Cas clinique infection fongique ORL

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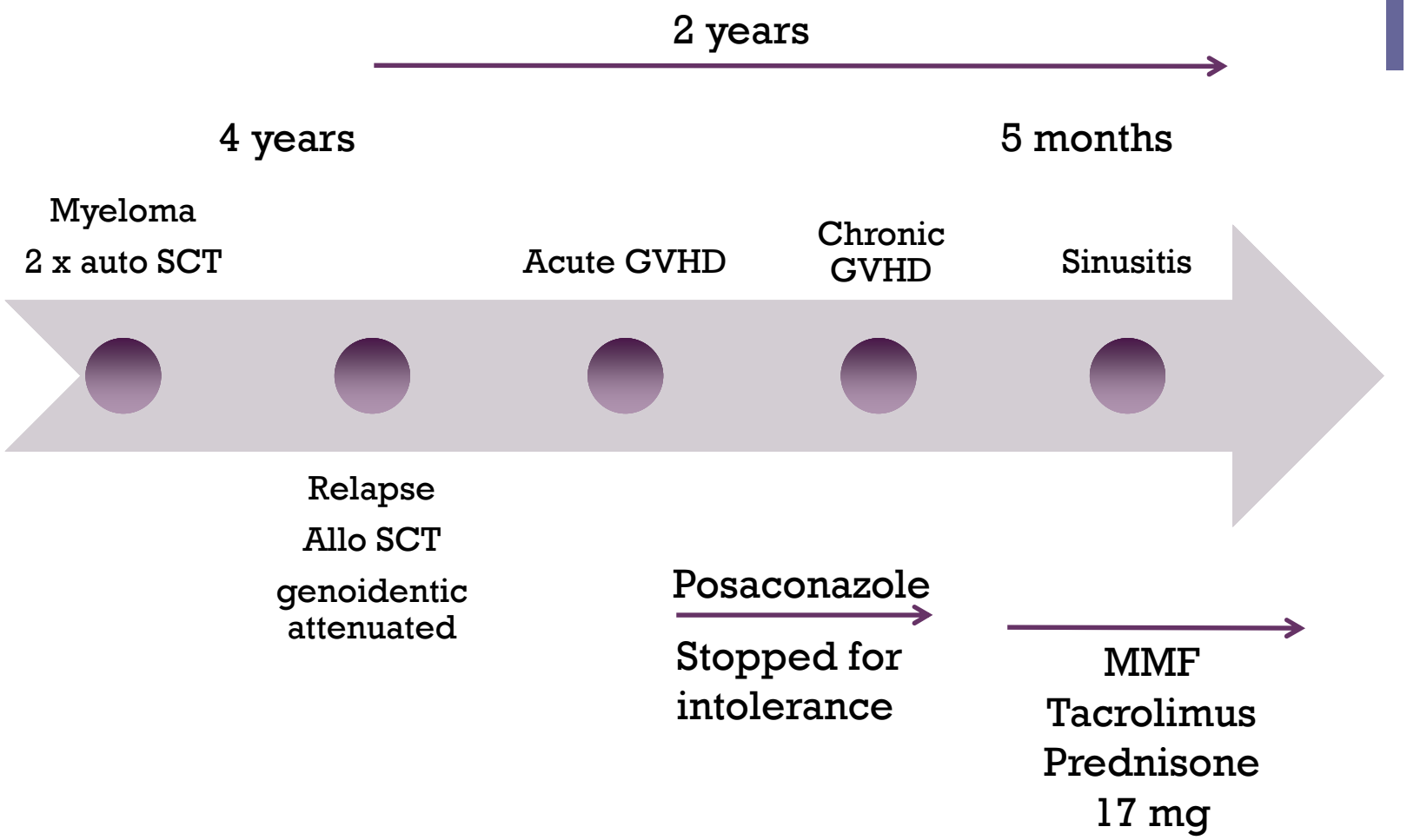
Patient history

- 53 year-old man from Western Africa
- Diabetes mellitus
  - Type II for 15 years
  - Requiring insulin therapy for 6 years
  - Complicated with nephropathy
  - Overweight
- IgA kappa myeloma diagnosed 6 years ago
- Auto SCT 5 years and 4 years before

SCT: stem cell transplant.

