Antifungal Therapy in Leukemia Patients

UPDATE ECIL 4, 6 September 2011

Raoul Herbrecht, Ursula Flückiger, Bertrand Gachot,

Patricia Ribaud, Anne Thiebaut, Catherine Cordonnier

UPDATE ECIL 4, 2011

The logo UPDATE ECIL 4, 2011 on top of a slide means that recommendations has be updated with either a change of grading, an addition or a confirmation of a previous grading

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

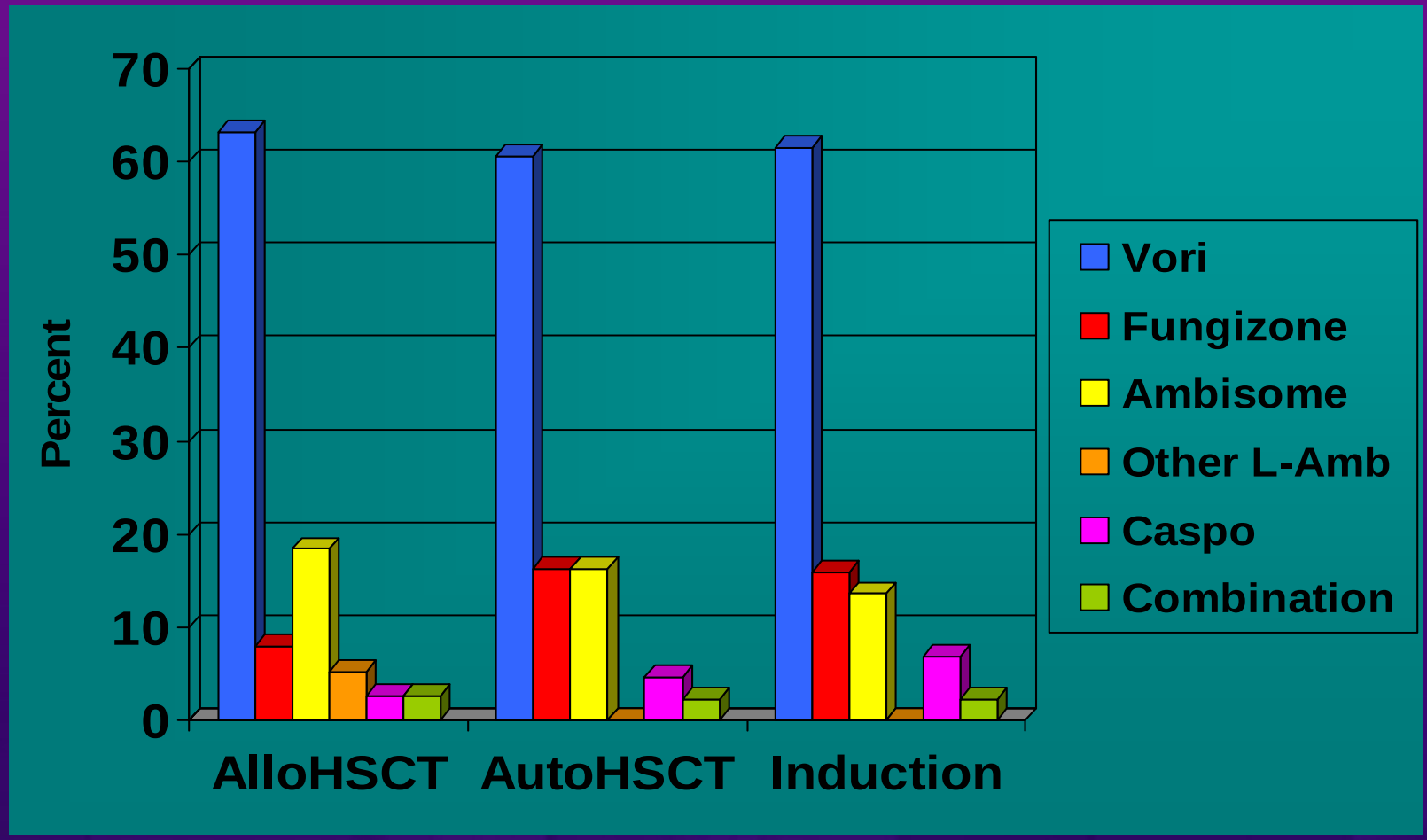
- Questionnaire on practice in Europe
- Literature review
  - Pubmed
  - Cochrane
  - ICAAC, ECCMID, ASH, ASCO, and EBMT
- CDC grading (I-III, A-E)

