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Antifungal Therapy in Leukemia Patients
2009 Update of the ECIL1 and ECIL 2 Guidelines

Raoul Herbrecht, Ursula Flückiger, Bertrand Gachot, Patricia Ribaud,
Anne Thiebaut, Catherine Cordonnier

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ELN LeukemiaNet European

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 Society for Human and Animal Mycology ISHAM ICHS

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: 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*

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*

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

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*

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

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/m² (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.