JN 25es Journées Nationales d'Infectiologie
DEAUVILLE et la région Normandie
du mercredi 12 au vendredi 14 juin 2024

Infections à filamenteux non-*Aspergillus* chez les adultes transplantés hépatiques, une cohorte rétrospective nationale française de 2007 à 2021

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Déclaration de liens d'intérêt avec les industriels de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

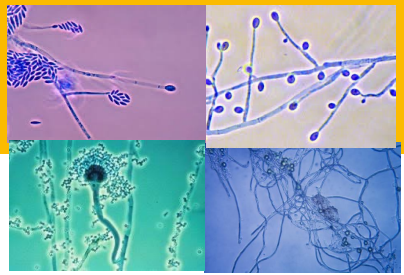
- **Intervenant** : Melenotte Cléa
- **Titre** : **Infections à filamenteux non-*Aspergillus* chez les adultes transplantés hépatiques, une cohorte rétrospective nationale française de 2007 à 2021**

Consultant ou membre d'un conseil scientifique	☐ OUI	☑ NON
Conférencier ou auteur/rédacteur rémunéré d'articles ou documents	☐ OUI	☑ NON
Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations	☑ OUI	☐ NON
Investigateur principal d'une recherche ou d'une étude clinique	☐ OUI	☑ NON

Déclaration d'intérêt de 2014 à 2023

- Intérêts financiers : Non
- Liens durables ou permanents : Non
- Interventions ponctuelles : Gilead
- Intérêts indirects : Non

Pourquoi cette étude?



Les infections fongiques invasives à filamenteux
(aspergillose, scédosporiose, mucormycose, fusariose)
représentent un problème de santé publique chez les patients transplantés d'organes.

=> Mortalité importante =>54% à 3 mois

⇒ Varie selon l'agent pathogène incriminé
100% mucormycose, 80% *non-Aspergillus* hyalohyphomycose, 54% aspergilloses et 20% phaeohyphomycoses (2013)

Peu de données sur les infections fongiques invasives à filamenteux hors aspergillose chez les patients transplantés hépatiques.

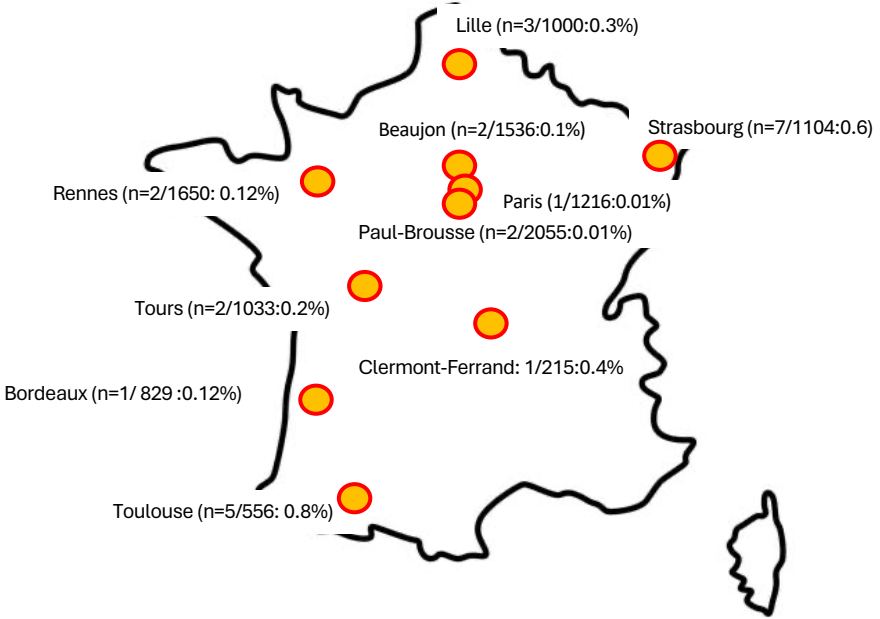
Table 3. Characteristics of HCT and SOT patients* with proven or probable invasive Mucorales, *Fusarium* spp., or *Scedosporium* spp. infection, as reported in TRANSNET, United States, 2001–2006†

Characteristic‡	Mucorales, no. (%), n = 105	*Fusarium* spp., no. (%), n = 37	*Scedosporium* spp., no. (%), n = 27	Total, no. (%), N = 169
Organ transplanted				
Heart	3 (10.7)	1 (16.7)	0	4 (8.9)
Lung	8 (28.6)	2 (33.3)	9 (81.8)	19 (42.2)
Kidney	9 (32.1)	1 (16.7)	2 (18.2)	12 (26.7)
Liver	9 (32.1)	2 (33.3)	0	11 (24.4)
Organ rejection within previous 30 d	13 (48.1)	3 (50)	8 (72.7)	24 (54.5)

*Includes 3 patients with 2 infections each; 2 patients had separate *Fusarium* and *Scedosporium* infections; 1 person had separate mucormycosis and

Shoham S, *Infect Dis Clin North Am*, 2013
Almyroudis NG, *Am Soc Transpl Surg*. 2006
Husain, *Clin Infect Dis*, 2013
Melenotte, *Transplant Infect Dis*, 2023
Park, *Emerg Infect Dis*, 2011

Infections à filamenteux non-*Aspergillus* chez les adultes transplantés hépatiques, une cohorte rétrospective nationale française de 2007 à 2021.



