practices

Are Your Choices Evidence-Based ?

n=47



Are Further Studies on Empirical Therapy Required ?

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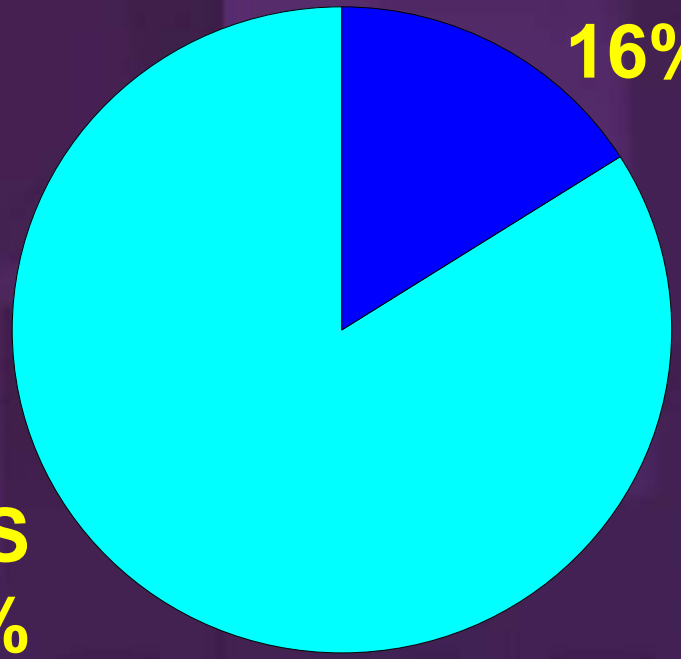

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2. Literature Review: Comparative Clinical Trials

COMPARATIVE TRIALS
n=25

1980s

Ampho B vs. No Therapy
n=2

1990 - 2005

Antifungal A vs. Antifungal B
n=23

IFI at baseline
n=4

Primary: Efficacy
n=11

Primary: Toxicity
n=8

Sample Size Based on Power Calculation
n=5

No Power Calculation
n=6

> 150 Pts
n=4

< 150 Pts
n=4

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Ampho B Deoxycholate vs. No Therapy

Pizzo, Am J Med, 1982; 72: 101-11
EORTC, Am J Med, 1989; 86: 668-72

1. Inclusion
   - Fever (FUO or CDI) > 38 °C during > 4-7 days +
   - Neutrophils < 0.1 - 0.5 G/L
2. Open randomization
   - Ampho B deoxycholate 0.5-0.6 mg/kg/d vs.
   - No therapy
3. Treatment duration
   - Afebrile +
   - Neutrophils > 0.5 G/L

