Mucormycoses

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Emergence des Mucormycoses

- Mucormycoses en France
- 1997-2006, 547 cas
- Incidence: 0,9/ 10^6 /yr
- 0,7 cas/10^6 in 1997
- 1,2 cas/10^6 in 2006

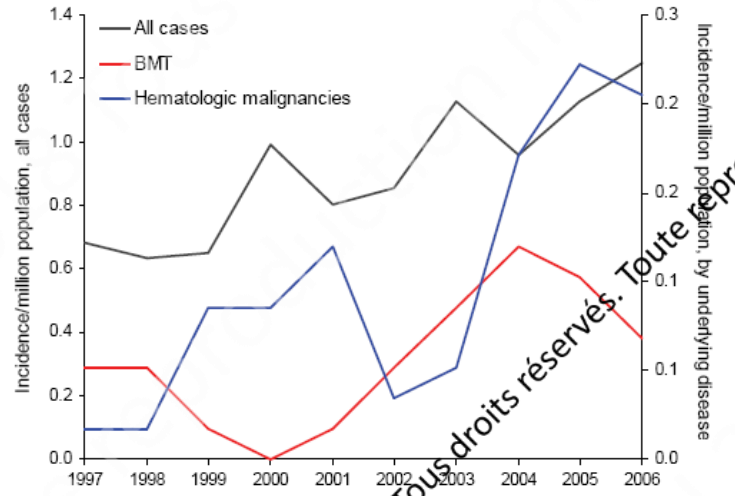
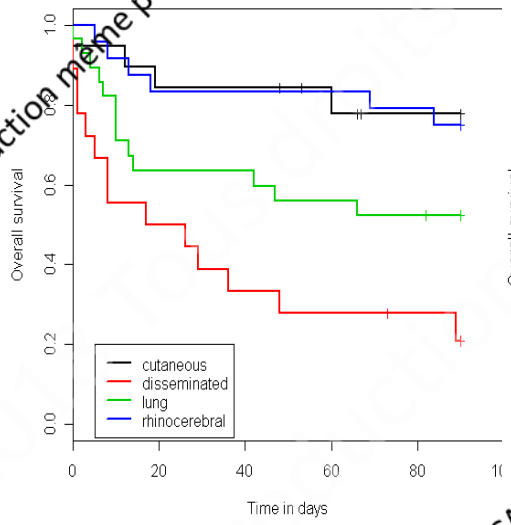
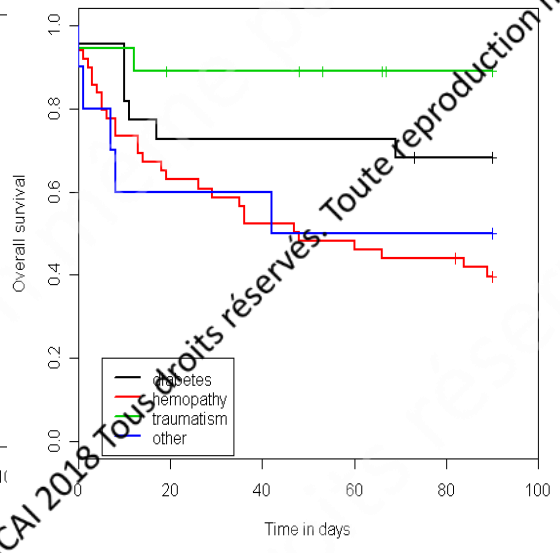


Figure 1. Evolution of the incidence of zygomycosis, France, 1997–2006. BMT, bone marrow transplantation.

© Bitar D, EID 2009

- Etude Retrozygo 101 mucormycoses
- 2005-2007
- Mortalité globale: 60%
- A M3: 44%





Lanternier, *CID*, 2012

Surveillance des mucormycoses en France

- Réseau de surveillance des infections fongiques en France
- 25 centres 2012-2014
- 88 mucormycoses
- Facteurs de risque:
  - Hémopathie (61,4%)
  - Diabète (15,9%)
  - Traumatisme/Brulures

