2nd European Conference on Infections in Leukemia

2007 Update of ECIL-1 Guidelines for Empirical Antifungal Therapy

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September 28 - 29 2007, Juan-les-Pins - France

ELN European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

ICHS International Society for Infectious Diseases in Compromised 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

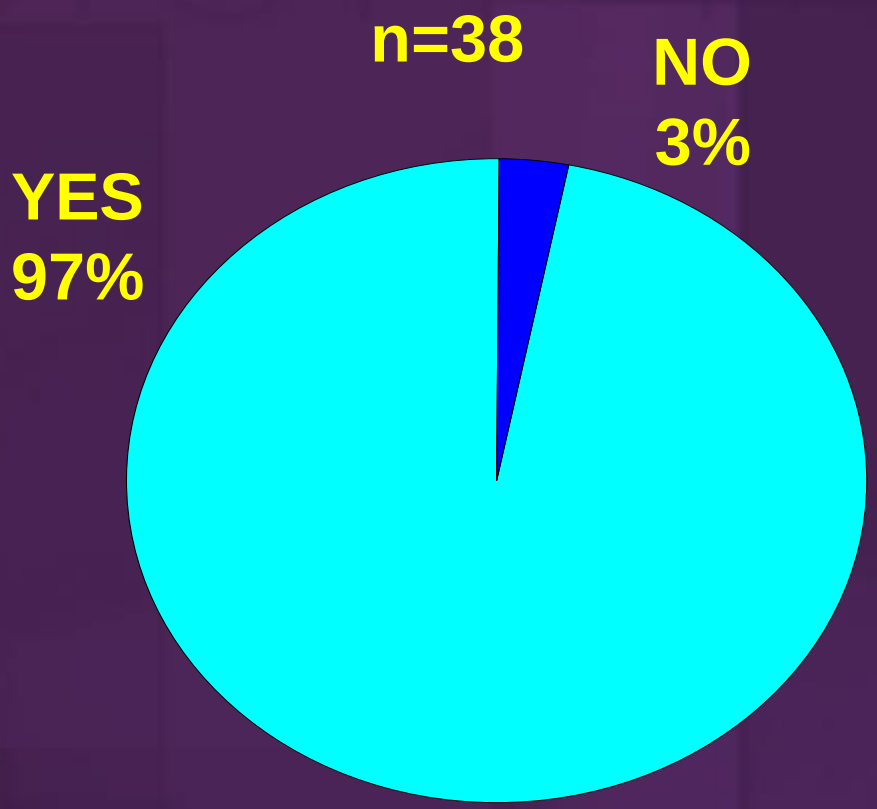
1. Questionnaire: European experts' practices
2. Literature review

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

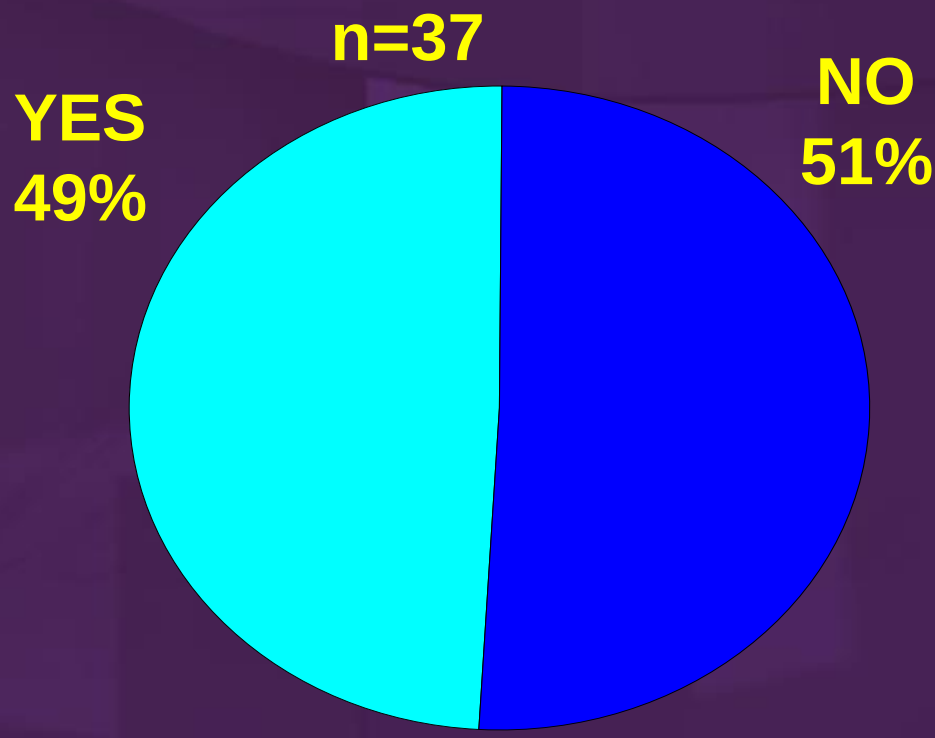
   Analysis of comparative clinical trials
3. CDC grading

1. Questionnaire: Experts' Practices

Do You Use Empirical Antifungal Therapy ?



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



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

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

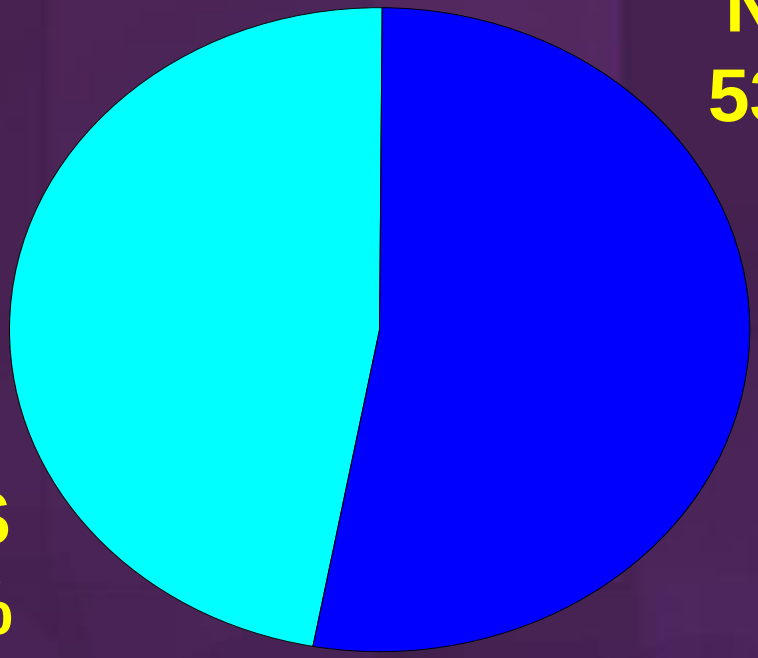
2. Clinical presentation
- FUO: Ampho B deoxycholate
- GI-tract colonization/Enterocolitis: Fluco / AmB-d / Caspo
- Pneumonia/Positive galacto-Mn: Voriconazole
- Clinical unstability: Liposomal AmB or Caspofungin