Invasive aspergillosis

Questionnaire

Summer 2005

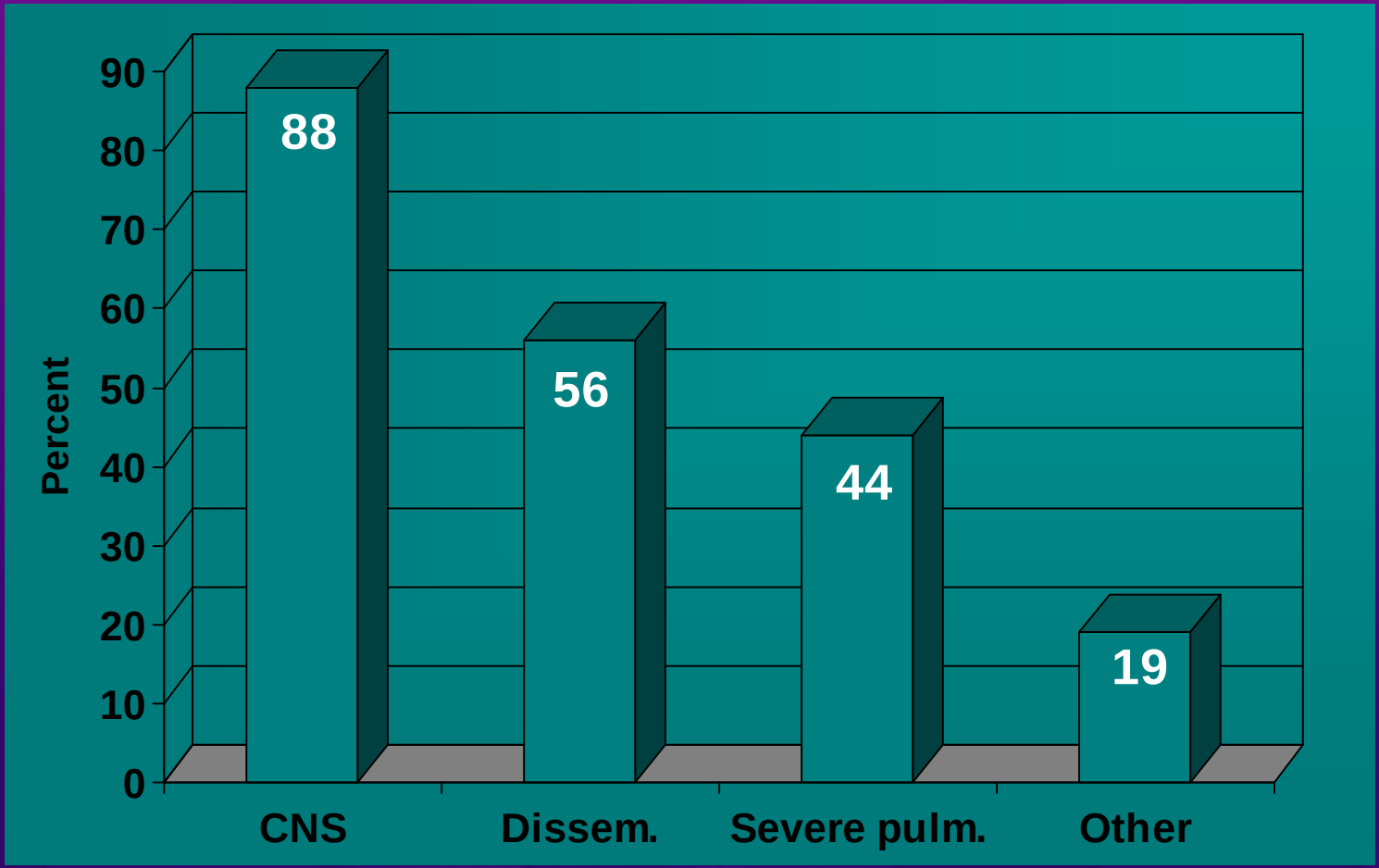
Questionnaire on current practice (38 responses)
First line therapy in invasive aspergillosis



