2nd European Conference on Infections in Leukemia

2007 update of the ECIL-1 guidelines for Antifungal therapy in leukemia patients

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Background

- Despite recent advances in antifungal therapy there is still a high failure rate in invasive aspergillosis and a 30 to 40% 3-month mortality rate in both candidemia and aspergillosis.

- In the past decades few options were available and there was no place to discuss the best primary or salvage therapy.

- With the development of new agents and strategies, there is now a need for guidelines.

Questions

- What is the optimal
  - first line antifungal therapy of candidemia / aspergillosis?
  - second line antifungal therapy of candidemia / aspergillosis?
  - duration of antifungal therapy in candidemia / aspergillosis?
- Should *in vitro* susceptibility testing be recommended to guide the choice of antifungals in candidemia / aspergillosis?
- Current indications for combination therapy in candidemia / aspergillosis ?

Methods

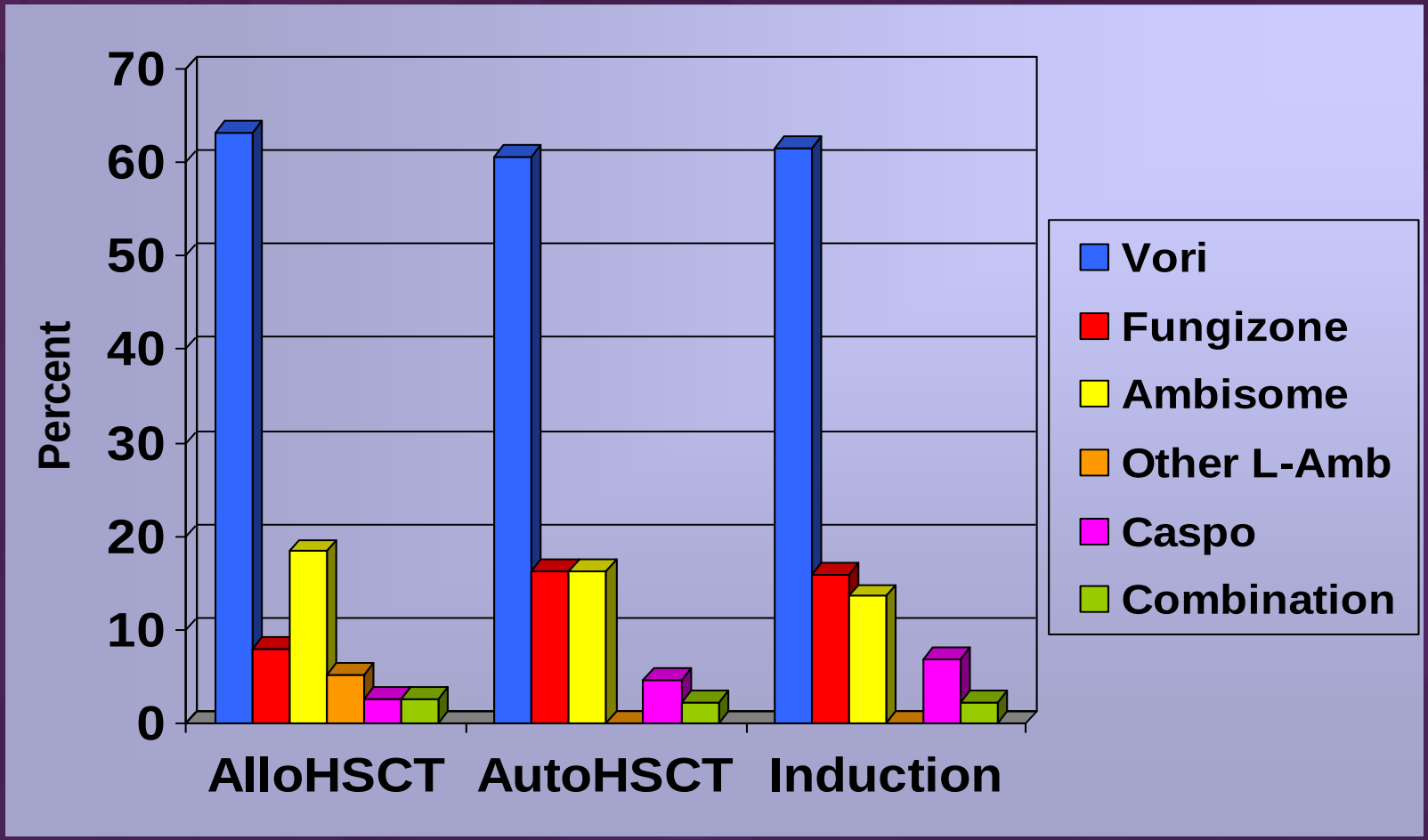
- Questionnaire on practice in Europe
- Literature review
  - Pubmed
  - Cochrane
  - ICAAC, ECCMID, ASH, ASCO, and EBMT
- CDC grading

Aspergillosis

Questionnaire

Summer 2005

Questionnaire on current practice (38 responses)
First line therapy in invasive aspergillosis



