UPDATE ECIL-3 2009

3rd European Conference on Infections in Leukemia

Empirical Antifungal Therapy
2009 Update of ECIL-1 / ECIL-2 Guidelines

O. Marchetti, C. Cordonnier, T. Calandra

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 (VZW)

International Immunocompromised Host Society ICHS

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 2009 Update
EMPIRICAL ANTIFUNGAL THERAPY

1. **Questionnaire:** European experts' practices ECIL1, 2005
2. **Literature review**

   - MEDLINE (Medical Subject Heading terms)
   - COCHRANE
   - PUBMED
   - Manual search in bibliography of reference publications
   - ECIL 1: ICAAC, ECCMID, ASH, ASCO, and EBMT 2002-2005
   - ECIL 3: ICAAC (2007-2009), ECCMID (2008-2009), ASH (2007-2008), ASCO (2008-2009), and EBMT (2008-2009)

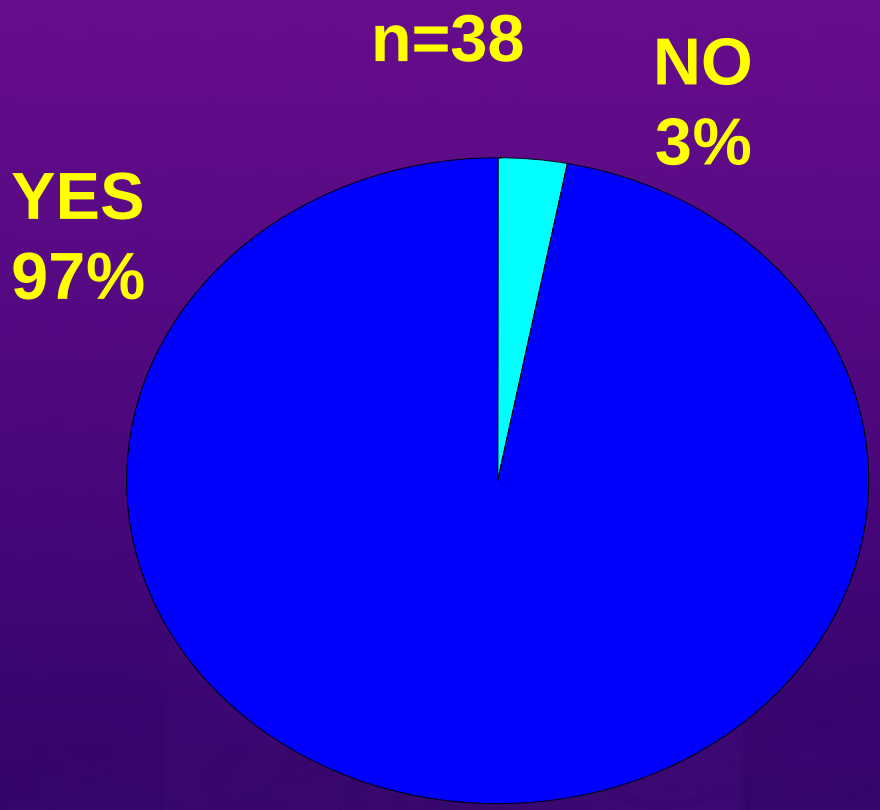
   Analysis of comparative clinical trials

3. **Keywords (MeSH):** neutropenia, agranulocytosis, febrile neutropenia, empirical, antifungal therapy, clinical trials
4. **CDC grading (I-III, A-E)**

1. Questionnaire: Experts' Practices

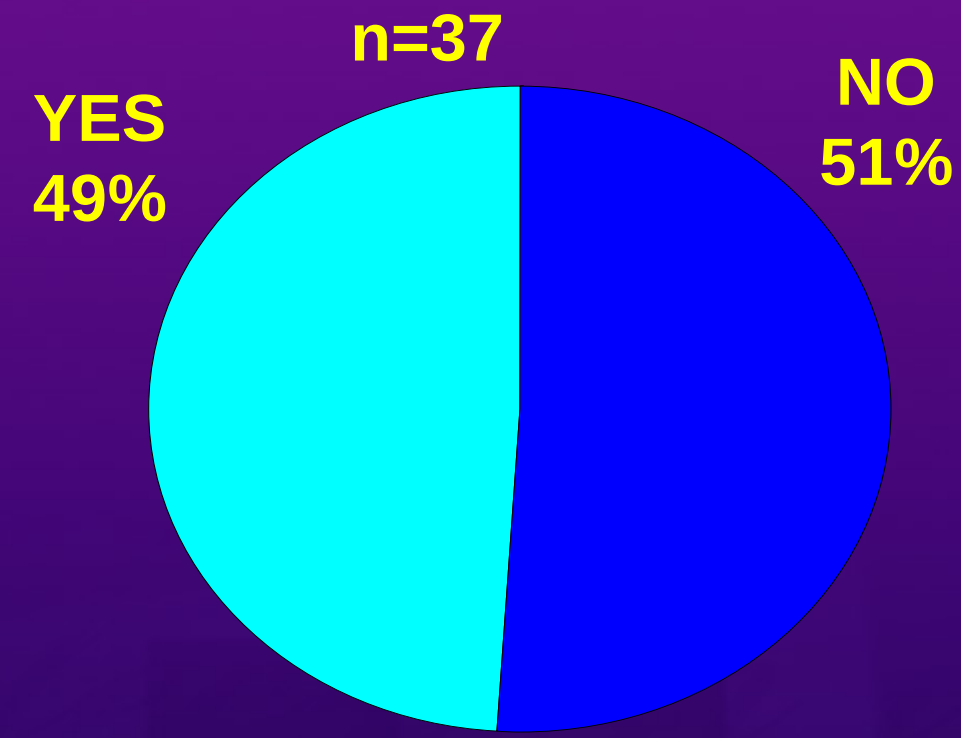
Summer 2005

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

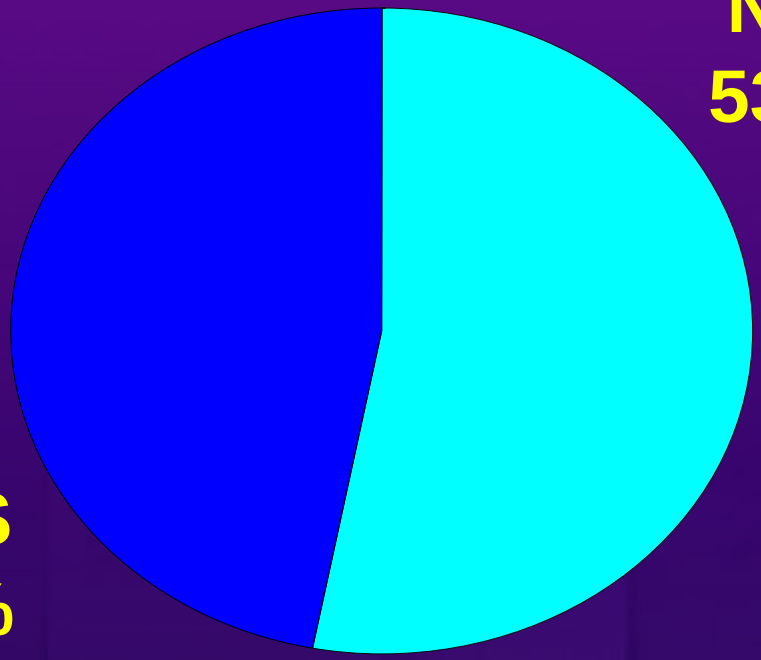
2. Clinical presentation
- FUO: Ampho B deoxycholate
- GI-tract colonization/Enterocolitis: Fluco / AmB-d / Caspo
- Pneumonia/Positive galacto-Mn: Voriconazole
- Clinical unstability: Liposomal AmB or Caspofungin