3rd European Conference on Infections in Leukemia

Results of the ECIL Questionnaire, September 2005

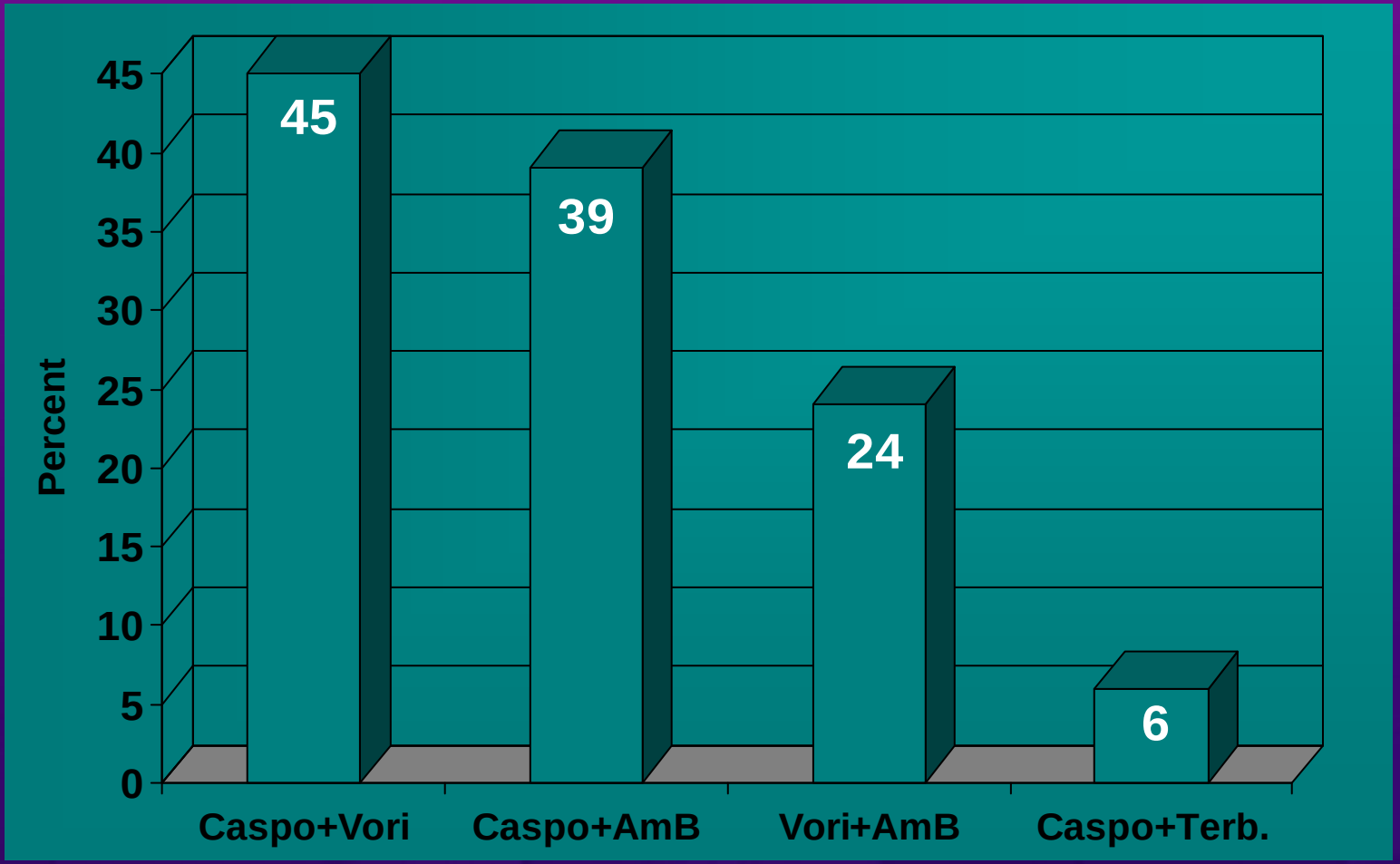
Questionnaire on current practice (38 responses)
Circumstances for use of combination therapy