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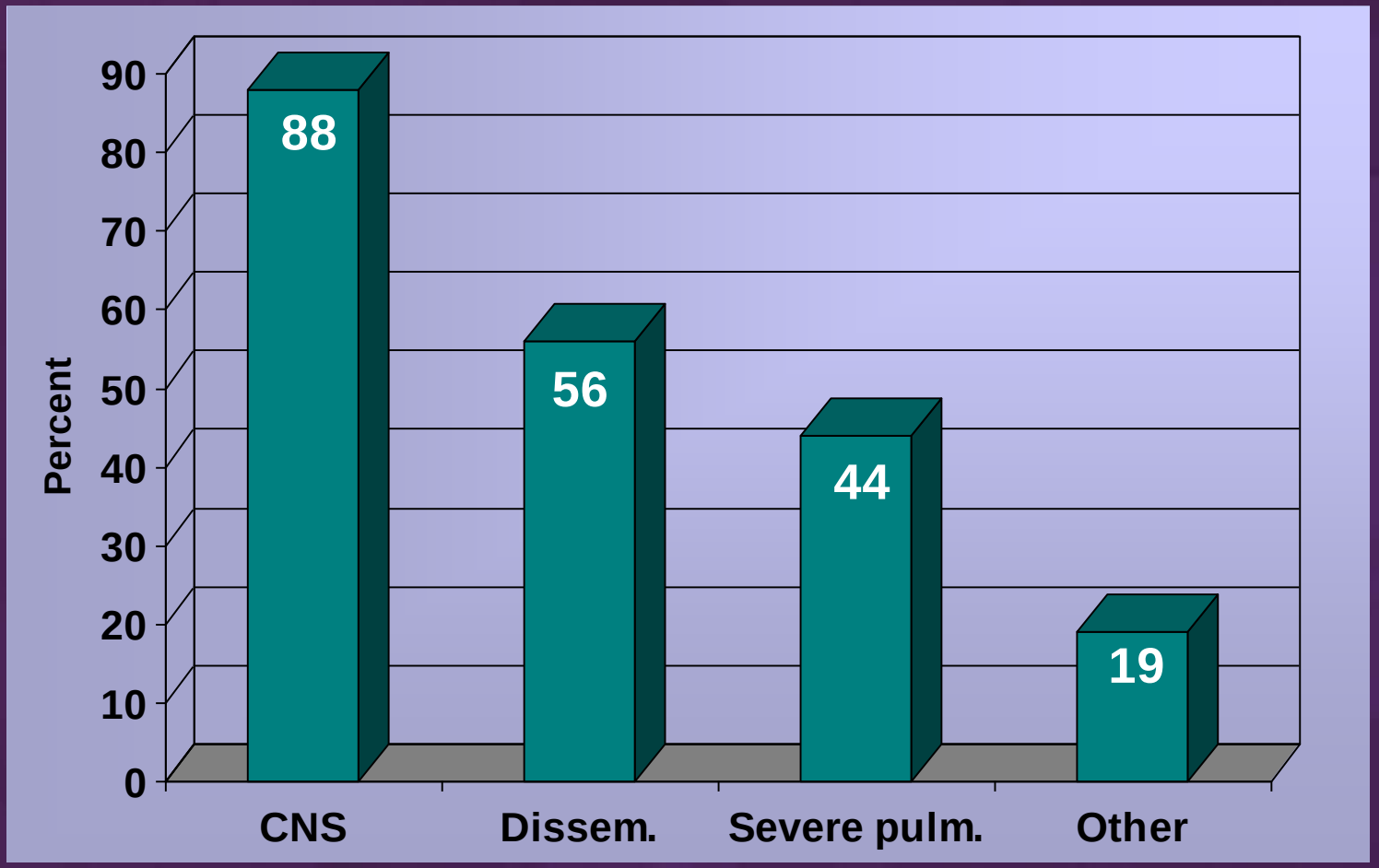
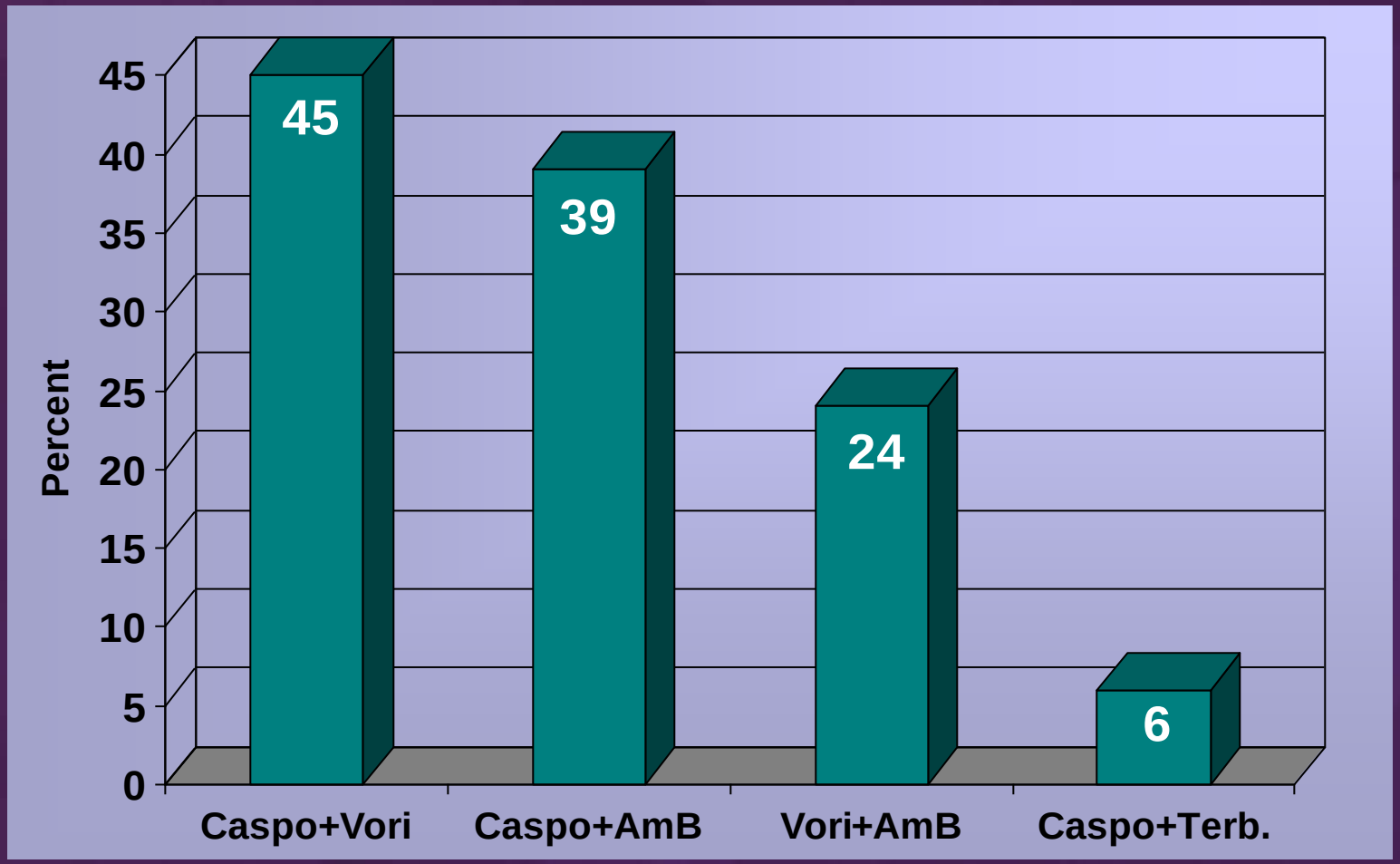
Results of the ECIL Questionnaire, September 2005