11 centres français ont participé

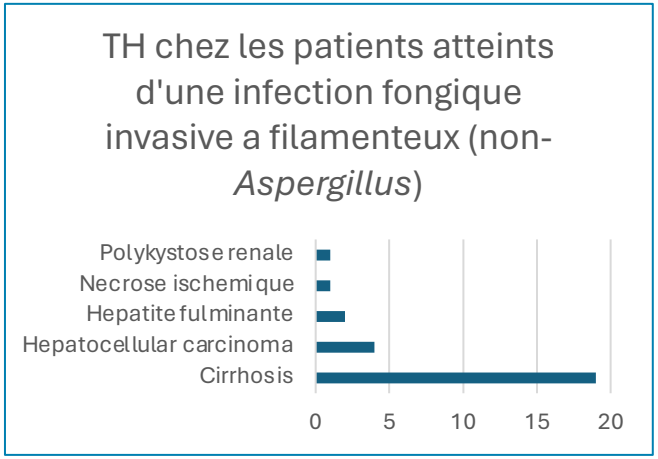
27 patients

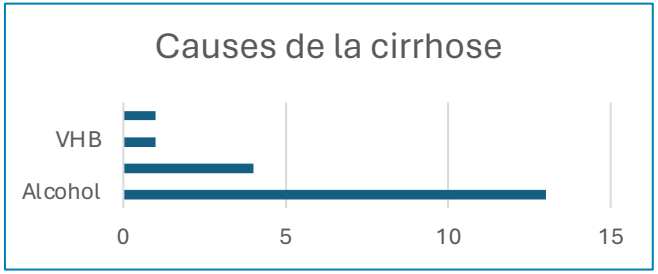
Nombre de TH sur la période 2007-2021: 11593

Incidence faible 0.23%

Etude Cas-Témoin 1:1

Facteurs de risque identifiés d'IFIF





Caractéristiques des patients, cas et témoins

	Control (n=27)	Cases (n=27)	P=
Sex	19 (70%)	19 (70%)	NS
Age at the date of LT (mean± SD)	55.72±11.8	55.57±13	NS
Body Mass Index	27.9±5.4	24.3±6.4	0.051
Autoimmune disease	3 (11%)	1 (0.3%)	NS
Tobacco	6 (22%)	4 (14.8%)	NS
Chronic renal insufficiency	2 (7%)	10 (37%)	0.009
Hemodialysis	1 (0.3%)	6 (22%)	0.037
Diabetes	7 (26%)	11 (40%)	NS
Cirrhosis	23 (85%)	19 (70%)	NS
Hepato cellular carcinoma	15 (55%)	8 (29%)	0.006
Fulminant hepatitis	2 (7%)	3 (11%)	NS
Hepatitis C	2 (7%)	6 (22%)	NS
Hepatitis B	1 (0.3%)	1 (0.3%)	NS
NASH	3 (11%)	1 (0.3%)	NS
Alcohol cirrhosis	15 (55%)	12 (44%)	NS

Facteurs de risques d'IFIF pré-opératoire

	Control (n=27)	Cases (n=27)	P=
ICU hospitalization waiting for LT	6 (22%)	14 (51%)	0.024
Hospitalization waiting for LT	6 (22%)	16 (57%)	0.006
At home waiting for LT	19 (70%)	9 (33%)	NS

Histoire médicale	Control (n=27)	Cases (n=27)	p=
CMV mismatch	13 (48%)	14 (51.8%)	NS
Previous fungal infection or colonization	1 (3%)	2 (7.4%)	NS
Previous liver transplantation	0 (0%	5(18.5%)	NS
Child Pugh C	9 (33.3%)	15 (55.5%)	NS
MELD>15	19 (70.3)	21 (77.7%)	NS
MELD >20	7 (25.9%)	19 (70.3%)	0.001
MELD>30	5 (18.5%)	10 (37%)	NS
Combined transplantation	1 (3.7%)	4 (14.8%)	NS

Facteur de risque d'IFIF en per-opératoire

	Control (n=27)	Cases (n=27)	P=
Transplantation surgical time (min)	348±106	434±156	0.075
Cold ischemia time (min)	403±117	425±179	NS
Length of stay in ICU	11±9.9	18±16.8	0.054
Amine post surgery	12 (44.4%)	21 (77.7%)	0.012
Amine >24 post surgery	7 (25.9%)	11 (40.7%)	NS
Mechanical ventilation post surgery	16 (59.5%)	23 (85.2%)	0.06
Mechanical ventilation >24h post surgery	6 (22.2%)	16 (59.2%)	0.06
Hemodialysis	4 (14.8%)	10 (37%)	NS
Red blood cell transfusion	14 (51.95%)	21 (77.7%)	0.009
Red blood cell transfusion>5	7 (25.9%)	14 (51.8%)	0.032

	Control (n=27)	Cases (n=27)	P=
Traitement IS			
Mycophenolate mofetil	24 (88.8%)	23 (85.18%)	NS
Basiliximab	4 (14.8%)	10 (37.1%)	NS
Sirolimus	5 (18.5%)	4 (14.8%)	NS
Tacrolimus	26 (96.3%)	22 (81.5%)	NS
Corticosteroids	22 (81.7%)	20 (74.1%)	NS