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

Questionnaire on European Experts' Practices

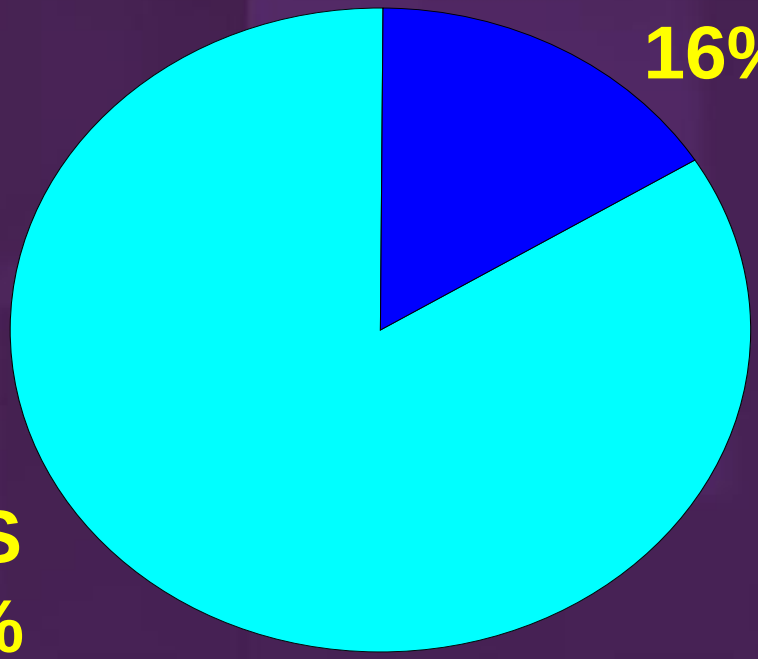
Are Your Choices Evidence-Based ?

n=37



Are Further Studies on Empirical Therapy Required ?

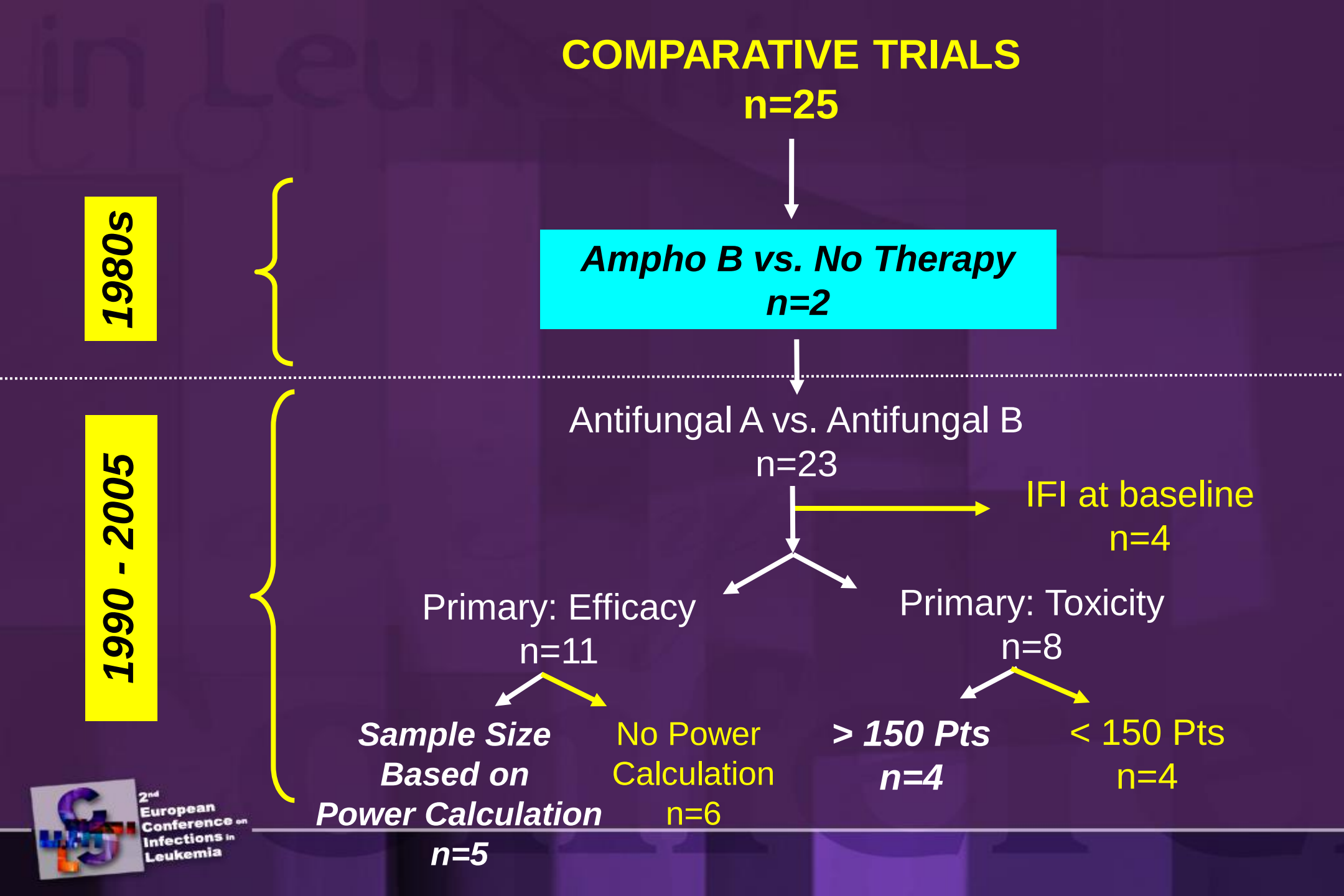
n=38



2. Literature Review: Comparative Clinical Trials

Question # 1

Is there evidence supporting the use of empirical antifungal therapy in neutropenic cancer patients with persistent fever in order to reduce the incidence, the morbidity and/or the mortality of invasive mycoses ?