Questionnaire on current practice (38 responses)
Circumstances for use of combination therapy



Questionnaire on current practice (38 responses)
Type of combination



In most cases AmB = Ambisome

Questionnaire on current practice (38 responses)
Second line therapy for aspergillosis

- Equally distributed between monotherapy and combination

- For monotherapy
  - Caspofungin: 50 to 75%
  - Ambisome: 15 to 18%
  - Voriconazole: 25 to 35%

- For combination
  - Caspofungin + Voriconazole: ≈ 40%
  - Caspofungin + AmB: ≈ 35%

Literature search

Aspergillosis: 1st line therapy with Voriconazole

Randomized, open label comparison

277 probable / proven IA for 391 pts randomized

Allo HSCT ≈ 25% ; Leukemia ≈ 43%

	Vori	Ampho B	Significant
Patients	144	133	
Dose (mg/kg/d)	7.87	0.97	
CR + PR	53%	32%	yes
Survival (week 12)	71%	58%	yes
Serious AEs	13%	24%	yes
Most frequent SAE	liver	renal	

Herbrecht et al. NEJM, 2002

Aspergillosis: 1st line with Ambisome

Double blind comparison of Ambisome 3mg/kg and Ambisome 10 mg/kg in primary therapy

	Ambisome 3	Ambisome 10
Number pts (ITT)	107	94
Median duration therapy	15 d	14 d
Response at EOT*	50%	46%
Survival at Wk 12	**72%**	**59%**
Nephrotoxicity	**14%**	**31%**

Ambisome is effective in invasive aspergillosis
No benefit to increase the dose to 10 mg/kg

No detailed indication on partial response in main paper and loose definition in reply to Denning et al. (CID 2007, 45:1109)

Cornely et al., CID 2007, 44: 1289

Aspergillosis: 1st line therapy with ABCD

Randomized, double-blind comparison

174 possible, probable, proven IA

Allo HSCT ≈ 42% ; Leukemia ≈ 70%

	ABCD	Ampho B	Significant
Patients (ITT population)	88	86	
Dose (mg/kg/d)	6	1 to 1.5	
CR + PR	13%	15%	no
Survival (week 12)	50%	45%	no
Doubling creatinine	11%	33%	yes
Most frequent AE	Chills	Creatinine	