Disease course

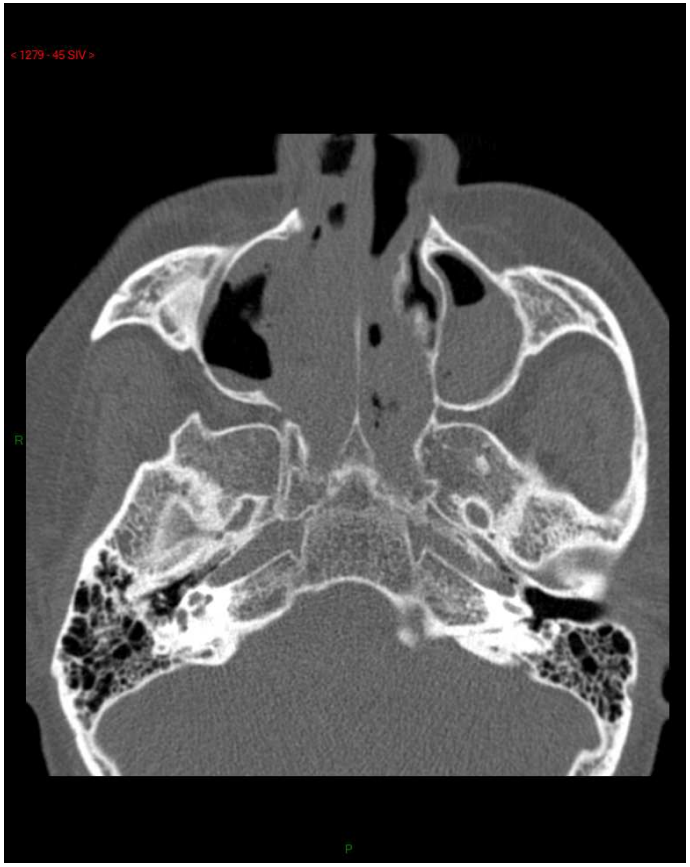


GVHD: graft versus host disease; MMF: mycophenolate mofetil; SCT: stem cell transplantation.

Presenting symptoms

- Nasal discharge
- Dry cough
- Frontal right pain
- Weight loss

CT imaging



Endoscopy

Question 1

- Quels diagnostics évoquez vous?
- Sur quels arguments?

Réponse 1

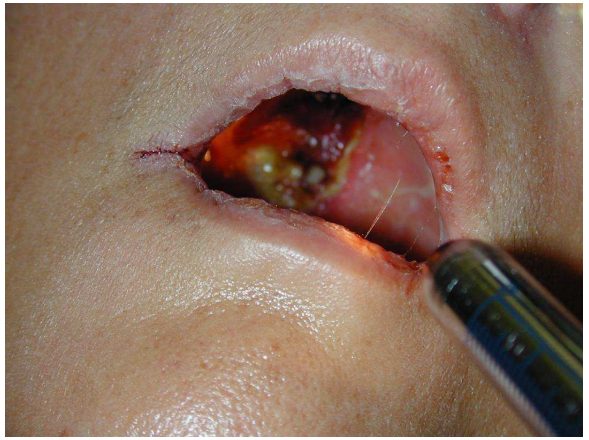
- Sinusite fongique invasive
- Aspergillose ou mucormycose
- Devant
  - Terrain
  - Imagerie: lyse osseuse signe invasion
  - Endoscopie sinusienne: tissu nécrotique

Rhino orbitocerebral mucormycosis Clinical presentation

22 patients with rhino orbitocerebral mucormycosis from Retrozygo study

Symptoms	%
Cranial nerve palsy	68%
Pain	86%
Oedema	58%
Turbinal or nasal necrosis	40%
Palatine necrosis	31%
Low visual acuity	36%
Exophtalmia	23%
Chemosis	18%

Vironneau P, CMI 2013



Question 2

- Quels examens demandez-vous pour appuyez votre diagnostic?