3rd European Conference on Infections in Leukemia

Results of the ECIL Questionnaire, September 2005

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 (voriconazole versus amphotericin B deoxycholate)

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 liposomal amphotericin B (Ambisome)

Double blind comparison of Ambisome 3mg/kg and Ambisome 10 mg/kg in primary therapy (Ambiload study)

	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 amphotericin B colloidal dispersion (ABCD)

Randomized, double-blind comparison (ABCD versus amphotericin B deoxycholate)

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 R et al. Clin Infect Dis, 2002

Caspofungin for primary therapy of invasive aspergillosis

- Two strata in an exploratory study. Results presented separately.
  1. Hematological malignancies: *Viscoli et al., Journal of Antimicrobial Chemotherapy, 2009*
  2. Allogeneic hematopoietic stem cell transplantations: *Herbrecht et al., Bone Marrow Transplantation, in press*

Caspofungin for primary therapy of invasive aspergillosis

Hematological malignancies

- 129 patients enrolled
- 61 patients eligible, all with a mycologically documented IA (probable or proven)
- Treated with standard dose of caspofungin
- Mostly acute leukemia; 85% neutropenic
- CR or PR: 20 / 61 (33%); (expected response rate at least 35%)
- 12-week survival: 53%

Viscoli et al., J Antimicrob Chemother, 2009

Caspofungin for primary therapy of invasive aspergillosis

Allogeneic HSCT recipients

- 42 patients enrolled
- 24 patients eligible, all with a mycologically documented IA (probable or proven)
- Early termination due to slow accrual
- Treated with standard dose of caspofungin
- CR or PR : 10 / 24 (42%)
- 12-week survival: 50%

Herbrecht et al., Bone Marrow Transplantation, in press

Caspofungin for primary therapy of invasive aspergillosis

Considering

- that study conducted in pts with hematological malignancies was well designed, that expected accrual was obtained and that response rate was below expectation
- that study in alloHSCT pts was stopped prematurely with only 24 pts

C II grading for primary therapy with caspofungin (previously caspofungin was graded C III for primary therapy)

Papers also considered (1)

ABLC versus liposomal AmB monotherapy for invasive aspergillosis in patients with hematologic malignancy.
Hachem et al., Cancer 2008

- Retrospective study of 381 consecutive patients with proven or probable invasive aspergillosis between Jun 93 and Dec 05
- 158 received primary therapy (106 L-AMB and 52 ABLC) and 81 received salvage therapy (51 L-AMB and 30 ABLC)
- Advanced stage and severity of underlying diseases in all groups
- Poor response rates (7.7 to 15.8%) to primary or salvage therapy in both study drug groups regardless of treatment modality.
- High mortality rates in all groups
- Higher nephrotoxicity with ABLC than L-AMB

No change in grading for
Liposomal AmB: B I for first line and B III for salvage
ABLC: B II for first line and BIII for salvage