Bowden et al. Clin Infect Dis, 2002

Aspergillosis: salvage therapy

- Only open-label, non comparative studies
- Pts failing or intolerant of ampho B or itraconazole
  - Ambisome, ABLC, ABCD, voriconazole, posaconazole, caspofungin are effective in 30 to 50% of the cases
  - Insufficient data for itraconazole
- Pts failing caspofungin
  - Voriconazole was effective in 8 / 12 patients (67%)

Ringden et al., J Antimicrob Chemother, 1991; Denning et al, CID, 2002; Perfect et al, CID, 2003; Maertens et al. CID, 2004 ; Kartsonnis et al, J Infect, 2005; Walsh et al., CID 1998; Oppenheim, CID, 1995; Candoni et al., Eur J Haematol, 2005; Patterson et al, ICAAC; Denning et al., Am J Med, 1994

Posaconazole in aspergillosis

- Paper published in CID (Walsh et al, 2007)
- Previously graded on abstract presented at ASH (Blood 2003, supplement)
- No change
  - No data in first line
  - B II for salvage

Aspergillosis: combination in 1st line

- Ampho B + placebo versus Ampho B + terbinafine
  - Results never published; Higher mortality with combination
- Ambisome + anidulafungin
  - Efficacy results not yet presented or published
  - No unexpected AEs but 57% (17 / 30) deaths
- Itra + lipid ampho B (n=11) compared retrospectively to lipid Ampho B alone (n = 101)
  - No response (0%) in combination therapy compared to 10% in monotherapy group
- Ambisome + caspofungin
  - 9 / 17 (53%) response in possible, probable, proven cases

Steinbach et al, CID, 2003; Herbrecht et al., ASBMT, 2004; Kontoyiannis et al., Cancer, 2005; Kontoyianis et al., CID, 2003

Aspergillosis: Salvage combination therapy

- Vori + caspo (n=16) versus historical control group of vori alone (n=31) after failure or ampho B or itra
  - Higher 3-month survival in patients receiving combination (HR 0.42)
- Ambisome + caspo (n=31) after failure of Ambisome
  - 57% response in possible, 18% in probable or proven cases
- Ambisome (or ampho B) + caspo in possible, probable or proven aspergillosis failing ampho B
  - 18 / 30 favorable response (60%); 67% survival to discharge

Marr et al., 2004; Kontoyiannis et al., 2003; Aliff et al., 2003; Maertens et al., 2006

Combination therapy in aspergillosis

Caspofungin with another antifungal agent (Maertens et al. Cancer 2007)

- 53 patients, salvage therapy
- Response rate at end of combination: 55%
- Day 84 survival: 55%

Lipid Amphotericin B + caspofungin (59 pts) or Voriconazole + caspofungin (33 pts) as salvage therapy (Raad et al, ICAAC, 2007)

- 12-week survival: 48% for Voriconazle + caspofungin compared to 25% for Lipid-Amphotericin B + caspofungin
- Retrospective comparison ; High rate of *Aspergillus terreus*

Updated grading of combination therapy as salvage for invasive aspergillosis: C II instead C III at ECIL 1

Recommendations Aspergillosis

Invasive pulmonary aspergillosis :1st line

Agent	Grade	Comments
Voriconazole	A I	2 x 6 mg/kg D1 then 2 x 4 mg/kg (initiation with oral: CIII)
Ambisome	B I	dose 3 – 5 mg/kg
ABLC	B II	dose 5 mg/kg
Caspofungin	C III	
Itraconazole	C III	start with iv
ABCD	D I	
Amphotericin B	D I	
Combination	D III	

In the absence of data in 1st line, Posaconazole has not been graded

Invasive aspergillosis: salvage

Agent	Grade	Comments
Ambisome	B III	no data in voriconazole failure
ABLC	B III	no data in voriconazole failure
Caspofungin	B II	no data in voriconazole failure
Itraconazole	C III	Insufficient data
Posaconazole	B II	no data in voriconazole failure
Voriconazole	B II	if not used in 1st line

Invasive pulmonary aspergillosis: antifungal combinations

- First line
  - Not recommended — DIII
- Salvage
  - Caspofungin + lipid ampho B — C II
  - Caspofungin + voriconazole — C II
  - Ampho B (any formulation) + azole: — no data

Aspergillosis

- Surgery (CIII) in case of
  - Lesion contiguous to a large vessel
  - Hemoptysis from a single lesion (embolization is an alternative)
  - Localized extrapulmonary lesion including central nervous system lesion (on case by case)