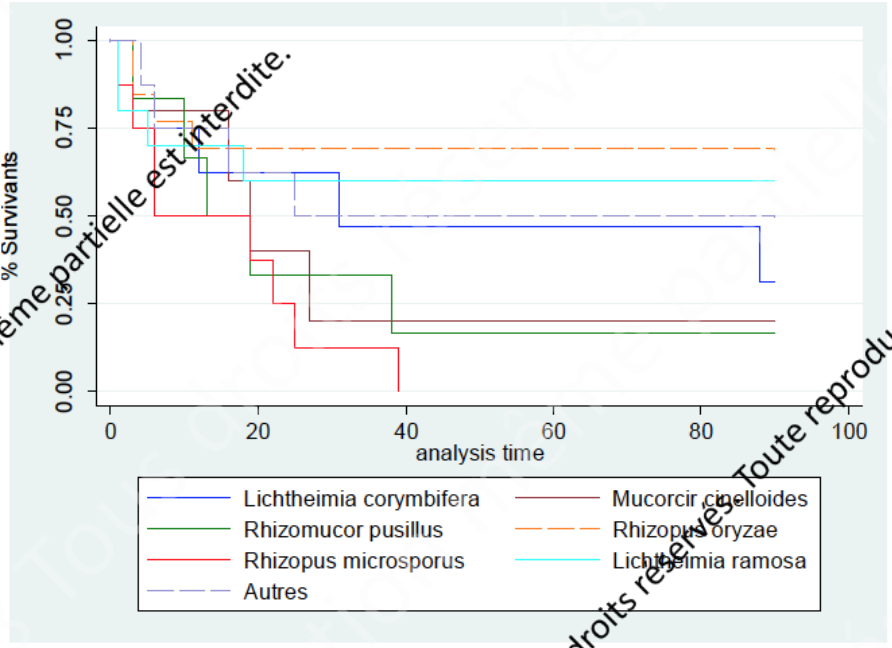


Figure 23 : Courbes de survie selon l'espèce de Mucorales isolée (RESSIF, 2012-2014)

Rapport 2015 CNRMA, unpublished data

Mucormycosis epidemiology in France

Table 1. Characteristics of 101 Patients With Proven or Probable Mucormycosis in France, 2005–2007

	No (%) of Patients
Mean (SD) age, years	50.7 (±19.9)
Male sex	59/101 (58)
Main risk factor	
Hematological malignancy[a]	50/101 (50)
+ HSCT	12/50 (24)
+ GVHD	5/50 (10)
+ Diabetes mellitus	9/50 (18)
+ Corticosteroids	13/50 (26)
+ Neutropenia	41/50 (80)
Diabetes mellitus[b]	23/101 (23)
Type 1	10/23 (43)
Ketoacidosis	8/23 (35)
Solid organ transplantation	3/101 (3)
Trauma	18/101 (18)
Other[c]	7/101 (7)

Lanternier, *CID*, 2012

Table 2. Clinical Localization of the Infection According to the Main Underlying Disease in 101 Cases of Mucormycosis

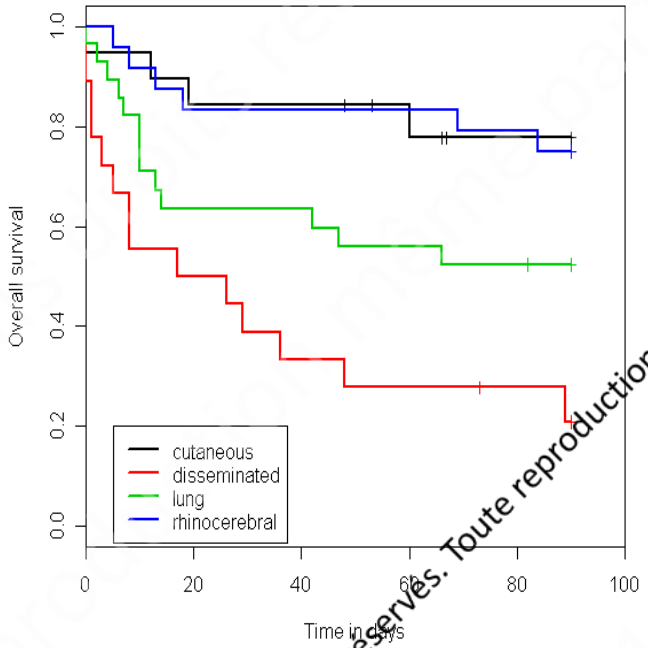
	No.(%) of Patients With Each Underlying Factor				
	Hematological Malignancy (n = 50)	Diabetes Mellitus (n = 23)	Trauma (n = 18)	SOT (n = 3)	Other (n = 7)
Lung	22 (44)	3 (13)	0	1	2
Rhinocerebral	6 (12)	16 (70)	1 (6)	0	2
Cutaneous	4 (8)	0	15 (83)	0	1
Disseminated	13 (26)	2 (9)	1 (6)	1	1
Other	5 (10)	2 (9)	1 (6)	1	1

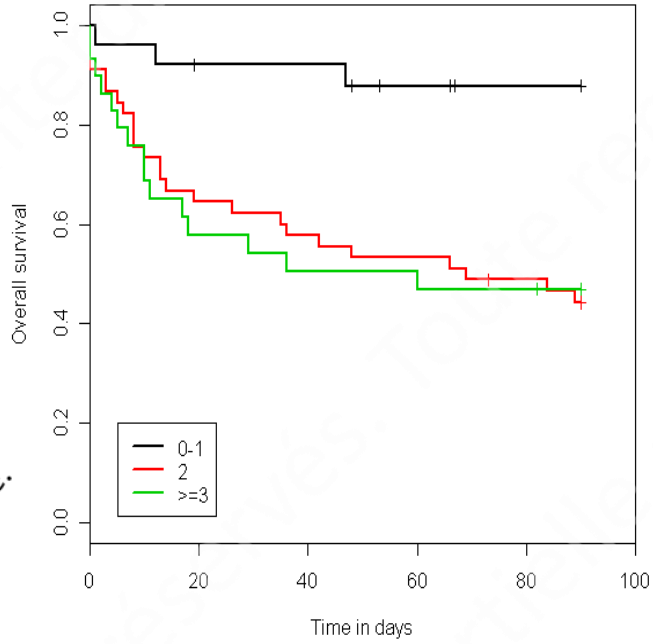
Rhizopus oryzae	(32%)
Lichtheimia spp	(29%)
Rhizopus microsporus	(17%)
Rhizomucor pusillus	(7%)
Cunninghamella spp	(7%)
Saksenaea vasiformis	(3%)
Mucor circillenoides	(3%)
Apophysomyces elegans	(2%)