Facteur de risque identifiés en post-opératoire

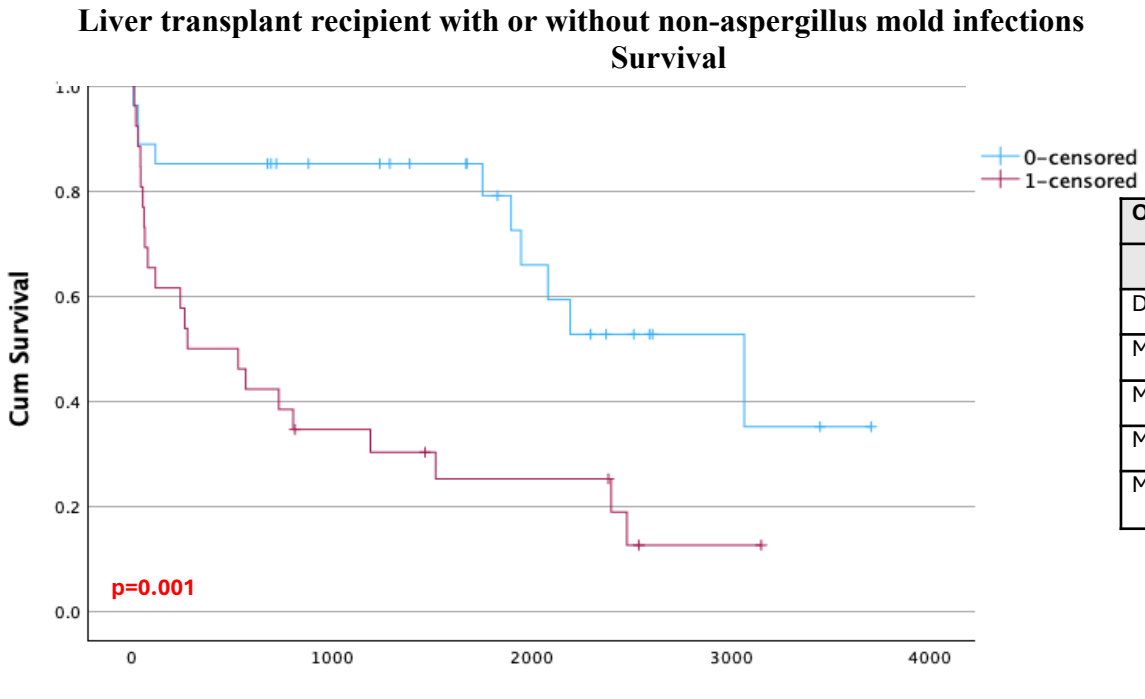
	Control (n=27)	Cases (n=27)	p=
Post LT complication			
Fungal infection yeast	3 (11%)	7 (25.9%)	NS
Mycobacterial infection	0	2 (7.4%)	NS
Clostridium difficile infection	0	2 (7.4%)	NS
P. aeruginosa infection	1 (3.7%)	2 (7.4%)	NS
Bacterial infection	13 (48%)	22 (81.4%)	0.01
Bacterial infection n=1	10 (37%)	9 (33.3%)	NS
Bacterial infection n=2	1 (3.7%)	5 (18.5%)	NS
Bacterial infection n=3	1 (3.7%)	4 (14.8%)	NS
Bacterial infection n>3	1 (3.7%)	4 (14.8%)	NS
CMV reactivation/infection	4 (14.8%)	5 (18.5%)	NS
Graft rejection	1 (3.7%)	3 (11.1%)	NS
Graft dysfonction	3 (11%)	3 (11.1%)	NS
Surgical revision	8 (29.8%)	14 (51.84%)	NS
Hemodialysis	2 (7.4%)	10 (37.03%)	0.007
Post operative bleeding	0	4 (14.81%)	NS
Post LT management			
Antifungal prophylaxis	4 (14.8%)	16 (59%)	0.001
Echinocandins prophylaxis	3 (11%)	12 (44%)	0.006
Fluconazole prophylaxis	3 (11%)	5 (18.5%)	NS

Facteur de risque identifiés en analyse multivariée

Risque d'IFIF *non-Aspergillus* chez les patients transplantés hépatiques

	OR	95% IC	P=
MELD>20	9.544	1.594-57.128	0.013
Fungal prophylaxis	14.931	1.516-147.017	0.021
Post LT bacterial infection	28.490	2.557-317.492	0.006

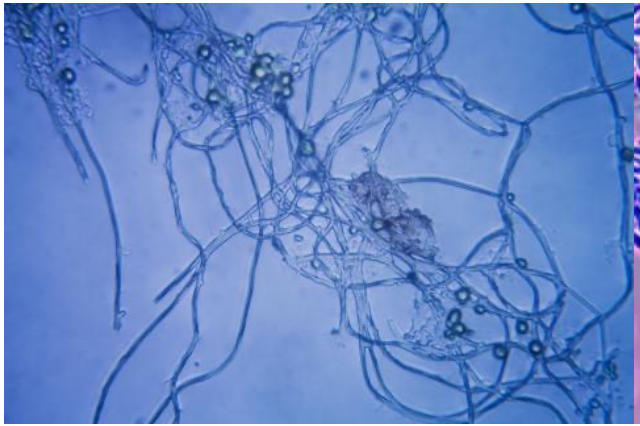
Mortalité post transplantation hépatique

