MALADIES BRONCHO-PULMONAIRES CHRONIQUES LIEES A L'*ASPERGILLUS*

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Pneumologie
Hôpital Bichat-Claude Bernard-APHP
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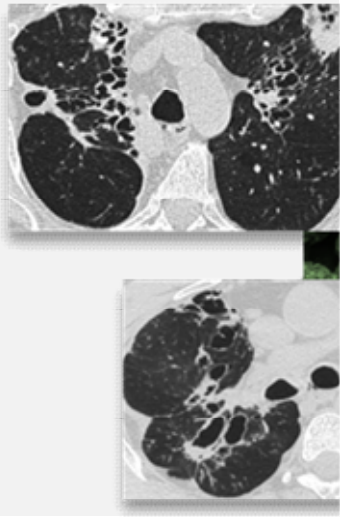

Déclaration liens d'intérêts

SUBVENTION ET AVANTAGES À TITRE COLLECTIF	RÉMUNÉRATION ET AVANTAGES À TITRE PERSONNEL
Pfizer Gilead MSD Astellas	Pfizer Gilead MSD Basilea Pulmatrix

Medical Mycology Advance Access published October 28, 2016

ISHAM
INTERNATIONAL SOCIETY FOR
HUMAN AND ANIMAL MYCOLOGY

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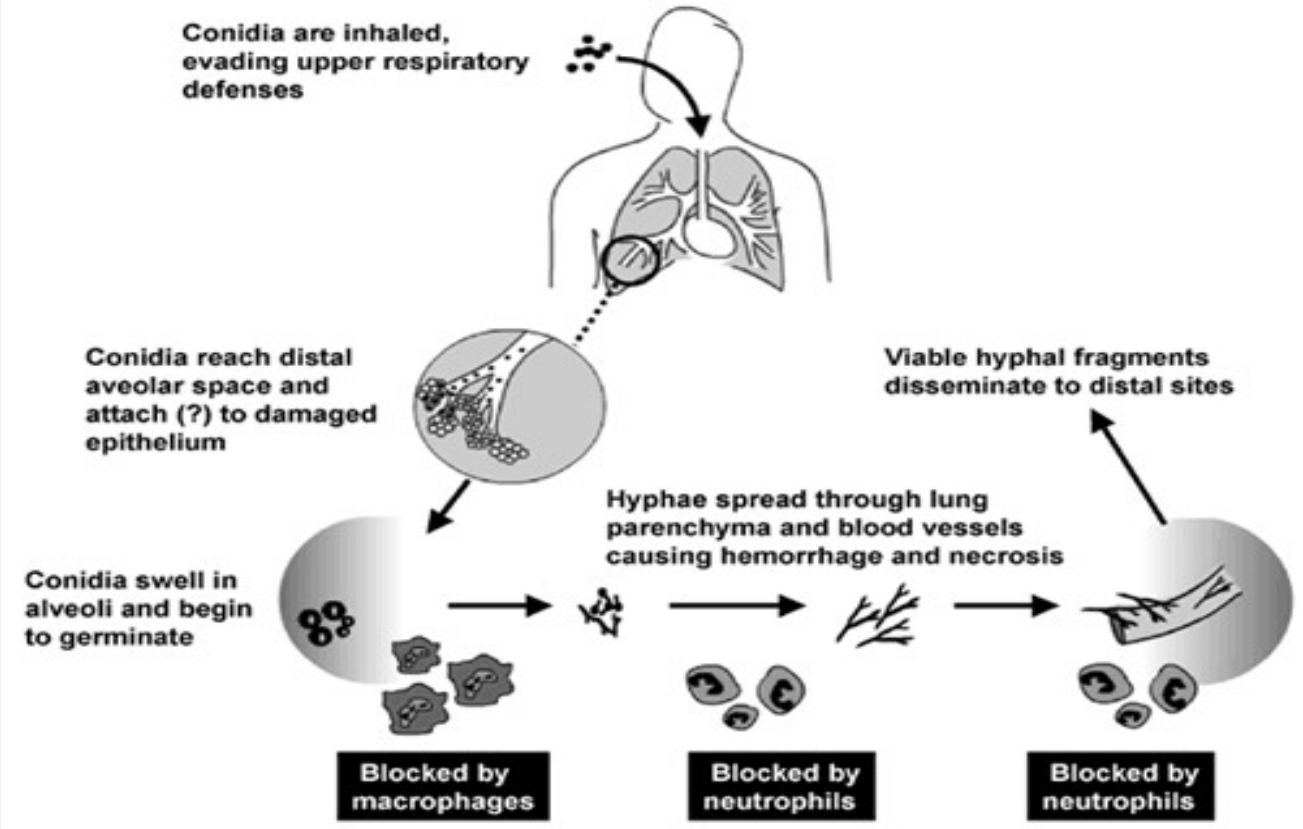
Advance Access Publication Date: 0 2016
Review Article

Review Article

Bronchiectasis and *Aspergillus*: How are they linked?