Ampho B Deoxycholate vs. No Therapy

Pizzo, Am J Med, 1982; 72: 101-11
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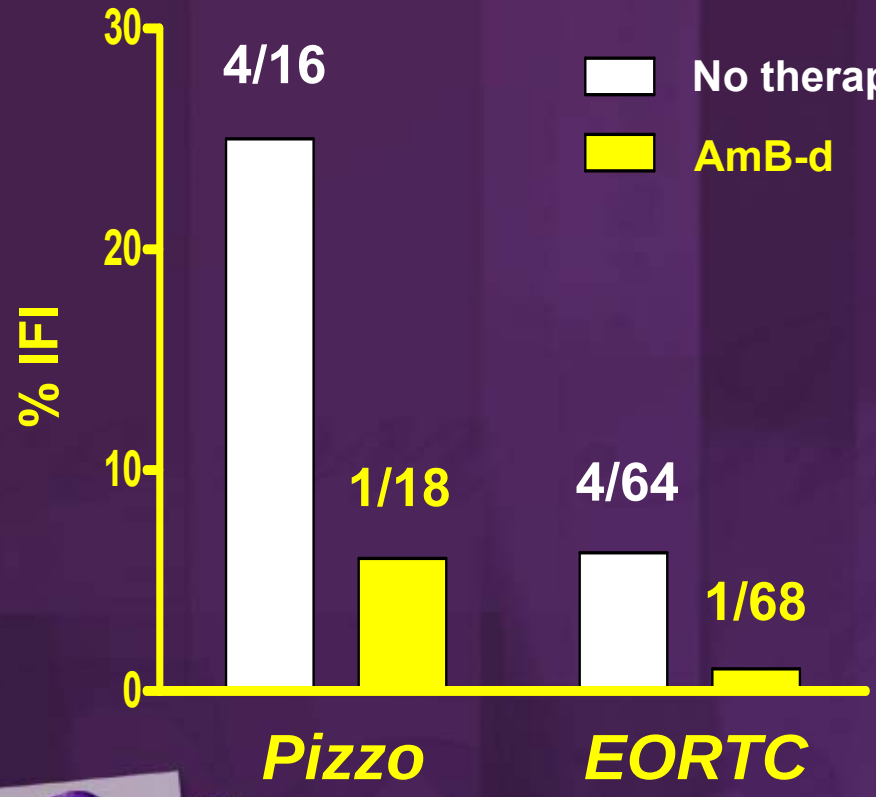
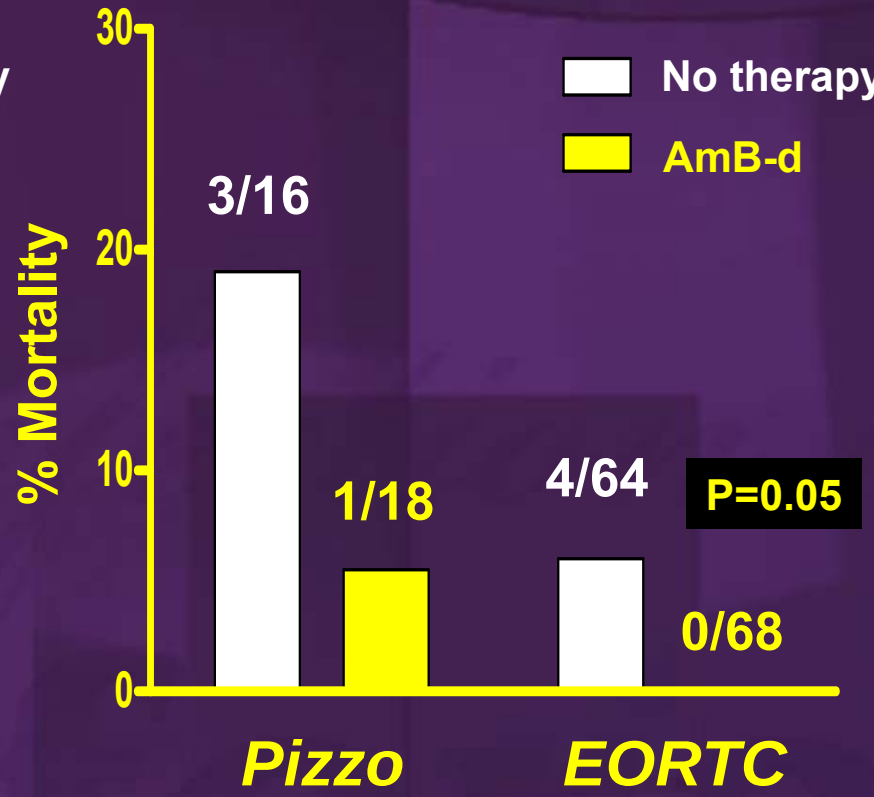
Invasive Fungal Infections (IFI)



Mortality IFI



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COMPARATIVE TRIALS
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1990 - 2005

Antifungal A vs. Antifungal B
n=23

IFI at baseline
n=4

Primary: Efficacy
n=11

Primary: Toxicity
n=8

Power OK
n=5

Underpower
n=6

> 150 Pts
n=4

< 150 Pts
n=4

Ampho B deoxy vs. Lipid ampho B, n=4
Azoles vs. Ampho B, n=4
Echinocandin vs. Ampho B, n=1

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Comparison of Two Empirical Antifungal Agents

FUO + > 38 °C during > 3-5 days (or relapsing) + Neutrophils <0.5 G/L

↓

Open or double-blind randomization

(Stratification: Risk + Antifungal Prophylaxis)

AMPHOTERICIN B	OTHER FORM AMPHO B or AZOLE or ECHINOCANDIN

Primary endpoint: EFFICACY (equivalence or non-inferiority) or TOXICITY

Assessment efficacy: COMPOSITE endpoint (3-6 criteria)