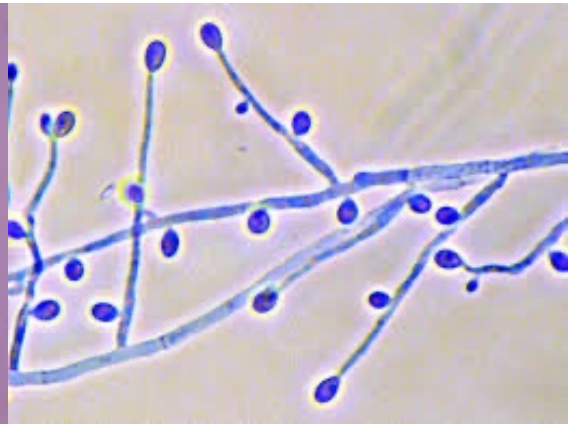


Time in days	0	1000	2000	3000	40000
Cases	27	10	8	6	6
Controls	27	23	20	18	17

Outcome			
	Control (n=27)	Cases (n=27)	p=
Death	10 (37%)	21 (77%)	0.001
Mortality at 1 month	3 (11%)	6 (22%)	NS
Mortality at 3 months	3 (11%)	9 (33%)	0.049
Mortality at 6 months	4 (14%)	11 (37%)	0.033
Mortality at 12 months	4 (14%)	14 (51.9%)	0.004

Qui sont ces 27 patients ?





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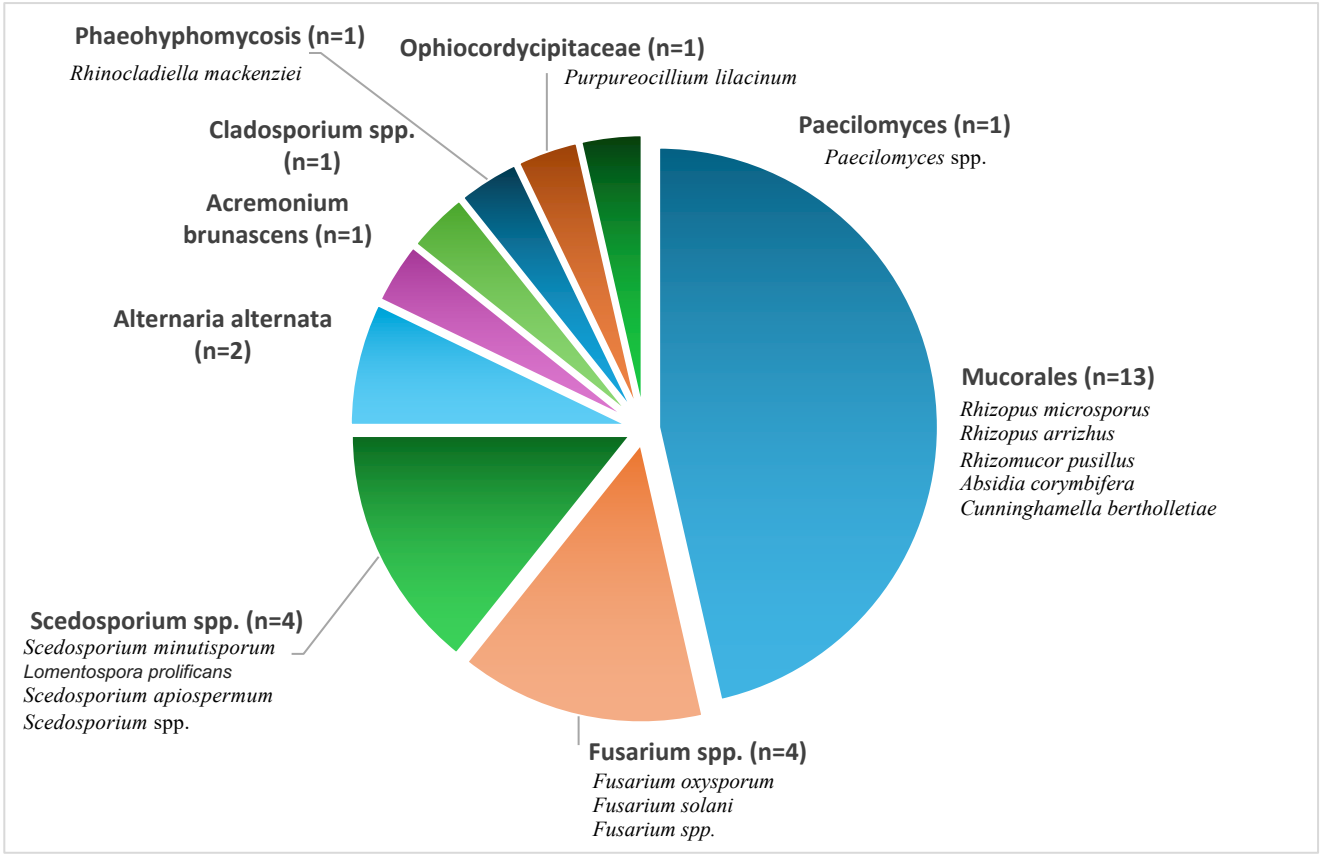
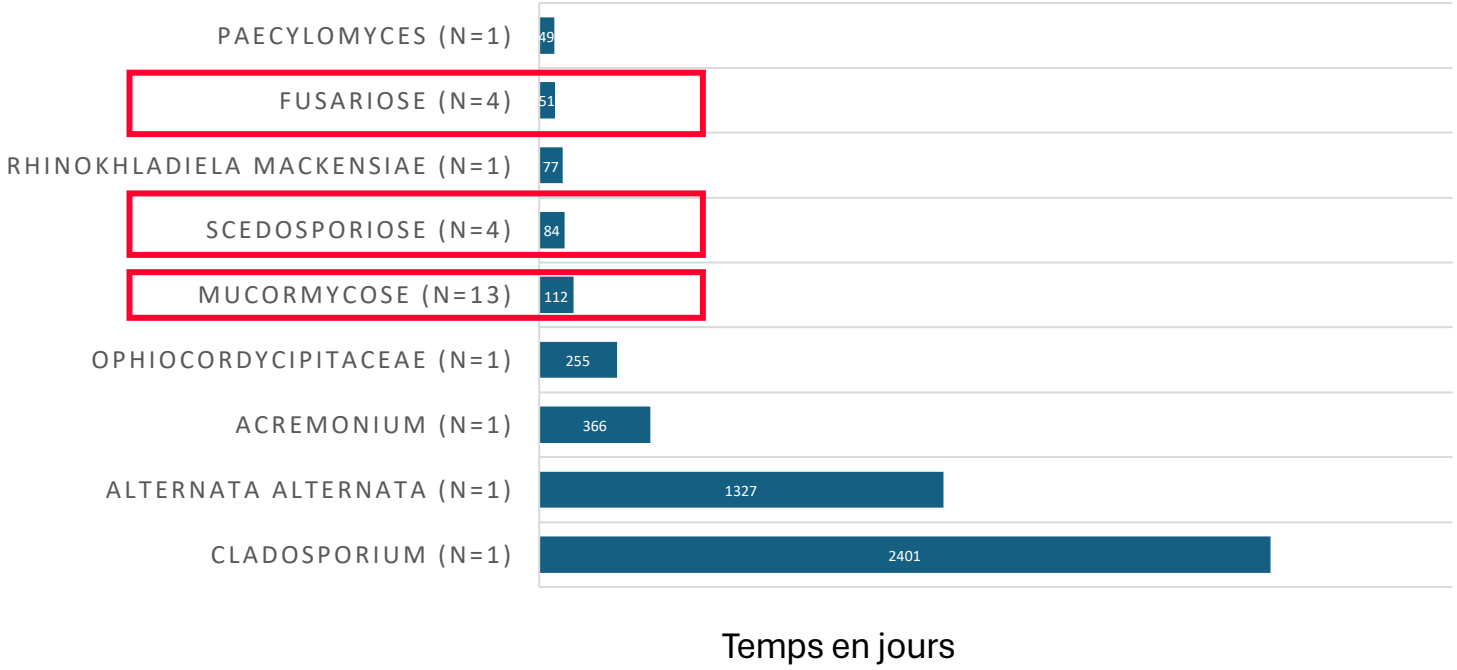