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

Questionnaire on European Experts' Practices

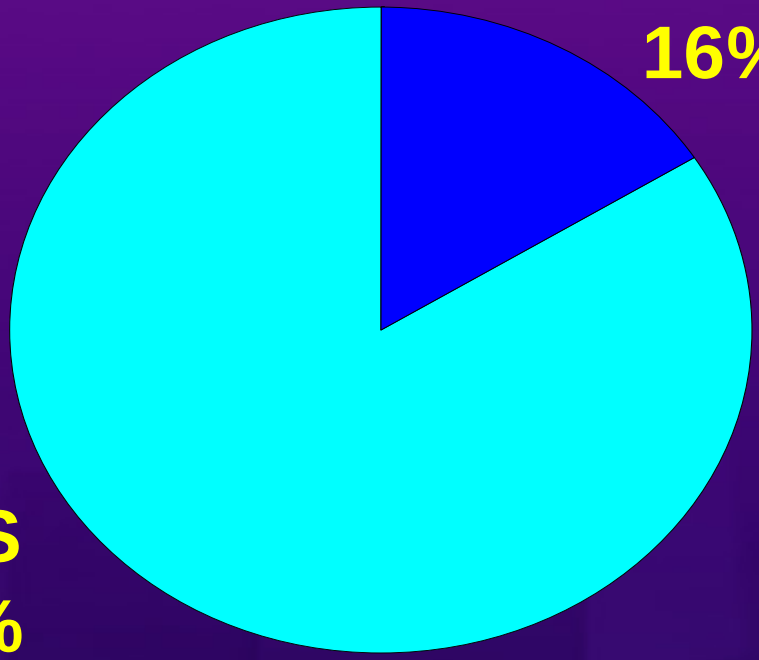
Are Your Choices Evidence-Based ?

n=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

3rd European Conference on Infections in Leukemia

Ampho B Deoxycholate vs. No Therapy

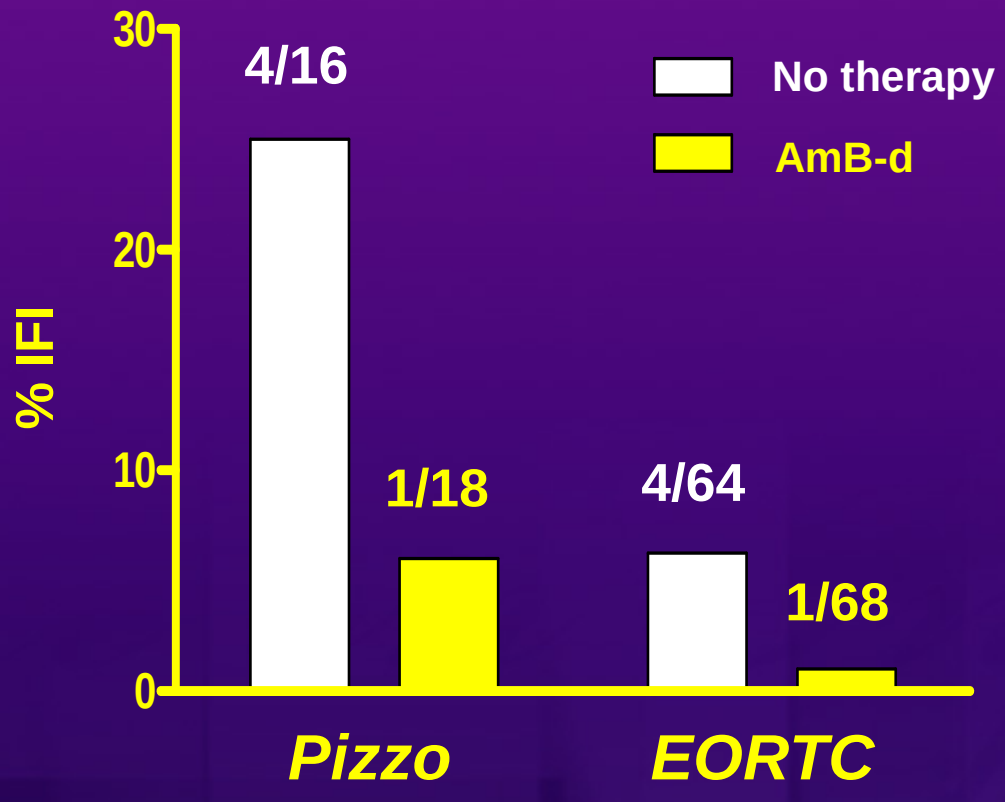
Pizzo, Am J Med, 1982; 72: 101-11
EORTC, Am J Med, 1989; 86: 668-72

1. Inclusion
   - Fever (FUO or CDI) > 38 ℃ 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

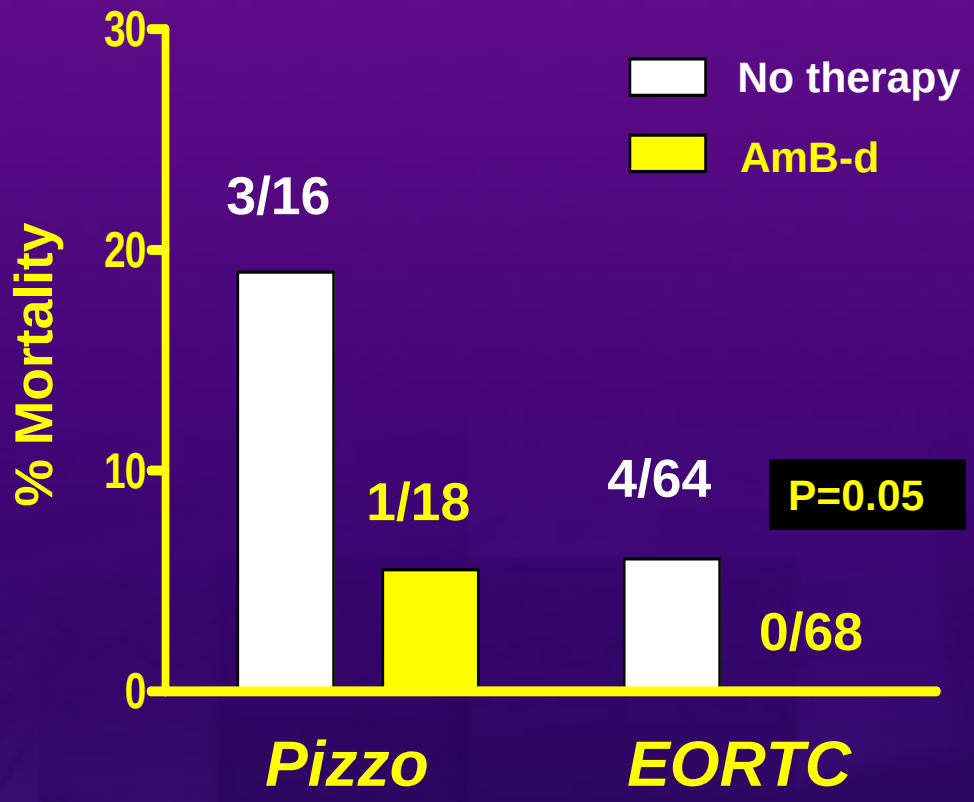
Ampho B Deoxycholate vs. No Therapy

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

Invasive Fungal Infections (IFI)

