2013-Update of the ECIL Guidelines for Antifungal Therapy in Leukemia and HSCT Patients (ECIL-5)

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Introduction

- First recommendations for the treatment of *Candida* and *Aspergillus* infections in hematological patients at ECIL-1 *(Herbrecht et al., Eur. J. Cancer Supplement, 2007)*, updated at ECIL-2 and 3 *(Maertens et al., Bone Marrow Transplant., 2010)*
- First recommendations for the treatment of *Mucorales* at ECIL-3 *(Skiada et al., Haematologica, 2013)*
- Goals for 2013 update
  - ✓ To update the recommendations with analysis of the new data for *Candida*, *Aspergillus* and *Mucorales* infections in hematological patients
  - ✓ To change the 5-level scale (A to E) for Strength of Recommendations for *Candida* and *Aspergillus* infections into a 3-level scale (A to C) already used for *Mucorales* infections with no modification in the scale for Quality of Evidence
- Three subgroups
  - ✓ Candidemia: F. Tissot, T. Calandra, C. Viscoli
  - ✓ Aspergillosis: A. Groll , S. Agrawal, L. Pagano
  - ✓ Mucormycosis: C. Lass-Flörl, G. Pettrikos, A. Skiada
  - ✓ Coordination: R. Herbrecht

All changes in grading appear in green on the next slides

Changes in grading scale for Aspergillus and Candida infections

ECIL-5 (2013)

Strength of Recommendations		
Grade	**ECIL-1 to 3**	**ECIL-5**
A	Strong evidence for efficacy and substantial clinical benefit: Strongly recommended	**Good evidence to support a recommendation for use**
B	Strong or moderate evidence for efficacy, but only limited clinical benefit: Generally recommended	**Moderate evidence to support a recommendation for use**
C	Insufficient evidence for efficacy; or efficacy does not outweigh possible adverse consequences (e.g. drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches: Optional	**Poor evidence to support a recommendation for use**
D	Moderate evidence against efficacy or for adverse outcome: Generally not recommended	**Omitted**
E	Strong evidence against efficacy or of adverse outcome: Never recommended	**Omitted**

Quality of Evidence	
Grade	**ECIL-1to 5 (no change)**
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytical studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Invasive candidiasis

Literature Search: candidemia, neutropenia

Clinical studies:	**Neutropenic patients**
1. Rex JH et al, N Eng J Med 1994	0
2. Nguyen MH et al, Arch Intern Med, 1995	NA
3. Anaissie EJ et al, Clin Infect Dis 1996	22/90 (24%)
4. Anaissie EJ et al, Am J Med, 1996	44/142 (31%)
5. Phillips P et al, Eur J Clin Microbiol Infect Dis, 1997	0
6. Mora-Duarte J et al, N Eng J Med 2002	24/224 (11%)
7. Rex JH et al, Clin Infect Dis 2003	0
8. Kullberg BJ et al, Lancet, 2005	0
9. Kartsonis NA et al, J Antimicrob Chemother 2004	5/37 (13%)
10. DiNubile et al, J Infect 2005 (subgroup analysis of 7)	24/74 (32%)
11. Ostrosky-Zeichner L et al. Eur J Clin Microbiol Infect Dis, 2005	25%
12. Reboli et al, N Eng J Med 2007	7/245 (3%)
13. Kuse et al, Lancet 2007	62/531 (12%)
14. Pappas et al, Clin Infect Dis 2007	50/578 (9%)
15. Betts et al, Clin Infect Dis 2009	15/204 (7%)

Literature Search: candidemia, neutropenia

Systematic review/meta-analyses (new data)	Neutropenic patients
16. Reboli et al, BMC Inf Dis 2011 (subgroup analysis of 12)	5/135 (4%)
17. Cornely et al, Mycoses 2011 (subgroup analysis of 13 and 14)	125/1067 (12%)
18. Andes et al, Clin Infect Dis 2012	139/1915 (9%)
19. Kanji et al, Leukemia Lymphoma 2013	342 (100%)

Anidulafungin in *C. albicans* candidiasis

Subgroup analysis of the anidulafungin randomized clinical trial (Reboli, NEJM 2007) in 135 adult patients with *C. albicans* infection (87% candidemia)

