3rd European Conference on Infections in Leukemia

September 25 - 26 2009, Juan-les-Pins - France

ELN European LeukemiaNet

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 IVZW

ICHS International Conference on Infections in Immunocompromised Host Society

Guidelines for treatment of zygomycosis by ECIL 3

A. Skiada, A. Groll, R. Herbrecht,
F. Lanternier, O. Lortholary,
L. Pagano, S. Zimmerli,
G. Petrikkos.

Background

- Zygomycosis is the third most common invasive fungal infection after candidiasis and aspergillosis.
- It has a high mortality, even when appropriately treated.
- There are no guidelines for the treatment of zygomycosis.

Questions

- What is the optimal
  - First line antifungal therapy for zygomycosis?
  - Second line antifungal therapy for zygomycosis?
  - Dosing and duration of antifungal therapy?
- What is the role of surgery in the treatment of zygomycosis?
- What are the indications for combination therapy or adjunctive treatments?

Methods

- Literature review
  - Pubmed
  - ICAAC, ECCMID, ASH, ASCO and EBMT

- IDSA grading system

IDSA-United States Public Health Service grading system for ranking recommendations

Quality of evidence	Strength of recommendation
I **Evidence from ≥ 1 properly randomized, controlled trial**	**A Good evidence to support a recommendation for use**
II **Evidence from ≥ well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments**	**B Moderate evidence to support a recommendation for use**
III **Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees**	**C Poor evidence to support a recommendation**

Proportion of hematological malignancies in zygomycoses case-series

	Years	Population	Cases	%
Roden et al, Clin Infect Dis 2005; 41:634-53	1887-2003	929 cases	154 HM 44 HSCT	17 5
Zaoutis et al, Ped Infect Dis J, 2007; 26:723-27	1939-2007	157 pediatrics	28 HM 9 HSCT	14 4
Skiada et al, CMI) (ECMM)	2005-2007	230 cases	123 HM	53
Ruping et al, ICAAC 2009 (M-1049) (Fungiscope)	2006-2009	41 cases	26	63.4

Incidence of zygomycoses in HMs treated with conventional approaches

	Years	Population	Cases	%
Pagano et al, Br J Haematol 1997;99: 331-6 (GIMEMA)	1987-1995	3148 acute leukemia	37	1
Nosari et al, Haematologica 2000; 85:1068-71	1987-1999	653 acute leukemia	13	1.6
Kontoyiannis et al, CID 2000; 30:851-6	1989-1998	624 autopsy in HMs	12	1.9
Kontoyiannis et al, CID 2000; 30:851-6	1989–1993 1994–1998	8 per 100,000 20 per 100,000		
Pagano et al, Haematologica 2006; 91:1068 (SEIFEM)	1999-2003	11802 HM	14	0.1

Incidence of zygomycoses in HSCTs

	Years	Population	Cases
Marr at al, CID 2002: 100:4358-66	1985-1999	5589 HSCT	29
Park et al, IDSA 2005 *(TRANSNET)*	2001-2004	9314 HSCT	37
Pagano et al, Clin Infect Dis 2007; 45:1161 (SEIFEM)	1999-2003	1249 alloHSCT 1979 autoHSCT	1
Garcia Vidal et al, Clin Infect Dis 2008; 47:1041–50	1998-2002	1248 HSCT	8
Neofytos et al., Clin Infect Dis 2009; 48:265–73 *(PATH-Alliance)*	2004-2007	alloHSCT autoHSCT	12 8

Role of amphotericin B in the treatment of zygomycosis

Amphotericin B - Activity *in vitro* *

	AMB % ≤1ug/mL	**PCZ** **% ≤0.5µg/mL**	ITC % ≤0.5µg/mL
Rhizopus sp (101)	100	**80**	62
Rhizopus arrhizus (20)	100	**64**	50
Rhizopus microsporus (12)	100	**78**	60
Mucor sp. (41)	94	**70**	57
Mucor circinelloides (6)	100	**0**	0
Rhizomucor sp.(5)	100	**67**	67
Absidia corymbifera (9)	100	**100**	100
Cunninghamella sp. (13)	63	**75**	29
Apophysomyces elegans (6)	100	**83**	80

* M38-A

Almyroudis et al., AAC 07

Amphotericin B - *in vitro* data

- For the *Mucorales* as a whole, amphotericin B was the most active antifungal agent, with the majority of strains displaying MICs near the suggested breakpoint of 1 g/ml.