Anthony De Soyza[1,*] and Stefano Aliberti[2]

Physiopathologie



Facteurs de risque des infections fongiques et bronchiectasies

Altération clairance muco-ciliaire

- Infections (bronchite aspergillaire)
- Antigènes aspergillaires et protéases (MUC5AC) / rétention mucus
- Réponse immune accrue TH2 (ABPA)

Déficit fonction neutrophile / monocytaire ou macrophagique

- Altération mécanismes d'apoptose neutrophiles : inflammation et infection

Particularités structurales de bronchectasie

- DDB cylindriques : cavités ➟ aspergillomes

Infection aspergillaire ➟ dommage paroi bronchique ➟ DDB

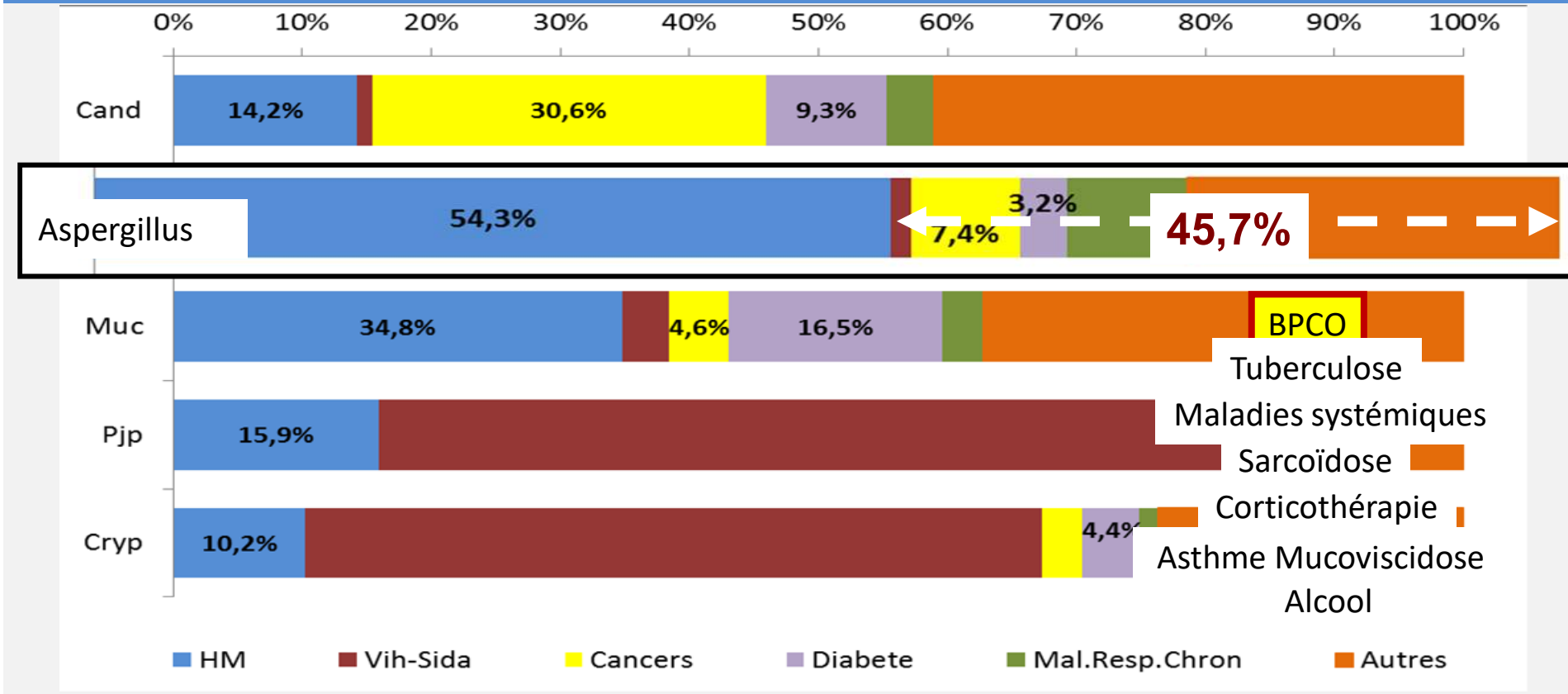
Susceptibilités génétiques

- Déficit en cellules dendritiques, Stat3 mutations, hyper IgE syndrome,
- Chronic Granulomatous Disease

De Soyza A, Medical Mycology, 2016

Facteurs de risque des infections fongiques

France 2004-10



Bitar, Lortholary et al. (Thanks to O. Lortholary)

An estimation of burden of serious fungal infections in France

Estimation du poids épidémiologique des infections fongiques graves en France

J.-P. Gangneux [a,*], M.-E. Bougnoux [b], C. Hennequin [c], C. Godet [d], J. Chandenier [e], D.W. Denning [f], B. Dupont [b], for the LIFE program, the Société française de mycologie médicale SFMM-study group [1]

Table 1 Burden of serious fungal infections in France.
Poids épidémiologique des infections fongiques graves en France.

Infection	Number of infections per underlying disorder per year					Rate/100K	Total burden
	None/other	HIV/AIDS	Respiratory	Cancer/Tx	ICU		
ABPA	–	–	95,331	–	–	145	95,331
SAFS	–	–	124,678			189	124,678
Chronic pulmonary aspergillosis	–	–	3450	–	–	5.24	3450
Invasive aspergillosis	151	17	97	800	120	1.8	1185
Mucormycosis	10	–	–	69	–	0.12	79
Pneumocystis pneumonia	61	449	4	144	–	1	658
Candidaemia	533	28	85	1134	590	3.6	2370
Candida peritonitis	249	–	–	–	237	0.74	486
							9075
							730,690
							131
							968,143