Papers also considered (2)

Safety and efficacy of a caspofungin-based combination therapy for treatment of proven or probable aspergillosis in pediatric hematologic pts. *Cesaro et al. BMC Infect Dis 2007*

- Retrospective analysis of caspofungin-based combination therapy in 40 pediatric pts (median age 11 y; range: 1-17 y)
- Mostly HSCT recipients and leukemia pts
- Probable IA in 20 (50%) and proven in 20 (50%) pts
- Caspofungin + liposomal AmB (n=18) or caspofungin + voriconazole (n=9) or both sequentially (n=9). Information is missing for 4 pts treated for < 7 days.
- Primary therapy: 20 cases ; salvage therapy: 20 cases
- Favorable response in 21 pts (53%). No difference according to type of combination
- Probability of 100-day survival was 70%

No change in grading for combination therapy (previously D III for first line and C II for salvage)

Papers also considered (3)

Treatment of invasive pulmonary aspergillosis in neutropenic patients by additional bronchoscopic amphotericin B instillation. *Winkler et al, Respiration 2007*

- 20 patients treated between February 1996 and October 2002
- First line therapy with AmB deoxycholate (8 pts) or AmB deoxycholate followed by liposomal AmB (10 pts) or liposomal AmB (23 pts)
- Most pts received in addition flucytosine, fluconazole or itraconazole
- Paper not further considered as reference for primary therapy of invasive aspergillosis has changed since this study

No recommendation

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

Aspergillosis

- Efficacy of caspofungin as salvage therapy for invasive aspergillosis compared to standard therapy in a historical cohort.
  Hiemenz et al. Eur J Clin Microbiol Infect Dis, 2010
  - Comparison of the 83 pts of the Caspofungin Salvage Invasive Aspergillosis Study (Maertens et al., Clin Infect Dis 2004) to a historical control group of 214 pts with documented IA refractory or intolerant to standard therapy (AmB, lipid-AmB, itra)
  - Favorable response rates: 45% with caspo and 16% in control group
- Caspofungin use in daily clinical practice for treatment of invasive aspergillosis: results of a prospective observational registry.
  Maertens et al. BMC Infect Dis, 2010
  - Prospective observational registry in 11 countries
  - 101 proven or probable invasive aspergillosis; caspo salvage therapy
  - Favorable response: 56%

No change in recommendation for caspofungin for salvage therapy: B II

UPDATE ECIL 4, 2011

Aspergillosis

- Caspofungin plus posaconazole as salvage therapy of invasive fungal infections in immunocompromised patients.
  Lellek et al. Mycosis, 2011, 54 Suppl 1
  - Retrospective, monocentric
  - 31 **HSCT** patients with refractory IA
  - Combination of caspofungin 50 mg/d and posaconazole 800 mg/d
  - Favorable response rate: 77%
- Micafungin alone or in combination with other systemic antifungal therapies in HSCT recipients with invasive aspergillosis
  Kontoyiannis et al., Transpl Infect Dis. 2009
  - 87 **HSCT** recipients with IA refractory (prior therapy mostly lipid AmB)
  - Micafungin 75 mg/d, mostly in combination with lipid-AmB
  - Successful response: 24%

No change in recommendation for combination therapy in second line: C II

Recommendations Aspergillosis

UPDATE ECIL 3, 2009

Invasive pulmonary aspergillosis :1st line

Agent	Grade	Comments
Voriconazole	A I	2x6 mg/kg D1 then 2x4 mg/kg (initiation with oral: CIII)
Ambisome	B I	dose 3 – 5 mg/kg
ABLC	B II	dose 5 mg/kg
Caspofungin	C II	
Itraconazole	C III	start with iv
ABCD	D I	
Amphotericin B deoxycholate	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
Posaconazole	B II	no data in voriconazole failure
Voriconazole	B II	if not used in 1st line
Itraconazole	C III	Insufficient data