Aspergillosis: unsolved questions

- **Duration of therapy**
  - **No fixed duration**

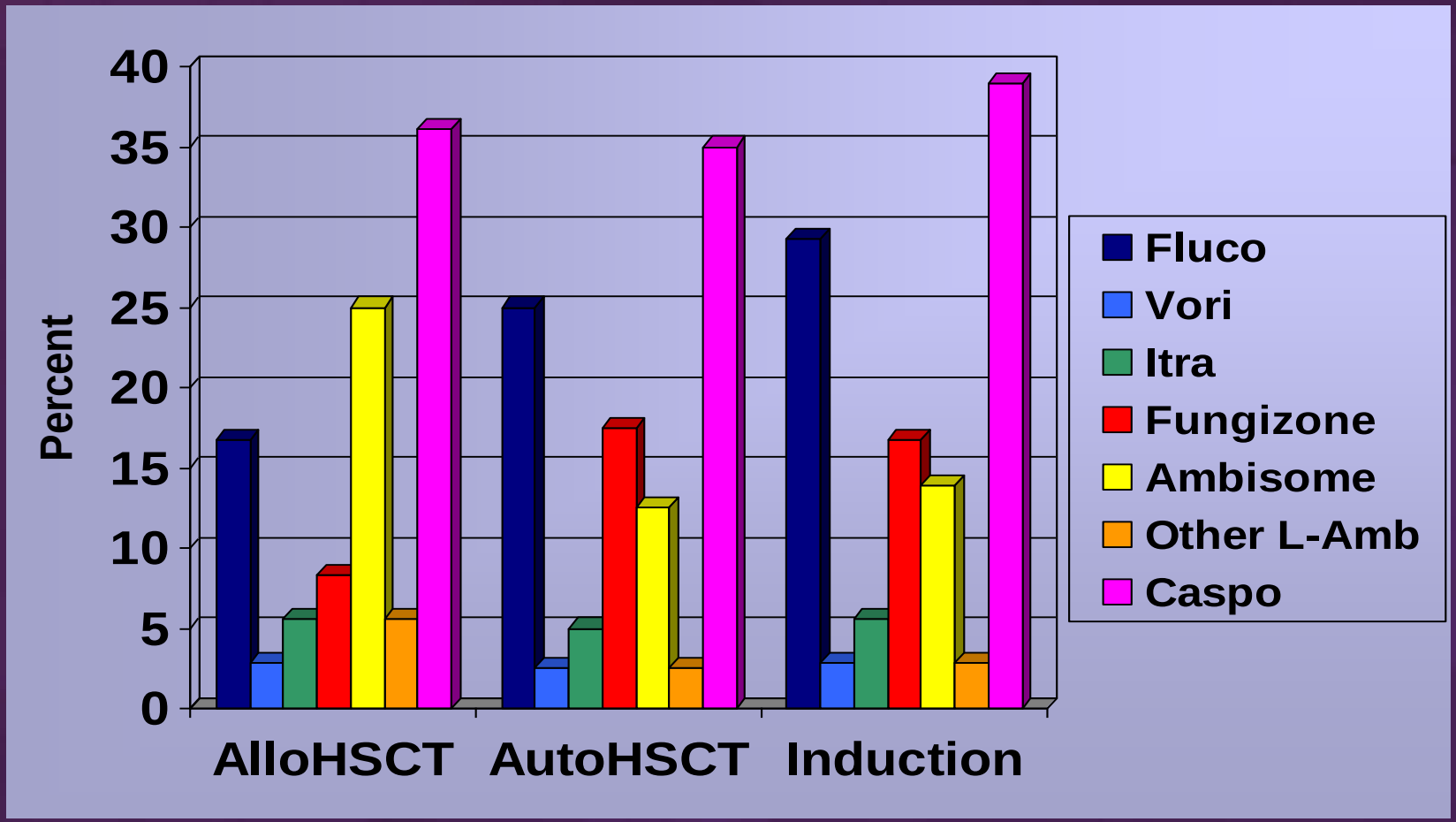
- **In vitro testing**
  - **Filamentous fungi are not routinely tested for susceptibility**
  - **No correlation between susceptibility testing and outcome**
  - ***Identification to the species level is recommended : C III***

Candidiasis

Questionnaire

Summer 2005

Questionnaire on current practice (38 responses)
Therapy in candidemia (before species identification)