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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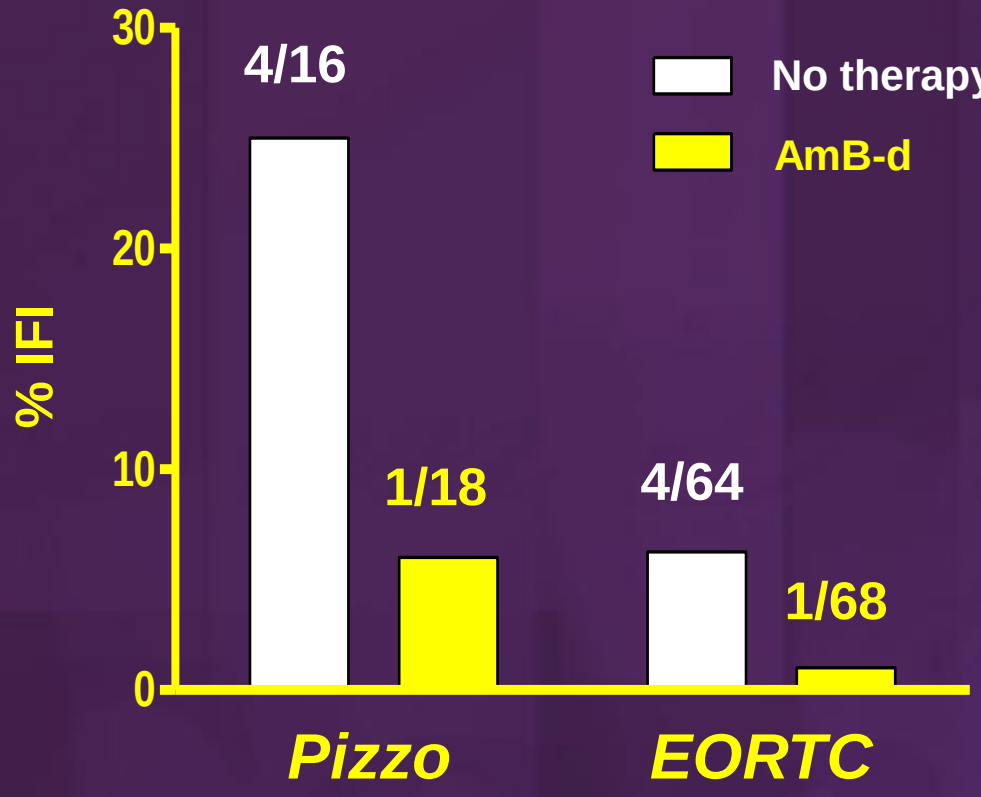
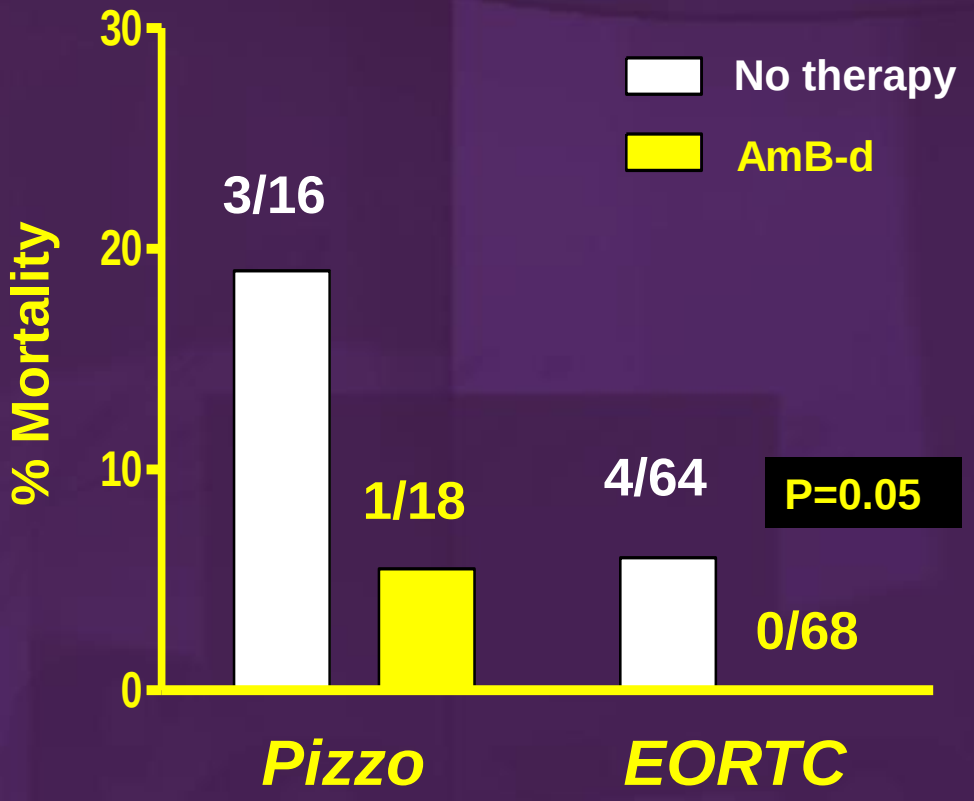
Invasive Fungal Infections (IFI)