- Only some strains of *Cunninghamella* sp. had higher MICs.

Almyroudis et al., AAC 07

Amphotericin B - Activity *in vitro*

- 37 strains / 7 species of zygomycetes
- NCCLS M38-P; 48h; 80% inhibition (azoles) / 100% (Amb)

Organism (no. of isolates) and agent	MIC (µg/ml)			
	Mean	Range	50%[a]	90%[a]
POS	1.22	0.015–8	0.25	4
ITC	1.95	0.015–8	0.5	8
VRC	41.14	0.5–>64	>64	>64
FLC	57.82	1–>64	>64	>64
AMB	0.33	0.03–2	0.25	0.5

[a] MIC at which 50% or 90% of the isolates were inhibited.

Sun et al., AAC 02

Amphotericin B - Activity *in vitro*

Table 4. Susceptibilities of zygomycetes to various antifungal agents*

Organism	Antifungal	MIC_{90} (mcg/mL)	Percent inhibited at MIC ≤1 mcg/mL
Rhizopus species	Posaconazole	1–4	40
	Voriconazole	1–8+	40
	Itraconazole	1–8+	20
	Amphotericin B	0.5–1	100
	Caspofungin	>8	0
Mucor species	Posaconazole	0.5–8+	67
	Voriconazole	1–8+	33
	Itraconazole	2–8+	0
	Amphotericin B	0.5–1	100
	Caspofungin	>8	0

Proc (Bayl Univ Med Cent) 2007;20:188–196

Amphotericin B- Efficacy *in vivo*

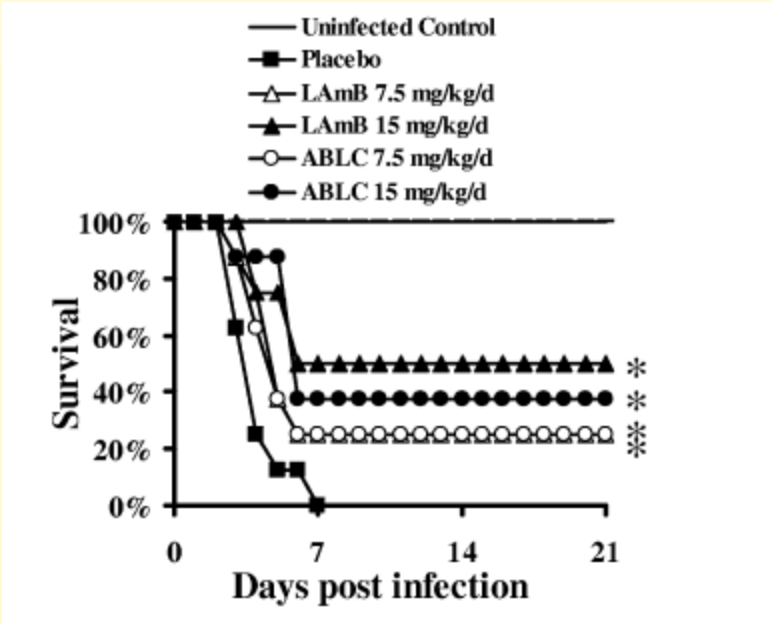
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2008, p. 1573–1576 Vol. 52, I
0066-4804/08/$08.00+0 doi:10.1128/AAC.01488-07

Comparison of Lipid Amphotericin B Preparations in Treating Murine Zygomycosis▽

Ashraf S. Ibrahim,[1,2]* Teclegiorgis Gebremariam,[1] Mohamed I. Husseiny,[1] David A. Stevens,[3,4] Yue Fu,[1,2] John E. Edwards, Jr.,[1,2] and Brad Spellberg[1,2]

Efficacy of LAmB and ABLC in the neutropenic mouse model of zygomycosis.

"There was no significant difference in survival among the mice treated with the different antifungals at the different doses, although, again, the highest number of surviving mice was in the group treated with LAmB at 15 mg/kg/day."



Clinical efficacy of Ampho-B

- Amphotericin B deoxycholate has been the “gold standard” for more than 40 years
- No randomized trials
- Only case-series available

Roden et al. CID 2005; 41:634–53

- In an overview of 929 case reports of zygomycosis, among **532** cases treated with AmB, the response rate was **61%**, compared to **69%** of the **116** patients treated with lipid compounds of AmB.
- Both haematological and non-haematological patients were included in this review

Improved Outcome of Zygomycosis in Patients with Hematological Diseases?