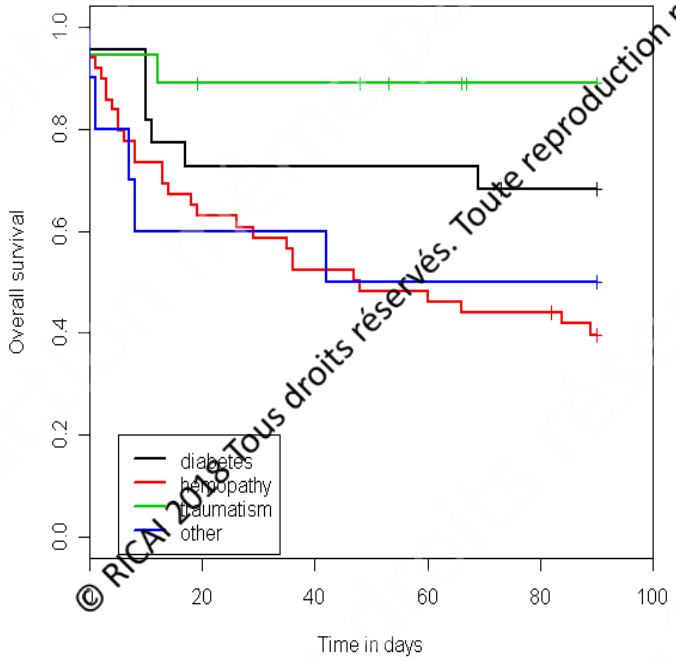
Rhizopus oryzae associated with rhino orbito cerebral location