Chronic pulmonary aspergillosis

Invasive aspergillosis

Incidence/100 000

5.24

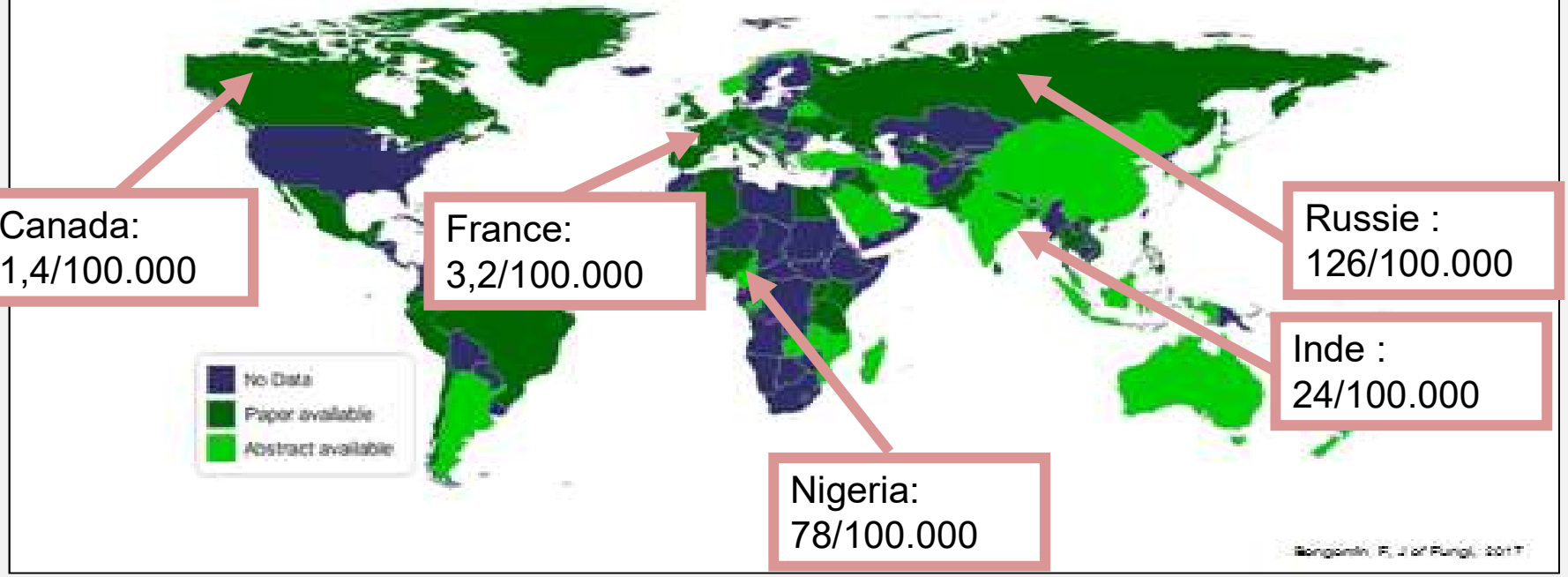
1.8

Gangneux et al., J. Med. Mycol.; 2016, 26, 385–390.

Aspergillosis	Invasive	Chronic	Allergic
Global Burden	200,000 – 400,000	1.5 M – 3M	6M – 20M
Untreated Mortality	~100%	~75% / 5 yrs	< 1%
Treated Mortality	30-85%	~45% / 5 yrs	< 1%
Orphan Drug Designation?	Yes	Yes	No (possible for Cystic Fibrosis)
Placebo-Controlled RCT Possible?	No	No	Yes
Surrogate Endpoint	Yes/No	No	No

Une épidémiologie de l'APC encore incomplète

3 millions de cas dans le monde



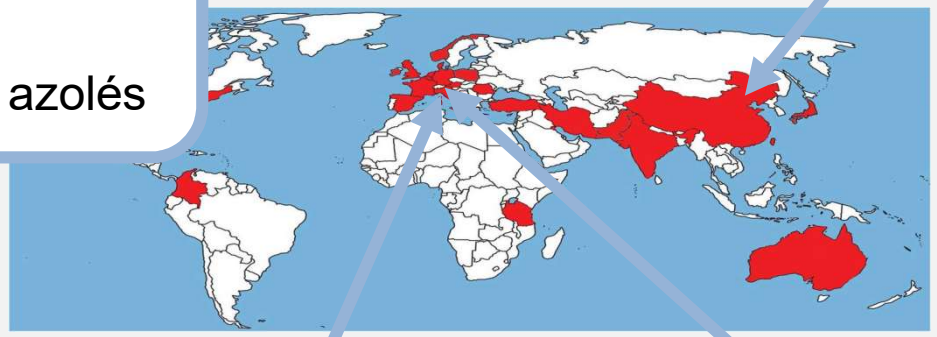
Résistance acquise (prétraités/environnementale)

Azole resistance in *Aspergillus fumigatus*: a side-effect of environmental fungicide use?