B. GLEISSNER[a,*], A. SCHILLING[b], I. ANAGNOSTOPOLOUS[c], I. SIEHL[a] and E. THIEL[a]

Leukemia & Lymphoma, July 2004 Vol. 45 (7), pp. 1351–1360

- Review of 120 cases from 1986 to 2002 with hematological malignancy and zygomycosis.
- 73 patients received d-AmB
- 26 patients received L-AMB
- 5 patients received ABLC
- 2 patients received ABCD
- **Survival: 39%** with d-AmB, **62%** with L-AmB and **75%** with d-AmB and sequential L-AmB.

Liposomal Amphotericin B

Study	No of cases	Antifungal median daily dose	Underlying disease	Survival (%)
Walsh et al (*2001*)	5	7.5-15 mg/kg	Not reported	**19/28 (68%)**
Pagano et al (*2004*)	12	3 mg/kg	HM	
Cordonnier et al (*2007*)	6	4 mg/kg	HM (including allo-HSCT)	
Cornely et al (*2007*)	3	3 mg/kg	HM	

Amphotericin B lipid complex

Study	No of cases	Antifungal median daily dose	Underlying disease	Survival (%)
Walsh *et al* (1998)	24	5 mg/kg	4 HM 2 allo-HSCT	**63/88 (71%)**
Larkin and Montero (2003)	64	4.82 mg/kg	17 HM 8 allo-HSCT	

Amphotericin B colloidal dispersion

Study	No of cases	Antifungal median daily dose	Underlying disease	Survival (%)
Oppenheim *et al* (1995)	4	6 mg/kg	HM	**16/24 (67%)**
Herbrecht *et al* (2001)	20	4.8 ± 1.8 mg/kg	5 HM 7 allo-HSCT	

Role of posaconazole in the treatment of zygomycosis

Posaconazole- Activity *in vitro*

- 37 strains / 7 species of zygomycetes
- NCCLS M38-P; 48h; 80% inhibition (azoles) / 100% (Amb)

	MIC_{50} [µg/mL]	MIC_{90} [µg/mL]
POS	0.25	4
ITC	0.5	8
VRC	>64	>64
FLC	>64	>64
AMB	0.25	0.5

Sun et al., AAC 02

Posaconazole- Activity *in vitro*

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AMB	0.33	0.03–2	0.25	0.5

[a] MIC at which 50% or 90% of the isolates were inhibited.

Sun et al., AAC 02

Posaconazole- Activity *in vitro*

In vitro activity against 45 zygomycetes isolates of 6 species obtained by the CLSI M38-A procedure at 48 h

	MIC_{50}	MIC_{90}	MEC[a]	MIC range
AMB	1	4		0.125–>16
ITC	4	>16		0.5–>16
VC	>16	>16		8–>16
POS	0.5	2		0.25–>16
CAS	>256	>256	256	128–>256

Torres et al., AAC 06

Posaconazole: Summary, Activity *in vitro*

- Zygomycetes are a heterogenous group of fungi with variable, but overall favorable susceptibility in vitro to posaconazole [1]
- Posaconazole fungicidal against *Rhizopus* and *Mucor* spp with <70% killing at 6 and 99.9% at 48h [2]
- No antagonism between posaconazole and AMB against zygomycetes in vitro [3]

[1] Sun AAC 02; Gil-Lamaignere JAC 05; Torres AAC 06; Antachopoulos JCM 06; Almyroudis AAC 07; [2] Krishnan DMID 09; [3] Arikan Med Mycol 08; Perkhofer AAC 08

Posaconazole- Efficacy *in vivo*

- **Lethal non-immunocompromised mouse model of diss. mucormycosis**
- **AmB 1, ITC 50 BID, POS 5, 25, 40 (100) QD**

- ***R. microsporus***
- ***R. oryzae***
- ***A. corymbifera***

Isolate	MIC (μg/ml)		
	Amphotericin B	Itraconazole	Posaconazole
R. microsporus AZN 1185	0.25	>16	1
R. oryzae AZN 6373	1	0.5	0.25
A. corymbifera AZN 4095	0.06	0.03	0.12

[a] MICs of amphoterin B and itraconazole against *R. microsporus* and *A. corymbifera* are from reference 3.