Diagnosis indirect

	Aspergillose	Mucormycose
Galactommannane	+	-
β-D glucane	_	-
Aspergillus fumigatus PCR serum	+	-
Mucorales qPCR serum	-	+

Surtout évalué en hématologie et chez les brulés

Prélèvement au site de l'infection

Examen direct	Filaments évocateurs
Anatomopathologie	Visualisation angioinvasion
Culture	Identification espèce
PCR sur tissu	

Quantitative Polymerase Chain Reaction Detection of Circulating DNA in Serum for Early Diagnosis of Mucormycosis in Immunocompromised Patients

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10 patients proven mucormycosis
Combination of 3 qPCR: *Mucor, Rhizopus, Lichteimia*
On serum
Positive 3 to 68 days before diagnosis confirmation

PHRC Modimucor

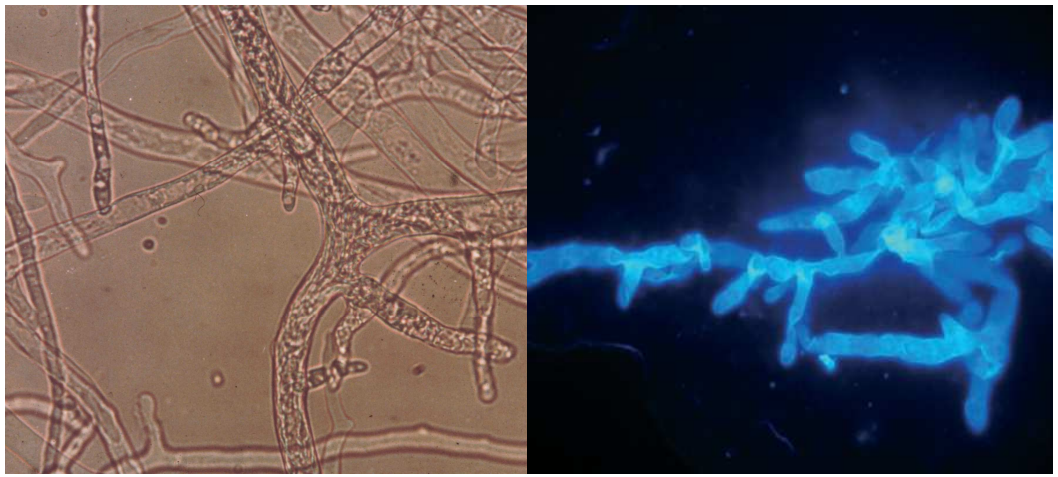
qPCR Mucorale: diagnostic et suivi

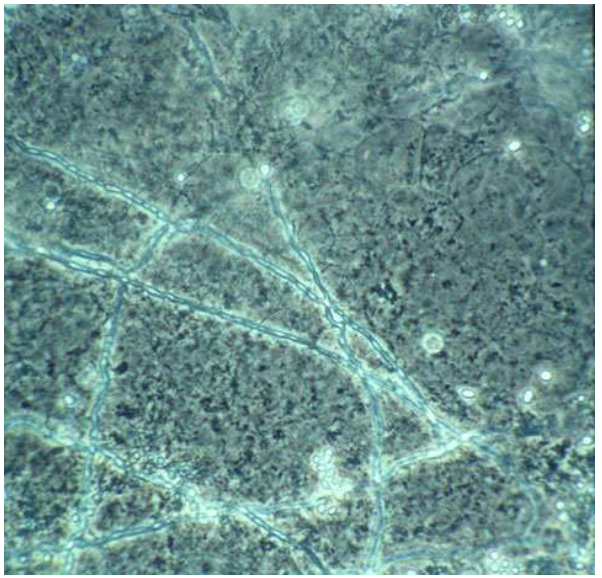
- Etude nationale rétrospective réalisée dans le réseau RESSIF (surveillance nationale des infections fongiques invasives) intérêt de la qPCR dans le diagnostic et le suivi de la mucormycose.
- 44 patients, 34 d'hématologie
- 81% avaient une qPCR positive (92% quand le PCR était réalisée dans des conditions techniques satisfaisantes et que l'espèce était prise en compte par la PCR).
- qPCR positive 9 jours avant le diagnostic mycologique et 2 jours avant le diagnostic radiologique.
- Survie à J84 plus élevée chez les patients négativant la qPCR (48% vs 4%).