Paul E Verweij, Eveline Snelders, Gert H J Kema, Emilia Mellado, Willem J G Melchers

- Monde 3,2% : sous-estimation
- absence de pratiques homogènes et standardisées inter-laboratoires pour surveillance émergence souches R aux azolés

- Aspergillose chronique :
  - UK : 7,7%,
  - France: 9%
- Résistance en France ITC sur mucoviscidose : 4,6% à 10,6%



Verweij CID 2016, Van der Linden EID 2015 *Bongomin et al, 2018* *Dauchy et al, 2018*

Maladies broncho- pulmonaires liées à l'*Aspergillus*

Manifestations infectieuses

- Colonisation aspergillaire
- Bronchite aspergillaire

- Aspergillome simple
- Aspergillose Pulmonaire Chronique Cavitaire (APCC)
- Aspergillose Pulmonaire Chronique Fibrosante (APCF)
- Aspergillose Pulmonaire Chronique Nécrosante (APCN)

- La forme invasive du non neutropénique

Manifestations d'hypersensibilité

- Aspergillose broncho-pulmonaire allergique (ABPA)
- Asthme sévère avec hypersensibilisation fongique (SAFS)
- Pneumopathie d' hypersensibilité à *Aspergillus*

Denning D et al, Eur Respir J, 2016
Patterson TF et al, CID, 2016

Formes de chevauchement

Maladies broncho- pulmonaires liées à l'*Aspergillus*

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Denning D et al, Eur Respir J, 2016
Patterson TF et al, CID, 2016

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Maladies broncho- pulmonaires liées à l'*Aspergillus*

Manifestations infectieuses

- **Colonisation** aspergillaire
- **Bronchite** aspergillaire

- Aspergillome simple
- Aspergillose Pulmonaire Chronique Cavitaire (APCC)
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Denning D et al, Eur Respir J, 2016
Patterson TF et al, CID, 2016

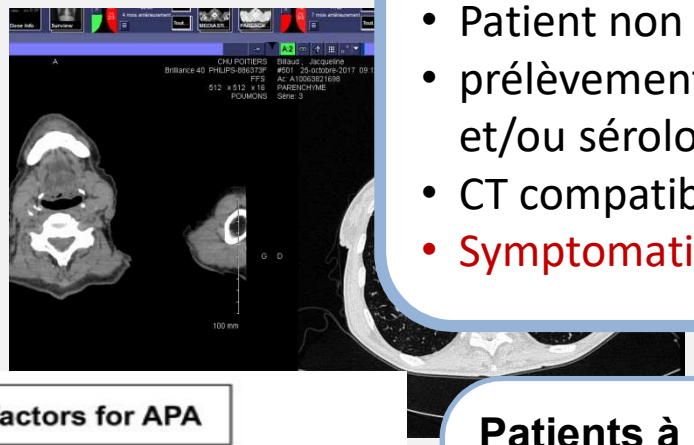
overlaps

Formes de chevauchement

Maladies broncho- pulmonaires liées à l'*Aspergillus*

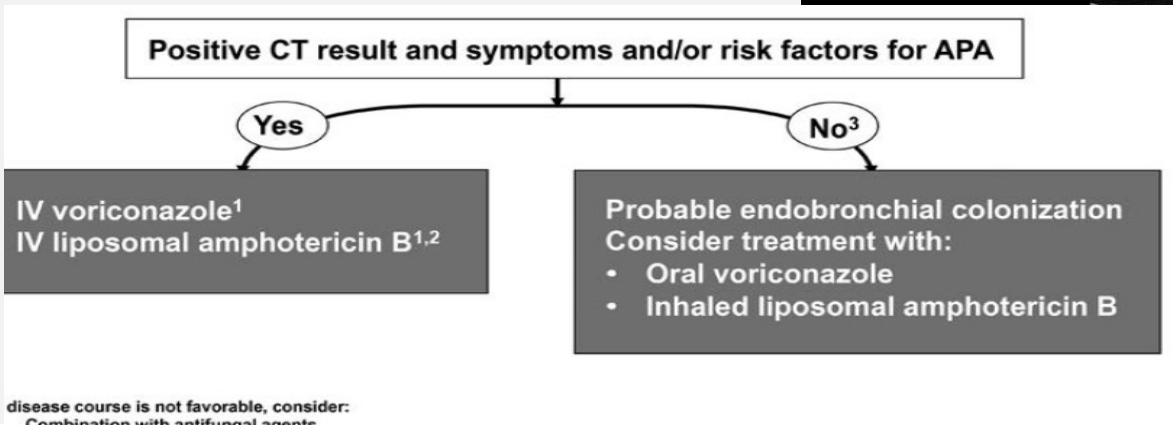
Colonisation aspergillaire

- Patient non immunodéprimé
- prélèvements respiratoires + et/ou sérologie +
- CT compatible
- Non symptomatique



Bronchite aspergillaire

- Patient non immunodéprimé
- prélèvements respiratoires + et/ou sérologie +
- CT compatible
- Symptomatique



Patients à risques :

- Corticoïdes
- BPCO (Gold≥3), Cavités
- virus influenza, CMV
- Cirrhose ++
- hospitalisation réanimation

Esp Quimoter, 2016; Burgel et al Infect and Drug Resis 2016

Maladies broncho- pulmonaires liées à l'*Aspergillus*

Manifestations infectieuses

- Colonisation aspergillaire
- Bronchite aspergillaire

- Aspergillome **simple**
- Aspergillose Pulmonaire Chronique **Cavitaire** (APCC)
- Aspergillose Pulmonaire Chronique **Fibrosante** (APCF)
- Aspergillose Pulmonaire Chronique **Nécrosante** (APCN)

