1st European Conference on Infection in Leukemia

Antifungal therapy

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

ELN European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

ICHS International Conference on Infection in Compromised Host

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 ?

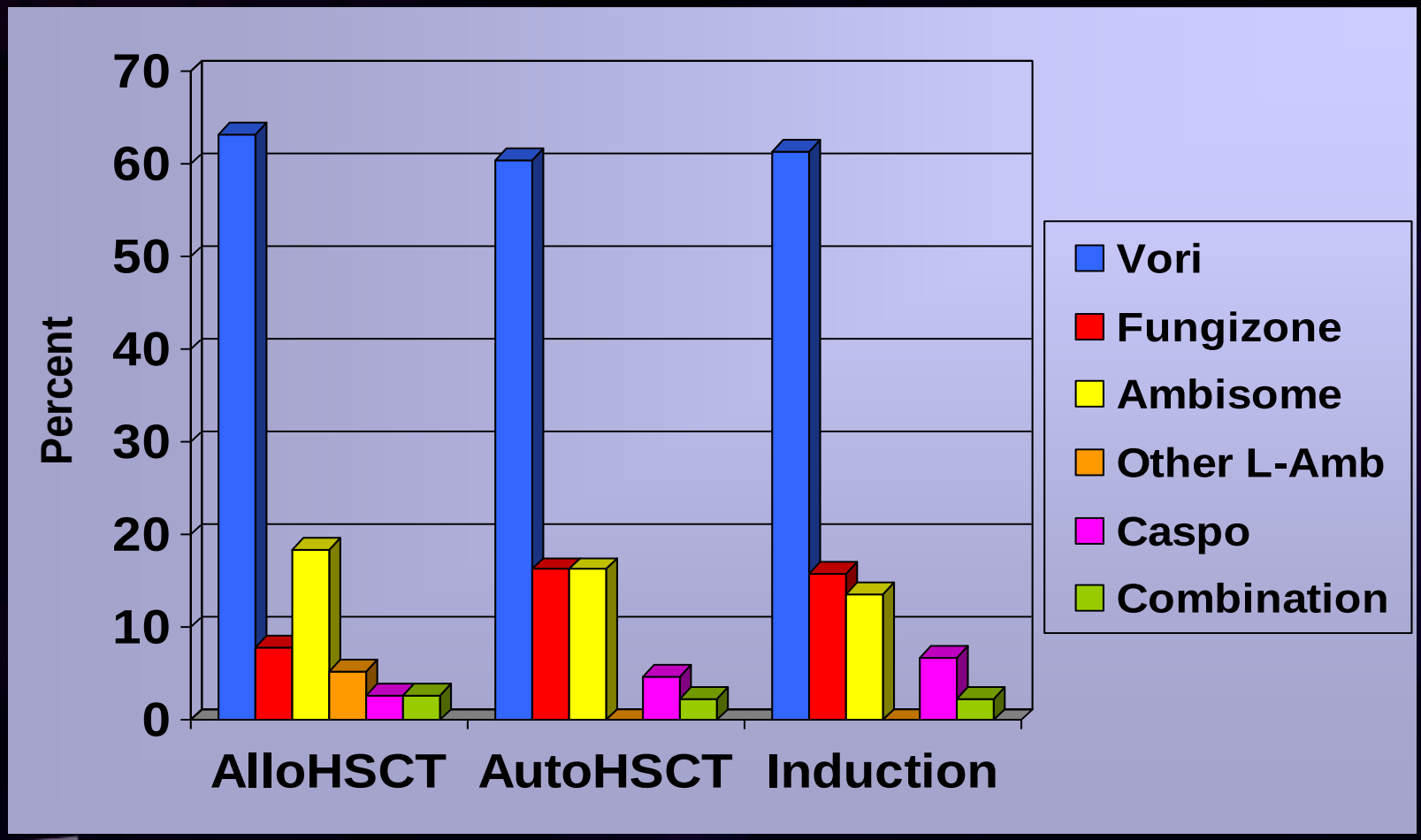
Methods

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

Aspergillosis

Questionnaire

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



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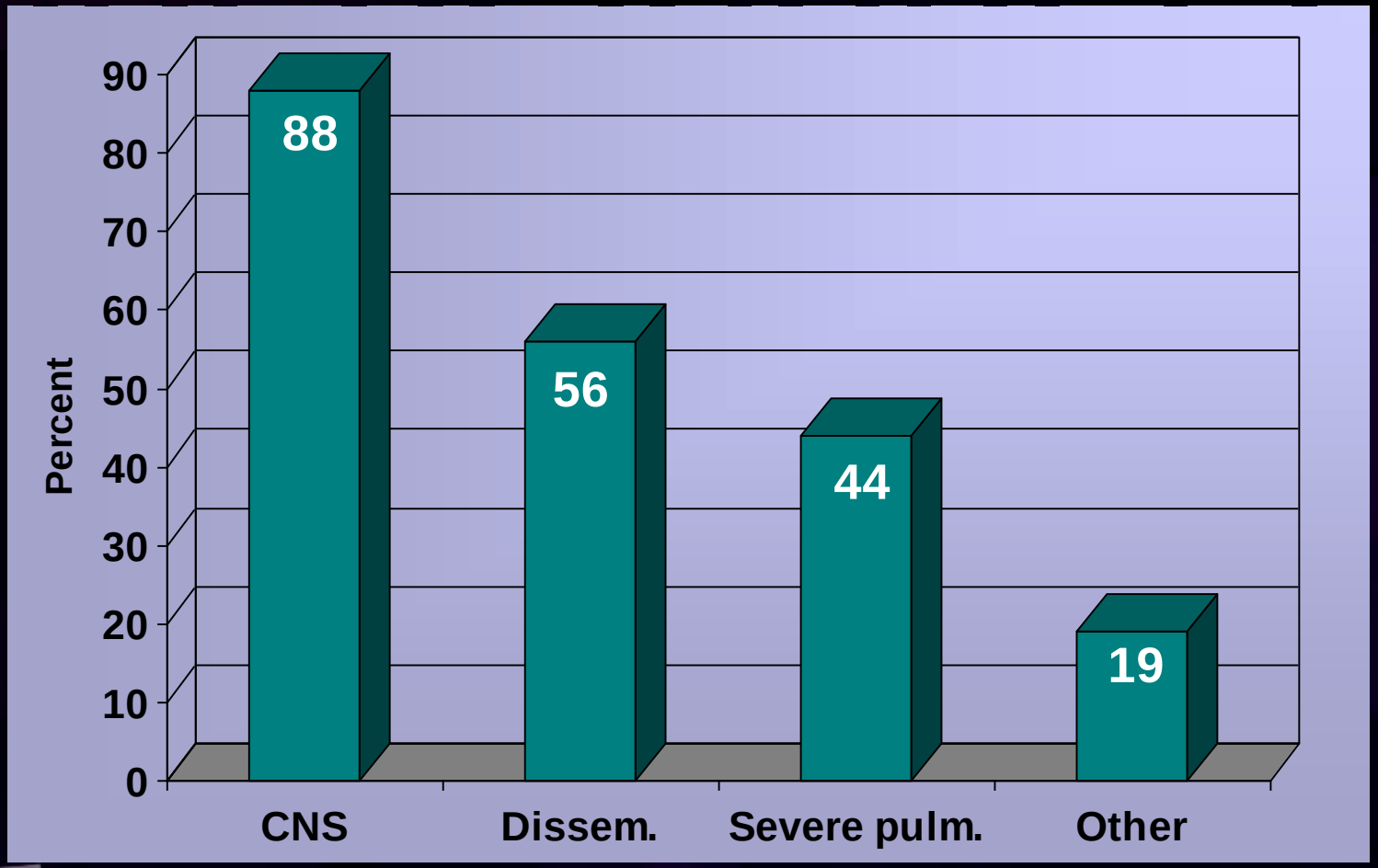
Results of the ECIL Questionnaire, September 2005