17 prouvés
10 probables

Délai entre la transplantation hépatique et la survenue de l'IFIF (*non-Aspergillus*)



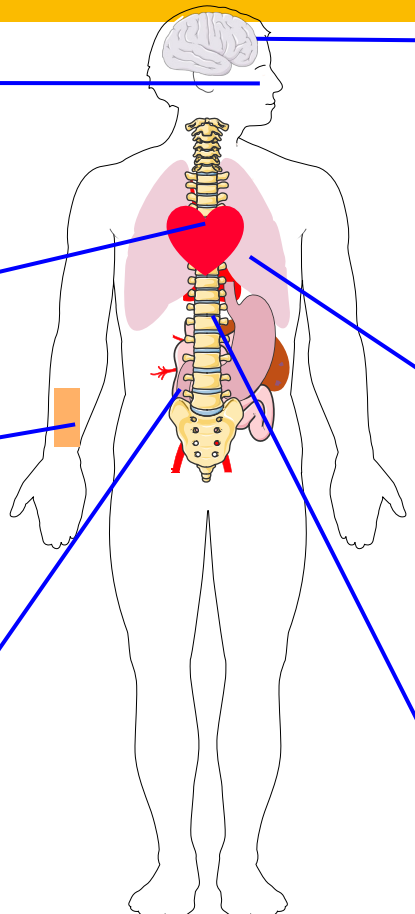
Présentation clinique: 6 disséminée, 21 localisées

Sinusienne (n=3)
Cunninghamella bertholletiae (+pulmonaire)
Rhizomucor pusillus
Rhizomucor spp.

Cardiaque (n=1)
Alternaria alternata (+cutanée)

Cutanée (n=5)
Fusarium spp. (+poumon)
Alternaria alternata (+cardiaque)
Fusarium solani
Cladosporium spp
Purpureocillium lilacinum

Digestive (n=4)
Scedosporium minutisporum
Absidia corymbifera
Rhizopus microsporus
Rhizopus microsporus
Paecilomyces spp.