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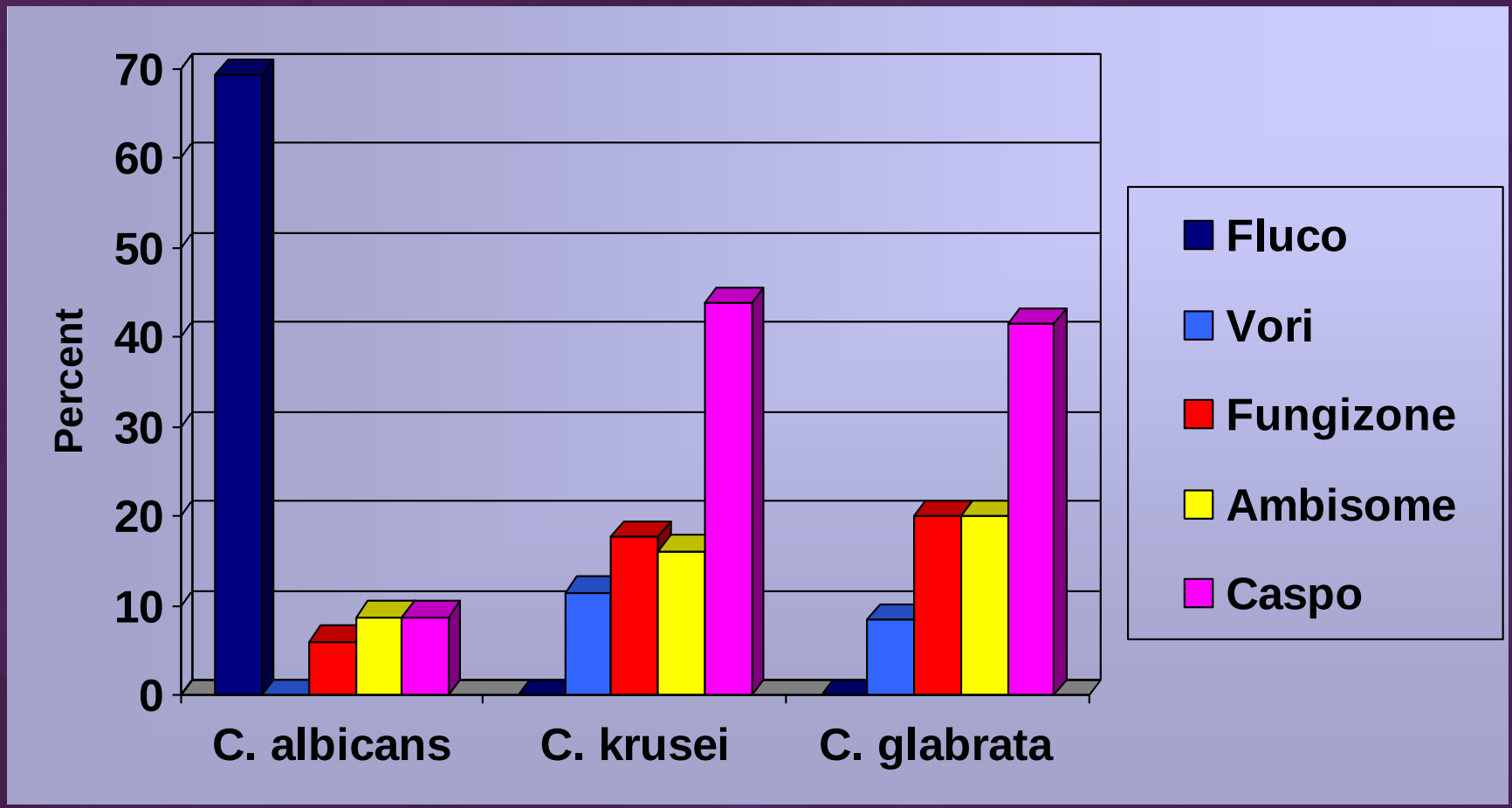

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Results of the ECIL Questionnaire, September 2005

Literature search

Neutropenia and Candidemia

The following 12 studies were analyzed:

- Rex, JH et al. N Engl J Med, 1994
- Nguyen, MH et al. Arch Intern Med, 1995
- Anaissie EJ et al. Clin Infect Dis, 1996
- Anaissie EJ et al. Am J Med, 1996
- Phillips P et al. Eur J Clin Microbiol Infect Dis, 1997
- Anaissie EJ et al. Am J Med, 1998
- Mora-Duarte J et al. N Engl J Med, 2002
- Rex JH et al. Clin Infect Dis, 2003
- Ostrosky-Zeichner L et al. Eur J Clin Microbiol Infect Dis, 2003
- Kullberg BJ et al. Clinical Microbiology and Infection, 2004
- Kartsonis NA et al. J Antimicrob Chemother, 2004
- DiNubile et al. J Infect 2005

Three Studies Including Neutropenic Patients

Author	Anaissie EJ	Mora-Duarte J.	Ostrosky-Zeichner
Patients	217 neutropenic 257 non neutropenic	24 neutropenic 200 non neutropenic	13 neutropenic 52 non neutropenic
Study design	retrospective	randomized	compassionate use
Antifungals	Fluconazole vs Amphotericin B	Caspofungin vs Amphotericin B	Voriconazole
Success	all patients 71% Fluconazole 73% Amphotericin B	(24 neutropenic) Caspofungin 6/8 Amphotericin B 3/8	13 neutropenic Voriconazole 6/13
Comments	neutropenic patients more likely tt Ampho B	tt at least 5d	83% previous tt with azole

tt: Treatment

Anaissie EJ et al. Am J Med, 1998 . Mora-Duarte J et al. N Engl J Med, 2002.
Ostrosky-Zeichner L et al. Eur J Clin Microbiol Infect Dis, 2003

Primary therapy in hematologic pts: current 2005 guidelines

Guidelines	Hematologic	Neutropenia
Germany 2003	Fluco 400 - 800 (B III) AmphoB ≥ 0.7 (B III) Caspo (B III)	-
Spain 2003	-	AmphoB, Fluco
UK 2003	-	Concerns about use of fluco (C II)
France 2004	-	AmphoB 1 mg/kg, Caspo, Ambisome 3 mg/kg
Australia 2004	-	Caspo (B I), Ambisome 3 mg/kg (AII), other lipid AmphoB (C III)
U.S.A. 2004	-	AmphoB 0.7 – 1.0 mg/kg Lipid AmphoB 3.0 – 6.0 mg/kg, Caspo, Fluco 6 – 12 mg/kg