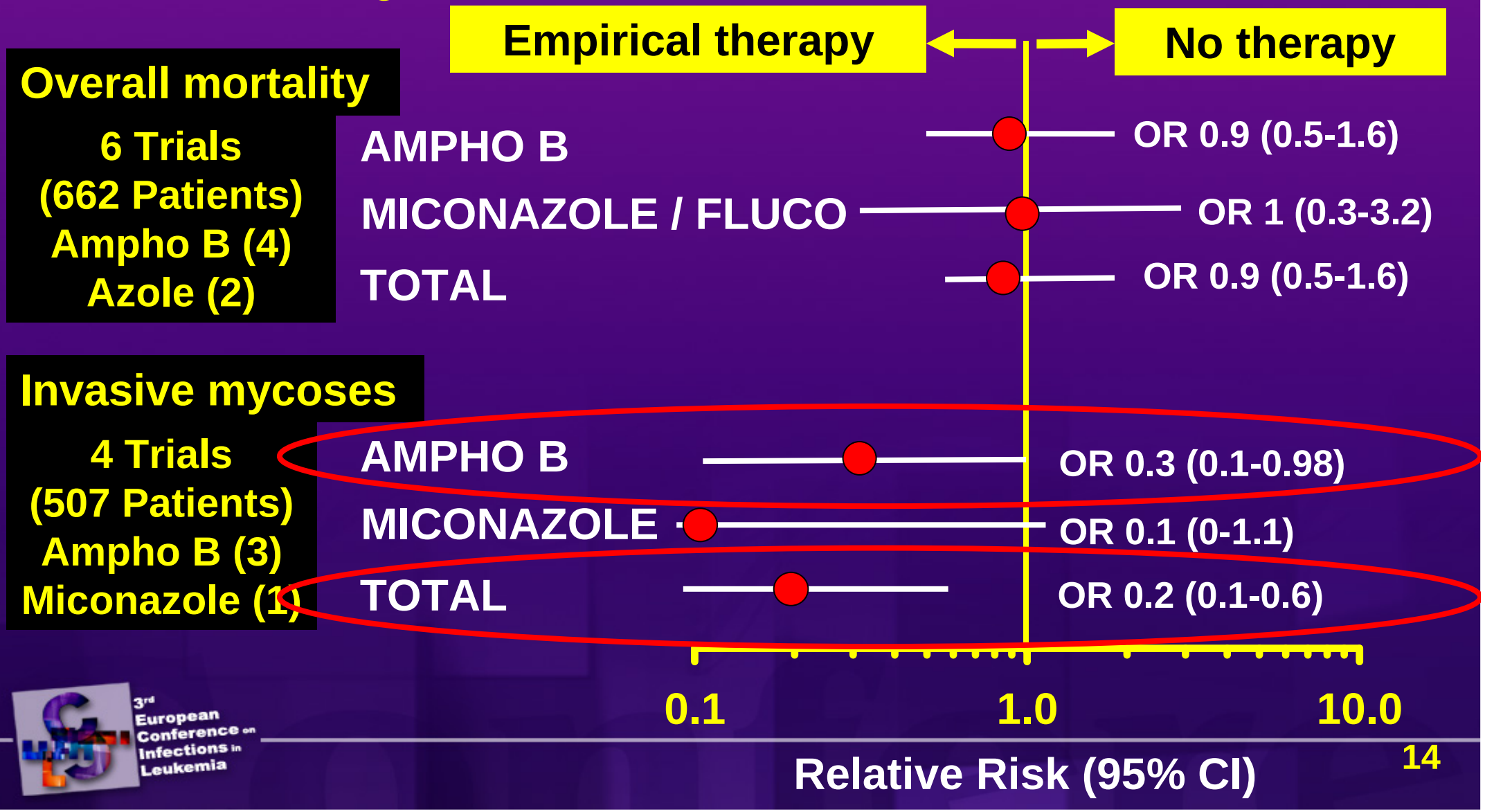


Mortality IFI



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%)	

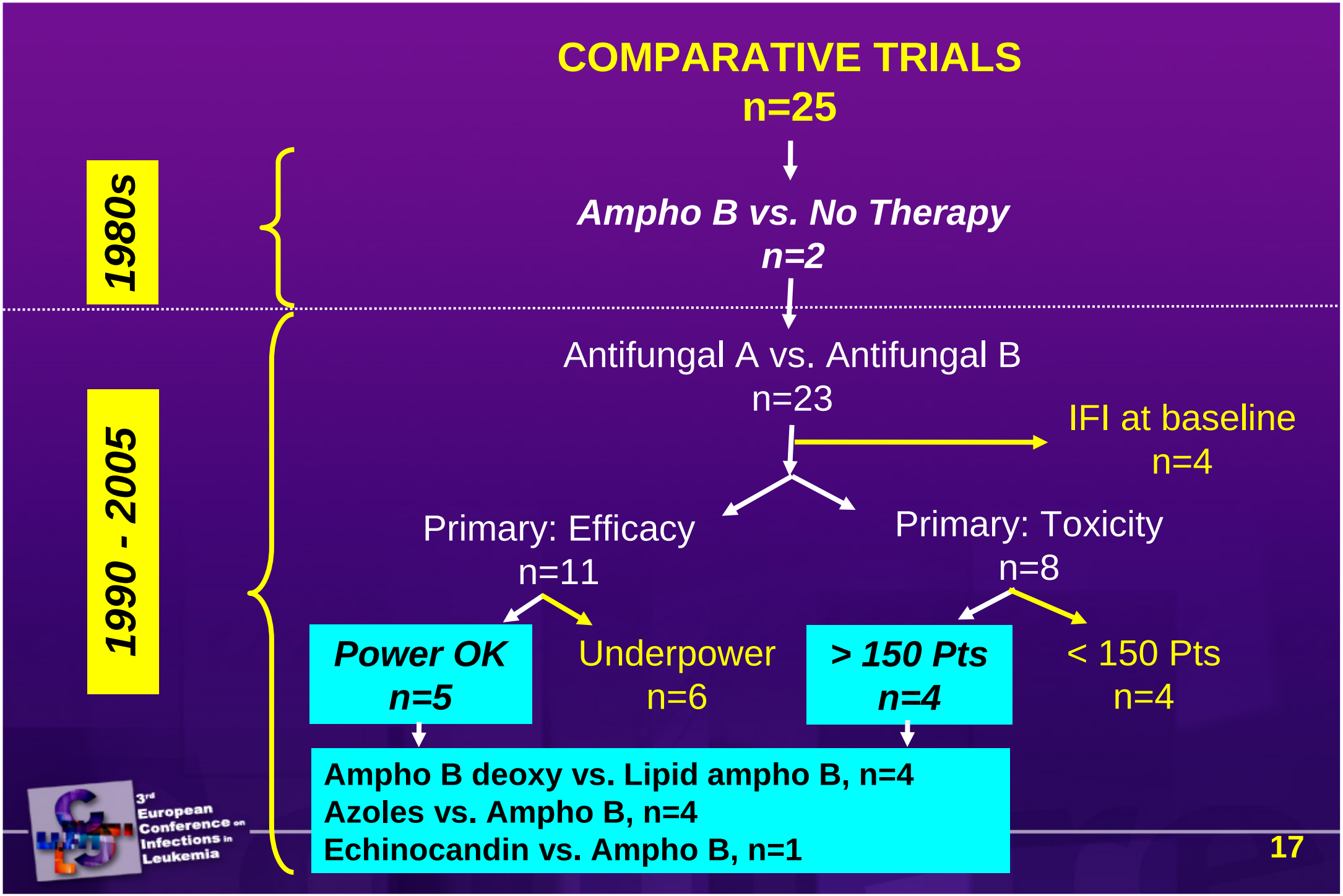
COMMENTS: OPEN DESIGN, LIPO-AMB 2 or 5 mg/kg/d on DAY 1 vs. 3 of fever
PROTOCOL VIOLATIONS, FEW DOCUMENTED IFI

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 ?


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
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
3rd European Conference on Infections in Leukemia
17

Comparison of Two Empirical Antifungal Agents

FUO + > 38 ℃ during > 3-5 days (or relapsing) + Neutrophi ls <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**