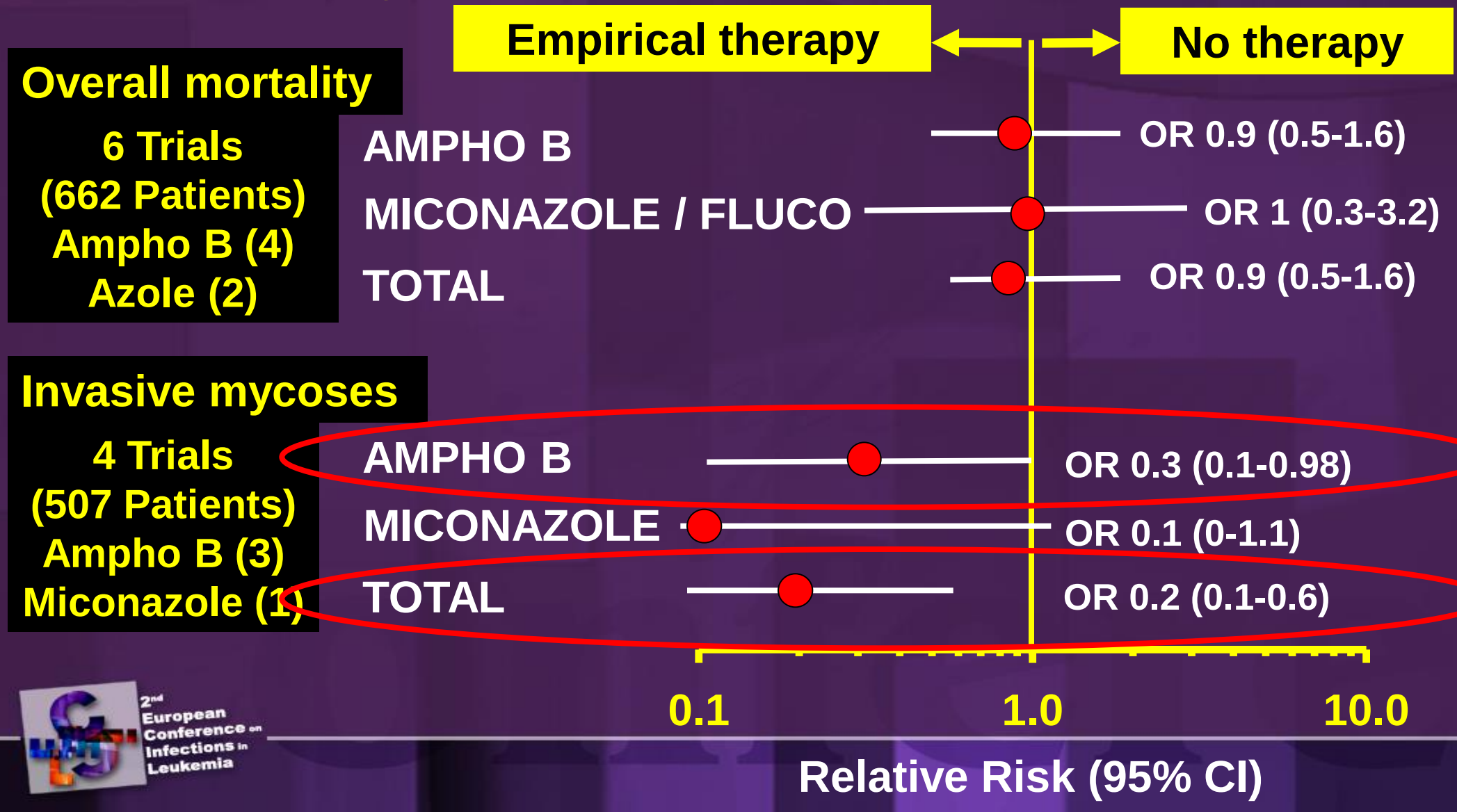


Mortality IFI



Empirical Antifungal Therapy vs. No Therapy: Meta-Analysis

Goldberg et al., 17th ECCMID 2007, Munich, Poster # P963



Empirical Antifungal Therapy vs. No Therapy: Meta-Analysis

Goldberg et al., 17th ECCMID 2007, Munich, Poster # P963

Wingard, AJM, 1987; 83: 1103-10	PLACEBO D1	MICONAZOLE D1	
INVASIVE MYCOSES	8/111 (7%)	1/97 (1%)	P=0.03
ATTRIBUTABLE MORTALITY	4/111 (4%)	0/97 (0%)	P=0.08

COMMENTS: UPFRONT EMPIRICAL ANTIFUNGAL THERAPY on DAY 1 of fever
ALL DOCUMENTED INVASIVE MYCOSES : CANDIDIASIS

Goldstone, BMT, 1994; 14 S5: S15-7	LIPO-AMB D1	LIPO-AMB D3
INVASIVE MYCOSES	1/64 (2%)	1/28 (4%)

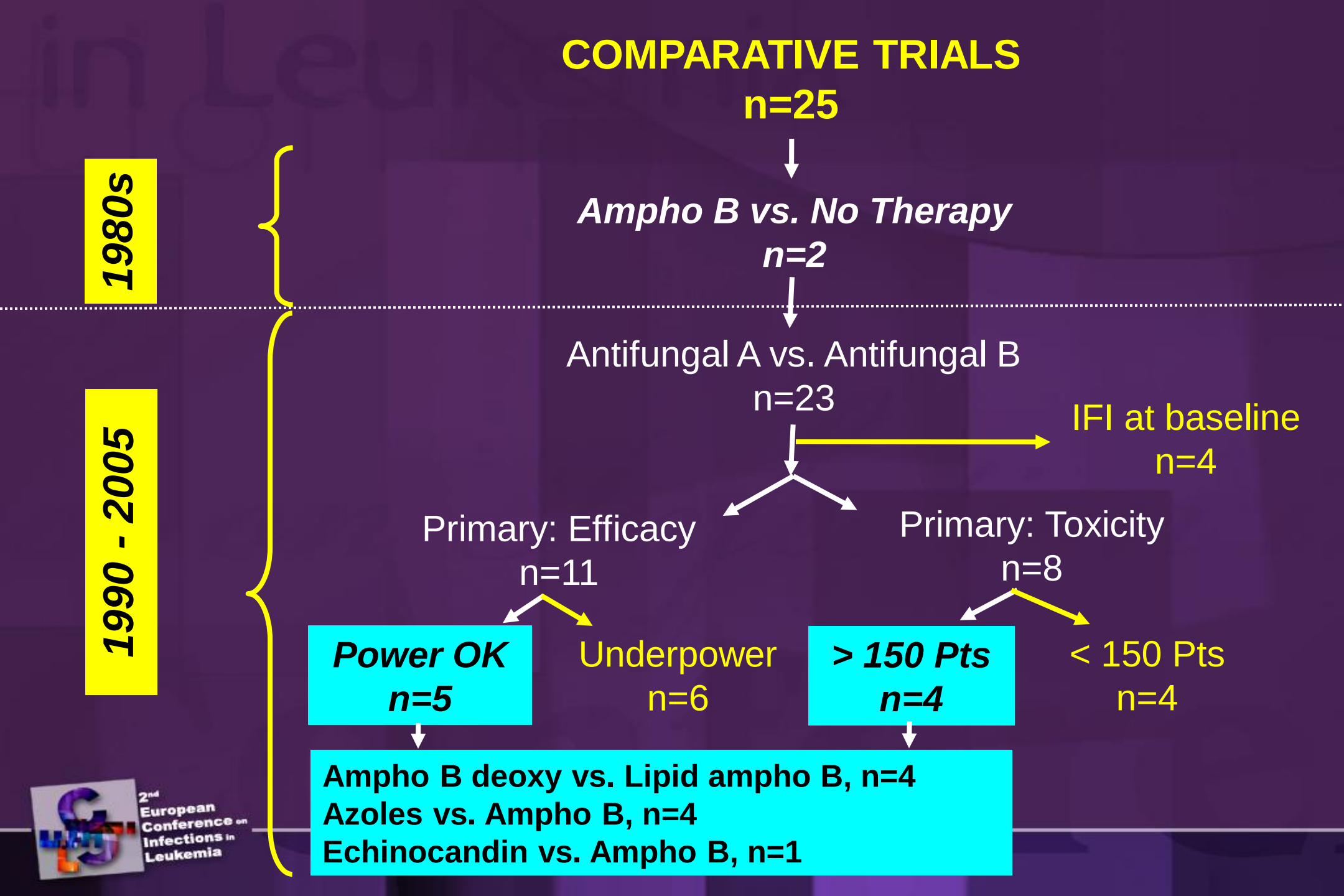
COMMENTS: OPEN DESIGN, LIPO-AMB 2 or 5 mg/kg/d on DAY 1 vs. 3 of fever
PROTOCOL VIOLATIONS, FEW DOCUMENTED IFI