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



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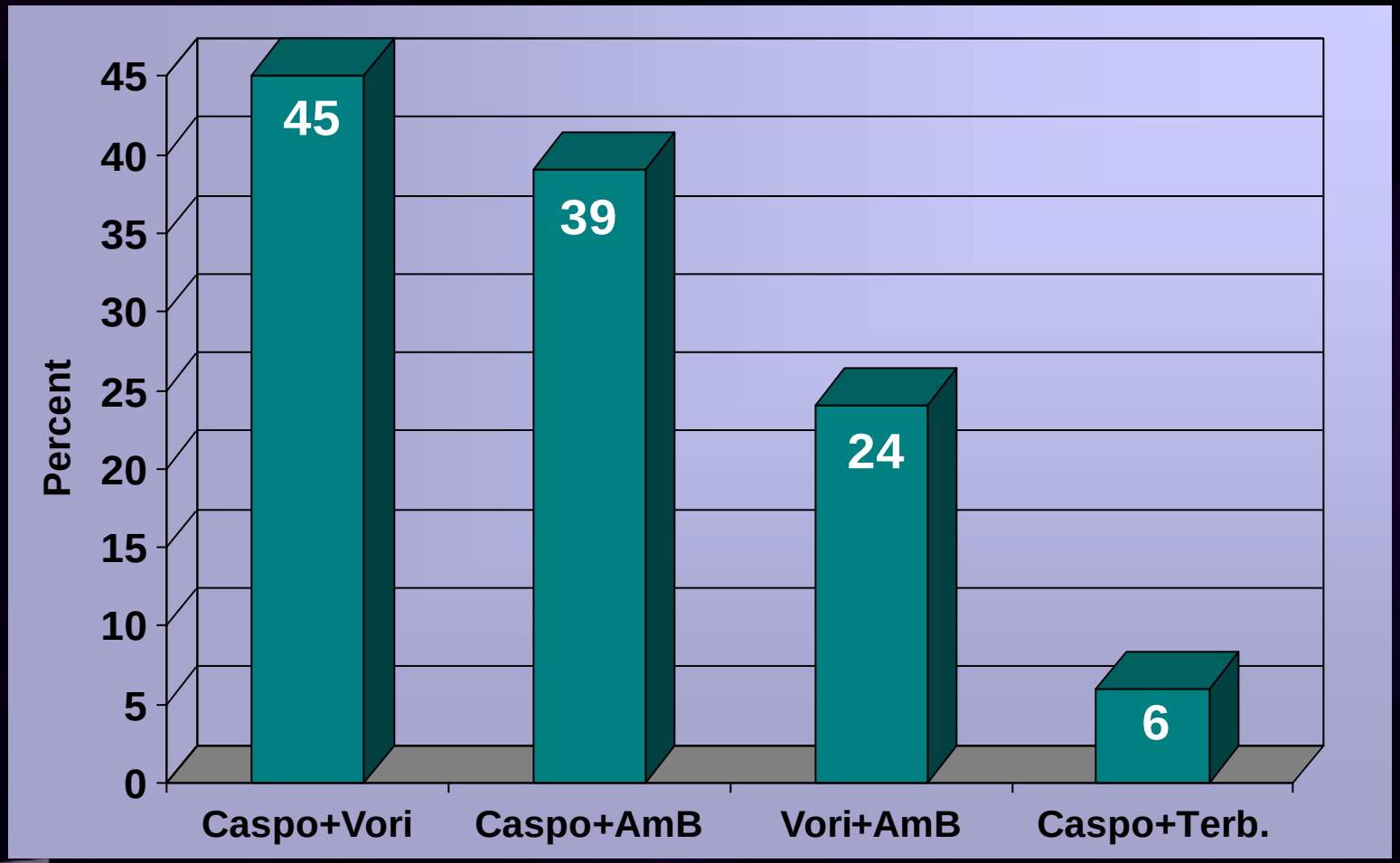
Results of the ECIL Questionnaire, September 2005