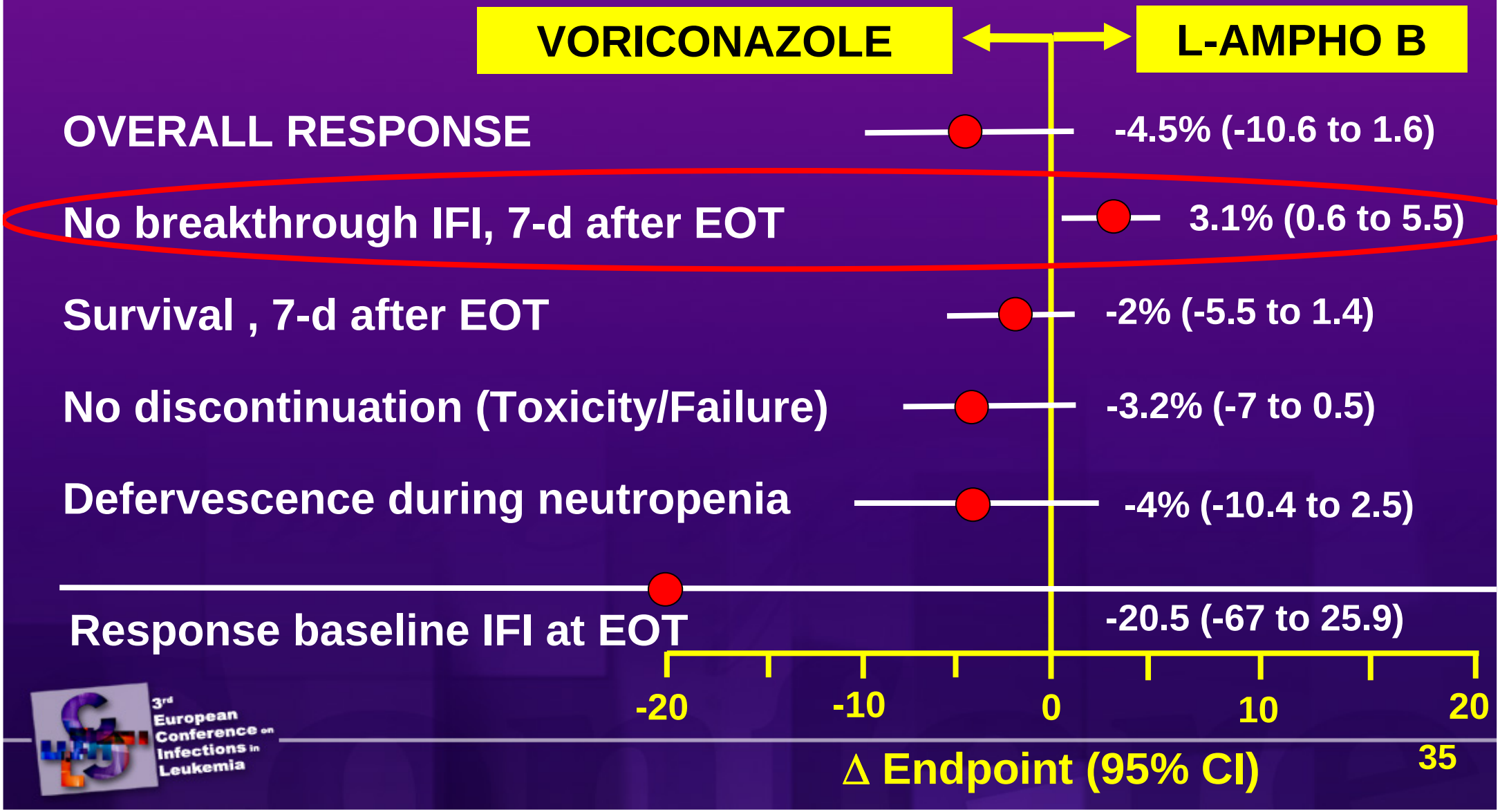
- **HOWEVER, EVIDENCE FOR THESE PRACTICES IS LACKING AND MOST EXPERTS AGREE THAT FURTHER STUDIES ARE NEEDED**

VORICONAZOLE

UPDATE ECIL-2 2007

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

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



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 ℃ during > 3 days + Neutrophils < 0.5 G/L exp ected > 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

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

	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%

Empirical Antifungal Therapy – 2009 UPDATE

Empirical Antifungal Therapy in High-Risk Neutropenic Patients

Publication	Design	Number Pts	Antifungal Agent(s)
Empirical AF therapy vs. no therapy	NO NEW STUDY		
Empirical AF therapy			
Comparison 2 antifungal agents			
Maertens ICAAC 2007	Prospective, multicenter double-blind, randomized, CHILDREN	54 + 25	Caspo vs. Liposomal AmB 2:1
Kubiak ICAAC 2008	Retrospective, multicenter	161 + 173	Caspofungin vs. Micafungin
1 single antifungal agent			
Tamura Leuk-Lymph 2009	Prospective, multicenter, no control arm	277	Micafungin
Ohta IJH 2009	Observational, single center, no control arm	68	Itraconazole IV
Lafaurie CMI 2009	Observational, single center, no control arm	56	Caspofungin

Caspofungin vs. Liposomal AmB for Empirical Therapy in Pediatric Neutropenic Patients with Persistent Fever: a Randomized, Double-Blind, Multicenter Trial

Maertens et al., 47th ICAAC 2007, Chicago, Abs. #M-621

Neutropenic, 2-17y, persistent fever >96h or relapsing fever, 2:1 randomization
Primary endpoint: safety / Secondary: composite efficacy endpoint (5 items)

	Caspofungin 70mg/m^2 D1, then 50mg/m^2 (n=56)	Liposonal AmB 3mg/kg/d (n=25)
Drug-related AE		
Clinical	48%	46%
Laboratory	11%	19%
Serious	2%	12%
Success (composite)	41% (95%CI 28-54)	28% (95%CI 10-46)
Survival 7-d post EOT	100%	100%
Response baseline IFI	0/1	0/0
Absence breakthourgh IFI	100%	96%
No stop for toxicity	91%	84%
Resolution fever	43%	32%

3rd European Conference Infections in Leukemia

Grading for empirical caspofungin or liposomal AmB in pediatric patients: <u>BII, new</u>

Caspofungin vs. Micafungin for Empirical Therapy in Adult Neutropenic Patients with Persistent Fever: a Retrospective Analysis

Kubiak et al., 48th ICAAC 2008, Washington D.C., Abs. #M-2168

3 centers in Boston, USA: retrospective analysis, 338 adults (196 HSCT)
empirical AF therapy for persistent neutropenic fever
2005-6: caspofungin 70 mg D1, then 50 mg/d vs. 2006-7: micafungin 100 mg/d

	Caspofungin (n=161)	Micafungin (n=173)
In-hospital mortality	7.5%	7.4%
Breakthrough IFI	10.6%	13.7%
Invasive aspergillosis	6.8%	6.3%
Invasive candidiasis	1.9%	4.6%

Grading for empirical micafungin : BII, new

Micafungin for Empirical Therapy in Adult Neutropenic Patients: a Prospective Multicenter Non-Comparative Study

Tamura et al., Leukemia and Lymphoma, 2009; 50: 92-100

87 centers, Japan, 2003-5 : prospective non-comparative,
277 adult neutropenic (2/3 HEM, 1/3 HSCT)
empirical AF for persistent fever > 48h (n=88) or AF therapy for possible (n=63) / probable (n=38) / proven (n=8) IFI: micafungin 50-150 mg/d (up to 300 mg)
(197 evaluable for efficacy: protocol violations, lack on inclusion criteria, follow-up < 5d)

Efficacy (composite clinical + microbiological + radiological + serological)	
Empirical	71/88 (80.7%)
Possible IFI	39/63 (61.9%)
Probable IFI	17/38 (44.7%)
Proven IFI	7/8 (87.5%)
Drug-related AE (81% hepatic)	**75/277 (27%)**
Mild	49/277 (17.8%)
Moderate	14/277 (5.1%)
Serious	12/277 (4.3%)

Grading for empirical micafungin : BII, new

UPDATE ECIL-3 2009

Empirical Antifungal Therapy in High-Risk Neutropenic Patients

Publication	Design	Number Pts	Antifungal Agent(s)
Empirical AF therapy			
1 single antifungal agent			
Ohta IJH 2009	Observational, single center, no control arm	68	Itraconazole IV No additional evidence vs. previous randomized trials NO CHANGE: BI
Lafaurie CMI 2009	Observational, single center, no control arm	56	Caspofungin Breakthrough aspergillosis - 3 probable (1 death) - 3 possible NO CHANGE: AI

3. Evidence-Based Recommendations

CDC Grading system

(ECIL-1 and ECIL-2, Updates ECIL-3)

Quality of evidence	Strength of recommendation
I Evidence from at least one well-executed randomized trial	**A** Strong evidence for efficacy and substantial clinical benefit Strongly recommended
II Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments	**B** Strong or moderate evidence for efficacy, but only limited clinical benefit Generally recommended
III Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees	**C** Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (e.g., drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches Optional
	D Moderate evidence against efficacy or for adverse outcome Generally not recommended
	E Strong evidence against efficacy or of adverse outcome Never recommended

2009 UPDATE - Indication for Empirical Antifungal Therapy in Persistently Febrile Neutropenic Patients

B II

« Generally recommended. Moderate evidence »

Unchanged grading

(no change in evidence)

2009 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
ABCD	4 mg/kg	B [2]	I	I
ABLC	5 mg/kg	B [2]	I	I
Itraconazole	200 mg iv	B [1,4]	I	I
Voriconazole	2x 3 mg/kg iv	B [1,3,4]	I	I
NEW: Micafungin	100 mg	B	II	II
AmB deoxycholate	0.5-1 mg/kg	B [2] / D [5]	I	I
Fluconazole	400 mg iv	C [1,4,6]	I	I

* A double-blind, randomized trial comparing caspofungin 50 mg/m^2 (n=56) with liposomal ampho B 3 mg/kg/d (n=25) (published in abstract form) suggests a provisional grading BII for children ; the constitution of a pediatric group specifically addressing antifungal prophylaxis and therapy in children will be considered for 2011 update of ECIL guidelines

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).