Mortality

- 60%, at M3: 44%

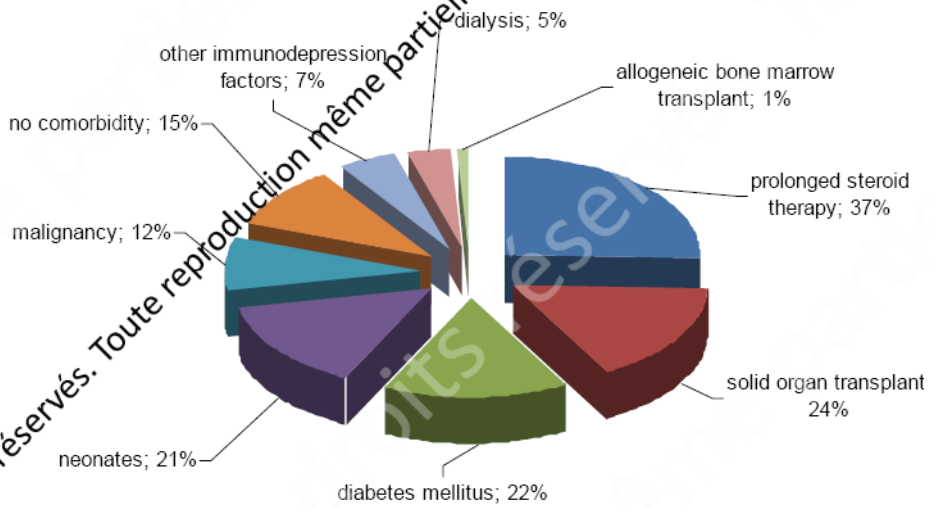


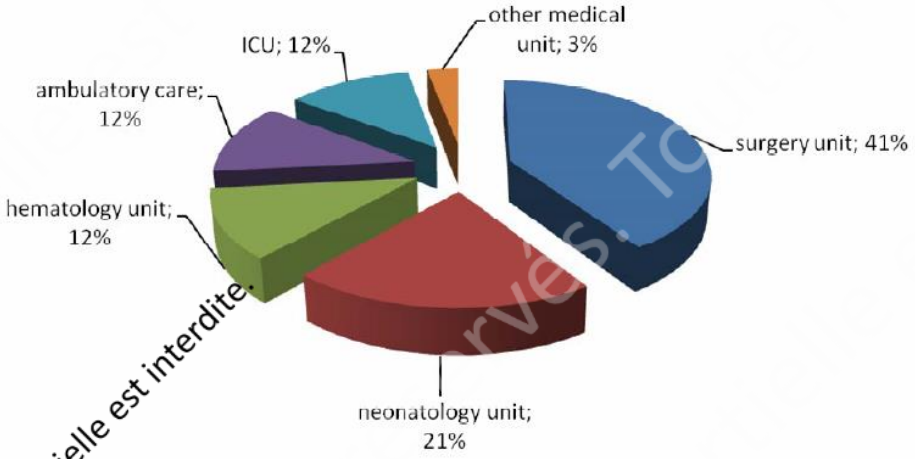


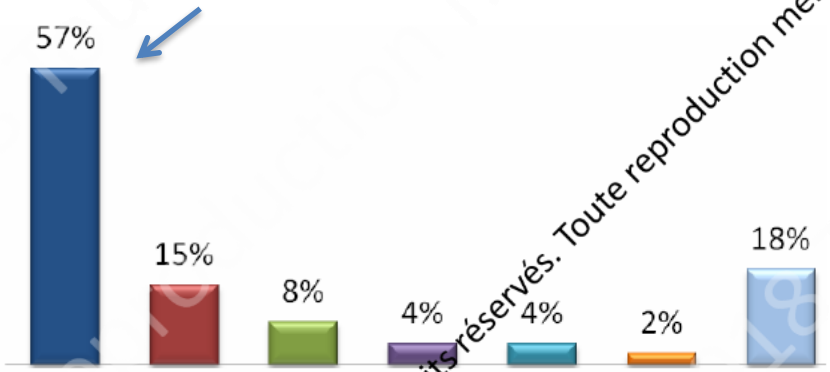


Lanternier, *CID*, 2012

Mucormycoses liées aux soins



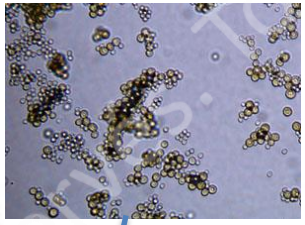


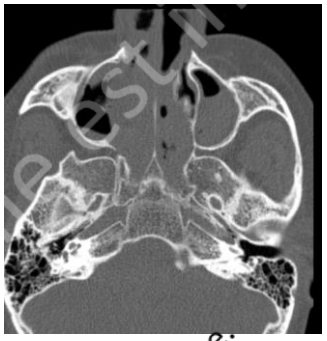


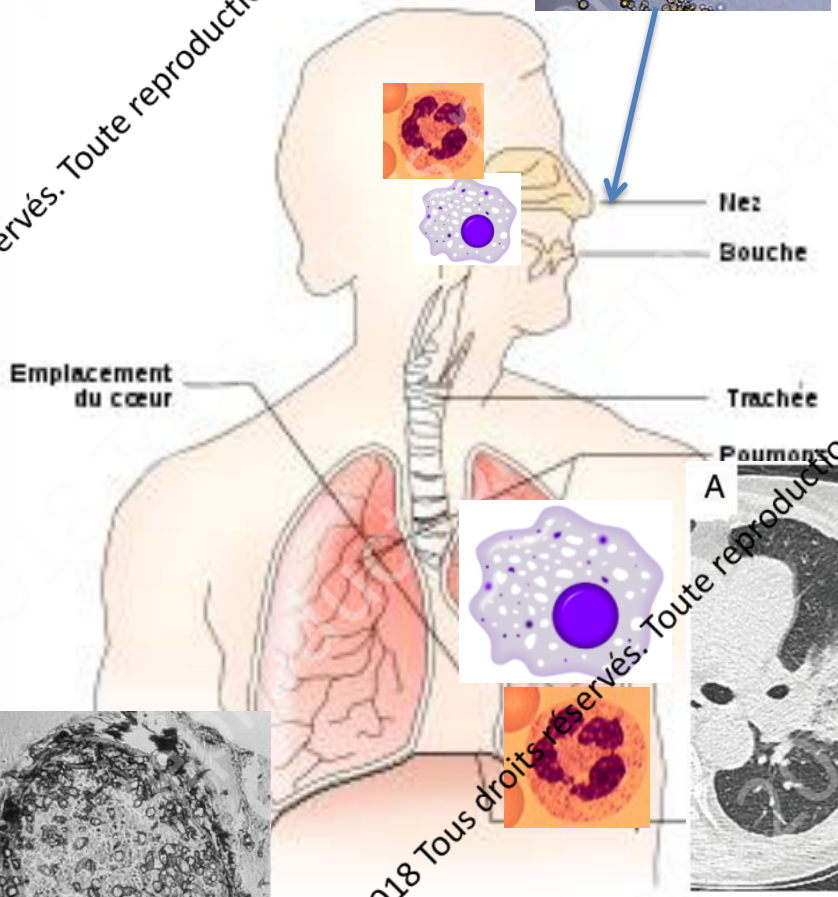
Rammaert, *Clin Infect Dis*, 2012

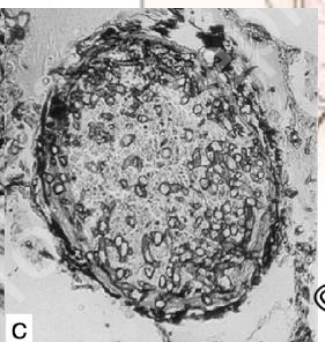
unpublished

Mucormycoses







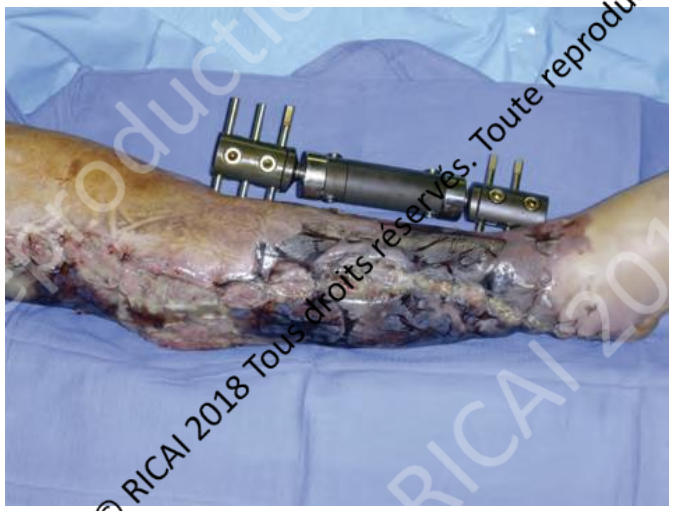


Angiotropisme+++ ⟶ Thrombose

Post traumatic mucormycosis