Questionnaire on current practice (38 responses)
Type of combination



In most cases AmB = Ambisome

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Results of the ECIL Questionnaire, September 2005

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 therapy with Ambisome

Randomized, open label comparison

106 possible, probable, proven IA and other suspected or documented invasive mold infections

Allo HSCT ≈ 15% ; Leukemia ≈ 80%

	Ambisome	Ampho B	Significant
Patients (IA only)	26	29	
Dose (mg/kg/d)	5	1	
CR + PR	69%	59%	no
Survival (week 12)	81%	62%	no
Doubling creatinine (all pts)	12%	41%	yes
Most frequent AE	HypoK^{+}	Creatinine	

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Leenders et al. Br J Haematol, 1998

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

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
- Caspo added to other antifungal agents in probable/proven cases
  - Caspo + ampho B or lipid Ampho B: 3 / 6 (50%) responses
  - Caspo + itra: 3 / 7 (43%) responses
  - Caspo + vori: 11 / 17 (65%) responses

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

Invasive aspergillosis: current guidelines

- Voriconazole is recommended as first line therapy by:
  - Australian guidelines (Slavin et al., Intern Med J, 2004)
  - British proposed standards of care (Denning et al., Lancet Infect Dis, 2003)
  - German guidelines (Bohme et al., Ann Hematol, 2003)
  - French consensus conference (Ann Fr Anesth Reanim, 2004)
  - Spanish guidelines (Gavalda et al., Enferm Infecc Microbiol Clin, 2003)

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)
Amphotericin B	D I	
Ambisome	B I	dose 3 – 5 mg/kg
ABLC	B II	dose 5 mg/kg
ABCD	D I	
Caspofungin	C III	
Itraconazole	C III	start with iv
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 III
  - Caspofungin + voriconazole — C III
  - 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