Cérebrale (n=4)
Rhizomucor spp (+sinus)
Scedosporium spp (+poumon)
Scedosporium apiospermum (+disseminée)
Rhinocladiella mackenziei (0)

Pulmonaire (n=15)
Rhizomucor spp (+sinus)
Scedosporium spp (+poumon)
Scedosporium apiospermum (+disséminée)
Fusarium spp. (+cutanée)
Rhizomucor spp
Cunninghamella bertholletiae
Rhizopus microsporus
Acremonium brunascens
Fusarium spp
Fusarium oxysporum
Alternaria alternata
Lomentospora prolificans
Rhizopus arrizhus

Osseuse (n=1)
Rhizomucor spp (+poumon)

Caractéristiques biologiques des patients

	N=	%
Numération formule sanguine		
Hb <11dg/dL	22	81%
Neutropénie<1.5G/L	3	11%
Lymphopénie<1 G/L	17/20	85%
Syndrome inflammatoire		
CRP >10 mg/L CRP mean± SD	18/22 96,63±92.7	81%
Fonction rénale		
Créatinne>110 Créatinine mean± SD	16/24 155 ±132	66.7%
Hypoalbuminémie	18/23	78%
Immunosuppression **Taux résiduel de tacrolimus**		
Normal Sous dosé Surdosé	17/22 2/22 3/22	77% 9% 13.6%

Anémie
Lymphopénie
Inflammation
Insuffisance rénale
Hypoalbuminémie

Thérapeutique

	N=27	%
Traitement antifongique	25/27	92%
AMBL en monothérapie	**8/25**	**32%**
Azolés en monothérapie	**9/25**	**36%**
AMBL+Azolés	2/25	8%
AMBL+5FC	2/25	8%
Caspofungine + azolés	3/25	12%
Caspofungine seule	1/25	4%
Traitement chirurgical	**8/27**	**29%**

Les décès dans le groupe IFIF

N=27	Mortalité à 3 mois du diagnostic d'IFIF N=14 (51%)
Atteinte cérébrale	2/4 (50%)
Infection prouvée	10/17 (58%)
Atteinte disséminée	4/6 (66%)
Co infection aspergillose	7/9 (77%)
Mucormycose	**9 (69%)**
Scedosporiose	**2/4 (50%)**
Fusariose	**1 /4(25%)**
MELD>20	7/19 (36%)
TH_combinée	0 (0%)
Transfusion >5 CGR	7/14 (50%)
Reprise chirurgicale	5/14 (35%)
Infection bactérienne post opératoire	8/22 (36%)
Basiliximab	4/10 (40%)
MMF	8/23 (35%)

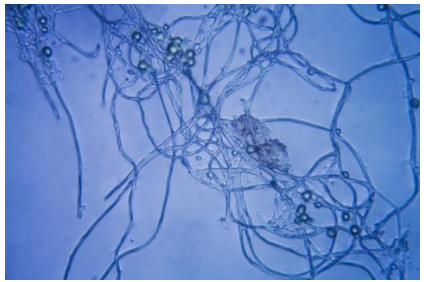
Key home messages

IFIF non-*Aspergillus*-> rare → 0.2%

Grave, mortalité à 3 mois post-TH 33% et à 12 mois 52%

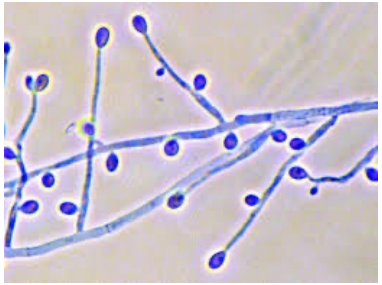
Mortalité à 3 mois du diagnostic d'IFIF: 51% et de 59% à 12 mois

Top 3 : mucormmycose, scedosporiose et fusariose



Mucormycose

Fusariose



Scedosporiose

Un grand merci !!!

Centre	Médecin référent
Beaujon (n=2)	P. Durand, C. Bonnal
Bordeaux (n=1)	C. Vignals, M. Lefranc
Clermont Ferrand (n=1)	R. Guérin, M. Moniot
Lille (n=3)	F. Vuotto, S. Loridant
Rennes (n=2)	P. Tattevin, J.P. Gangneux
Strasbourg (n=7)	F. Lefebvre, C. Le Hyaric, R, Herbrecht
Toulouse (n=5)	N. Kamar, X. Iriart
Tours (n=2)	M. Barbaz, A. Chesnay
Besancon (n=1)	D. Weil, A.P. Bellanger-Clerget
Paris (n=5)	Arnaud Fekkar, F. Botterel, F. Saliba
Paul-Brousse (n=2)	F. Saliba, Nada El Domiaty

L'équipe de recherche

Coralie Le Hyaric, Céline Guichon, Olivier Lortholary, François Danion, Agnès Lefort

Pr Françoise Botterel, président de la Société Française de Mycologie Médicale

Dr Bernard CASTAN, président de la SPILF
Pr Pierre Tattevin, vice-président de la SPILF

Les facteurs de risque de décès à 3 mois chez les patients transplantés hépatiques

	Pas de décès à M3 (n=42)	Décès a M3 (n=12)	p=
Infection fongique invasive non-Aspergillus	3 (7.1%)	9 (75%)	0.049
Co infection avec Aspergillus	5 (11%)	4 (0.33%	NS
Scedosporiose	1 (0.2%)	2 (16%)	NS
Mucormycose	8 (19%)	5 (41%)	NS
MMF	37 (88%)	10 (83%)	NS
Tacrolimus	37 (88%)	11 (91%)	NS
Basiliximab	10 (23%)	4 (33%)	NS
Infection bactérienne post TH	26 (61%)	9 (75%)	NS
Reactivation/infection CMV	9 (21%)	0 (0%)	NS
Transfusion >=5 CGR	13 (30%)	8 (66%)	0.008
Amine post opératoire	23 (54%)	10 (83%)	0.04
Amines post opératoire >24h	11 (28%)	7 (58%)	0.026
VM post opératoire	28 (68%)	11 (91%)	NS
VM post opératoire >24h	14 (33%)	8 (66%)	0.025
Hemodialyse	8 (19%)	6 (50%)	0.017
MELD>20	19 (45%)	7 (58%)	NS
MELD>30	9 (21%)	6 (0.5%)	NS