	Anidulafungin	Fluconazole	p value
Number pts (mITT)	74	61	
- Neutropenic patients	1	4	
Global response			
- End of iv therapy	81.1%	62.3%	0.02
- End of all therapy	79.7%	55.7%	0.048
Time to negative blood culture (median)			
- *C. albicans*	2 days	5 days	<0.05
- *C.* non *albicans*	EXCLUSION	CRITERIA	
All cause 6-week mortality	20.3%	21.3%	NS

Anidulafungin was published as being non inferior to fluconazole with a claim that it was superior to fluconazole

Reboli et al., BMC Inf Dis 2011

Micafungin for invasive candidiasis

Subgroup analysis of the micafungin randomized clinical trial (Kuse, Lancet 2007; Pappas, CID 2007) in 359 patients with vs. 942 without malignancy

Treatment success (mITT)	Micafungin / L-AmB trial		Micafungin / caspofungin trial		
	MICA 100 (n=244)	L-AmB (n=245)	MICA 100 (n=191)	MICA 150 (n=199)	CASPO (n=188)
Neutropenic pts	**37 (15%)**	**38 (16%)**	**22 (11%)**	**17 (8%)**	**11 (6%)**
Malignancy	62/87 (71.3)	69/96 (71.9)	51/68 (75)	33/56 (58.9)	37/52 (71.2)
Neutropenic	21/34 (61.8)	21/34 (61.8)	17/20 (85)	9/17 (52.9)	6/9 (66.7)
Non-neutropenic	41/53 (77.4)	48/62 (77.4)	34/48 (70.8)	24/39 (61.5)	31/43 (72.1)
No malignancy	118/157 (75.2)	107/149 (71.8)	95/123 (77.2)	109/143 (76.2)	99/136 (72.8)
C. albicans					
Malignancy	80.5%	77.1%	74.2%	62.5%	74.1%
No malignancy	78.1%	73.5%	79%	74%	72.4%
C.* non-*albicans					
Malignancy	66.7%	68.7%	78.4%	55.2%	63.3%
No malignancy	73.3%	68.7%	75.4%	78.4%	72.9%

Similar efficacy of micafungin vs. caspofungin and L-AmB in patients with and without malignancy

Cornely et al, Mycoses 2011

Echinocandins for invasive candidiasis

- **Patient-level, quantitative review of 7 randomized clinical trials :**
  - 1915 patients ; 139 (9%) neutropenic
  - Invasive candidiasis: candidemia (84%)
  - *Candida* spp: *C. albicans* (44%), *C. tropicalis* (18%), *C. parapsilosis* (16%), *C. glabrata* (11%), *C. krusei* (2%)
- **30-day mortality (univariate analysis):**
  - Echinocandins vs. others: 27% vs. 36% (p<0.0001)
  - Triazoles vs. others: 36% vs. 30% (p=0.006)
  - Polyenes vs. others: 35% vs. 30% (p=0.04)
- **30-day mortality (logistic regression):**
  - Echinocandin use (OR=0.50, 95% CI=0.35-0.72, p=0.0001) and central venous catheter removal (OR=0.65, 95% CI=0.45-0.94, p=0.02) are associated with decreased mortality
  - Increasing age (OR=1.01, 95% CI=1.00-1.02, p=0.02), APACHE II score (OR=1.11, 95% CI=1.08-1.14, p=0.0001), immunosuppressive therapy (OR=1.69, 95% CI=1.18-2.44, p=0.001), infection with *C. tropicalis* (OR=1.64, 95% CI=1.11-2.39, p=0.01) are associated with increased mortality

Andes et al, CID 2012

Candidemia in hematologic patients before species identification (Changes in ECIL-5 compared to ECIL-1 to 3)

	Overall population		Hematological pts	
Micafungin[1]	A I		~~B II~~	A II
Anidulafungin	A I		~~B II~~	A III
Caspofungin	A I		~~B II~~	A II
AmBisome	A I		~~B II~~	A II
ABLC, ABCD	B II		B II	
AmB deoxycholate [2]	~~A I~~	C I	~~C III~~	C II
Fluconazole[3,4]	A I		C III	
Voriconazole[4]	A I		B II	

[1] See warning box in European label
[2] Close monitoring for adverse event is required
[3] Not in severely ill patients
[4] Not in patients with previous azole exposure

(Herbrecht et al, Eur J Cancer Supplement, 2007; Maertens et al, Bone Marrow Transplant, 2011)

Candidemia after species identification (ECIL-5 update)

ECIL-5 (2013)