Dannaoui et al.,AAC 03

Posaconazole: Summary, Efficacy *in vivo*

- **Zygomycetes are a heterogenous group of fungi with variable virulence and variable host responses** [1]
- **Posaconazole prolonged was effective for disseminated *Mucor* spp. and *R.microsporus* in neutropenic mice, had no effects against *R. oryzae*, and partial benefit against *A. corymbifera* in non-immunocompromised mice** [2]
- **No consistent in vitro-in vivo correlation against *R.oryzae, A.corymbifera,* and *R.microsporus*** [3]
- **Combination of POS and L-AMB / DAMB no better than L-AMB or DAMB against *R.oryzae* in ketoacidotic or neutropenic mice** [4]

[1] Petraitiene ICAAC 08; [2] Sun AAC 02; Dannaoui AAC 03; Ibrahim AAC 09; [3] Dannaoui AAC 03; Rodriguez AAC submitted ; [4] Rodriguez AAC 08; Ibrahim AAC 09;

Posaconazole vs. Zygomycosis

- Ergosterol biosynthesis valid target
- however
  - Zygomycetes are heterogeneous in terms of susceptibility
  - Challenge of in vitro / in vivo correlation
- Posaconazole effective in patients ?

Posaconazole Clinical – *Greenberg et al. (2006)*

- 24 patients receiving POS on protocols for pts. with refractory infections or intolerance to standard therapies
- Proven rhinocerebral (11); single site (9); and disseminated infections (4)
- allo-BMT/HM,15; other: 9
- Pretreatment with AMBs: 22/24; surgery: 18/24
- Dosage: 800 mg/d for median of 182 d (8-1004)

→ Overall successful outcome (I.D.): 19/24 (79 %)
Estimated survival at day +90: 78 %

- Survival associated with surgery, stabilization of underlying condition, and absence of dissemination

Posaconazole Clinical – *Van Burik et al. (2006)*

- Retrospective analysis of SPRI compassionate use protocol including 91 pts. with proven (69)/probable (22) zygomycosis refractory (81) or intolerant (10) to prior antifungal therapy
  - 62% single site, 38% > one site
  - 53% HM, 33% IDDM
  - >85% pretreatment with LFABs, 70% surgical resection
- 800 mg in divided dosages for 6-1005 days

➡ CR/PR at 12 weeks (ITT): 55/91 (60%)

- 14 % CR, 46% PR, 21% stable disease

Posaconazole Clinical: *Chamilos et al. (2008)*

Outcome among 70 consecutive patients with hematologic malignancy who had zygomycosis at MDACC during 1989–2006:

Characteristic	Outcome[a]		Univariate analysis		Multivariate analysis	
	Death (n = 46)	Survival (n = 24)	OR (95% CI)	P	OR (95% CI)	P
Treatment						
Delayed treatment (≥6 days after diagnosis)	29 (63)	6 (25)	8.6 (1.7–43.4)	.009	8.1 (1.7–38.2)	.008
AMB-deoxycholate[h]	8 (17)	4 (17)	…	.8	…	
Lipid AMB	14 (30)	6 (25)	…	.7	…	
Liposomal AMB	24 (52)	14 (58)	…	.8	…	
Duration of treatment, median days (range)	12 (1–96)	35 (1–133)	…	<.001	…	
≥7 days of AMB-based treatment	29 (63)	24 (100)	0.03 (0.001–0.6)	<.001	…	
AMB-based treatment plus caspofungin	11 (24)	10 (42)	…	.1	…	
Salvage posaconazole treatment[i]	5 (11)	10 (42)	0.1 (0.04–0.7)	.005	0.1 (0.01-0.66)	.01
WBC transfusions	12 (26)	3 (13)	…	.2	…	
GM-CSF or G-CSF	37 (80)	14 (58)	…	.08	…	
IFN-γ	4 (9)	2 (8)	…	.6	…	
Surgery[k]	13 (28)	9 (38)	…	.4	…	

Role of surgical treatment

Rationale: to reduce fungal mass; to debride necrotic tissue

- **Surgery may be of benefit in localized zygomycosis, particularly cutaneous-soft tissue and rhino-orbital-cerebral disease, fewer data on pulmonary disease**