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

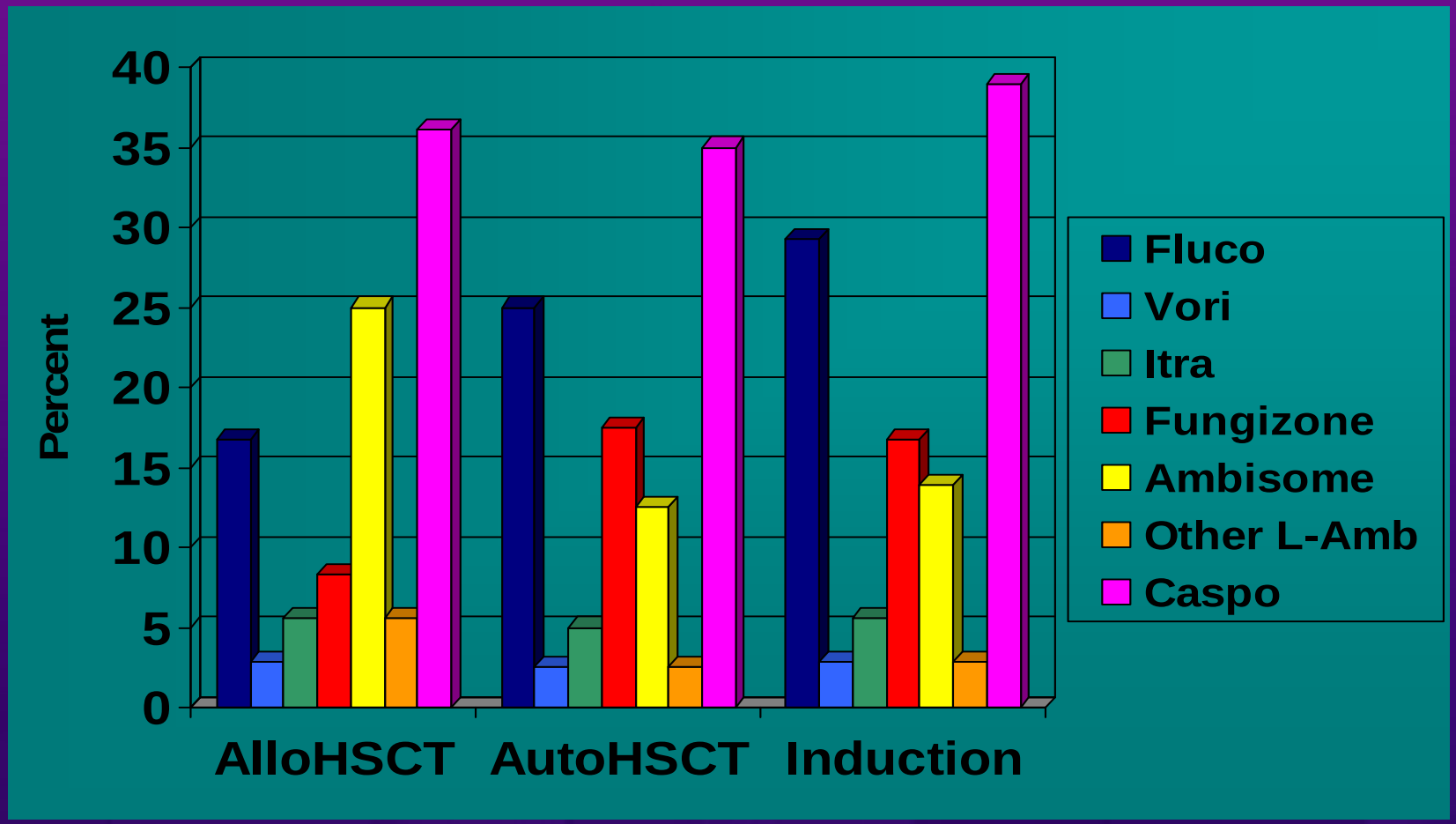
- **Duration of therapy**
  - **No fixed duration**
- **Drug monitoring, especially for azoles, may be indicated in case of failure or of adverse events**
- **In vitro testing**
  - **Filamentous fungi are not routinely tested for susceptibility**
  - **No correlation between susceptibility testing and outcome**
  - ***Identification to the species level is recommended : C III***