Synopsis of Clinical Trials

	Size	Design	Regimens	Primary endpoint
Prentice, 1997	338	Open	Lipo AmB 1 or 3 vs AmB-d 1	Severe toxicity
White, 1998	196	Double-Blind	ABCD 4 vs AmB-d 0.8	Nephrotoxicity
Walsh, 1999	687	Double-Blind	Lipo AmB 0.6 vs AmB-d 0.6	Equivalent efficacy (± 10%)
Wingard, 2000	244	Double-Blind	Lipo AmB 3 or 5 vs ABLC 5	Infusion-related toxicity
Winston, 2000	317	Open	Fluco 400 vs AmB-d 0.5	Equivalent efficacy (± 15%)
Boogaerts, 2001	360	Open	Itra 200, then 400 vs AmB-d 0.7-1	Equivalent efficacy (± 15%)
Ehninger, 2002	162	Open	Itra 200, then 400 vs AmB-d 0.7-1	Severe toxicity
Walsh, 2002	837	Open	Vori 6, then 400 vs Lipo AmB 3	Non-inferior efficacy (± 10%)
Walsh, 2004	1095	Double-Blind	Caspo 50 vs Lipo AmB 3	Non-inferior efficacy (± 10%)

Overall Response (Composite Endpoint)

	EXPERIMENTAL		CONTROL		
Prentice, 1997	Lipo AmB 1	58%	AmB-d 1	49%	P=0.09
	Lipo AmB 3	64%			
White, 1998	ABCD 4	50%	AmB-d 0.8	43%	NS
Walsh, 1999	Lipo AmB 3	50%	AmB-d 0.6	49%	NS
Wingard, 2000	ABLC 5	33%	Lipo AmB 3	40%	NS
			Lipo AmB 5	42%	
Winston, 2000	Fluco 400	68%	AmB-d 0.5	67%	NS
Boogaerts, 2001	Itra 200	47%	AmB-d 0.7	38%	Δ 9 (CI -1 to 13)
Ehninger, 2002	Itra 200	63%	AmB-d 0.7	43%	P=0.0001
Walsh, 2002	Vori 6	26%	Lipo AmB 3	31%	Δ -4 (CI -11 to 2)
Walsh, 2004	Caspo 50	34%	Lipo AmB 3	34%	Δ 0 (CI -6 to 6)

Outcome of Baseline IFI

	Endpoint	EXPERIMENTAL		CONTROL		
Walsh, 1999	Success	Lipo AmB 3	9/11 (82%)	AmB-d 0.6	8/11 (73%)	NS
Winston, 2000	Success	Fluco 400	3/10 (30%)	AmB-d 0.5	5/9 (55%)	NS
	Mortality		4/10 (40%)		4/9 (44%)	NS
Walsh, 2002	Success	Vori 6	6/13 (46%)	Lipo AmB 3	4/6 (67%)	NS
Walsh, 2004	Success	Caspo 50	14/27 (52%)	Lipo AmB 3	7/27 (26%)	0.04
	Mortality		3/27 (11%)		12/27 (44%)	0.01

Breaktrough IFI

	EXPERIMENTAL		CONTROL		
Prentice, 1997	Lipo AmB 1 Lipo AmB 3	3% 2%	AmB-d 1	2%	NS
White, 1998	ABCD 4	17%	AmB-d 0.8	18%	NS
Walsh, 1999	Lipo AmB 3*	3%	AmB-d 0.6	8%	P=0.005
Wingard, 2000	ABLC 5	4%	Lipo AmB 3 Lipo AmB 5	4% 2%	NS
Winston, 2000	Fluco 400	4%	AmB-d 0.5	4%	NS
Boogaerts, 2001	Itra 200	3%	AmB-d 0.7	3%	NS
Walsh, 2002	Vori 6	2%	Lipo AmB 3	5%	Δ 3 (CI 1 to 5), P=0.02
Walsh, 2004	Caspo 50**	5%	Lipo AmB 3	5%	Δ -1 (Δ -3 to 2)

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* *Lipo AmB: Mortality IFI 36% vs. 41%, NS*

** *Caspo: Mortality IFI 34% vs. 42%, NS*

Nephrotoxicity (>2x Baseline Creatinine)