- La forme invasive du non neutropénique

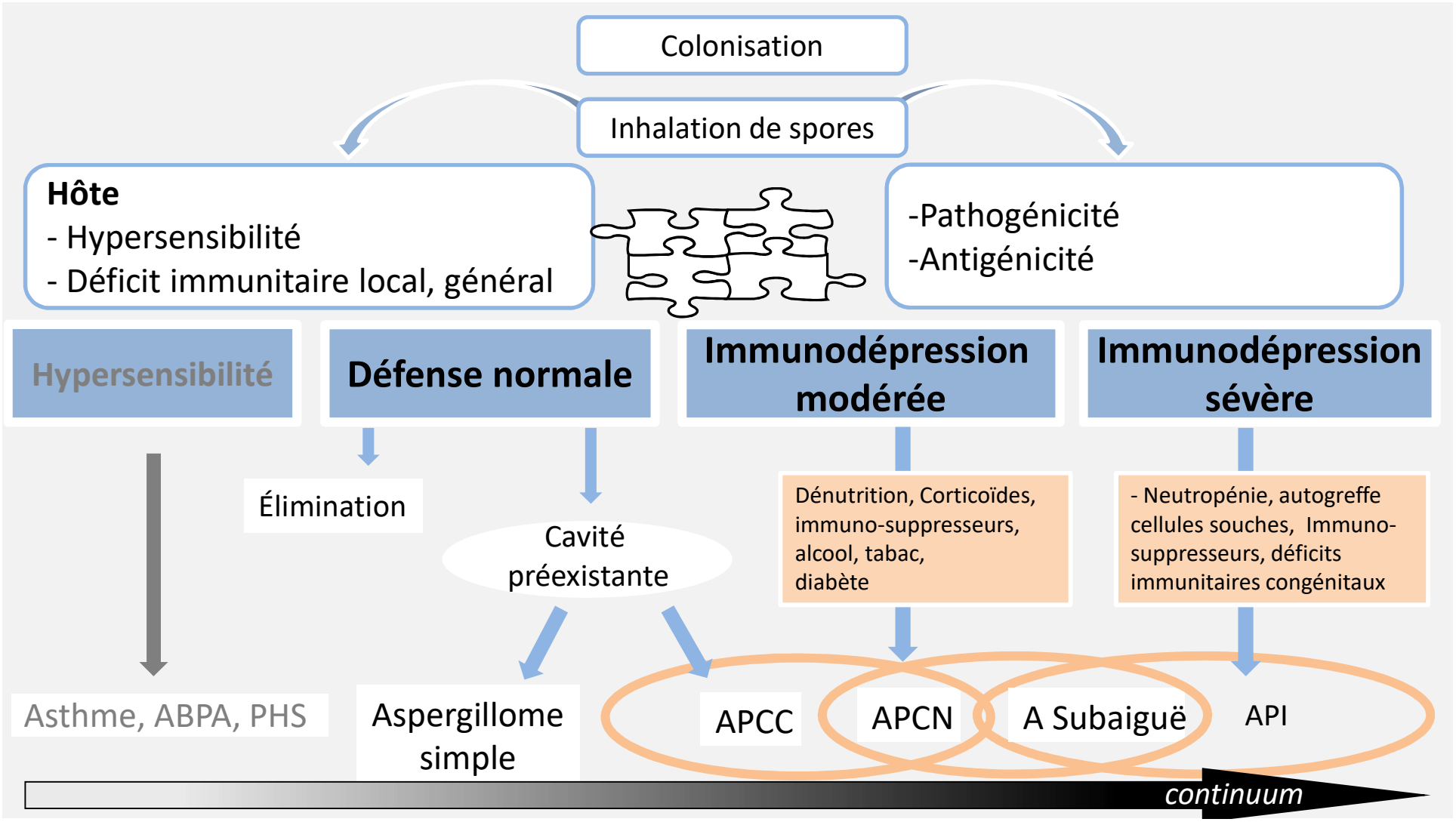
Manifestations d'hypersensibilité

- Aspergillose broncho-pulmonaire allergique (ABPA)
- Asthme sévère avec hypersensibilisation fongique (SAFS)
- Pneumopathie d'hypersensibilité à *Aspergillus*

Denning D et al, *Eur Respir J,* 2016
Patterson TF et al, CID, 2016

overlaps

Formes de chevauchement


Colonisation
Inhalation de spores
Hôte
- Hypersensibilité
- Déficit immunitaire local, général
-Pathogénicité
-Antigénicité
Hypersensibilité
Défense normale
Immunodépression modérée
Immunodépression sévère
Élimination
Cavité préexistante
Dénutrition, Corticoïdes, immuno-suppresseurs, alcool, tabac, diabète
- Neutropénie, autogreffe cellules souches, Immuno-suppresseurs, déficits immunitaires congénitaux
Asthme, ABPA, PHS
Aspergillome simple
APCC
APCN
A Subaiguë
API
continuum

EFISG ESCMID FUNGAL INFECTION STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases

Chronic Pulmonary Aspergillosis - subsets

Simple/single Aspergilloma

Aspergillus nodule(s)

Chronic Cavitary Pulmonary Aspergillosis/Complex Aspergilloma (CCPA)

Chronic Fibrosing Pulmonary Aspergillosis (CFPA)

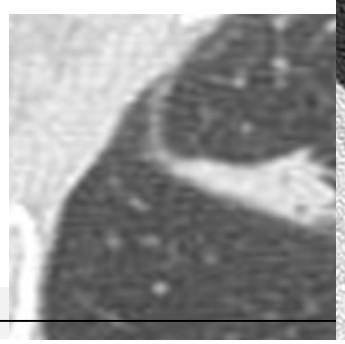
Subacute invasive(SIA)/Semi-Invasive/Chronic Necrotizing Pulmonary Aspergillosis (CNPA)