Schiel, Infect, 2006; 34: 118-26	NO RX D4-6	AMB-D +/- 5-FC D4-6	FLUCO D4-6
OVERALL MORTALITY	0/54 (0%)	1/45 (2%)	1/56 (2%)

COMMENTS: COMPLEX OPEN DESIGN WITH 3-STEP INTERVENTION
START ANTIFUNGAL THERAPY ON DAY 4-6 of fever
DOCUMENTED IFI ?

Question # 2

Based on efficacy and safety data, is there evidence supporting the use of the different antifungal agents for empirical therapy in neutropenic cancer patients with persistent fever ?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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	3%	AmB-d 1	2%	NS
	Lipo AmB 3	2%			
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	4%	NS
			Lipo AmB 5	2%	
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)

* *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 Success

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**

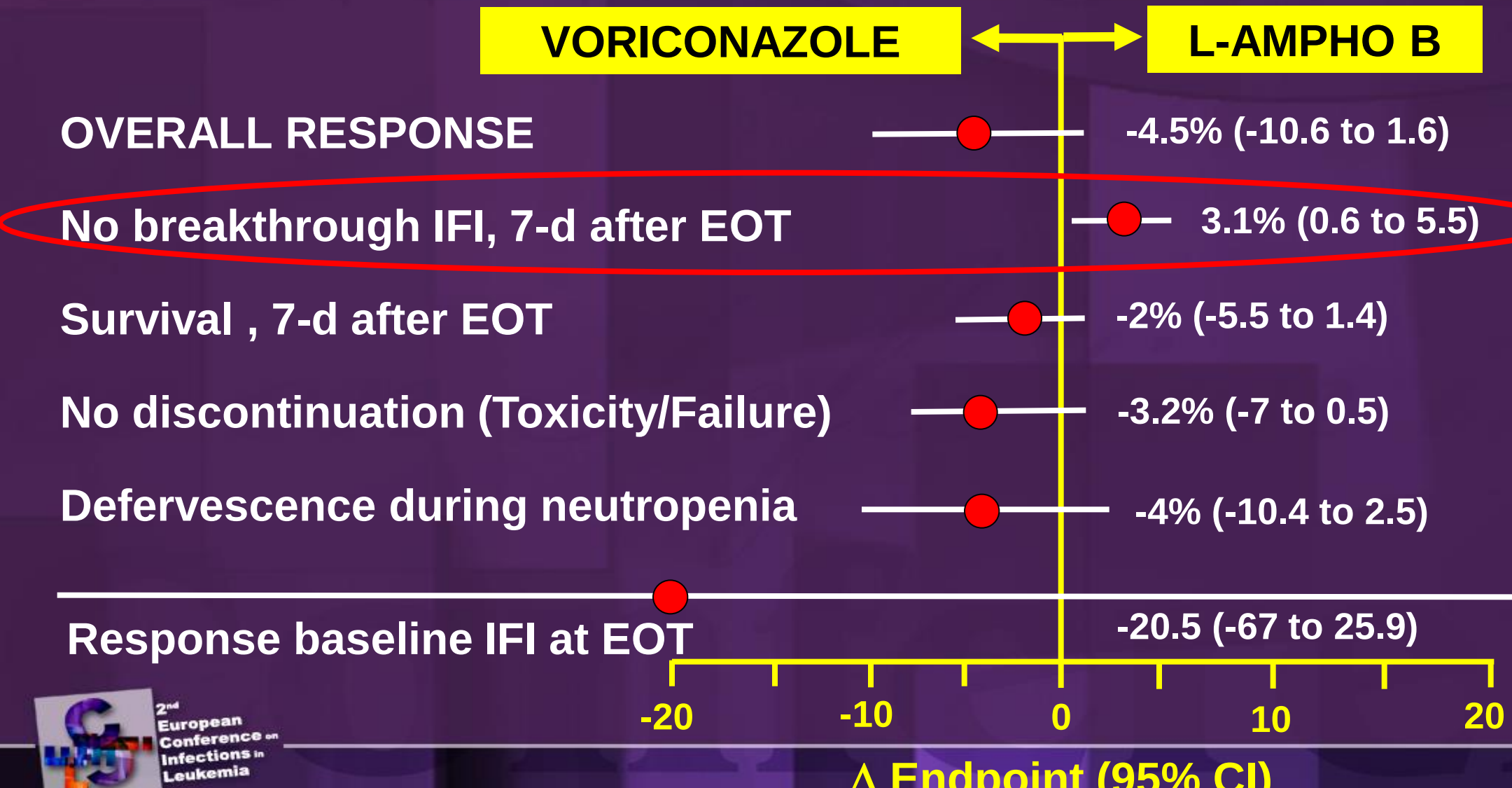
- **HOWEVER, EVIDENCE FOR THESE PRACTICES IS LACKING AND MOST EXPERTS AGREE THAT FURTHER STUDIES ARE NEEDED**