- **Benefit of surgery diminishes in disseminated disease**

Other antifungal agents beside amphotericin B and posaconazole

- **Flucytosine, fluconazole, voriconazole and terbinafine have no meaningful activity**
- **Itraconazole**
  - Some variable in vitro and experimental activity, best activity being reported against Absidia spp. (Dannaoui et al, 2002)
  - Rare case reports (Eisen et al, 2004; Liao et al., 1995; Parthiban et al., 1998; Zhao et al., 2009), insufficient to support its use in zygomycosis
- **Isavuconazole**
  - Broad spectrum triazole including Mucorales with MIC50 values of 1 to 4 mg/mL and MIC90 values of 4 to 16 mg/mL (Verweij et al., 2009)
  - So far no clinical data
- **Caspofungin, anidulafungin and micafungin**
  - No efficacy in vitro against Zygomycetes (Almyroudis et al., 2007; Espinel-Ingroff et al., 1998; Isham et al., 2006)
  - Caspofungin has shown efficacy in an animal model but with an inverse-dose response relationship: low dose more effective high dose (Ibrahim et al., 2005)
  - No clinical data are available with echinocandin in monotherapy

No recommendation for the use of any of these agents as monotherapy

Combination therapy: experimental data

- **Amphotericin B lipid complex combined to caspofungin (Spellberg et al., 2005)**
  - Improved survival of diabetic ketoacidotic mice infected with *Rhizopus oryzae*
- **Liposomal amphotericin combined to anidulafungin or micafungin (Ibrahim et al, 2008)**
  - Improved survival in mice infected intravenously with *Rhizopus oryzae* compared to placebo or monotherapy arms
  - Paradoxical effect (low dose more active than high dose) with micafungin but not with anidulafungin
- **Liposomal amphotericin B combined to posaconazole (Ibrahim et al., 2009)**
  - In mice infected with *Rhizopus oryzae*
  - Combination did not improve survival compared to liposomal amphotericin B alone

Combination therapy: clinical data

- **Retrospective study in rhino-orbito-cerebral zygomycosis (Reed et al., 2008)**
  - Monotherapy with AmB formulation (31 patients) or a combination of caspofungin and ABLC or L-AmB (6 patients)
  - Patients receiving a combination had a higher response rate and survival
  - Limitations: rhinocerebral only, most pts had diabetes and all had surgery
- **Combination of deferasirox and L-AmB (Spellberg et al, 2009)**
  - 8 patients received deferasirox in addition to their antifungal therapy
  - Only events attributable to deferasirox were skin rashes in 2 patients.
  - 7 of the 8 patients responded to therapy.
  - Limitations: low number of pts, various combinations used in this study
- **Combination of deferasirox and L-AmB (Spellberg et al, 2012)**
  - A double-blinded, randomized, placebo-controlled phase II clinical trial of the safety and exploratory efficacy of adjunctive deferasirox therapy for patients with mucormycosis treated with L-AmB (the deferasirox-AmBisome therapy for mucormycosis [DEFEAT Mucor] study) failed to demonstrate a benefit of combination therapy

Adjunctive treatments (deferasirox)

Rationale: Chelation of iron (by chelators that are not siderophores for zygomycetes) decreases availability of this factor essential for growth and pathogenicity of zygomycetes

- Chelation of iron may be beneficial.
  - The Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor) Study failed to demonstrate a benefit.
- Further studies are needed in order to clarify the potential of deferasirox to add benefit to lipid polyene therapy for mucormycosis

- **Current data do not support establish conclusively that deferasirox or deferiprone should be used in the treatment of mucormycosis.**

Adjunctive treatments

Hyperbaric oxygen

Rationale: *in vitro* suppressive effect on growth of zygomycetes. Reduction of tissue hypoxia and acidosis: enhanced killing of zygomycetes by neutrophils, reduced availability of free iron, enhanced oxydative action of amphotericin B.

- Hyperbaric oxygen may be beneficial, particularly in diabetic patients

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.

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

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[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.

Recommendation for second line and maintenance therapy

Second line

Management includes antifungal therapy, control of underlying disease and surgery.	A II
Posaconazole	BII
Combination lipid AmB and caspofungin	BII
Combination lipid AmB and posaconazole	CIII
Combination with deferasirox	CIII

Maintenance therapy

Posaconazole	B III [5]

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