Lelievre et al, Medicine 2014

	Patients with PTM n=16	Other patients n=85	p
Median (IQC) age, years	42.9 (19-68.5)	55.5 (40.5-65.3)	0.42
Underlying disease	5 (31.2)	81 (95.3)	< 0.0001
Cutaneous localization	14 (87.5)	6 (7.1)	< 0.0001
Median time between symptoms and diagnosis, days	4.5 (0-317)	21 (0-210)	0.0002
Surgical treatment	15 (93.7)	39 (47)	0.0006



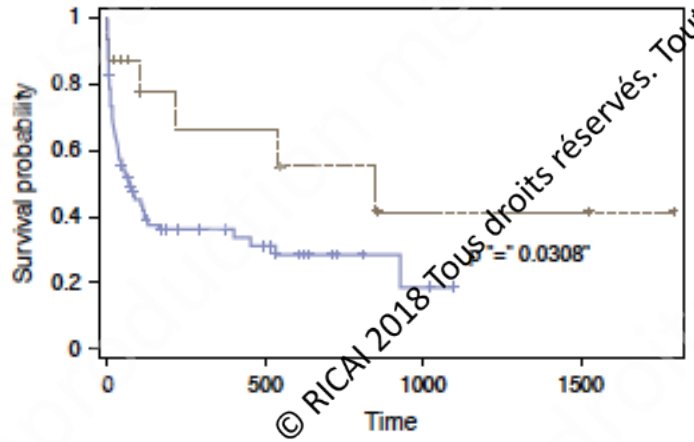
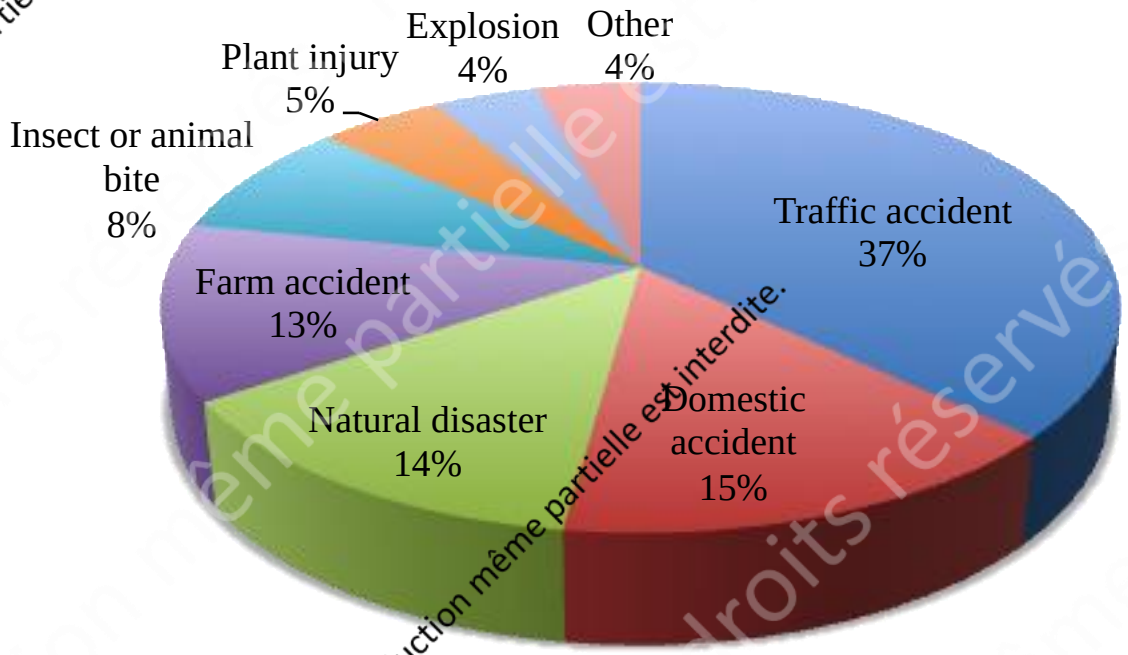


FIGURE 3. Survival of posttraumatic (dotted line) versus other forms of mucormycosis (blue line) in the RetroZygo study.