Pas de résultats significatifs en analyse multivariée

Co infection avec l'aspergillose 33%

Non-*Aspergillus*

Poumon

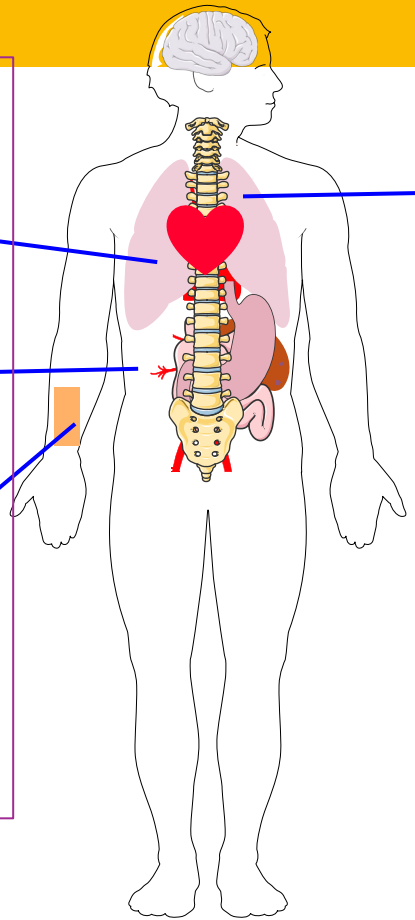
Scedosporium prolificans
Rhizomucor spp
Scedosporium apiospermum

Liquide d'ascite

Paecilomyces spp.
Scedosporium apiospermum

Peau

Cladosporium spp (peau)
Scedosporium apiospermum



***Aspergillus* infection n=9**

Poumon

Aspergillus fumigatus

Aspergillus niger

Aspergillus nidulans

Les causes du décès dans le groupe IFIF

	Décès (n=21)
Attribuables à l'IFIF	8/21 (38%)
Possiblement en lien avec l'IFIF (dans les 2 mois suivant le diagnostic)	6/21 (28%)
Autres causes	7/21 (28%)

Agent pathogène responsable du décès	**Localisations infectieuses**
Mucormycose (n=5)	Poumon-Os Sinusienne Pulmonaire (x2) Digestive
Fusariose (n=1)	Cutanée et pulmonaire
Scedosporiose-Aspergillose (n=1)	Disséminée
Rhinocladiella mackenziei (n=1)	Cérébrale

N=27	**Mortalité à 3 mois N=9**
Atteinte cérébrale	2 (22%)
Infection prouvée	3 (33%)
Atteinte disséminée	3 (44%)
Co infection aspergillose	4 (44%)
Mucormycose	**5 (55%)**
Scedosporiose	**2 (22%)**
Fusariose	**1 (11%)**
MELD>20	7 (77%)
TH_combinée	0 (0%)
Transfusion >5 CGR	7 (77%)
Reprise chirurgicale	5 (55%)
Infection bactérienne post opératoire	8 (88%)
Basiliximab	4 (44%)
MMF	8 (88%)

Phaeohyphomycosis (n=1)

Rhinocladiella mackenziei

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1 Cite Share

Fungal thalamic abscess caused by **Rhinocladiella mackenziei** in an immunocompetent patient.

Gupta S, Srivastava A, Vyas N, Kaur H, Sharma BS, Rudramurthy SM.

Indian J Med Microbiol. 2024 May 23;49:100605. doi: 10.1016/j.ijmmb.2024.100605. Online ahead of print.

PMID: 38734140

In the present study, authors describe the first case of left thalamic fungal abscess due to **Rhinocladiella mackenziei** in an immunocompetent 39-year-old male patient in Jaipur, Rajasthan. ...

2 Cite Share

Post covid cerebral phaeohyphomycosis by **Rhinocladiella mackenziei**: An unusual association.

Khandhar AV, Warade A, Agrawal U, Shetty A, Sunavala A, Desai K.

Indian J Med Microbiol. 2023 Nov-Dec;46:100430. doi: 10.1016/j.ijmmb.2023.100430. Epub 2023 Jul 25.

PMID: 37945123

Cerebral phaeohyphomycosis (CP) is a rare but a highly morbid fungal infection of the central

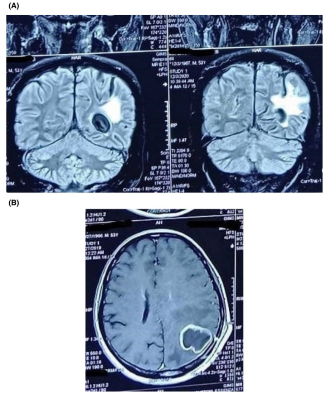
Case Reports > Clin Case Rep. 2022 Dec 5;10(12):e6691. doi: 10.1002/ccr3.6691. eCollection 2022 Dec.