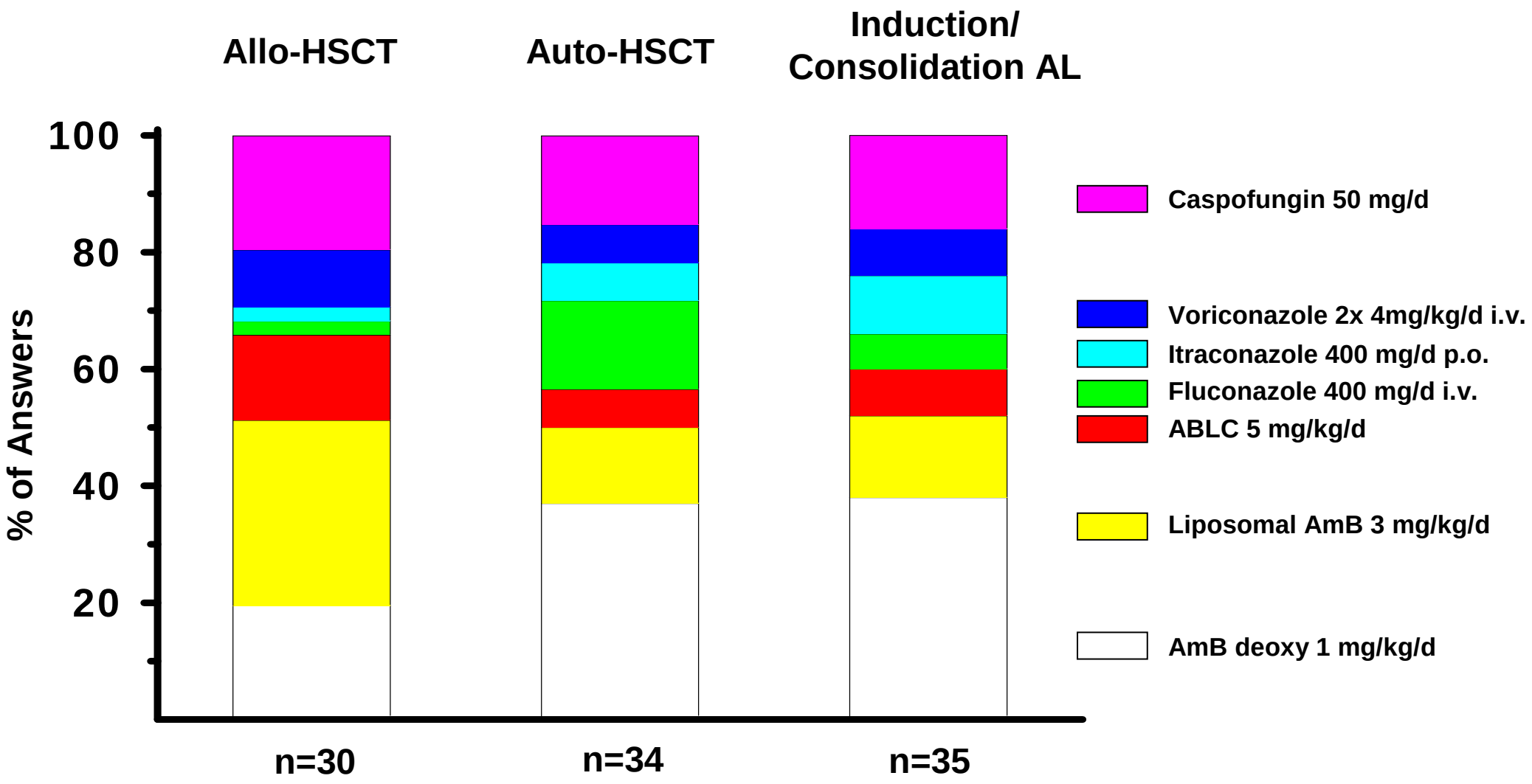
6 No activity against *Aspergillus* and other moulds. Not approved by the FDA for this indication.

Choice of Antifungal Drugs for Empirical Therapy in Allo-HSCT

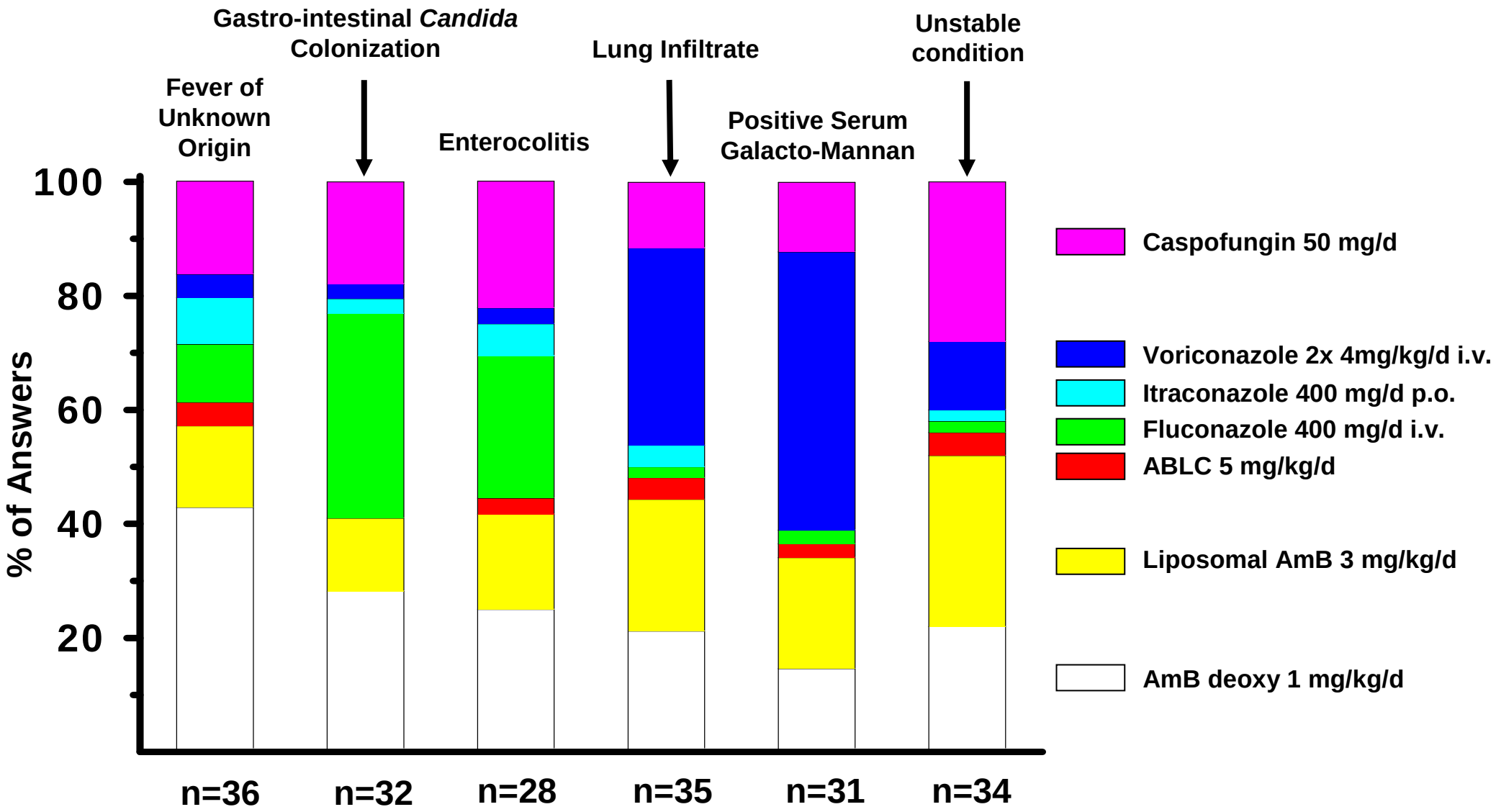
- Data unclear or limited, value of subgroup analyses for efficacy or toxicity ?
- Amphotericin B deoxycholate: high nephrotoxicity
- Itraconazole: data lacking
- Fluconazole: large use of prophylaxis ↑ risk of resistant *Candida* spp., no activity on *Aspergillus*