Efungumab (Mycograb)

- **A human recombinant antibody (Fv fragment) that binds to HSP90 of Candida**

- **Double-blind, placebo-controlled, randomized, multicentre study of patients with culture-confirmed candidiasis**
  - Pilot study (n=21) and a confirmatory study (n=137)
    - All patients received AmBisome (3mg/kg/d) or Abelcet (5mg/kg/d)
    - Patients were randomized to received Efungumab (1 mg/kg bid) or placebo
  - Only very limited number of neutropenic patients
  - Some methodological concerns
  - So far not approved. Not graded by the ECIL2

Pachl et al. CID 2006, 42: 1404

Anidulafungin in candidiasis

Double-blind comparison of anidula 200 mg then 100 with fluco. 800 mg then 400 in invasive candidiasis in adults

	Anidulafungin	Fluconazole	p value
Number pts (MITT)	118	127	<.02
Response			
- End of therapy	74.0%	56.8%	
- Limited number of neutropenic patients: 3 and 4 respectively			
Mycological eradication			
- *C albicans*	77/81 (95%)	57/70 (81%)	
- *C glabrata*	15/20 (75%)	18/30 (60%)	
- *C krusei*	EXCLUSION	CRITERIA	
- *C parapsilosis*	9/13 (69%)	14/16 (88%)	
All cause mortality	23%	31%	0.13

Anidulafungin has shown non-inferiority to fluconazole

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Reboli et al., NEJM 2007

Micafungin in candidiasis (1)

Double-blind comparison of micafungin with Ambisome in invasive candidiasis in adults

	Micafungin 100 mg	Ambisome 3 mg/kg	
Number pts (MITT)	247	247	
Response			
- Overall	74.1%	69.6%	
- Neutropenic pts	19/32 (59.4%)	14/25 (56.0%)	
Mycological persistence at EOT			
- *C albicans*	9/85 (11%)	8/73 (11%)	
- *C glabrata*	3/22 (14%)	3/15 (20%)	
- *C krusei*	1/6 (17%)	1/5 (20%)	
- *C parapsilosis*	5/35 (14%)	3/29 (10%)	
Deaths at Week12	40%	40%	
Infusion related AEs	17.0%	28.8%	p=.001
Nephrotoxicity	10.3%	29.9%	p<.0001

Micafungin has shown non-inferiority to Ambisome and better tolerance

Kuse et al., Lancet 2007, 369 : 1519

Micafungin in candidiasis (2)

Double-blind comparison of micafungin (100 mg or 150 mg) to caspofungin (70 D1 then 50 mg) in invasive candidiasis in adults

	Micafungin 100	Micafungin 150	Caspofungin
Number pts (MITT)	191	168	188
Response			
- Overall	87.4%	87.4%	87.2%
- Neutropenic pts	18/22(82%)	9/17(53%)	7/11(64%)
Mycological response			
- *C albicans*	71/92 (77%)	71/102 (69.6)	61/83 (74%)
- *C glabrata*	24/28 (86%)	30/34 (88%)	22/33 (67%)
- *C krusei*	6/8 (75%)	5/8 (63%)	3/4 (75%)
- *C parapsilosis*	22/29 (76%)	15/21 (71%)	27/42 (64%)

No difference in adverse events, in mortality, or in relapses

Micafungin 100 mg and micafungin 150 mg are non-inferior to caspofungin in invasive candidiasis

No benefit to increase micafungin dose to 150 mg

Pappas et al, CID 2007, 45 : 883

Micafungin in candidiasis (3)

Double-blind comparison of micafungin with Ambisome in invasive candidiasis in pediatric patients

	Micafungin	**Ambisome**
Daily dose	2 mg/kg	3 mg/kg
Number pts (ITT)	52	54
Response		
- Overall	69.2%	74.1%
- Neutropenic pts	5/7 (71.4%)	10/13 (76.9%)
Discontinuation for AE	3.8%	16.7%

Arrieta et al., 17th ECCMID 31 March-3 April 2007, Munich

Recommendations Candidiasis

Candidemia in hematologic patients before species identification

	Overall population	Haematological pts
Micafungin	A I	B II
Anidulafungin	A I	B II
Caspofungin	A I	B II
Ambisome	A I	B II
Other lipid-AmB	A II	B II
Fluconazole	A I *	C III
Voriconazole	AI **	BII

** Not in severely ill patients or in patients with previous azole prophylaxis*

*** Not in patients with previous azole prophylaxis*

Candidemia after species identification (1/2)

		Overall population	Haematological pts
Micafungin	*C albicans*	A I	B II
	C glabrata	B I	B II
	C krusei	B I	B II
Anidulafungin	*C albicans*	A I	B II
	C glabrata	B I	B II
	C krusei	B I	B II
Caspofungin	*C albicans*	A I	B II
	C glabrata	B I	B II
	C krusei	B I	B II