Candida species	Overall population	Hematological patients
C. albicans	Echinocandins (A I) Fluconazole (A I)[1] Voriconazole (A I) L-AmB (A I) / ABCD (A II) / ABLC (A II) / d-AmB (C I)	Echinocandins (A II)[2] Fluconazole (C III) Voriconazole (C III) L-AmB (B II) / ABCD (B II) / ABLC (B II) / d-AmB (CII)
C. glabrata	Echinocandins (A I) L-AmB (B I) / ABCD (B II) / ABLC (B II) / d-AmB (C I)	Echinocandins (A II)[2] L-AmB (B II) / ABCD (B II) / ABLC (B II) / d-AmB (C II)
C. krusei	Echinocandins (A II) L-AmB (B I) / ABCD (B II) / ABLC (B II) /d-AmB (C I) Voriconazole (B I)	Echinocandins (A III) L-AmB (B II) / ABCD (B II) / ABLC (B II) /d-AmB (C II) Voriconazole (C III)
C. parapsilosis	Fluconazole (A II) Voriconazole (B I) Echinocandins (B II) L-AmB (B I) / ABCD (BI I) / ABLC (B II) /d-AmB (C I)	Fluconazole (A III) Voriconazole (C III) Echinocandins (B III) L-AmB (B II) / ABCD (B II) / ABLC (B II) /d-AmB (C II)

[1]C I in severely ill patients

[2]A III for anidulafungin

Recommendations for catheter removal in candidemia

Literature search: catheter removal

Clinical studies (old data):	**% neutropenic patients**
1) Nguyen et al, Arch Int Med 1995	NA
2) Rex et al, CID 1995	0 %
3) Anaissie EJ et al. Am J Med, 1996	44/142 (31%)
4) Anaissie EJ et al, Am J Med 1998	217/472 (46%)
5) Mora-Duarte J et al. NEJM, 2002	24/224 (11%)
6) Rex et al, CID 2003	0 %
7) Raad et al, CID 2004	192/404 (48%)
8) Kuse et al, Lancet 2007	62/531 (12%)
9) Pappas et al, CID 2007	50/578 (9%)
10) Betts et al, CID 2009	15/204 (7%)
Systematic review/meta-analyses (new data):	
11) Nucci et al, CID 2010 (substudy of 8 and 9)	85/842 (10%)
12) Horn et al, Eur J Clin Micro Inf Dis 2010 (substudy of 8 and 9)	107/1070 (10%)
13) Andes et al, CID 2012	139/1915 (9%)
14) Garnacho-Montero et al, JAC 2013	13/188 (7%)

Early catheter removal in candidemia

Subgroup analysis of micafungin RCT (Kuse, Lancet 2007; Pappas, CID 2007) of 842 patients with candidemia and CVC (10% neutropenic)

	Removed within 48h	Not removed or removed > 48h	p value
Number pts (mITT)	354	488	
Overall success	75.1%	66.8%	0.02
Persistent candidemia	34/328 (10.4%)	62/457 (13.6%)	0.18
Recurrent candidemia	6.2%	7.8%	0.42
Survival at 28 days	77.4%	69.4%	0.01
Survival at 42 days	72.3%	64.1%	0.01

No difference in time to negative blood culture

By multivariate analysis: no difference in treatment success or mortality

No beneficial effect of early catheter removal on treatment success, mycological eradication and survival

Nucci et al., CID 2010

Catheter removal for candidemia

- **1915 patients**:
  - 1492 (78%) with CVC
  - 1134/1492 (76%) removed
- ***Candida* spp:** *C. albicans* (44%), *C. tropicalis* (18%), *C. parapsilosis* (16%), *C. glabrata* (11%), *C. krusei* (2%)
- **Univariate analysis:**
  - 30-day mortality: 28% vs. 41% (p<0.0001) when CVC removed
- **Sensitivity analysis:**
  - impact of CVC removal significant for the 3 lowest APACHE II quartiles, but not for the highest quartile (> 32)
- **Multivariate analysis**
  - 30-day mortality: OR 0.65 (95%CI 0.45 - 0.94), p=0.02

Catheter removal was associated with reduced mortality after adjustment for severity of infection (APACHE II < 32)

Andes et al., CID 2012

Early catheter removal for primary and secondary candidemia

Prospective observational study of consecutive candidemia in patients with CVC at a single center (*C. albicans:* 46%, *C. parapsilosis :* 20%)