Perspectives for the Future

Underlying Condition and Choice of Empirical Antifungal Therapy



Clinical Presentation and Choice of Empirical Antifungal Therapy



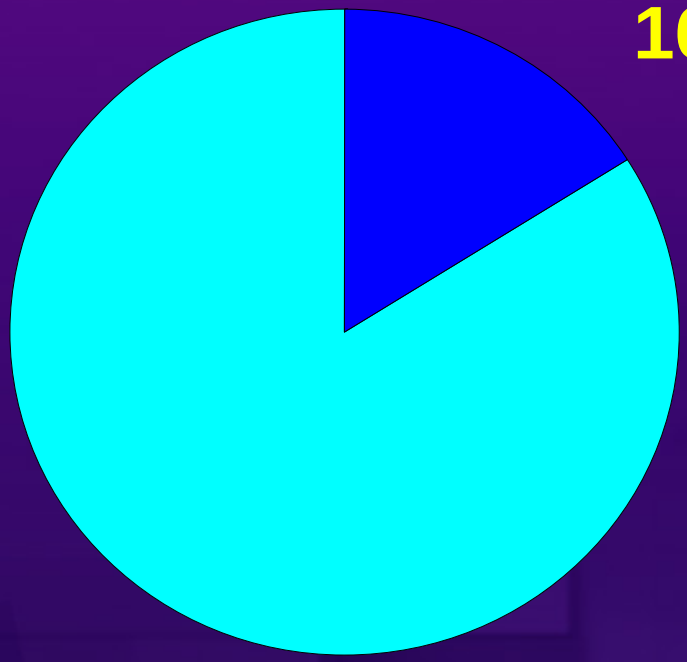
Questionnaire on European Experts' Practices

Are Further Studies on Empirical Therapy Required ?

n=38

YES
84%

NO
16%



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 ?

Pre-Emptive Antifungal Strategies

2009 UPDATE

Empirical Antifungal Therapy

- The early diagnosis of IFI is difficult: delayed treatment of IFI increases mortality
- Consensus guidelines: standard of care for persistent or relapsing fever during neutropenia

BUT,

- Many cases of non-fungal fever result in over-treatment: 60% treated for 5-15% IFI
- Empirical strategy with new drugs expensive
- New non-invasive methods for diagnosis of IFI

Pre-Emptive Antifungal Therapy

Definition of pre-emptive therapy not standardized:

- Different in ICU ≠ hematological patients
- Confusion in the literature on timing of pre-emptive vs. empirical therapy: pre-emptive earlier (i.e. high-risk conditions in absence of fever and clinical symptoms/signs of infection) or later (i.e. high-risk conditions with fever and other clinical symptoms/signs of infection)

Objectives

- ↓ Number of patients treated with the fever-driven empirical approach: treat only the "true" cases, but BEFORE overt invasive fungal infection (IFI)
- ↓ Costs and toxicity

Risks of this alternative strategy compared with the empirical treatment ?

- More deaths ?
- More IFIs ?

What criteria for a pre-emptive strategy ?

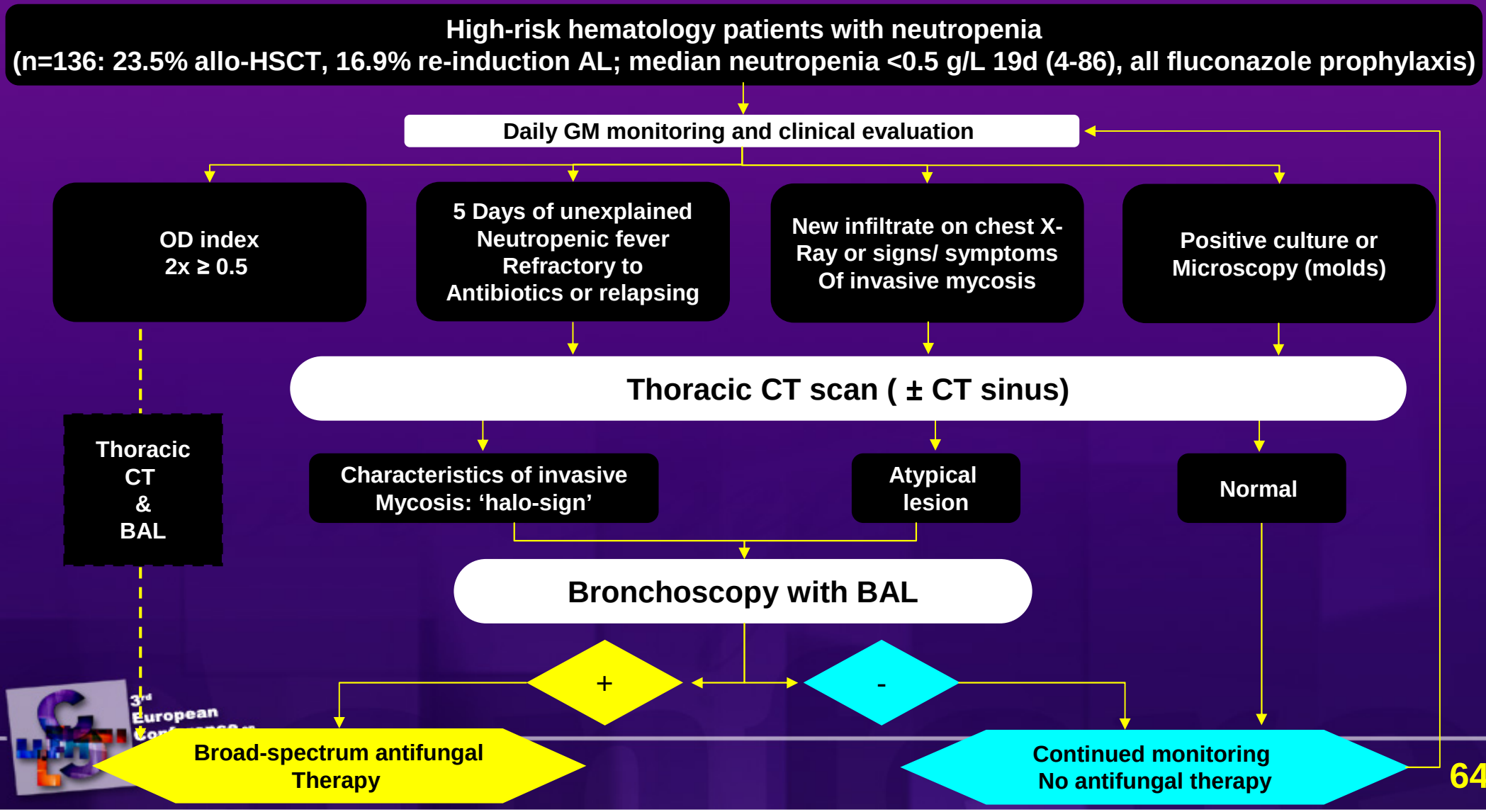
- Clinical +/- radiological +/- microbiological ?