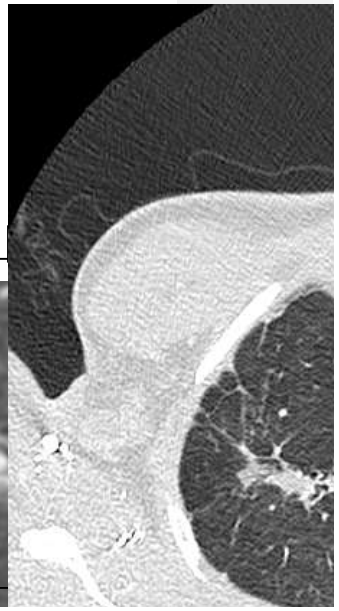
Note – fungal balls (aspergilloma) may be seen in any of these conditions, except *Aspergillus* nodule

Aspergillome simple

- Prolifération de spores aspergillaires organisées en feutrage mycélien dense ou « balle fongique » dans une cavité préexistante (pulmonaire, bronchique, pleurale) sans envahir le poumon
- Absence de tissu pulmonaire nécrosé
- Présence de tissu inflammatoire avec phénomènes d'hypervascularisation
- Sérologie aspergillaire positive +/- examen direct/culture

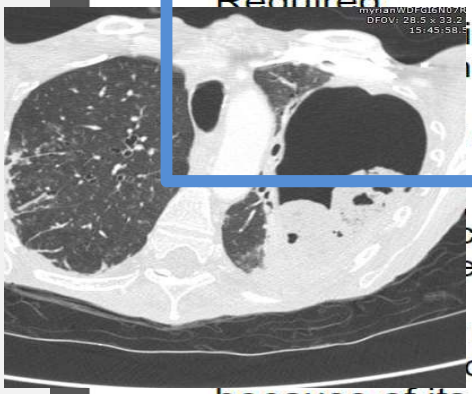
Aspergillome simple :
lésion unique
avec cavité
à paroi fine

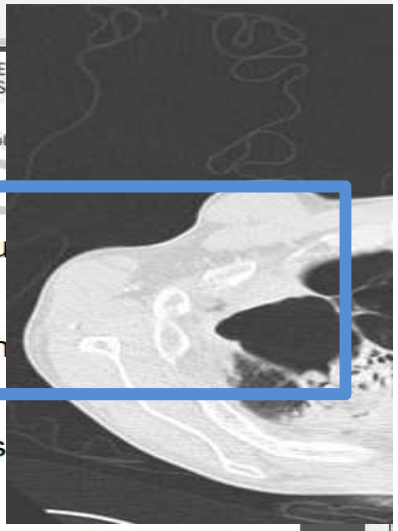




Kim YT, Ann Thorac Surg 2005

Chronic Pulmonary Aspergillosis – Diagnostic criteria





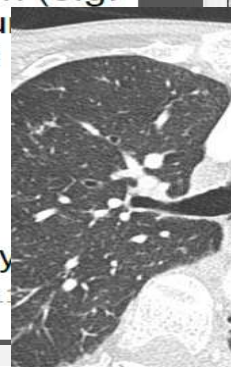
Required:

istic CT appearance of a fungus ball in a pulmonary or pleu
ius,

or indirect microbiological evidence of *Aspergillus* infection

cal features consistent with chronic pulmonary aspergillosis
eural thickening, extensive fibrosis or nodule)

radiological evidence of at least 3 months disease (sometimes inferred)
durations of disease may be seen in SIA/CNPA, which becomes CPA because of its chronicity],
AND
2.3 Histological or microbiological or immunologic evidence of *Aspergillus* infection (e.g. histological evidence of *Aspergillus*-like hyphae in lung biopsy or *Aspergillus* cultu from a percutaneous cavity aspiration; strongly positive BAL antigen; positive IgG antibody/precipitins). Respiratory tract culture or PCR positive for *Aspergillus* is supportive.
Required:
Exclusion of histoplasmosis, coccidioidomycosis and paracoccidiodomycosis in endemic areas or those with pertinent travel history; actinomycosis.
Active bacterial infection, including mycobacterial infection and/or malignancy occur concurrently. Mycobacterial infections or malignancy may mimic CPA.