	Primary candidemia (no portal of entry/catheter-related)	Secondary candidemia (not catheter-related)
Number pts	148	40
- neutropenic pts	12 (8.1%)	1 (2.5%)
- CVC removal <48h	64/138 (43%)	7/39 (17%)
In-hospital mortality (HR, 95% CI, p value)		
- APACHE II score	1.13 (1.07-1.20, p<0.001)	1.09 (0.96-1.23, p=0.16)
- CVC removal	0.39 (0.16-0.93, p=0.03)	0.76 (0.15-3.75, p=0.74)
- antifungal therapy	0.46 (0.19-1.08, p=0.07)	0.4 (0.23-0.83, p=0.03)

Early catheter removal was associated with reduced mortality for primary, but not secondary candidemia

Garnacho-Montero et al., JAC 2013

Candidemia: Catheter removal

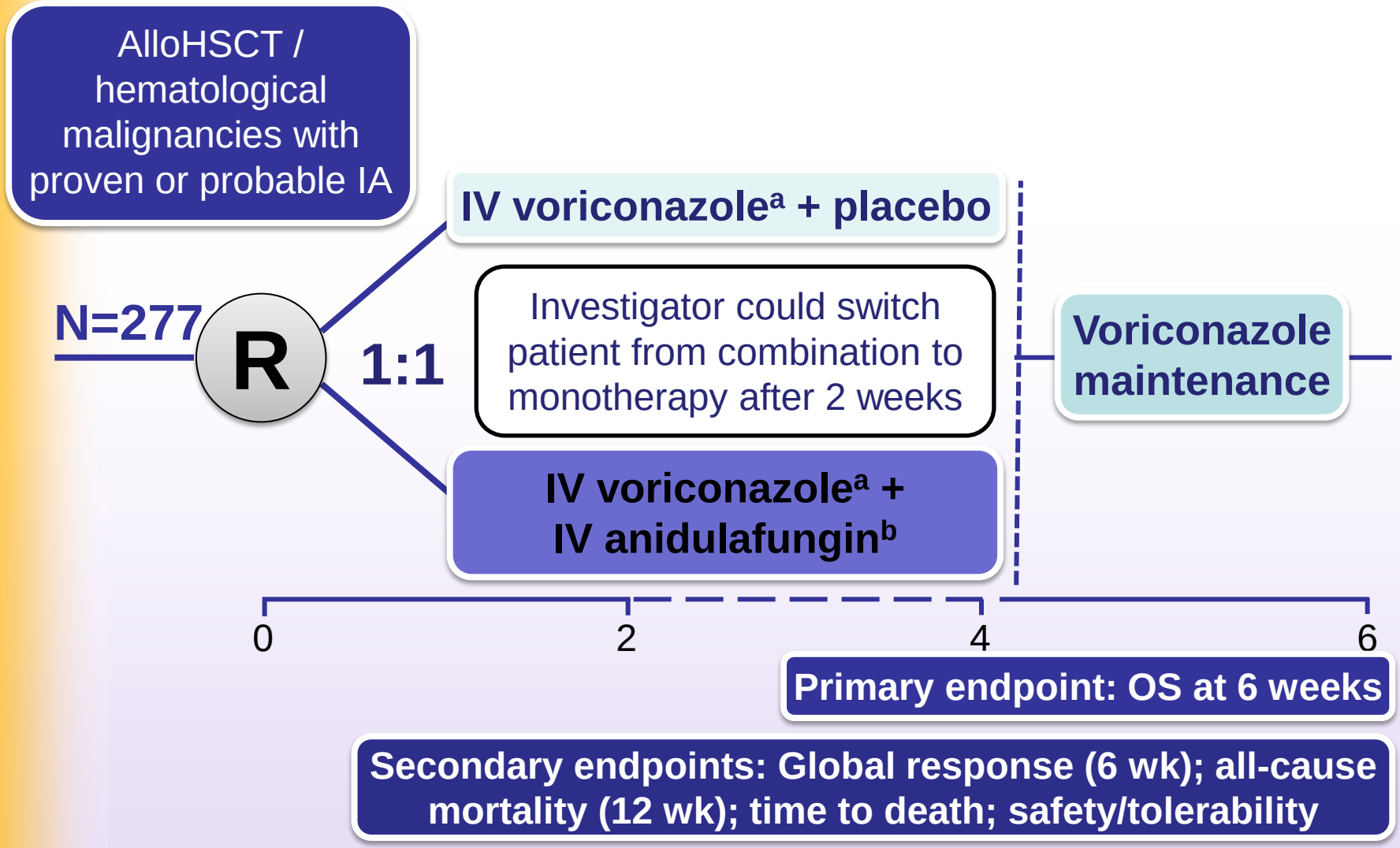
- Removal of central venous line
  - In non-hematological patients **A II**
  - In hematology patients ~~**B III**~~ **B II**
  - ~~Removal is always recommended when *C parapsilosis* is isolated **A II**~~
- When catheter cannot be removed, treatment with an echinocandin or a lipid formulation of amphotericin B is preferred **B III**