VORICONAZOLE

UPDATE ECIL-2 2007

Voriconazole vs. Liposomal Ampho B : Assessment of Primary and Secondary Endpoints

Walsh et al., NEJM, 2002; 346: 225-34



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UPDATE ECIL-2 2007

Voriconazole vs. Liposomal Ampho B : Should Data on Baseline and Breakthrough IFI be Challenged ?

Jorgensen, Gotzsche, and Johansen, Cochrane Jan. 2006, 1; 1-9

www.thecochranelibrary.com

	VORI (n=415)	LIPO AMB (n=422)	Δ (95%CI), P-value
BASELINE IFI (< 24 h)	13 (3%)	6 (1.5%)	NA, P=0.11
Response	6/13 (46%)	4/6 (67%)	-21% (-67 to 26), P=0.63
BREAKTHROUGH IFI (> 24 h)	8 (1.9%)	21 (5%)	3.1% (0.6 to 5.5), P=0.02
ALL IFI			
Original data	21	27	NR, P=0.46
Cochrane review (Persistent BL + Breakthr.)	15	23	1.8% (-1 to 4.7), P=0.27

Voriconazole vs. Liposomal Ampho B : Should Data on Baseline and Breakthrough IFI be Challenged ?

Response to Cochrane Review by Walsh et al. & Pfizer

Baseline IFI:

- 19/19 diagnosed before the first dose of study drug

Breakthrough IFI:

- 24-h cut-off identical to that of trial L-AmB vs. AmB-deoxycholate
- 29/29 IFI diagnosed > 48 h after the first dose of study drug (mean 13 days for voriconazole and 6 days for L-AmB)

Inappropriate to combine in a post-hoc analysis baseline IFI (study underpowered for evaluation of response) and breakthrough IFI (pre-defined efficacy endpoint)

ITRACONAZOLE

UPDATE ECIL-2 2007

Itraconazole vs. Ampho-Deoxycholate

Boogaerts et al., Ann Intern Med, 2001; 135: 412-22
Schuler et al., Onkologie, 2007; 30: 185-91

Fever > 38 °C during > 3 days + Neutrophils < 0.5 G/L expected > 7 days

↓

Open multicenter 1:1 randomization (stratification: HSCT, Pneumonia)

AMPHO B-DEOXYCHOLATE 0.7-1 mg/kg/d I.V.	ITRACONAZOLE 400 mg D1-2, 200 mg D3-14 I.V. then 400 mg D14-EOT P.O.
Boogaerts's study 60 CENTERS, EUROPE + NORTH AMERICA 1996-1997, PUBL. 2001 **PRIMARY : EQUIVALENT EFFICACY** **Failure therapy > 3 d :** Breakthrough IFI (NOT EORTC-MSG) Death due to any cause Persistent fever > 28 d STOP for toxicity	**Schuler's Study** 27 CENTERS, GERMANY 1999-2001, PUBL. 2007 **PRIMARY : STOP for TOXICITY** **Failure therapy > 3 d :** Breakthrough IFI or progressing pneumonia Death due to IFI (NOT EORTC-MSG) Persistent fever > 28 d STOP for toxicity STOP on investigator's decision

Itraconazole vs. Ampho-Deoxycholate

Boogaerts et al., Ann Intern Med, 2001; 135: 412-22
Schuler et al., Onkologie, 2007; 30: 185-91

	Boogaerts, 2001		*Schuler, 2007*	
	ITRA n=192	AmB-D n=192	ITRA n=81	AmB-D n=81
Defervescence	73%	70%	69%	60.5%
	Δ 3% (-6 to 12)		P < 0.001	
Days to afebrile	7 (1-26)	6 (1-22)	4	3
Breakthrough IFI	3%	3%	6%	6%
Mortality	11%	14%	17%	16%
Due to infection	8%	9%	6%	11%
Creatinine 2x Baseline	5% P < 0.001	24%	4% P < 0.001	41%
STOP FOR TOXICITY	19% P < 0.001	38%	22% P < 0.001	57%
Success	47%	38%	62%	42%
	Δ 9% (1 to 19)		P < 0.001	
Success composite endpoint (Walsh's criteria)	53%	46%	55%	27%
	Δ 7% (-3 to 17)		Δ 29% (14 to 43)	

AMPHO B COLLOIDAL DISPERSION is on the market in some European countries

Ampho B Colloidal Dispersion (ABCD) vs. Ampho B-Deoxycholate

White et al., Clin Infect Dis, 1998; 27: 296-302

	ABCD 4 mg/kg/d (n=98)	AMB-D 1-1.5 mg/kg/d (n=95)	P-value
DEMOGRAPHICS			
Acute leukemia	23%	30.5%	NS
Allo- / Auto-HSCT	45% / 31%	39% / 26%	NS
Neutrophils < 0.1 G/L	89%	88%	NS
RESPONSE			
Overall	50%	43%	NS
Defervescence	53.5%	58%	NS
IFI (Mortality)	3% (1%)	3% (1%)	NS
TOXICITY			
Creat. 2x BL, CyA/Tacrolimus	31%	68%	< 0.001
NO CyA/Tacrolimus	8%	35%	< 0.001
Chills	80%	65%	0.018
Hypoxemia	12%	3%	0.013
DISCONTINUATION	18%	21%	NS

Safety Profile of Different Ampho B Forms

Prentice BJH 1997; White CID 1998; Walsh NEJM 1999-2003-04; Wingard CID 2000; Winston AJM 2000; Boogaerts Ann Intern Med, 2001; Schuler Onkol 2007