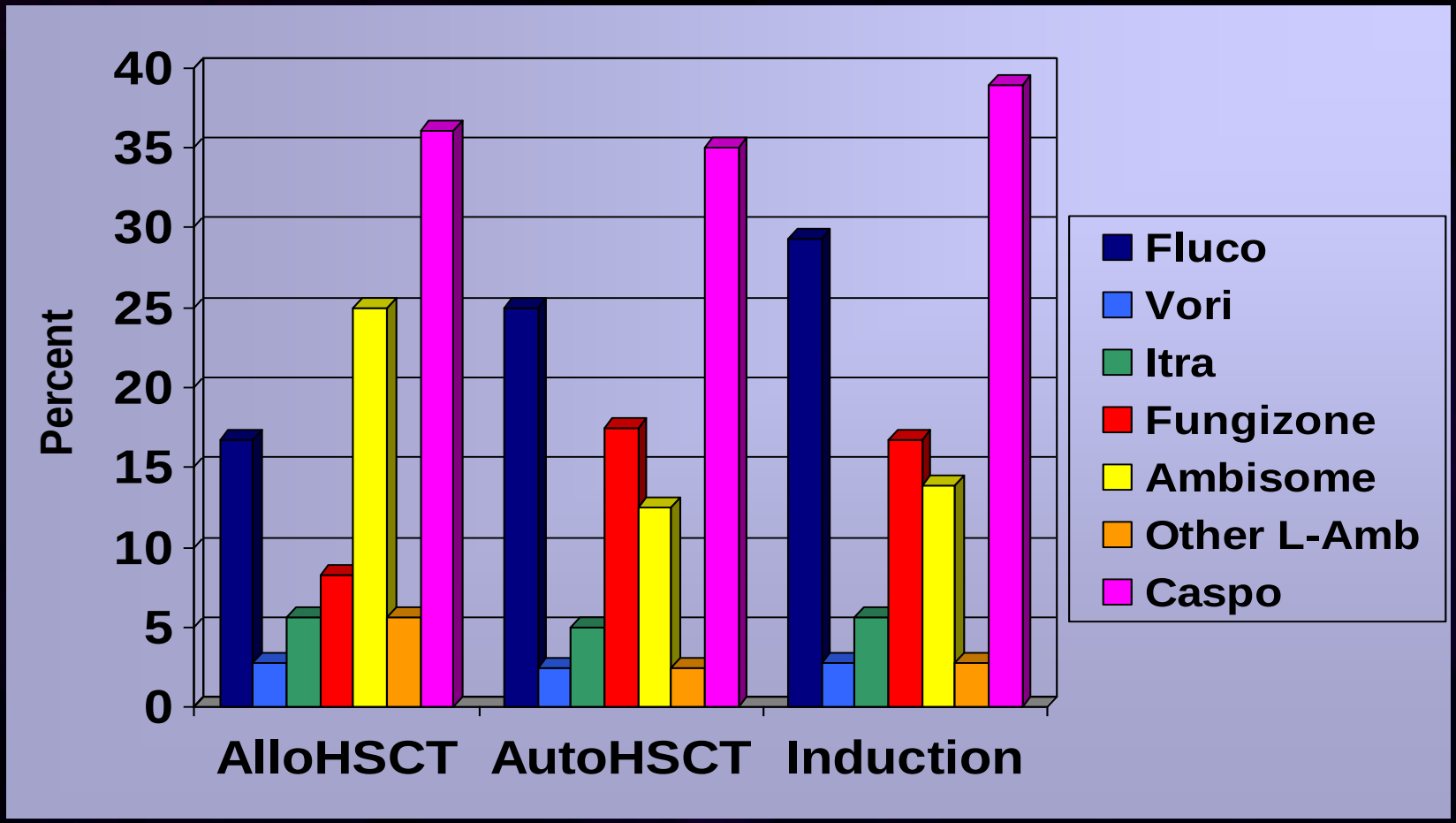
- **Duration of therapy**
  - **No fixed duration**