Invasive aspergillosis

Invasive aspergillosis – front-line

Reference	Kind of study	Antifungal agent	N° cases of aspergillosis	OR	OS
Ellis et al CID 1998	Prospective, randomized, multicentric	L-AmB 1 mg/kg L-AmB 4 mg/kg	41 48	58% 52%	43% 37%
Caillot et al CID 2001	Prospective, observational, multicentric	Itraconazole	31	48%	87%
Bowden et al CID 2002	Prospective, randomized, multicentric	ABCD d-AmB	88 86	52% 51%	64% 55%
Herbrecht et al NEJM 2002	Prospective, randomized, multicentric	d-AmB Voriconazole	133 144	32% 53%	58% 71%
Candoni et al Eur J Hem 2005	Prospective, observational, monocentric	Caspofungin	32	56%	53%
Viscoli et al JAC 2009	Prospective, multicentric, AMLs	Caspofungin	61	33%	54%
Cornely et al CID 2007	Prospective, randomized, multicentric, 59% possible	L-AmB 3 mg/kg L-AmB 10 mg/kg	107 94	50% 46%	72% 59%
Herbrecht et al BMT 2010	Prospective, multicentric, alloHSCTs	Caspofungin	24	42%	50%
Cornely et al. AAC 2011	Prospective, multicentric, 89% hematol malignancies	Caspofungin 70-200 mg QD	46	54%	72%
Marr et al ESCMID 2012	Prospective, randomized, multicentric	Voriconazole Voriconazole+anidulafungin	135 142		61% 71 %

Combination for primary therapy of IA



[a]6 mg/kg q12h Day 1, then 4 mg/kg q12h (a switch to oral voriconazole [300 mg q12h] was allowed after ≥7 days of IV therapy)
[b]200 mg on Day 1, then 100 mg q24h

(Marr et al, ECCMID, London, 2012)