Pre-Emptive Antifungal Therapy in High-Risk Neutropenic Patients

Publication	Design	Number Pts	Antifungal Agent(s)
Maertens CID 2005	Prospective, single center, no control arm	136 high-risk cohort → 19 treated	Liposomal AmB
Cordonnier CID 2009	Prospective multicenter open random. vs. EMP	150 + 143 AL + Auto-HSCT	AmB-deoxy or Liposomal AmB
Hebart BMT 2009	Prospective multicenter open random. vs. EMP	207 + 196 Allo-HSCT	Liposomal AmB
Girmenia JCO 2009	Observational, « real-life » in single center	74 persistent fever → 49 treated	Voriconazole or Liposomal AmB
Barnes JCP 2009	Observational, « real-life » in single center	125 high-risk neutropenic fever	Caspo / L-AmB / Vori
Dignan BMT 2009	Observational, « real-life » in single center	53 persistent fever → 17 treated	Caspofungin → L-AmB or Vori
Aguilar-Guisado BMT 2009	Observational, « real-life » in single center	66 persistent fever → 26 treated	4 different drugs
Riva ICAAC 2008	Observational, « real-life » in single center	143 persistent fever	AmB-deoxy or Liposomal AmB

Galactomannan and CT-Based Pre-Emptive Antifungal Therapy: Prospective Feasibility Study

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



Galactomannan and CT-Based Pre-Emptive Antifungal Therapy: Prospective Feasibility Study

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

4'170 galactomannan measurements: median 28 (range 5-96)/patient

117 FEVER, 58 (49.6%) qualified for empirical antifungal therapy [30 (25.6%) for persistent fever and 28 (23.9%) for relapsing fever]: only 9 (7.7%) preemptive lipo-AmB
19 NO FEVER: 10 preemptive liposomal AmB for positive galactomannan

Preemptive liposomal AmB 5 mg/kg/d in 19 episodes:
- Galactomannan trigger in 16, persistent fever + CT-scan trigger in 3
- 7 proven inv. aspergillosis, IA (6 died, 2 due to IA), 12 probable IA (1 died, not IA)
- 3-month survival in IA 63.1% (76.9% if HEM remission, 30% if HEM refractory)

No antifungal therapy in 117 neutropenic episodes:
- 2 *C. glabrata* breakthrough fungemia, 1 disseminated zygomycosis, no IA
- 9 deaths (1 due to zygomycosis)

Empirical vs. Pre-Emptive Antifungal Therapy for High-Risk, Febrile Neutropenic Patients (PREVERT): Multicenter, Open-Label Randomized Trial

Cordonnier et al., Clin Infect Dis, 2009; 48: 1042-51

Prospective, 12 French centers, 2003-6 in adult, hematological cancer, myeloablative chemotherapy or auto-HSCT, expected neutropenia <0.5 G/L during >10 D, no previous IFI

↓

Stratified (center / chemotherapy / prophylaxis)
randomization strategy 1:1 applied from day 4 to day 14 of fever

Empirical Antifungal Rx

Fever-driven

↓

AmB-deoxy (1mg/kg/d) if Cr-Cl > 60 or 40-59 ml/min and NO nephrotoxic agents
Liposomal AmB (3mg/kg/d) if Cr-Cl 40-59 + nephrotoxic agent or Cr-Cl <40 ml/min

Pre-Emptive Antifungal Rx

If pneumonia, septic shock, skin lesions, acute sinusitis/orbital signs, unexplained CNS signs, hepatosplenic abscesses, grade 3-4 mucositis, severe diarrhea, *Aspergillus* colonization, or ≥ 1x GM Ag ≥ 1.5 (2x/week)

↓

AmB-deoxy (1mg/kg/d) if Cr-Cl > 60 or 40-59 ml/min and NO nephrotoxic agents
Liposomal AmB (3mg/kg/d) if Cr-Cl 40-59 + nephrotoxic agent or Cr-Cl <40 ml/min

PRIMARY ENDPOINT: SURVIVAL 14 D AFTER RECOVERY NEUTROPENIA (60 D if no recovery), expected 90%, NON-INFERIORITY IF D < 8% (228 pts needed in each arm)
SECONDARY ENDPOINT: OCCURRENCE OF PROVEN/PROBABLE IFI

Empirical vs. Pre-Emptive Antifungal Therapy for High-Risk, Febrile Neutropenic Patients (PREVERT)

Cordonnier et al., Clin Infect Dis, 2009; 48: 1042-51

Reason for starting antifungal therapy

Days fever onset to antifungal therapy

Days antifungal therapy

Table 3. Antifungal therapy in the intention-to-treat population (n = 293).

End point	Empirical treatment group	Preemptive treatment group	P^a
Antifungal treatment	92/150 (61.3)	56/143 (39.2)	<.001
Reason for starting antifungal treatment[b]			
Isolated fever between day 4 and day 14 after antibacterial treatment initiation	55 (59.8)	1 (1.8)	<.001[c]
Pneumonia	6 (6.5)	26 (46.4)	
Severe mucositis	8 (8.7)	10 (17.9)	
Isolated fever beyond day 14	11 (12.0)	7 (12.5)	
Septic shock	5 (5.4)	3 (5.4)	
Positive result of galactomannan antigen test	2 (2.2)	3 (5.4)	
Skin lesion	2 (2.2)	2 (3.6)	
Sinusitis or periorbital inflammation	0 (0.0)	3 (5.4)	
Neurological symptoms	2 (2.2)	0 (0.0)	
Diarrhea	1 (1.1)	1 (1.8)	
Duration of fever before antifungal treatment,[b] median days (IQR)	7 (5–11)	13 (6–17)	<.01
Duration of fever after antifungal treatment,[b] median days (IQR)	9 (4–15)	7 (5–13)	NS
Duration of antifungal treatment, mean days ± SD			
Any antifungal agent	7.0 ± 8.5	4.5 ± 7.3	<.01
High-cost antifungal agents (liposomal AmB, caspofungin, or voriconazole)	3.7 ± 7.6	2.6 ± 5.8	NS
Low-cost antifungal agents (AmB deoxycholate)	3.5 ± 5.2	2.0 ± 4.6	<.01
Cost of antifungal drugs, 2005 €			
Mean ± SD	2252 ± 4050	1475 ± 3329	<.001
Range	0–20,726	0–18,500	
Estimated cost of antifungal drugs if liposomal AmB had been used instead of AmB deoxycholate, 2005 €			<.001
Mean ± SD	4261 ± 4760	2509 ± 4099	

Empirical vs. Pre-Emptive Antifungal Therapy for High-Risk, Febrile Neutropenic Patients (PREVERT)

Cordonnier et al., Clin Infect Dis, 2009; 48: 1042-51

Primary Endpoint: Survival

Secondary Endpoint: Invasive fungal infection (IFI)

Total days fever

Table 2. Efficacy end points in the intention-to-treat 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	…	