Candidemia after species identification (2/2)

		Overall population	Haematological pts
Ambisome	*C albicans*	A I	B II
	C glabrata	B I	B II
	C krusei	B I	B II
Other lipid-AmB	*C albicans*	A II	B II
	C glabrata	B II	B II
	C krusei	B II	B II
AmB deoxycholate	*C albicans*	A I	C III
	C glabrata	B I	C III
	C krusei	B I	C III
Fluconazole	*C albicans*	A I	C III
	C glabrata	C III	D III
	C krusei	E III	E III
Voriconazole	*C albicans*	A I	C III
	C glabrata	C III	C III
	C krusei	B I	C III

Duration of antifungal therapy in candidemia

Duration of antifungal therapy in candidemia : overview of selected studies

- 12 studies 1994 – 2005
- 3/12 prospective, randomized & double-blinded
- Duration of AFT designed *a priori* in 4 studies
- Total effective duration of therapy 10-21 d. except for « salvage » studies (30-60 d.)
- No specific study in leukemia / neutropenia
- No well-designed trial specifically studying duration of therapy

Duration of antifungal therapy in candidemia : current guidelines

Guideline	Duration recommended	Specific guidelines in neutropenia
Germany 2003	2 w. OR 10-14 d. after 1st –ve BC with adapt. to possible organ manif.	None
Spain 2003	2 w. after last +ve BC AND resol. of sympt. AND ≥ 4 w. if dissem.	None
France 2004	2 w. after last +ve BC AND resol. of sympt.	≥ 7 d. after resolution of neutropenia
U.S.A. 2004	2 w. after last +ve BC AND resol. of signs & sympt. of infection	2 w. after resolution of neutropenia

Recommendations for duration of therapy in candidemia

Duration of antifungal therapy in candidemia : recommendations

Non-neutropenic adults: at least 14 days after the last +ve blood culture and resolution of signs and symptoms : **B III**

Neutropenic patients: at least 14 days after the last +ve blood culture and resolution of signs and symptoms and resolved neutropenia: **C III**

Importance of an active search for dissemination of infection in leukemic patients following neutrophil recovery (ocular fundus + abdominal imaging)

Antifungal susceptibility testing in candidemia

Antifungal susceptibility testing in candidemia : *in vitro* / clinical correlation

- 11 studies 1988-2005
- 7/11 prospective (or data extracted from prospective studies)
- Heterogeneous populations
- Various number of episodes analyzed (24 – 262)
- Amphotericin B and/or fluconazole
- Attempts to correlate *in vitro* AFST or inappropriate AF therapy and outcome (death or clinical / microbiologic treatment failure)

Ref	Method	N	AF	Method	Correlation
Powderly 88	retrosp	29	Ampho	Tube dil.	Yes (MIC – mortality)
Rex 95	prosp.	232	Ampho /FCZ	NCCLS	No
Nguyen 98	prosp.	105	Ampho	NCCLS	Yes (MLC - microb. failure)
Clancy 99	prosp.	99	Ampho	E-test	Yes (MIC – microb. failure)
Kovacicova 00	?	262	FCZ	Agar E-test	Yes (attributable mortality)
Lee 00	prosp.	32	FCZ	NCCLS	Yes (success rate)
Wenisch 01	prosp.	24	Ampho /FCZ	NCCLS Flow cyt	Yes (AFST by flow cytometry – outcome)
Antoniadou 03	Retrosp Mult an	80 272	Ampho /FCZ	NCCLS	Yes (inappr. AFT – outcome)
Baddley 04	prosp.	119	FCZ	NCCLS	Yes (AFST - outcome)
Chen 05	retrosp	56	Ampho /FCZ	E-test	No
Clancy 05	prosp.	32	FCZ	NCCLS	Yes (MIC & dose/MIC - outcome)

Antifungal susceptibility testing in candidemia: current « guidelines »

Guideline	Recommendation	Comment on choice of therapy
Germany 2003	None	NA
Spain 2003	AFST (not graded)	None
France 2004	Routine E-test (B-II)	None
U.S.A. 2004	NCCLS M27A & FCZ Not a standard of care Helpful in deep or hematogenous infection	Helpful in case of lack of clinical response May support oral switch to azole (long-term therapies)

Not graded

Recommendations for antifungal susceptibility testing

Antifungal susceptibility testing (AFST)

AFST should be performed in hematological patients on isolates from blood or normally sterile sites, in order to:

- evaluate a possible cause of lack of clinical response or microbiologic eradication A II
- support a change in initial antifungal therapy B II
- support a switch from an IV antifungal to an oral azole A II

Recommendations for catheter removal in candidemia

Candidemia: catheter removal

- Removal of central venous line
  - is a consensus recommendation for the non-hematological patients **A II**
  - in hematology patients the quality of evidence is lower **B III**
  - removal is always recommended when *C parapsilosis* is isolated **A II**