	AmB-Deoxy	ABLC	ABCD	Liposomal-AmB
Nephrotoxicity (2x baseline)	24 - 41%	42%	8%	8 - 19%
Cyclosporin/Tacrolimus	68%	NR	31%	NR
Infusion-related AE	36 - 65%	51% (79%)	80%	5 - 52%
Hypoxia	3%	20%	13%	0 - 6%
Hypotension	NR	19%	NR	7%
Discontinuation	7 - 57%	32%	18%	5 - 13%

3. Evidence-Based Recommendations

UPDATE ECIL-2 2007

Indication for Empirical Antifungal Therapy in Persistently Febrile Neutropenic Patients

B II

« Generally recommended. Moderate evidence »

Unchanged grading

(no change in evidence)

2007 UPDATE : 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 [2]	I	I
NEW: ABCD	4 mg/kg	B [2]	I	I
Voriconazole	2x 3 mg/kg iv	B [1,3,4]	I	I
UPGRADE: Itraconazole	200 mg iv	B [1,4]	I	I
AmB deoxycholate	0.5-1 mg/kg	B [2] / D [5]	I	I
Fluconazole	400 mg iv	C [1,4,6]	I	I

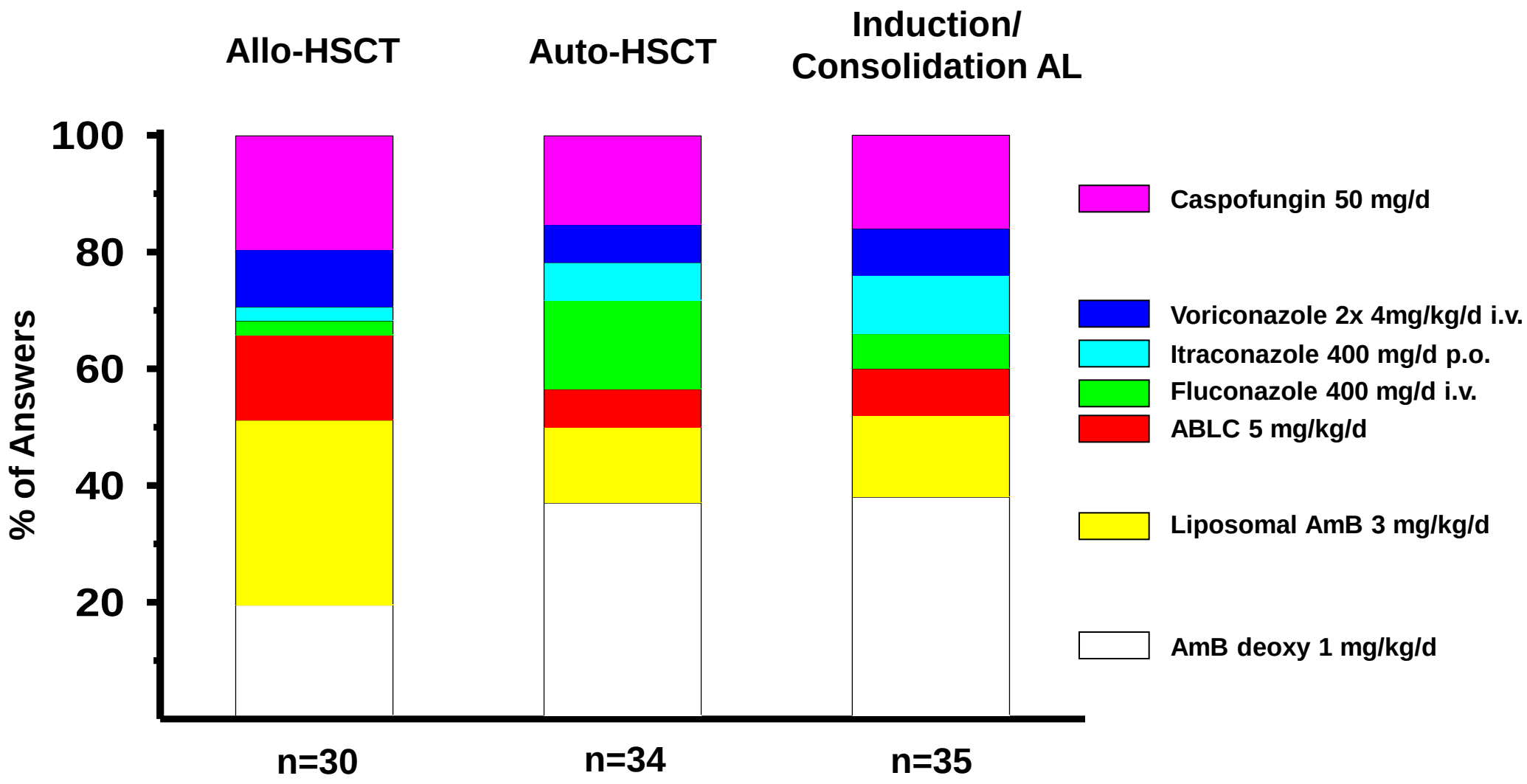
1 No activity against mucorales
2 Infusion-related toxicity (fever, chills, hypoxia)
3 Failed the 10% non-inferiority cut-off when compared with liposomal AmB (and thus not approved by the FDA for this indication), but first-line for aspergillosis, effective therapy for candidiasis, and efficacious for prevention of breakthrough IFI.
4 Activity of azoles empirical therapy for persistent fever may be limited in patients receiving prophylaxis with an agent of the same class.
5 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).
6 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