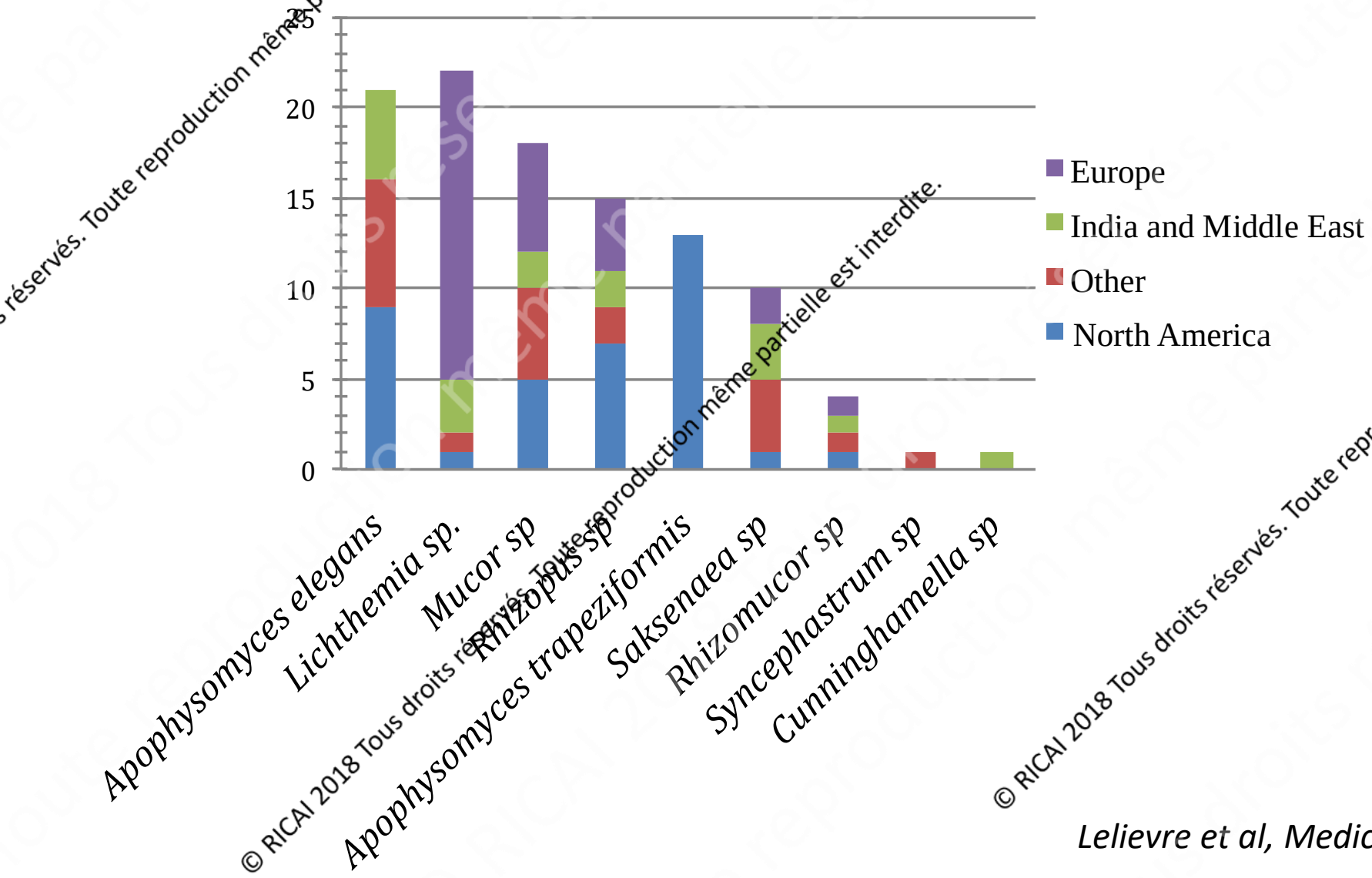
Circumstances of trauma of 122 cases of PTM from literature review.



	RetroZygo (n =16), n (%)	Literature (n=122), n (%)
Necrosis	10 (62.5)	93 (76.2)
Bacteria recovered from culture of wound	8 (50)	50 (41.0)

Lelievre et al, Medicine 2014

Distribution of Mucorales species according to the geographical origin (n=122)



Lelievre et al, Medicine

Diagnostic de mucormycose pulmonaire
Signe du halo inversé

- Etude monocentrique
- Leucémie aigue

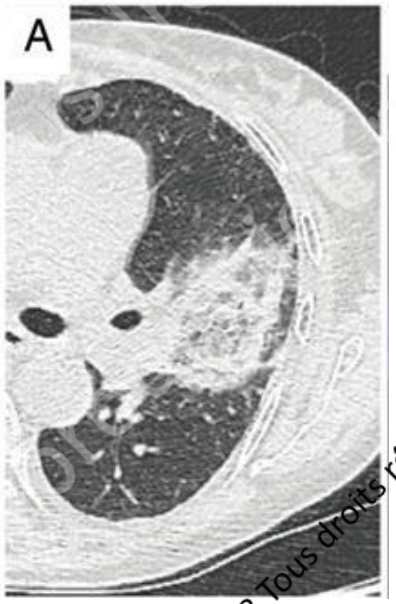


Table 3. Evolution of Computed Tomographic Scans of 16 Patients With Proven Pulmonary Mucormycosis