Invasive candidiasis

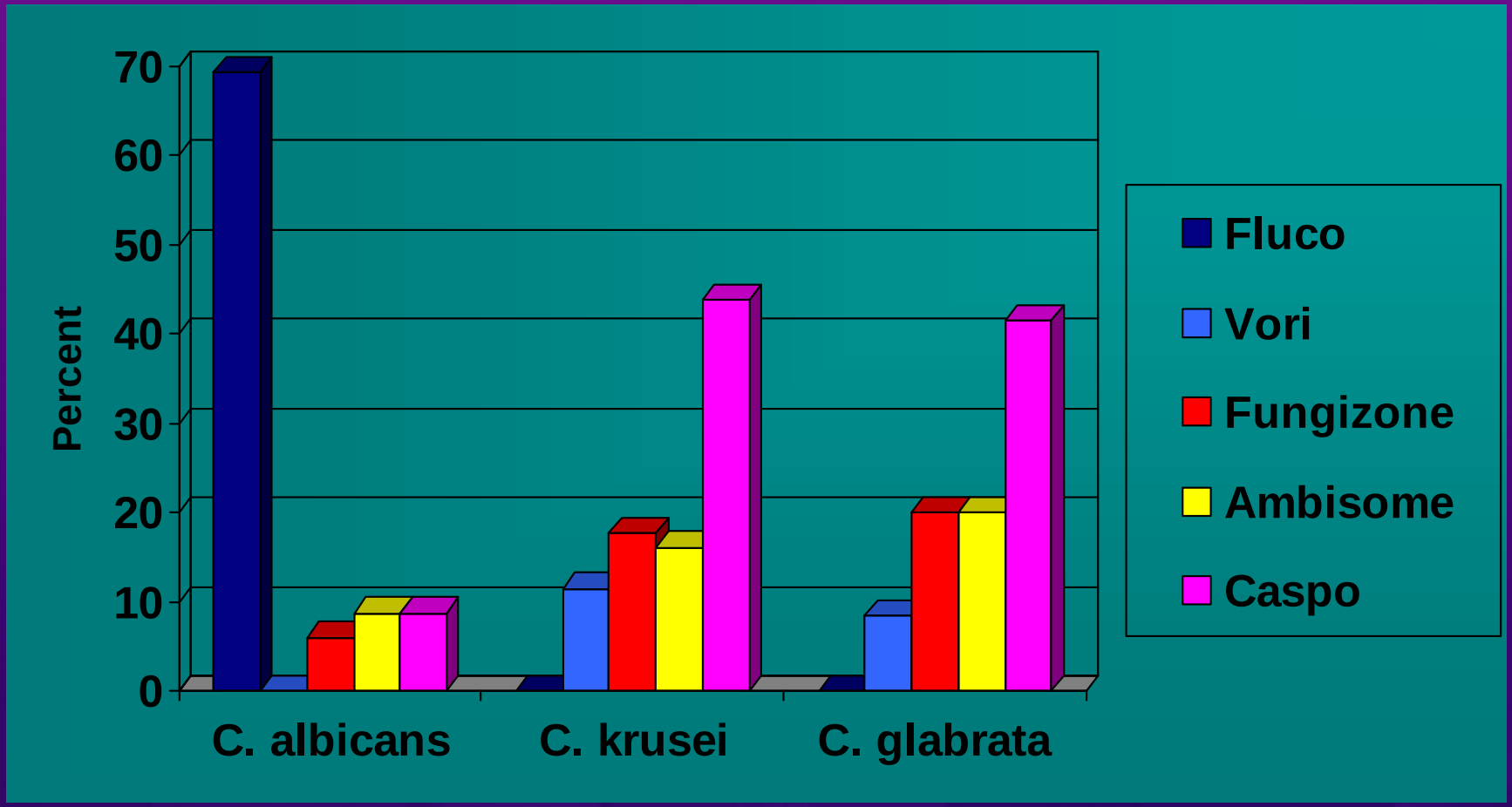
Questionnaire

Summer 2005

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



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



3rd European Conference on Infections in Leukemia

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

UPDATE ECIL 2, 2007

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. Sofar not graded by the ECIL

Pachl et al. CID 2006, 42: 1404

UPDATE ECIL 2, 2007

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

3rd European Conference on Infections in Leukemia

Reboli et al., NEJM 2007

UPDATE ECIL 2, 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

3rd European Conference on Infections in Leukemia

Kuse et al., Lancet 2007, 369 : 1519

UPDATE ECIL 2, 2007

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

High dose caspofungin in candidiasis

- Double-blind comparison of two doses of caspofungin in invasive candidiasis.
  - 104 pts received standard dose (SD) : 70 mg on d1 then 50 mg/d
  - 100 pts received high dose (HD): 150 mg/d
  - 60 pts with active malignancy but only 15 neutropenic and 10 transplant recipients
  - 42% *C. albicans*, 21% *C. parapsilosis*, 10% *C. glabrata*

Betts et al., Clin Infect Dis, 2009

High dose caspofungin in candidiasis

Safety outcomes

	SD (n=104)	HD (n=100)
Treat. duration	14.5 d	14.2 d
Drug related AE	20 (19%)	19 (19%)
- leading to discontin.	2 (2%)	2 (2%)

No differences in frequency and type of events

Betts et al., Clin Infect Dis, 2009

UPDATE ECIL 3, 2009

High dose caspofungin in candidiasis

Efficacy outcomes

	SD (n=102)	HD (n=95)
Favorable response		
Overall	73/102 (72%)	74/95 (78%)
Neutropenic pts	2/6 (33%)	4/7 (57%)

No differences in
- time to clear blood cultures
- in 8 weeks mortality rate (33 and 38% respectively)

Betts et al., Clin Infect Dis, 2009