Cerebral phaeohyphomycosis in liver transplant recipient: A case report

Kaleem Ullah [1], Muhammad Asif Baig [1], Abdul Wahab Dogar [1], Shams Uddin [1], Chaudhary Abdul Fatir [2], Ali Asad [3], Muhammad Junaid Tahir [2], Ka Yiu Lee [4], Khabab Abbasher Hussien Mohamed Ahmed [5], Zohaib Yousaf [6]

Affiliations + expand

PMID: 36483863 PMCID: PMC9723403 DOI: 10.1002/ccr3.6691



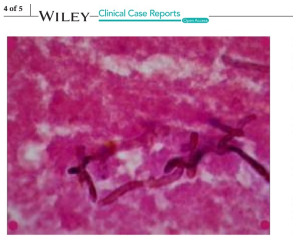


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FIGURE 2 Gram stain and hematoxylin and eosin (H&E) stain showing fungal septate hyphae with a diffuse mixed inflammatory infiltrate (10× and 40× magnification)

Purpureocillium lilacinum

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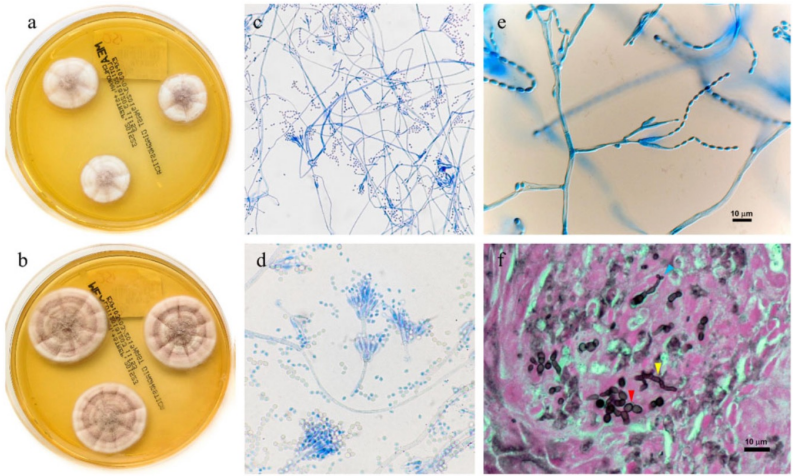

Figure 3. Macroscopic, microscopic and histopathological presentation of *Purpureocillium lilacinum*. (a and b) Malt extract agar plate incubated at 26°C showing white to lilac colonies of *P. lilacinum* after 5 days and 7 days of culture. (c and d) Lactophenol cotton blue staining. Typical phialides with a distinct neck bearing conidia. Conidia are ellipsoidal to fusiform with a smooth wall. Magnification: ×400 and ×1000. (e) Lactophenol cotton blue staining. *P. lilacinum* isolate showing elongated phialides producing chains of lemon-shaped conidia. Magnification ×600. (f) Histopathological examination (Grocott stain) reveals three different aspects of *P. lilacinum* growing within infected tissue: globose yeast-like structures (red arrowhead), septate hyphae (yellow arrowhead) and conidia that arise from the apical orifice of a phialide (blue arrowhead). Magnification ×600. Images (a–d) courtesy of Jörg Steinmann and images (e–f) courtesy of René Pelletier.

Characteristics and outcome of invasive *Purpureocillium lilacinum* infections JAC

Table 1. *Continued*

Characteristic	Total ($n = 101$)		Deaths in the respective cohort, n (%)		Mortality ($n = 101$)
Bronchial stent	3	3.0%	–	–	–
Central venous catheter	10	9.9%	–	–	–
Prosthetic aortic valve	3	3.0%	3	100.0%	3.0%
Organ involvement[e]					
Blood	18	17.8%	6	33.3%	5.9%
Bone and joints	6	5.9%	1	16.7%	1.0%
Central nervous system	5	5.0%	1	20.0%	1.0%
Deep tissue	24	23.8%	3	12.5%	3.0%
Heart	5	5.0%	4	80.0%	4.0%
Lung	26	25.7%	4	15.4%	4.0%
Peritoneum	4	4.0%	1	25.0%	1.0%
Sinuses	13	12.9%	1	7.7%	1.0%
Skin	37	36.6%	6	16.2%	5.9%
Dissemination					
Adjacent organs	15	14.9%	1	6.7%	1.0%
Disseminated	22	21.8%	7	31.8%	6.9%
Not disseminated	64	63.4%	13	20.3%	12.9%

Abbreviations: EORTC/MSG, European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium; GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; SOT, solid organ transplantation.
Data may be superadditive.
[a]Other underlying conditions included hepatitis C ($n = 3$), rheumatoid arthritis ($n = 2$), acute SOT rejection and PTLD ($n = 1$), chronic hepatitis B ($n = 1$), chronic lung allograft dysfunction ($n = 1$), chronic persisting hepatitis of unknown aetiology ($n = 1$), Guillain-Barré Syndrome ($n = 1$), and Sweet's syndrome ($n = 1$).
[b]Including five non-specified cases, three cases with acute myeloid leukaemia and two cases with biphenotypic leukaemia.
[c]Including two cases of osteosarcoma and one case each with breast cancer, neuroblastoma, pancreatic cancer, retinoblastoma, rhabdomyosarcoma, testicular cancer.
[d]Including four cases with chronic lymphocytic leukaemia, one case with non-Hodgkin lymphoma, one case with not further specified lymphoma, and one case with multiple myeloma.
[e]Other organ involvements include eye ($n = 2$), kidney ($n = 2$), and vessels ($n = 1$).

Rosanne Sprute, JC, 2021