Million L, CMI, 2015

Mucormycosis-Diagnostic Smear

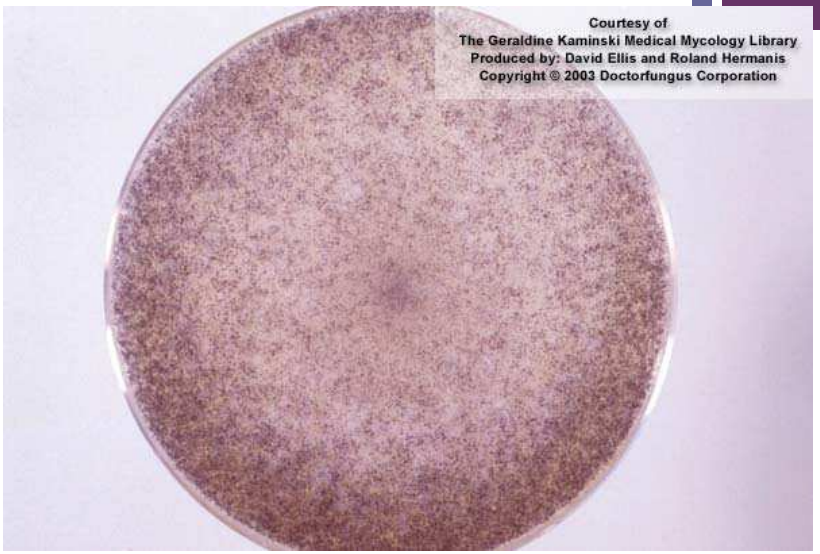
Mucormycosis	Aspergillose
Ribbon like hyphae	Hyphae
Large 6-16µm	Large 2-3µm
No or pauci septated	Septated
Right angle	
Calcofluor	





Mucormycosis-Diagnostic Culture

- 37°
- No grinding ++++
- Species diagnosis
- Antifongigram
- Identification:
  - Phenotypic
  - Molecular (ITS)
  - MALDI-TOF MS

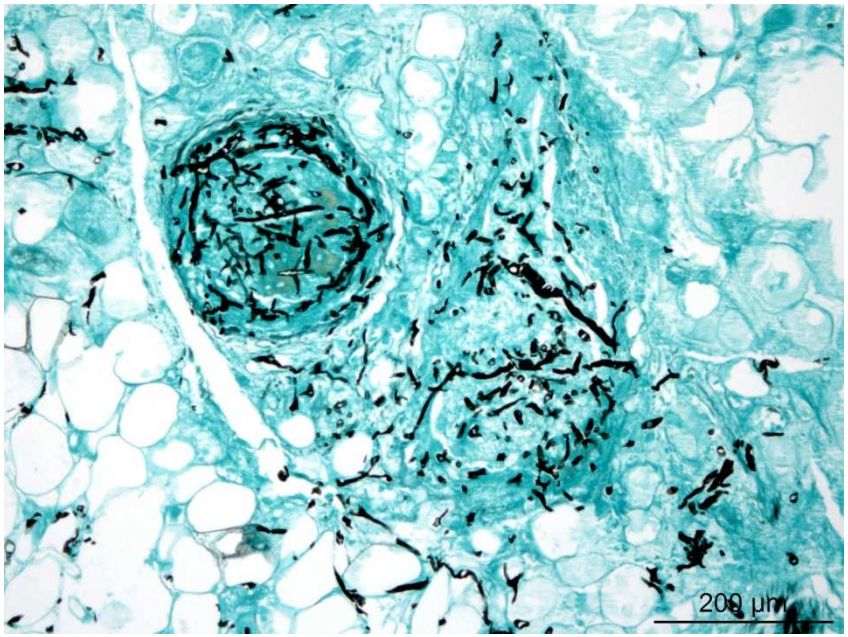


Mucormycosis: diagnosis

- **Histology:**
  - Proven
  - Mucorales hyphae (coloration HES +++; PAS)
  - Immunohisto
  - No sp diagnosis except PCR on tissue

Diagnosis

- Surgery:
  - Right maxillar sinus biopsy
  - Direct exam: hyphae
  - Culture: *Rhizopus oryzae*