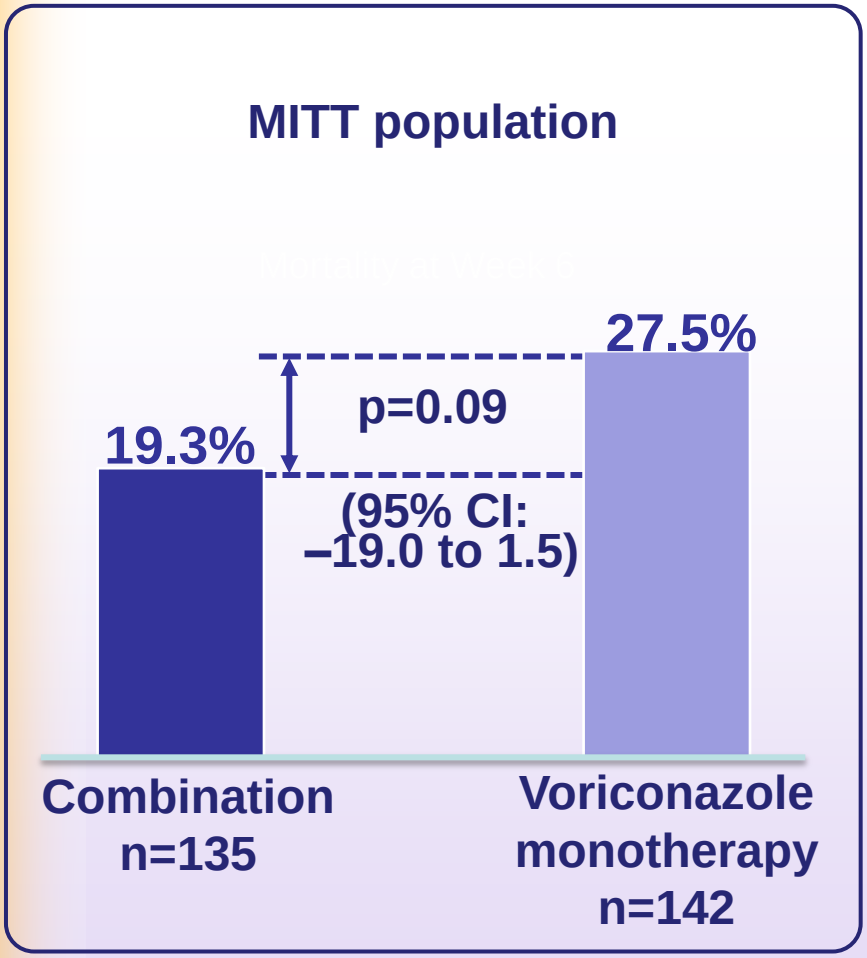
IA diagnoses at baseline

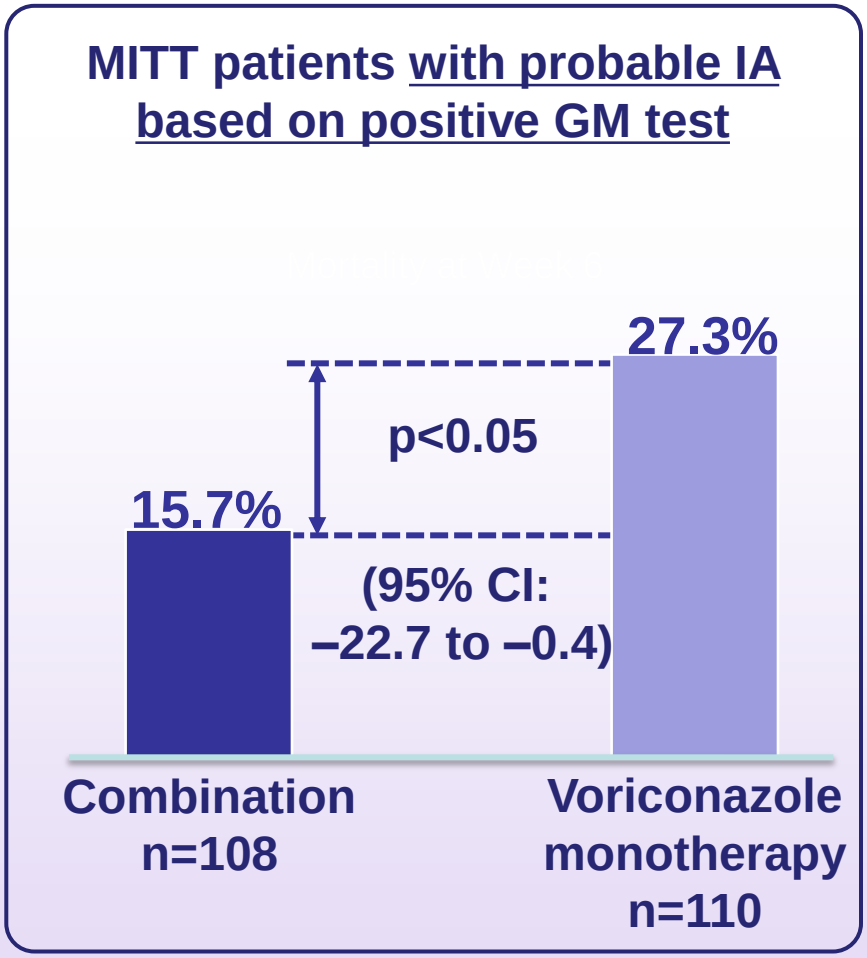
Modified ITT population	Combination N=135	Voriconazole monotherapy N=142
Probable IA, n (%		
Histopathology without culture	4 (3)	0
Culture or cytology of BAL	20 (15)	30 (21)
Positive GM only	**108 (80)**	**110 (77)**
Positive BAL GM and serum GM	7 (5)	12 (8)
Positive serum GM only	61 (45)	64 (45)
Positive BAL GM only	40 (30)	34 (24)
Proven IA, n (%)		
Histopathology with culture	1 (1)	0
Culture of tissue	2 (1)	0
Histopathology without culture	0	2 (1)

GM: galactomannan

(Marr et al, ECCMID, London, 2012)