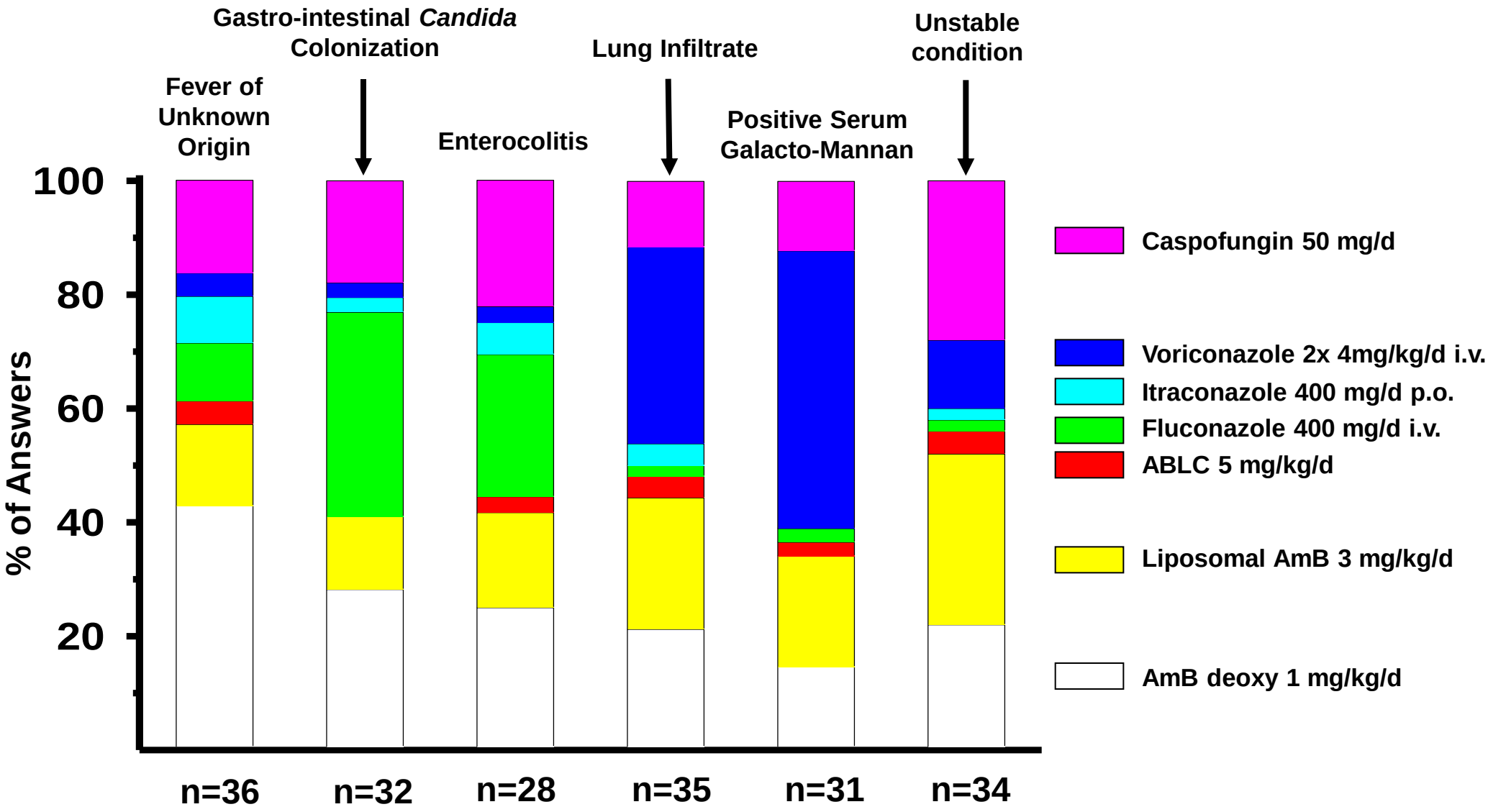
- Data unclear or limited, value of subgroup analyses for efficacy or toxicity ?
- Amphotericin B deoxycholate: high nephrotoxicity
- Itraconazole: data lacking
- Fluconazole: large use of prophylaxis ↑ risk of resistant *Candida* spp., no activity on *Aspergillus*

Perspectives for the Future

Underlying Condition and Choice of Empirical Antifungal Therapy

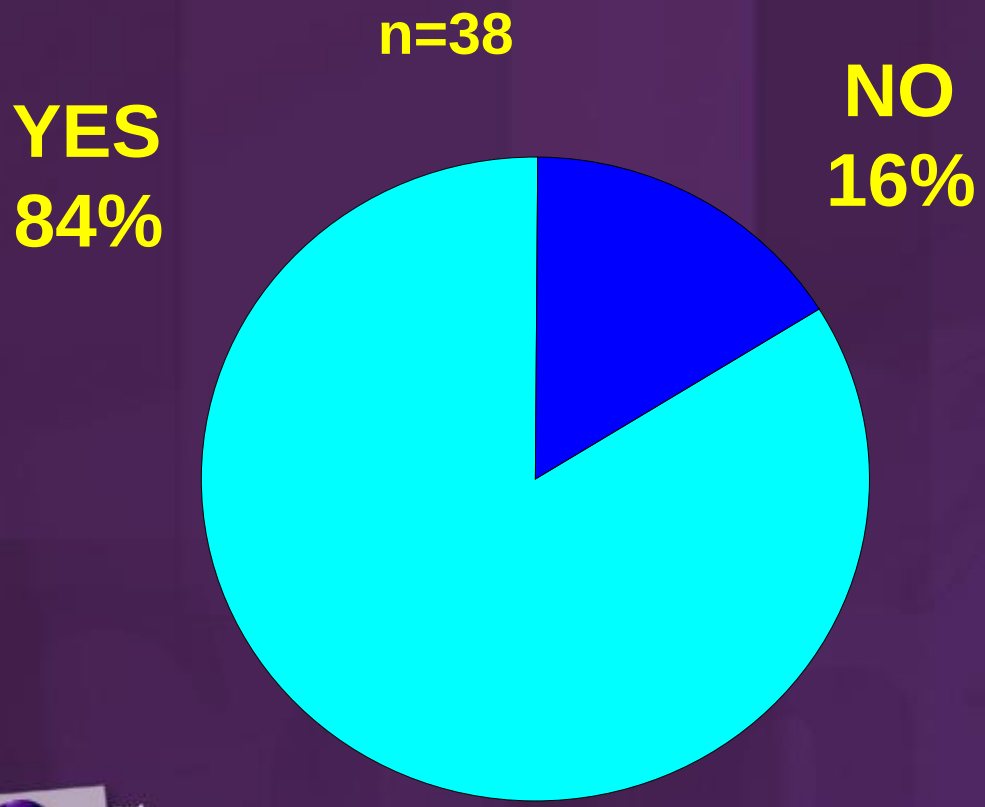


Clinical Presentation and Choice of Empirical Antifungal Therapy



Questionnaire on European Experts' Practices

Are Further Studies on Empirical Therapy Required ?



NEED FOR PREEMPTIVE ANTIFUNGAL STRATEGIES ?

Pre-emptive strategies

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

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