Rhinosinusal mucormycosis

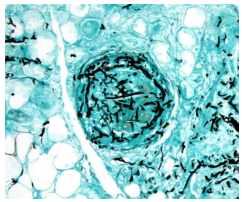
Image provided by F. Lanternier

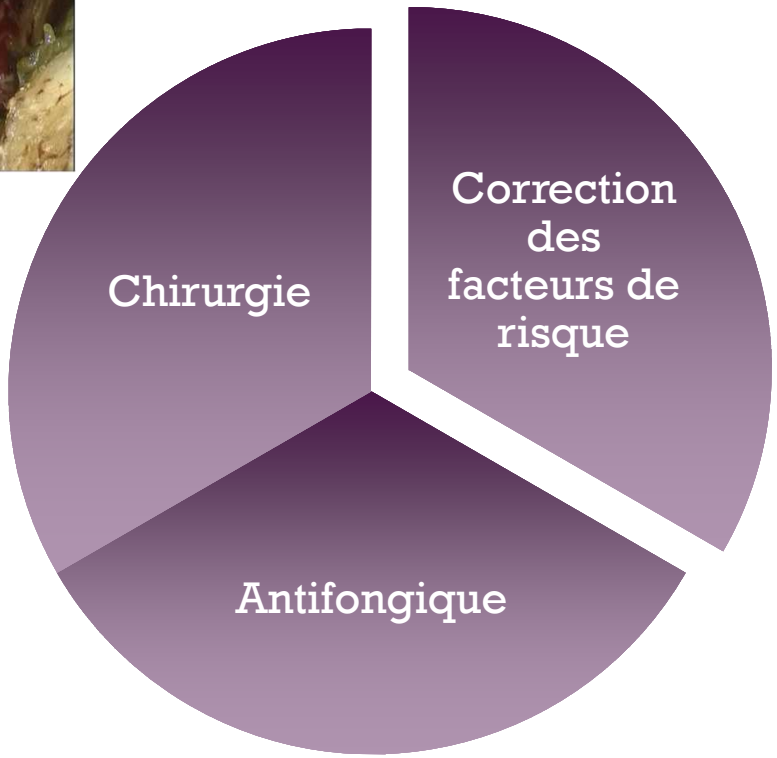
PCR: polymerase chain reaction.

Question 3

- Quel traitement poursuivez-vous avec ces résultats?