	EXPERIMENTAL		CONTROL		
Prentice, 1997	Lipo AmB 1	10%	AmB-d 1	24%	0.01
	Lipo AmB 3	12%			
White, 1998	ABCD 4	8%	AmB-d 0.8	35%	0.001
	+ Cy or Tacro	31%	+ Cy or Tacro	68%	0.001
Walsh, 1999	Lipo AmB 3	19%	AmB-d 0.6	34%	0.001
Wingard, 2000	ABLC 5	42%	Lipo AmB 3	14%	0.001
			Lipo AmB 5	15%	
Winston, 2000	Fluco 400	1%	AmB-d 0.5	33%	0.001
Boogaerts, 2001	Itra 200	5%	AmB-d 0.7	24%	0.001
Ehninger, 2002	Itra 200	4%	AmB-d 0.7	41%	0.001
Walsh, 2002	Vori 6	7%	Lipo AmB 3	8%	NS
Walsh, 2004	Caspo 50	3%	Lipo AmB 3	11%	0.001

Impact of Empirical Antifungal Therapy in Different Clinical Settings

1. In AL vs. allo- vs. auto-HSCT ?

2. In FUO vs. microbiologically or clinically documented infection ?

3. In patients receiving or not receiving antifungal prophylaxis ?

- **No consistent differences**
- **Data lacking**

Comments

HISTORICAL STUDIES IN THE 1980s

- Current standard of care based on two open studies comparing ampho B deoxycholate to nihil
- Limited number of patients: underpowered
- Benefit of empirical antifungal therapy on occurrence of IFI and mortality due to IFI not unequivocally proven
- Evolution of cytotoxic and immunosuppressive therapies, HSCT, supportive care, imaging techniques, and laboratory tests. Results from these trials applicable to current practice ?

Comments (Cont'd)

COMPARATIVE STUDIES 1990 - 2000

- Comparison of ampho B to other form of ampho B or agent of a different class. No direct comparison of azoles and echinocandins
- No substantial superiority of any antifungal agent for overall response, mainly based on resolution of fever
- Effect on IFI or mortality due to IFI difficult to assess in small numbers of events
- Ampho B deoxycholate more toxic than lipid forms, azoles or echinocandins, but 10-20x less expensive
- No metanalysis available

Issues in Comparative Studies

- Case mix, lower risk of IFI may favor demonstration of equivalence of two regimens
  - Short duration of fever at inclusion
  - Documented bacterial infection
  - Auto- vs. AL vs. allo-HSCT
  - Short duration of neutropenia
  - Overtreatment in the majority of patients
- Methodology
  - Open design: doubt on efficacy may ↑ failure rates
  - Primary endpoint:
    - Equivalent/non-inferior efficacy in composite endpoint
    - Toxicity, underpowered for assessment of efficacy

Issues in Comparative Studies (Cont'd)

- Neutrophil recovery <7 days after inclusion → short duration antifungal therapy → lower rate of defervescence
- Pertinence of composite primary endpoint ?
  - Defervescence during or after recovery of neutropenia non-specific, but major driver for success
  - Overall survival influenced by multiple factors
  - Difference baseline and breakthrough IFI ?
  - Combination of stop due to lack of efficacy or toxicity ?
  - Adjustment for risk stratification ?
- Underpowered to evaluate efficacy in sub-groups (e.g. high-risk patients or IFI or mortality of IFI): only explorative value

Duration of Neutropenia and Outcome

Cordonnier, ASH 2004, Abs # 1339

	LIPO AMB	AMB DEOXY	Δ (95%CI)
OVERALL RESPONSE			
Neutropenia < 7 days	42/136 (31%)	57/155 (37%)	NS
> 7 days	28/205 (62%)	112/187 (60%)	NS
OVERALL MORTALITY			
Neutropenia < 7 days	5/136 (6%)	12/155 (8%)	NS
> 7 days	19/205 (9%)	24/187 (13%)	NS
BREAKTHROUGH IFI			
Neutropenia < 7 days	3/136 (2%)	8/155 (5%)	NS
> 7 days	7/205 (3%)	18/187 (10%)	0.01

Impact of Resolution of Fever on Composite Endpoint for Response

De Pauw, ECCMID 2004, Abs # O423

	CASPOFUNGIN	LIPO AMB	Δ (95%CI)
48h afebrile during neutropenia	34%	34%	0 (-5 to 6)
24h afebrile during neutropenia	52%	48%	4 (-2 to 10)
Afebrile 7 d after start antifungal Rx	55%	53.5%	2 (-4 to 8)
Afebrile NOT in composite endpoint	82%	75%	7 (2 to 12)