May 10, 2014

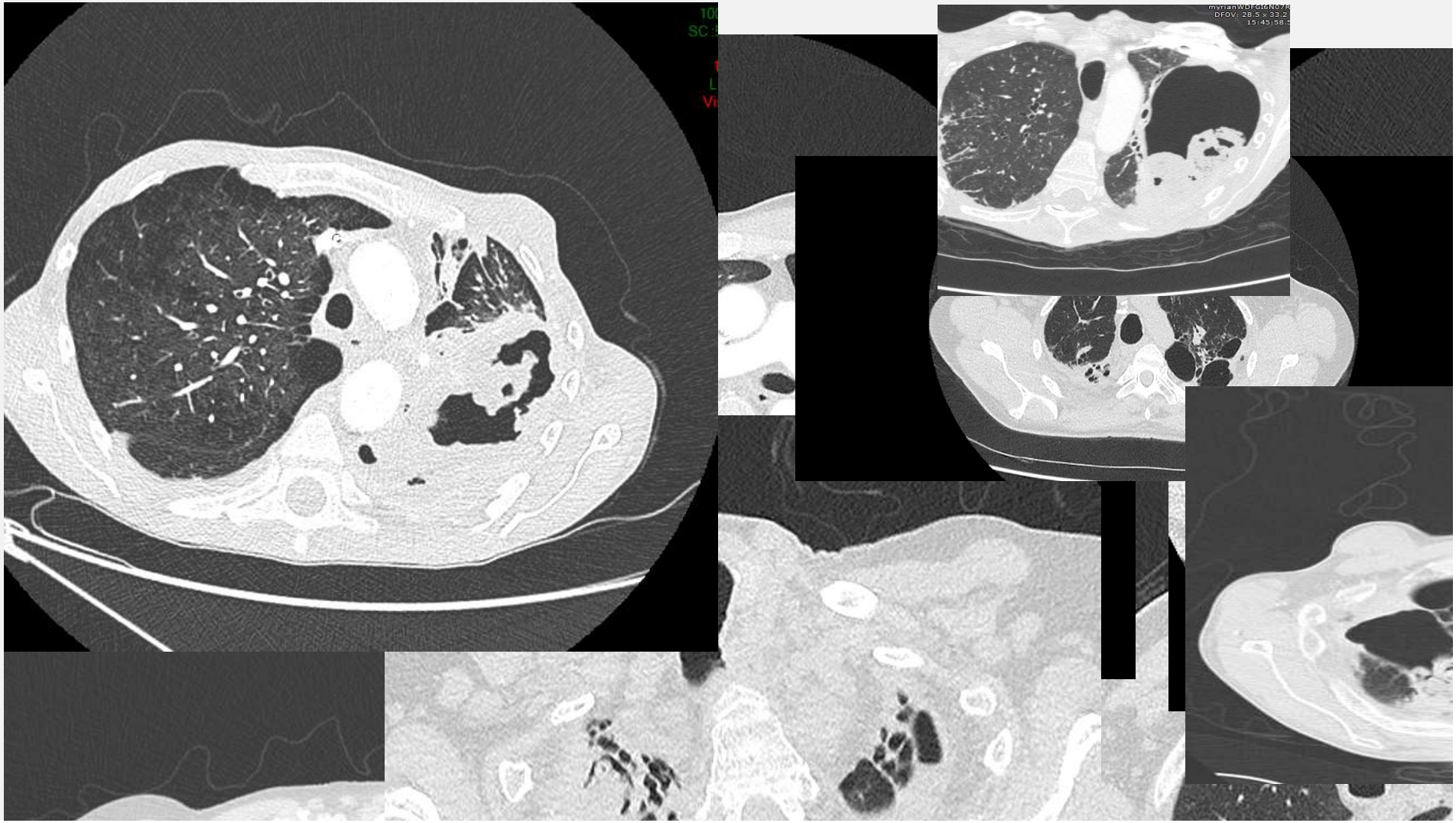


TABLE 6 Antibody diagnosis of chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Ref.	Comment
Cavitary or nodular pulmonary infiltrate in non-immunocompromised patients	Diagnosis or exclusion of CPA	*Aspergillus* IgG antibodies	A	II	[42, 43, 44]	IgG and precipitins test standardisation incomplete
		Aspergillus precipitins	A	II	[29, 43, 45–47]	Mostly in-house tests and poorly validated; uncertain sensitivity is the major problem

TABLE 4 Key tests on respiratory samples for patients with cavitary or nodular pulmonary infiltrate in non-immunocompromised patients

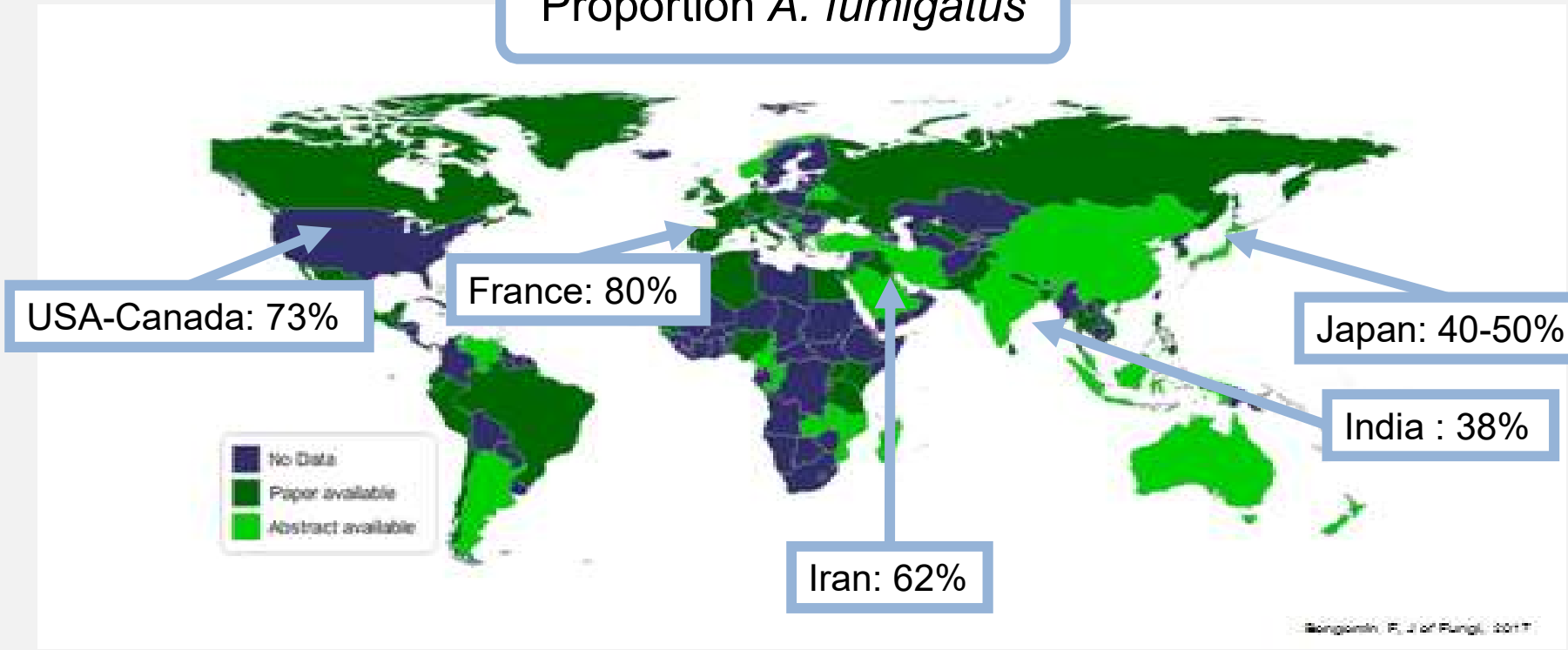
Test	Strength of recommendation	Quality of evidence
Direct microscopy for hyphae[#]	A	II
Fungal culture (sputum or BAL)[¶]	A	III
Histology	A	II
Fungal culture (transparietal aspiration)	B	II
Aspergillus PCR (respiratory secretion)[+]	C	II
Bacterial culture (sputum or BAL)	C	IIt