CT characteristics	Days 0–5	Days 6–14	Days 15–26
No. of patients with CT performed	16/16 (100)	11/16 (69)	11/16 (69)
No. of CTs performed	25	14	11
No. of patients with CT during neutropenia	15/16 (94)	9/11 (82)	4/11 (36)
Typical RHS	15/16 (94)	7/11 (64)	0/11 (0)
Diameter of lesion ≤3 cm	2/16 (12)	0/11 (0)	1/11 (9)
Diameter of lesion >5 cm	7/16 (44)	8/11 (73)	9/11 (82)
Micronodules	1/16 (6)	7/11 (64)	10/11 (91)
Pleural effusion	2/16 (12)	6/11 (55)	7/11 (64)
Air-crescent sign or cavitation	0/16 (0)	1/11 (9)	4/11 (36)

Data are presented as No. of scans with characteristic/No. of scans with available data (%). Day 0 corresponds to the day of the first CT scan. Micronodules are defined by diameter <1 cm.

Abbreviations: CT, computed tomography; RHS, reversed halo sign.

Legouge, CID, 2014

qPCR Mucorale sur sérum: diagnostic et suivi

- Etude nationale rétrospective
- 44 patients avec mucormycose, 34 avec hémopathie
- Combinaison de 3 qPCR sur sérum: *Mucor, Rhizopus, Lichteimia*
- 81% qPCR positive
  - 92% quand technique correcte
- qPCR positive 9 jours avant diagnostic mycologique et 2 jours avant diagnostic radiologique
- Survie à J84 plus élevée chez les patients avec qPCR négative (48% vs 4%)
- qPCR pour le diagnostic et le suivi de mucormycose

PHRC Modimucor

Million L, CMI, 2015

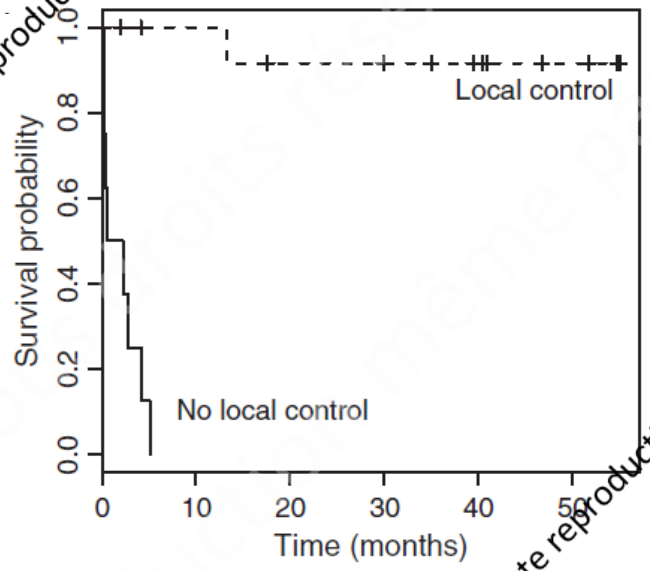
Clinical presentation

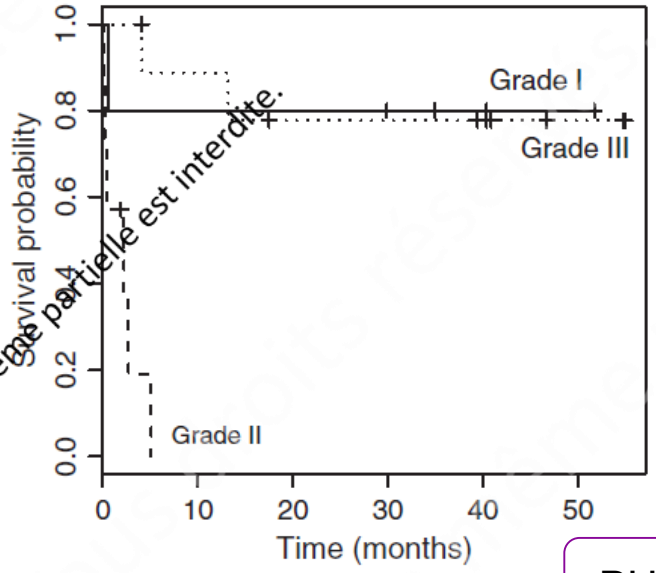
22 patients with rhino orbitocerebral mucormycosis from Retrozygo study

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

Place de la chirurgie dans les mucormycoses rhino-orbito-cérébrales





PHRC MICCA

Grade	N (%)
I: Biopsy	5 (22)
II: Resection of necrosis	7 (32)
III: Extended surgery	10 (45)

Vironneau P et al. *Clin Microbiol Infect* 2014;20:O336–O339.