Impact of Type of Statistical Analysis on Succes

Walsh, NEJM, 2002; 346: 225-34 and 1746-7
Powers (FDA), NEJM, 2002; 346: 289-90

	VORICONAZOLE	LIPO AMB	Δ (95%CI)
Unadjusted, composite endpoint	26%	31%	-4.5 (-10.6 to 1.6)
Adjusted, composite endpoint	24%	30%	-6.1 (-12 to 0.1)
Defervescence not included in endpoint	82%	85%	-2.3 (-7.7 to 2.3)

Outcome of Baseline IFI

	Endpoint	LIPO AMB		COMPARATOR		
Walsh, 1999	Success	Lipo AmB 3	9/11 (82%)	AmB-d 0.6	8/11 (73%)	NS
Walsh, 2002	Success	Lipo AmB 3	4/6 (67%)	Vori 6	6/13 (46%)	NS
Walsh, 2004	Success IFI	Lipo AmB 3	7/27 (26%)	Caspo 50	14/27 (52%)	0.04
	Aspergillosis		***1/12 (8%)***		***5/12 (42%)***	
	Candidiasis		***5/12 (42%)***		***8/12 (67%)***	
	Mortality IFI		12/27 (44%)		3/27 (11%)	0.01

Issues in Current Practices

- Current experts' practices are differentiated according to the clinical setting :
  - First vs. relapsing fever
  - Underlying conditions
  - Clinical presentation (FUO vs. site of infection)
  - Previous antifungal prophylaxis

- HOWEVER, EVIDENCE FOR THESE PRACTICES IS LACKING AND MOST EXPERTS AGREE THAT FURTHER STUDIES ARE NEEDED

3. Evidence-Based Recommendations

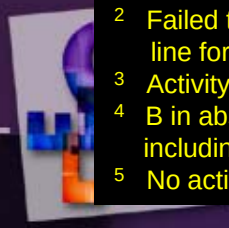
Indication for Empirical Antifungal Therapy in Persistently Febrile Neutropenic Patients

B II

Choice of Antifungal Drugs for Empirical Therapy

Antifungal agent	Daily dose	CDC Grading		
		Level of Recommendation	Evidence for	
			Efficacy	Safety
Liposomal AmB	3 mg/kg	A	I	I
Caspofungin	50 mg	A [1]	I	I
ABLC	5 mg/kg	B	I	I
Voriconazole	2x 3 mg/kg iv	B [1,2,3]	I	I
AmB deoxycholate	0.5-1 mg/kg	B / D [4]	I	I
Itraconazole	200 mg iv	C [1,3]	I	I
Fluconazole	400 mg iv	C [1,3,5]	I	I

1 No activity against mucorales.
2 Failed the 10% non-inferiority cut-off when compared with liposomal AmB (and thus not approved by the FDA for this indication), but first-line for aspergillosis and efficacious for prevention of breakthrough IFI.
3 Activity against *Candida* may be limited in patients receiving azole prophylaxis.
4 B in absence of / D in presence of risk factors for renal toxicity (e.g. impaired renal function at baseline, nephrotoxic co-medication including cyclosprin or tacrolimus in allogeneic HSCT recipients, aminoglycoside antibiotics, history of previous toxicity).
5 No activity against *Aspergillus* and other moulds. Not approved by the FDA for this indication.



Choice of Antifungal Drugs for Empirical Therapy in Allo-HSCT

- Data unclear or limited, value of subgroup analyses for efficacy or toxicity ?
- Amphotericin B deoxycholate: high nephrotoxicity
- Itraconazole: data lacking
- Fluconazole: large use of prophylaxis ↑ risk of resistant *Candida* spp., no activity on *Aspergillus*

Perspectives for the Future

Pre-emptive strategies

- Risk profile / Underlying conditions
- Previous antifungal prophylaxis
- Clinical presentation: site, severity
- Radiology: high-resolution CT-scan
- Cultures, including colonization
- Modern non-invasive laboratory/molecular markers

↓

1. No therapy in absence of positive findings:
↓ AEs, resistance and costs ?
2. Targeted therapy according to presentation ?