



**3rd
European
Conference on
Infections in
Leukemia**

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

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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	<i>C albicans</i>	A I	B II
	<i>C glabrata</i>	B I	B II
	<i>C krusei</i>	B I	B II
Anidulafungin	<i>C albicans</i>	A I	B II
	<i>C glabrata</i>	B I	B II
	<i>C krusei</i>	B I	B II
Caspofungin	<i>C albicans</i>	A I	B II
	<i>C glabrata</i>	B I	B II
	<i>C krusei</i>	B I	B II

Candidemia after species identification (2/2)

		Overall population	Hematological pts
Ambisome	<i>C albicans</i>	A I	B II
	<i>C glabrata</i>	B I	B II
	<i>C krusei</i>	B I	B II
Other lipid-AmB	<i>C albicans</i>	A II	B II
	<i>C glabrata</i>	B II	B II
	<i>C krusei</i>	B II	B II
AmB deoxycholate	<i>C albicans</i>	A I	C III
	<i>C glabrata</i>	B I	C III
	<i>C krusei</i>	B I	C III
Fluconazole	<i>C albicans</i>	A I	C III
	<i>C glabrata</i>	C III	D III
	<i>C krusei</i>	E III	E III
Voriconazole	<i>C albicans</i>	A I	C III
	<i>C glabrata</i>	C III	C III
	<i>C krusei</i>	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	<u>NO NEW STUDY</u>		
Empirical AF therapy			
Comparison 2 antifungal agents			
Maertens ICAAC 2007	Prospective, multicenter double-blind, randomized, CHILDREN	54 + 25	<u>Caspo vs. Liposomal AmB 2:1</u>
Kubiak ICAAC 2008	Retrospective, multicenter	161 + 173	<u>Caspofungin vs. Micafungin</u>
1 single antifungal agent			
Tamura Leuk-Lymph 2009	Prospective, multicenter, no control arm	277	<u>Micafungin</u>
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
ABL C	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
<u>NEW: Micafungin</u>	<u>100 mg</u>	<u>B</u>	<u>II</u>	<u>II</u>
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 amphotericin 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 cyclosporin 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.