Forte posologie d'amphotéricine B liposomale (10 mg/kg/j) dans le traitement de première ligne de la mucormycose

	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.

Doublement créatinine: 40%

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

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, 2014

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

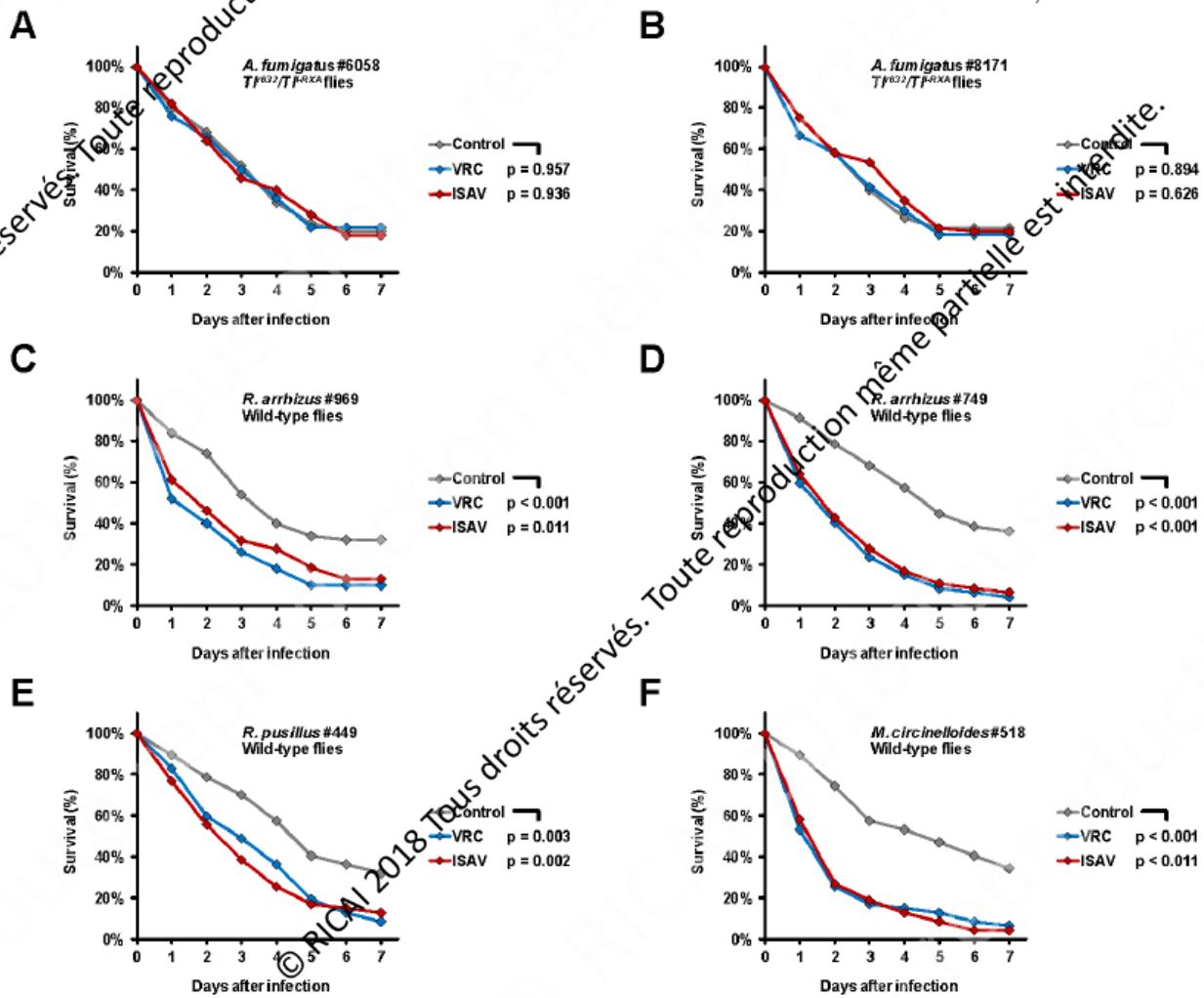
Arendrup, AAC 2015

Pre-Exposure to Isavuconazole Increases the Virulence of Mucorales but not *Aspergillus fumigatus* in a *Drosophila melanogaster* Infection Model

Running Title: Isavuconazole-associated hyper-virulence in *Drosophila*

Sebastian Wurster[1], Russell E. Lewis[2], Nathaniel D. Albert[1], Dimitrios P. Kontoyiannis[1#]

AAC, 2018



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%

Conclusion

Mucormycosis suspicion
- Radio-clinical presentation and Risk factors: diabetes mellitus

Diagnosis emergency
- Serum PCR
- Specimen at infection site

Therapeutic emergency:
- Surgery
- Antifungal:
  - Liposomal Amphotericin B ≥ 5mg/kg
  - Isavuconazole if not tolerated

When to step down?
- Negative PCR
- Radio clinical stabilization

Which antifungal to step down with?
- Isavuconazole
- Posaconazole

Pilmis .. Lanternier, F1000 research 2018

Remerciements

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