+ Traitement de la mucormycose



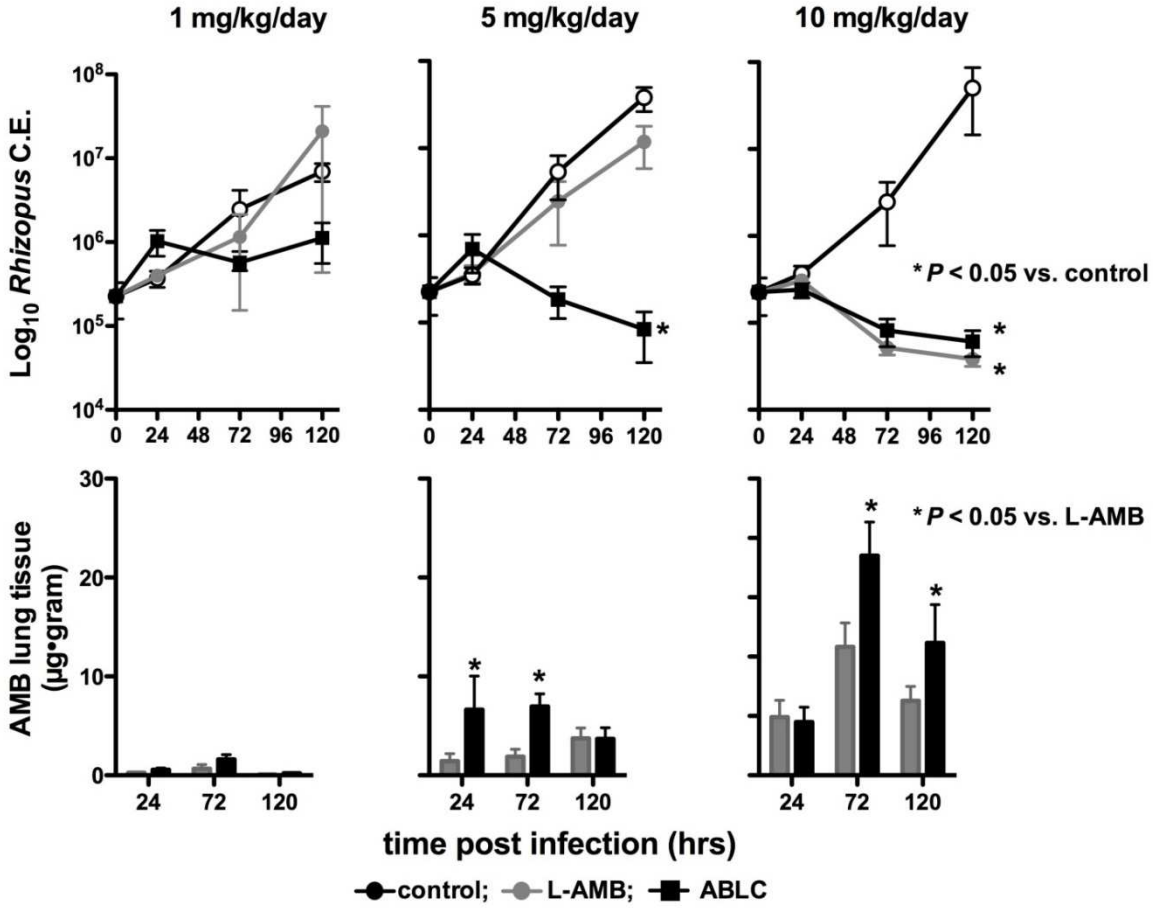


Antifungal activity

	Polyènes	Isavuconazole	Posaconazole	Voriconazole	Candine
Aspergillus	+	+	+	+	+
Mucorales	+	+	+	-	-/+

Mucormycoses
L-AmB: high dose

- Souris ID infected with *Rhizopus oryzae*



R. E. LEWIS, AAC 2009

+ Forte posologie d'amphotéricine B liposomale

	Herbrecht, W4 or EOT if before ($n=33$)[a]	Segal, W4 or EOT if before ($n=32$)[b]	Herbrecht, W12 ($n=31$)[c]	Segal, W12 ($n=31$)[c]
Favourable response	12/33 (36%)	10/32 (31%)	14/31 (45%)	15/31 (48%)
partial response	6/33 (18%)	4/32 (13%)	4/31 (13%)	6/31 (19%)
complete response	6/33 (18%)	6/32 (19%)	10/31 (32%)	9/31 (29%)
Failure	21/33 (64%)	22/32 (69%)	17/31 (55%)	16/31 (52%)
stable	4/33 (12%)	7/32 (22%)	2/31 (6%)	1/31 (3%)
failure without death	10/33 (30%)	8/32 (25%)	2/31 (6%)	2/31 (6%)
death[d]	7/34 (21%)	7/34 (21%)	13/34 (38%)	13/34 (38%)
related to mucormycosis	5/34 (15%)		9/34 (26%)	
not related to mucormycosis	2/34 (6%)		4/34 (12%)	

L-AmB: liposomal amphotericin B
EOT: end of treatment.