Mortality at Week 6





p-value for mortality estimates adjusted for randomisation strata

(Marr et al, ECCMID, London, 2012)

Invasive aspergillosis: First-line

Agent	Grade	Comments
Voriconazole	A I	2x6 mg/kg D1 then 2x4 mg/kg (initiation with oral: CIII)
Ambisome	B I	dose 3 mg/kg
ABLC	B II	dose 5 mg/kg
Caspofungin	C II	
Itraconazole	C III	
ABCD	C I	
Combination voriconazole + anidulafungin	C I [1]	
Other combinations	C III	

AGAINST THE USE

Amphotericin B deoxycholate	A I

[1] *provisional*

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

Invasive aspergillosis – Salvage treatment

Reference	Kind of study	Antifungal agent	N° cases of aspergillosis	OR	OS
Maertens et al CID 2004	Prospective, observational, multicentric	Caspofungin	83	45%	52%
Kontoyannis et al Cancer 2001	Prospective, observational, monocentric	Caspofungin + L-AmB	31	35%	nr
Walsh et al CID 2007	Prospective, observational, multicentric	Posaconazole	107	42%	38%
Caillot et al Acta Haematol 2003	Prospective, observational, multicentric	Itraconazole	21	52%	86%
Marr et al CID 2004	Retrospective, observational, monocentric	Voriconazole	31	nr	34%
		Vori + Caspo	16	nr	61%
Denning et al J Infect 2006	Prospective, observational, multicentric	Micafungin	22	41%	nr
Raad et al Leukemia 2008	Retrospective	Posaconazole	53	40%	57%
Denning et al CID 2002	Prospective, multicentric	Voriconazole	56	48%	45%

Invasive aspergillosis: salvage

Agent	Grade		Comments
Ambisome	~~B III~~	B II	no data in voriconazole failure
ABLC	~~B III~~	B II	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
Combination	~~C II~~	B II	different studies, not randomized

Mucormycosis: diagnosis and treatment

Rhizopus, *Mucor*, *Lichtheimia* (previously classified as *Absidia*), *Cunninghamella*, *Rhizomucor*, *Apophysomyces*, and *Saksenaea* are most important [1].

Cunninghamella, may be associated with a higher mortality rate in patients [2] and have been shown to be more virulent in experimental models [3].

No evidence that identification of the causative Mucorales to the genus and/or species level led to guide antifungal treatment [4]. Species identification important for outbreak-investigations [5].

The differentiation between Mucorales and Non-Mucorales infection is of importance as it has major therapeutic implications.

1. Kwon-Chung KJ. *Clin Infect Dis* 2012; **54 Suppl 1**: S8-S15.
2. Gomes MZ, Lewis RE, Kontoyiannis DP. *Clin Microbiol Rev* 2011; **24**: 411-45.
3. Petraitis V, Petraitiene R, Antachopoulos C, Hughes JE, Cotton MP, Kasai M et al. *Med Mycol* 2013; **51**: 72-82.
4. Salas V, Pastor FJ, Calvo E, Alvarez E, Sutton DA, Mayayo E et al. *Antimicrob Agents Chemother* 2012; **56**: 2246-50.
5. Rammaert B, Lanternier F, Zahar JR, Dannaoui E, Bougnoux ME, Lecuit M et al. *Clin Infect Dis* 2012; **54 Suppl 1**: S44-54.

Diagnosis: new approaches

- Mucorales specific T cells detection
- Molecular tests on
  - Formalin fixed tissue
  - Clinical samples
  - Serum
  - Cultures
- MALDI-TOF

Although very promising, these methods still need more investigation. No grading so far

Potenza L, Vallerini D, Barozzi P, Riva G, Forghieri F, Zanetti E et al. *Blood* 2011; **118**: 5416-9

Buitrago MJ, Aguado JM, Ballen A et al. Clin Microbiol Infect 2013; 19: E271-7

Bernal-Martínez L, Buitrago MJ, Castelli MV, et al. Clin Microbiol Infect 2013, 19:E1-7

Walther G, Pawłowska J, Alastruey-Izquierdo A, et al. Persoonia 2013, 30:11-47.

Lass-Flörl C, Mutschlechner W, Aigner M, et al. J Clin Microbiol. 2013, 51:863-8.

Millon L, Larosa F, Lepiller Q, et al. Clin Infect Dis 2013;56: e95-e101.