- **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

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



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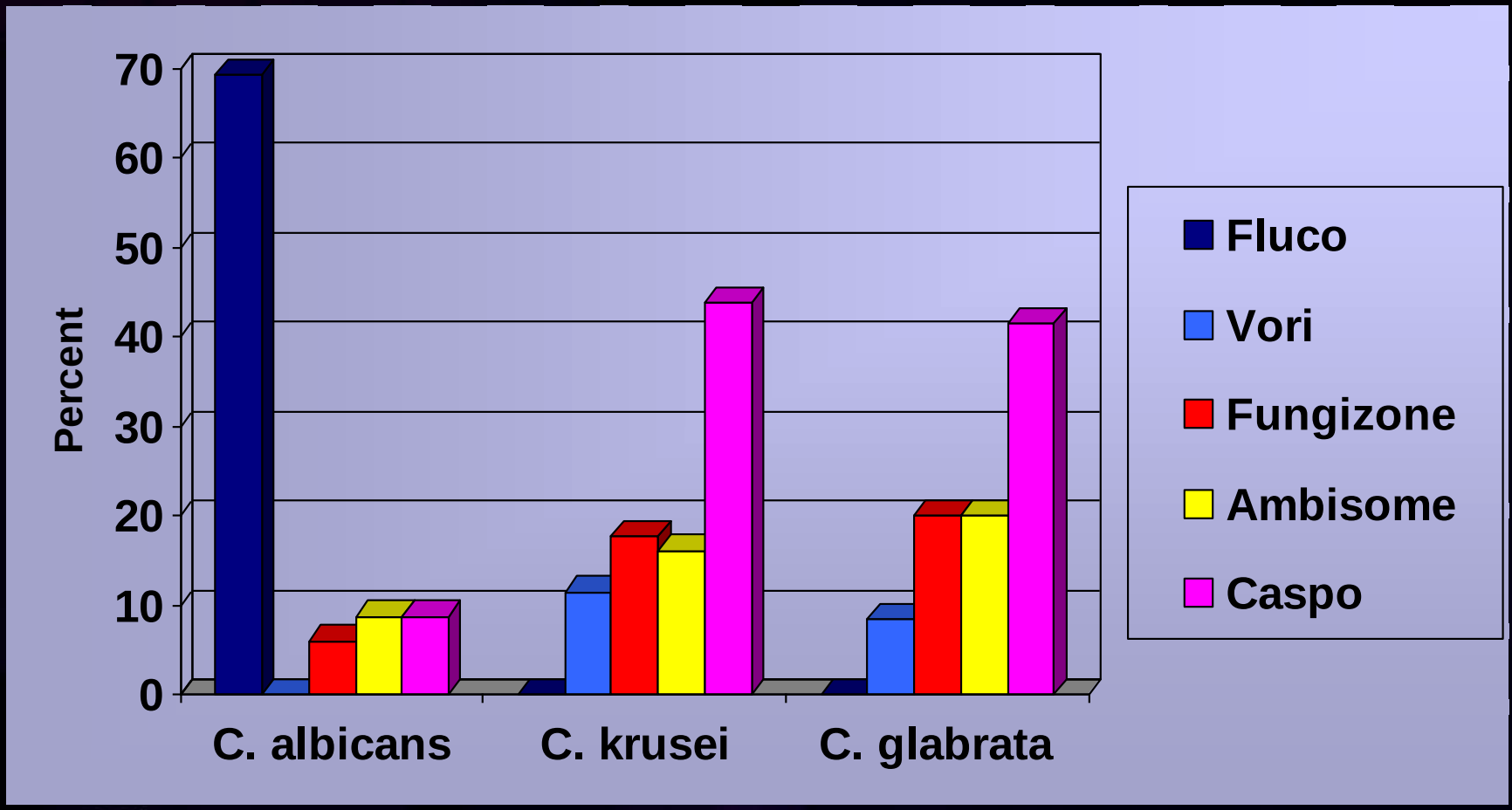
Results of the ECIL Questionnaire, September 2005

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



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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 guidelines

Guidelines	Hematologic	Neutropenia
Germany 2003	Fluco 400 - 800 (B III) AmphoB $\geq$ 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 (A II), 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

Recommendations Candidiasis

Candidemia in hematologic pts ***before identification***

Agent	General*	Comments for hematology pts
Fluconazole	A I	C III D III if azole prophylaxis or colonization with *C glabrata* E III if colonization with *C krusei*
Ampho B	A I	C III if concomitant nephrotox. drug E III if renal impairment
Lipid amphoB	A II	B II
Caspofungin	A I	B II
Voriconazole	A I	B II

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**** Overall population at risk for candidemia not restricted to hematology or neutropenic patients***

After identification: Candidemia due to *C. albicans*

Agent	General*	Comments for hematology pts
Fluconazole	A I	C III
Ampho B	A I **	C III **
Lipid amphoB	A II	B II
Caspofungin	A I	B II
Voriconazole	A I	C III

Overall population at risk for candidemia not restricted to hematology or neutropenic patients

****** ***D III if concomitant nephrotoxic drug and E III if renal impairment***

After identification: Candidemia due to *C. glabrata* or *C. Krusei*

Agent	General*	Comments for hematology pts
Fluconazole	C III E III	D III for *C glabrata* E III for *C krusei*
Ampho B	B I **	C III** for *C glabrata* and *C krusei*
Lipd amphoB	B II	B II for *C glabrata* and *C krusei*
Caspofungin	B I	B II for *C glabrata* and *C krusei*
Voriconazole	C III B I	C III for *C glabrata* C III for *C krusei*

Overall population at risk for candidemia not restricted to hematology or neutropenic patients

****** ***D III if concomitant nephrotoxic drug and E III if renal impairment***

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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 no. 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 looser B III
  - removal is always recommended when *C. parapsilosis* is isolated A II