Lanternier et al, French Mycosis Study Group, JAC, 2015

Isavuconazole

- Nouvel azolé large spectre
- IV et PO
- Pas de cyclodextrine

Antifungal compound and species (no. of isolates)	EUCAST, day 1 Range (mg/liter)	EUCAST, day 1 MIC_{50} (mg/liter)	EUCAST, day 1 % of MICs below *A. fumigatus* ECOFF[c]	EUCAST, day 2 Range (mg/liter)	EUCAST, day 2 MIC_{50} (mg/liter)	EUCAST, day 2 % of MICs below *A. fumigatus* ECOFF[c]
Amphotericin B						
Lichtheimia corymbifera (12)	≤0.03 to 0.125	≤0.03	100	≤0.03 to 0.25	0.125	100
Lichtheimia ramosa (4[a]/5)	≤0.03	≤0.03	100	≤0.03 to 0.06	0.06	100
Mucor circinelloides						
Group I (4/5[b])	≤0.03 to 0.125	≤0.03	100	≤0.03 to 0.125	0.06	100
Group II (9)	≤0.03 to 0.125	0.06	100	0.06 to 0.25	0.125	100
Rhizomucor pusillus (8[a]/9)	≤0.03	≤0.03	100	≤0.03 to 0.25	0.06	100
Rhizopus microsporus (26)	0.06 to 0.5	0.125	100	0.25 to 1	0.5	100
Rhizopus oryzae (6)	0.125 to 0.5	0.25	100	0.5 to 1	0.5	100
Total (70/72[a,b])	≤0.03 to 0.5	0.06	100	≤0.03 to 1	0.125	100
Isavuconazole						
Lichtheimia corymbifera (12)	0.5 to 2	1	100	1 to 4	2	67
Lichtheimia ramosa (4[a]/5)	0.125 to 0.5	0.25	100	0.5 to 4	2	60
Mucor circinelloides						
Group I (4/5[b])	4 to 8	8	0	2 to 16	16	20
Group II (9)	1 to 16	8	11	4 to >16	16	0
Rhizomucor pusillus (8[a]/9)	0.5 to 1	0.5	100	1 to 2	2	100
Rhizopus microsporus (26)	0.5 to 4	1	92	1 to 8	4	35
Rhizopus oryzae (6)	0.5 to 4	1	83	0.5 to 8	4	33
Total (70/72[a,b])	0.125 to 16	1	77	0.5 to >16	4	44
Posaconazole						
Lichtheimia corymbifera (12)	0.06 to 0.25	0.125	100	0.125 to 0.5	0.25	75
Lichtheimia ramosa (4[a]/5)	≤0.03 to 0.125	≤0.03	100	0.06 to 0.5	0.5	40
Mucor circinelloides						
Group I (4/5[b])	0.25 to 1	0.5	40	0.5 to 8	1	0
Group II (9)	0.125 to >16	2	11	1 to >16	>16	0
Rhizomucor pusillus (8[a]/9)	≤0.03 to 0.125	0.06	100	0.125 to 0.5	0.25	78
Rhizopus microsporus (26)	0.25 to 1	0.5	12	0.5 to >16	2	0
Rhizopus oryzae (6)	0.25 to 2	0.5	50	0.25 to >16	0.5	17
Total (70/72[a,b])	≤0.03 to >16	0.25	47	0.06 to >16	1	26

Arendrup, AAC 2015

Données de l'étude VITAL

- Disponible par voir IV ou orale
- Absence de cyclodextrine dans la formulation intraveineuse
- Etude ouverte de phase III évaluant l'efficacité de l'isavuconazole dans infections fongiques invasives dont mucormycoses
- >18 ans
- Première ou deuxième ligne
- Isavuconazole 200mg X 3/j J1-J2, puis 200mg/j
- 37 patients, 59% hémopathie

Marty, Idweek 20014

Isavuconazole dans le traitement de mucormycoses: étude VITAL

24/37 arrêts de traitement

- Décès: 11 (30%)
- Effets indésirables: 6 (16%)
- Non compliance: 4 (11%)
- Non réponse: 3

	Primary treatment group (N=21)	Refractory group (N=11)	Intolerant to other antifungals group (N=5)	Total (N=37)
DRC-assessed overall response at day 42				
Complete response	0	0	0	0
Partial response	3 (14%)	1 (9%)	0	4 (11%)
Stable disease	9 (43%)	4 (36%)	3 (60%)	16 (43%)
Progression of disease	1 (5%)	0	0	1 (3%)
Death	7 (33%)	4 (36%)	2 (40%)	13 (35%)
Missing data	1 (5%)	2 (18%)	0	3 (8%)
DRC-assessed overall response at day 84				
Complete response	1 (5%)	1 (9%)	0	2 (5%)
Partial response	1 (5%)	3 (27%)	1 (20%)	5 (14%)
Stable disease	9 (43%)	0	2 (40%)	11 (30%)
Progression of disease	0	1 (9%)	0	1 (3%)
Death	9 (43%)	4 (36%)	2 (40%)	15 (41%)
Missing	1 (5%)	2 (18%)	0	3 (8%)
DRC-assessed overall response at EOT†				
Complete response	3/19 (16%)	2 (18%)	0	5/35 (14%)
Partial response	3/19 (16%)	2 (18%)	1 (20%)	6/35 (17%)
Stable disease	6/19 (32%)	2 (18%)	2 (40%)	10/35 (29%)
Progression of disease	7/19 (37%)	5 (45%)	2 (40%)	14/35 (40%)
DRC-assessed success rate at EOT				
Clinical response	10/18 (56%)	2/9 (22%)	2/4 (50%)	14/31 (45%)
Mycological response	6/19 (32%)	4/11 (36%)	2/5 (40%)	12/35 (34%)
Radiological response	3/18 (17%)	2/10 (20%)	1/5 (20%)	6/33 (18%)
All-cause mortality through day 42‡	7 (33%)	5 (45%)	2 (40%)	14 (38%)
All-cause mortality through day 84‡	9 (43%)	5 (45%)	2 (40%)	16 (43%)