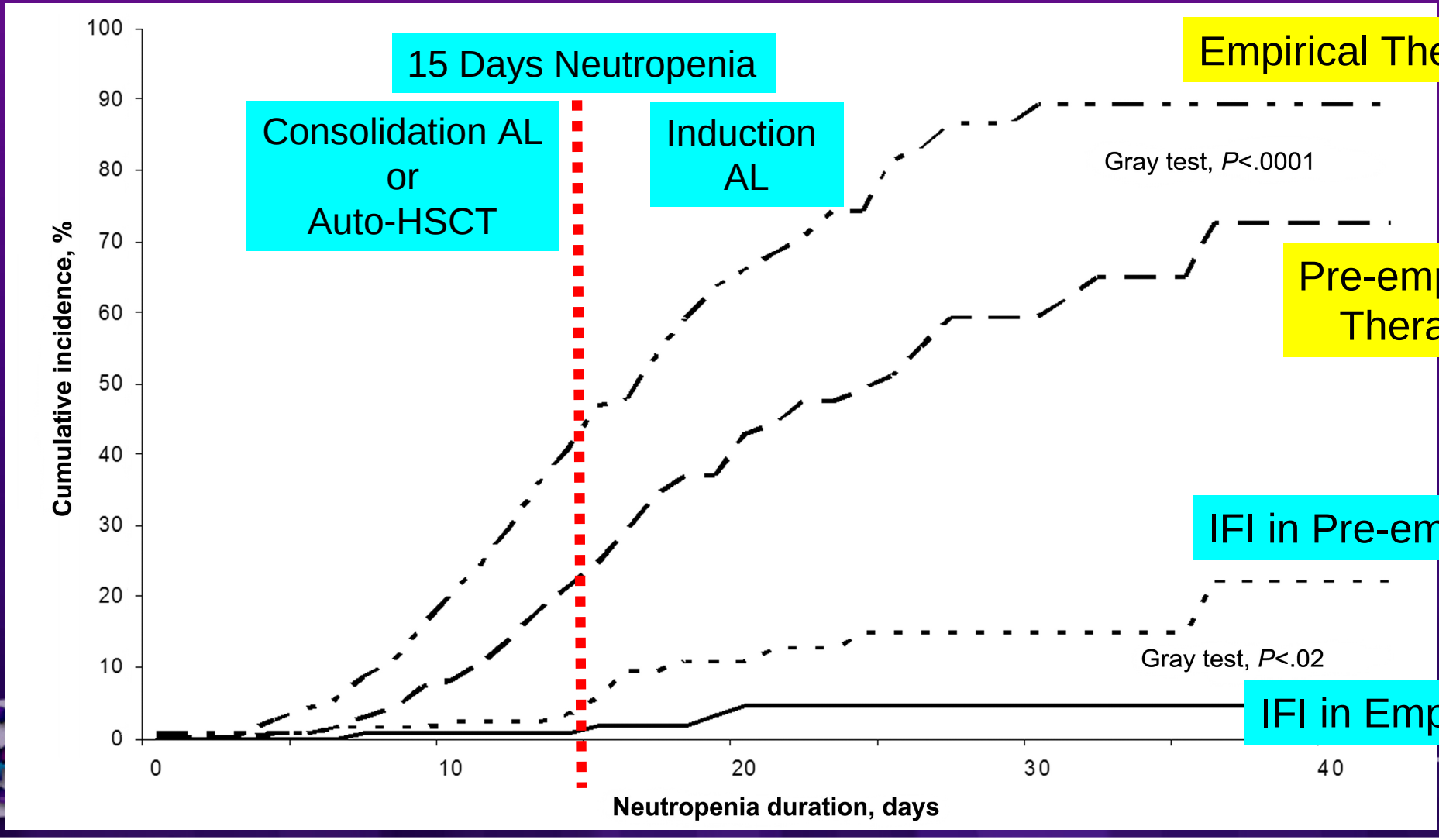
NOTE. Data are no. (%) of patients, unless otherwise indicated. IFI, invasive fungal infection; IQR, interquartile range; NS, not significant.

[a] By Cochran-Mantel-Haenszel test for qualitative variables; by Wilcoxon sum-rank test for skewed quantitative variables.

[b] Excludes 14 patients without fever (8 in the empirical treatment group and 6 in the preemptive treatment group).

Empirical vs. Pre-Emptive Antifungal Therapy for High-Risk, Febrile Neutropenic Patients (PREVERT)

Cordonnier et al., Clin Infect Dis, 2009; 48: 1042-51



PCR-Based Pre-Emptive Antifungal Therapy in Allo-HSCT: A Multicenter Randomized Study

Hebart et al., Bone Marrow Transplant, 2009; 43: 553-61

409 allo-HSCT, fluconazole prophylaxis, 100-day follow-up

↓

Randomization

Empirical antifungal therapy
(n=211, ITT 207)

↓

Persistent fever >5 d:
Lipo Ampho B 3 mg/kg/d
(day 30: n=64/207, 30.3%)

↓

30-d proven IFI 8/207, 3.9%
30-d mortality 13, 6.3%
(5/207 due to IFI, 2.4%)

PCR monitoring
(n=198, ITT 196)

↓

1x PCR+ OR persistent fever >5 d:
Lipo Ampho B 3 mg/kg/d
(day 30: n=89/196, 45.4%, p=0.003)

↓

30-d proven IFI 7/196, 3.6% (NS)
30-d mortality 4, 1.5% (p=0.046)
[1/198 due to IFI, 0.5% (p=0.21)]

UPDATE ECIL-3 2009

Clinically-Driven Diagnostic Antifungal Approach in Neutropenic Patients: a Prospective Feasibility Study

Girmenia C et al., J Clin Oncol, 2009 Oct 19. [Epub ahead of print]

Observational 1-center experience, 2006-7, AL / auto-HSCT pts (n=146),
220 neutropenic episodes (NE) after intensive chemoth., 159 febrile episodes (FE)

↓

Baseline Diagnostic Work-Up (BDWU) at onset of fever:
3 sets of blood cultures + other clinically indicated investigations

↓

Persistent Fever ≥ 4 d or Relapsing Fever or « Clinical Suspicion » of IFI

↓

Intensive Diagnostic Work-Up (IDWU):
Galactomannan on 3 consecutive days + chest CT-scan +
other clinically indicated investigations

Antifungal therapy if:
Positive BDWU or IDWU (i.e. proven-probable-possible IFI)
or empirically for persistent fever + « clinical deterioration »

Clinically-Driven Diagnostic Antifungal Approach in Neutropenic Patients: a Prospective Feasibility Study

Girmenia et al., J Clin Oncol, 2009, in Press

OBSERVED ANTIFUNGAL THERAPY Diagnostic-driven approach Empirical fever-driven	48 / 159 (30.2%) febrile episodes 47 / 159 (29.6%) 1 / 159 (0.6%)
ESTIMATED empirical fever-driven antifungal therapy (standard of care recommended by guidelines)	84 / 159 (52.8%) febrile episodes
ESTIMATED REDUCTION OF ANTIFUNGAL USE IN DIAGNOSTIC-DRIVEN VS. EMPIRICAL FEVER-DRIVEN APPROACH	- 36 / 159 (- 22.6%) febrile episodes

Clinically-Driven Diagnostic Antifungal Approach in Neutropenic Patients: a Prospective Feasibility Study

Girmenia et al., J Clin Oncol, 2009, in Press

	3-Month Mortality
Overall	36* / 146 pts. (24.6%)
Cancer	15.1%
Bacterial infection	4.1%
IFI	2.7%
Other	2.7%
IFI	17** / 49 (34.6%)
Possible IFI	3/16 (23%)
Proven/probable IFI	14/33 (42.4%)
Proven/probable IA	10/27 (37%)
Proven zygomycosis	3/3 (100%)
Candidemia	1/3 (33.3%)

* 7 Autopsies

** 4 attributed to IFI
10 IFI active at time of death, but primary cause refractory leukemia

Median days fever onset to antifungal therapy:
- IFI, survived 5.2 days (1-9)
- IFI, died 5.8 days (1-15)
- Only 1 zygomycosis untreated, died 6 d after fever onset

UPDATE ECIL-3 2009

Comments

A pre-emptive antifungal strategy is “FEASIBLE”

- Clinical + GM/CT-scan based pre-emptive: overall survival as with empirical
- Decreased use of antifungal therapy vs. empirical
- Risk of increased occurrence of IFI (*Aspergillus, Candida*) vs. empirical therapy, especially in patients with neutropenia during more than 15 days: prognostic impact of IFI ?
- Potential for early therapy of IFI in absence of fever with pre-emptive approach (missed by fever-driven empirical approach)
- No grading of evidence/recommendation for pre-emptive due to the lack of defined standard criteria and variability of results among studies

Comments (Cont'd)

UPDATE ECIL-3 2009

Parameters possibly influencing the results of different pre-emptive strategies:

- Patient population / duration of neutropenia
- Local epidemiology of IFI: environment, hospital protective measures
- Timing and type of microbiological and radiological investigations : monitoring vs. clinical-/fever-driven (grading of recommendations for fungal markers)
- Risks of diagnostic work-up
- Drug for pre-emptive antifungal therapy (prophylaxis ?) / Comparative strategy / Timing of antifungal therapy
- Further prospective randomized studies with a well-defined design are needed:
  - To validate clinical, microbiological, radiological criteria used for the strategy
  - To assess the cost-effectiveness of pre-emptive therapy