De Carolis E, Posteraro B, Lass-Flörl C, et al. *Clin Microbiol Infect* 2012; **18**: 475-84.

Schrodl W, Heydel T, Schwartze VU, et al. *J Clin Microbiol* 2012; **50**: 419-27.

Diagnosis: Susceptibility testing

In general, amphotericin B and posaconazole are the most active drugs *in vitro* [14, 16].

Recently, in vitro combination studies have been performed to explore the interaction of antifungals against *Mucorales*. However, the clinical significance of these combination data remains uncertain [17].

Currently, no validated minimum inhibitory concentrations breakpoints for any of the drugs are available and thus determination of susceptibility categories is not possible.

Drogari-Apiranthitou M, Mantopoulou FD, Skiada A ,et al. *J Antimicrob Chemother* 2012; **67**: 1937-40.
Vitale RG, de Hoog GS, Schwarz P, et al. *J Clin Microbiol* 2012; **50**: 66-75.
Zhang S, Li R, Yu J. *Antimicrob Agents Chemother* 2013.

RetroZygo study

Retrospective ; registry

First-line therapy

L-AmB	(n = 53)
Amphotericin B deoxycholate	(n = 6)
Amphotericin B lipid complex posaconazole	(n = 12)
Amphotericin B lipid complex or L-AmB and posaconazole	(n = 11)
L-AmB and caspofungin	(n = 3)
L-AmB, posaconazole and caspofungin	(n = 1)

The type of first-line antifungal treatment was not associated with survival (P =0.25)

No impact on grading

Lanternier F, Dannaoui E, Morizot G et al. *Clin Infect Dis* 2012; **54 Suppl 1**: S35-43.

Posaconazole

- 96 cases collected in a case-report revision
  - 67 cases plus surgery
  - 2 cases only posaconazole
  - 39 cases posaconazole plus lipid compound of AmB
- Response
  - Complete response: 62 (64%)
  - Partial response: 7 (7%)
  - Stable: 1 (1%)

No impact on grading

Vehreschild JJ, Birtel A, Vehreschild MJ et al. *Crit Rev Microbiol* 2012.

Combination treatment

- Review of 32 cases from the SEIFEM and FUNGISCOPE registries treated with a combination of posaconazole with a lipid formulation of amphotericin B (ABLC , n=5 ; liposomal amphotericin B, n=27)
- Posaconazole was mainly used as salvage treatment
- Response rate: 56%

Pagano L, Cornely O, Busca A et al. *Haematologica* 2013.

Mucormycosis
Recommendation for first line (part 1)

Management includes antifungal therapy, control of underlying conditions and surgery	**A II**
Antifungal therapy	
- AmB deoxycholate	**C II**
- Liposomal AmB	**B II [1]**
- ABLC	**B II [1]**
- ABCD	**C II**
- Posaconazole	**CIII[2]**
- Combination therapy	**CIII**

[1] Liposomal amphotericin B should be preferred in CNS infection and/or renal failure.

[2] No data to support its use as first line treatment. May be used as an alternative when amphotericin B is absolutely contraindicated.

Mucormycosis
Recommendation for first line (part 2)

Management includes antifungal therapy, control of underlying conditions and surgery.	A II
Control of underlying condition	A II [3]
Surgery	
- rhino-orbito-cerebral	A II
- soft tissue	A II
- localized pulmonary lesion	B III
- disseminated	CIII[4]
Hyperbaric oxygen	CIII

[3] Control of underlying condition includes control of diabetes, hematopoietic growth factor if neutropenia, discontinuation/tapering of steroids, reduction of immunosuppressive therapy

[4] Surgery should be considered on a case by case basis, using a multi-disciplinary approach

Mucormycosis
Recommendation for salvage therapy (failure of first line)

Salvage (failure of first line)

Management includes antifungal therapy, control of underlying disease and surgery. A II

Posaconazole BII

Combination lipid AmB and caspofungin ~~BII~~ B III

Combination lipid AmB and posaconazole ~~CIII~~ B III

AGAINST THE USE

Combination with deferasirox A II

Mucormycosis
Recommendation for maintenance therapy or in case of intolerance to first line therapy

Maintenance therapy (prior response or stable disease)

Or intolerance to first line therapy

Posaconazole **B II [1]**

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[1] whenever possible, overlap of a few days (at least 5) with first line therapy to obtain appropriate serum levels. Monitoring of serum levels might be indicated