Marty, LID, 2016

Isavuconazole et mucormycose

	Vital study 1st line Isavuconazole N=21	AmBizygo study L AmB high dose N=33
Chirurgie	**43%**	**71%**
Response W4		**31%**
Partial response		13%
Complete response		19%
Décès		21%
Response W6	**14%**	
Partial response	0	
Complete response	14%	
Stable	43%	
Décès	33%	
Response W12	**10%**	**48%**
Partial response	1 (5%)	19%
Complete response	1 (5%)	29%
Stable	9 (43%)	6%
Décès	43%	38%

Mucormycosis: posaconazole treatment

- Retrospective study, second line
- Posaconazole: 800mg/j
- N=91
- 52% hemopathy, 30% allo
- Response W12: 60% (RC:14%, RP:46%)
- Survival at 3 months: 62%

Van Burik, CID, 2006

Posaconazole
Nouvelles formulations disponibles

- Pas d'étude en première ligne
- Comprimés:
  - Indépendant de la prise alimentaire
  - Une prise par jour
  - 300mg/j
  - Comparison 300mg comprimé vs 400mg X 2/j solution:
    - Solution 748 ng/ml; comprimé, 1,910 ng/ml; P<0.01
- IV:
  - Sur voie centrale

Jung AAC, 201

Recommandations pour le traitement de première ligne de la mucormycose

ECIL6

Population	Intervention	SoR	QoR
	AmB deoxycholate	C	II
Any	L-AmB 5–10 mg/kg	B	II
CNS	L-AmB 10 mg/kg	B	II
	ABLC 5–7.5 mg/kg	B	III
	ABCD	C	II
Any	Posaconazole 400 mg twice daily	C	III
	Combination therapy	C	III

EFISG-ECMM

Population	Intention	Intervention	SoR	QoR
Any	Cure and increase survival	AmB, liposomal ≥5mg/kg	A	IIu
CNS	Cure	AmB, liposomal ≥10 mg/kg, initial 28 days	A	II
Any, except CNS	To cure	AmB, lipid complex ≥5mg/kg	B	IIu
Any	To cure	Posaconazole 200 mg X 4/d	B	IIu
Any	To cure	Lipid-based AmB + caspofungin	C	III

Recommandations pour le traitement de première ligne de la mucormycose

ECIL6

Population	Intervention	SoR	QoR
	AmB deoxycholate	C	II
Any	L-AmB 5–10 mg/kg	B	II
CNS	L-AmB 10 mg/kg	B	II

Isavuconazole en cas d'intolérance ou d'échec de l'amphotéricine B liposomale

Place du posaconazole comprimé et IV?

EFISG-ECMM

Any	Cure and increase survival	AmB, liposomal ≥5mg/kg	A	IIu
CNS	Cure	AmB, liposomal ≥10 mg/kg, initial 28 days	A	II
Any, except CNS	To cure	AmB, lipid complex ≥5mg/kg	B	IIu
Any	To cure	Posaconazole 200 mg X 4/d	B	IIu
Any	To cure	Lipid-based AmB + caspofungin	C	III

Mucormycose rhino orbito cérébrale Les points clés

- URGENCE DIAGNOSTIQUE ET THERAPEUTIQUE
- Terrain: diabète+++
- Clinique: douleur sinusienne, epistaxis unilatérale, signes neurologiques
- Diagnostique: PCR Mucorales sérique, biopsie au site de l'infection (ED, culture, anapath, PCR sur tissu)
- Traitement: correction facteurs de risque, chirurgie, amphotéricine B liposomale forte dose