No change in grading for caspofungin
(previously: A I in overall population
B II in hematological pts)

3rd European Conference on Infections in Leukemia

Candidemia

- Monotherapy with caspofungin for candidaemia in adult patients with cancer: a retrospective, single institution study
  Sipsas et al. Int J Antimicrob Agents, 2009
  - Retrospective, non-comparative, single center
  - 63 adults with cancer and candidemia; caspofungin monotherapy
  - Clinical response rate 78%
- Caspofungin for the treatment of candidaemia in patients with haematological malignancies.
  Pagano et al. Clin Microbiol Infect, 2010
  - Prospective, non-comparative, 11 hematology centers
  - 24 neutropenic patients with candidemia treated with caspofungin
  - Favorable overall response rate: 58%

No change in recommendation for caspofungin
A I (overall population), B II (hematological pts)

Recommendations Candidiasis

UPDATE ECIL 3, 2009

Candidemia in hematologic patients before species identification

	Overall population	Hematological 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
AmB deoxycholate		A I * C III *
Fluconazole	A I **	C III
Voriconazole	A I ***	B II

** DIII if concomitant nephrotoxic drug and EIII if renal impairment*
*** Not in severely ill patients or in patients with previous azole prophylaxis*
*** Not in patients with previous azole prophylaxis*

3rd European Conference on Infections in Leukemia

Candidemia after species identification (1/2)

		Overall population	Hematological 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

UPDATE ECIL 3, 2009

Candidemia after species identification (2/2)

		Overall population	Hematological 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

** DIII if concomitant nephrotoxic drug and EIII if renal impairment*

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**