TABLE 5 Contribution of antigen to the diagnosis of chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Ref.	Comment
Cavitary or nodular pulmonary infiltrate in non-immunocompromised patients	Diagnosis of exclusion of CPA	Antigen BAL	B	II	[38]	Antigen studied in BAL and serum, but not in sputum
		Antigen (serum)	C	II	[28, 38, 39]	
		Antigen (sputum)	No data			

Bio-diversité des *Aspergillus*

- *Aspergillus* non-*fumigatus* : fréquents en dehors de l'Europe et de l'Amérique du Nord
- Résistance innée et acquise

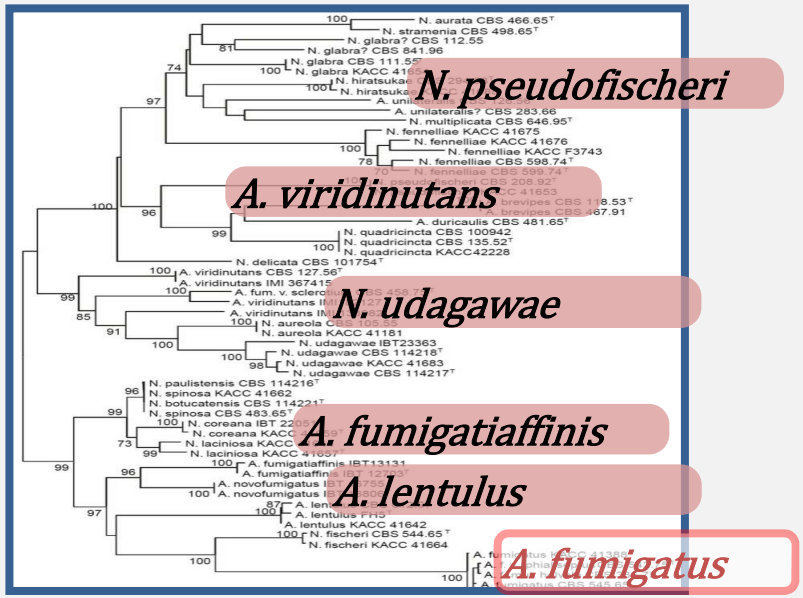


Pourquoi faire la culture ?

⇒ **Prendre en compte la variabilité inter-espèces**
⇒ **Détection des résistances**

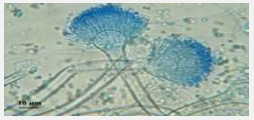
Genera *Aspergillus*

Section	*Fumigati*	*Flavi*	*Nigri*	*Terrei*	*Nidulantes*

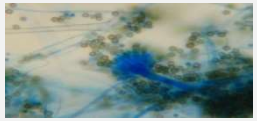


Hong *et al.*, 2008

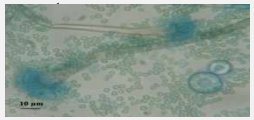
Technique de routine : gradient sur bandelette (E-test)
PCR ciblée : détection d'A*spergillus* et de quelques mutations
Pour aller plus loin : séquençage moléculaire du gène *cyp51A* :



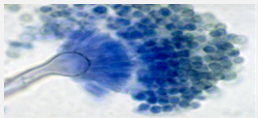
A.



A. ustus



A. nidulans



A. flavus

Remerciements JP Gangneux

Biodiversité et résistance

Section *Fumigati* : hétérogénéité des profils de sensibilité

Espèces	Section	Profil de sensibilité				
		AmB	ITZ	VCZ	POS	Candines
A. lentulus	Fumigati	R	V	V	V	R
N. pseudofischeri	Fumigati	S	V	V	V	S
A. felis/viridinutans	Fumigati	V	R	V	V	S
A. tubingensis	Nigri	S	V	S	S	-
A. calidoustus	Usti	S	R	R	R	V
A. alliaceus	Flavi	R	S	S	-	R

Remerciements JP Gangneux

V : variable

EUROPEAN RESPIRATORY journal
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

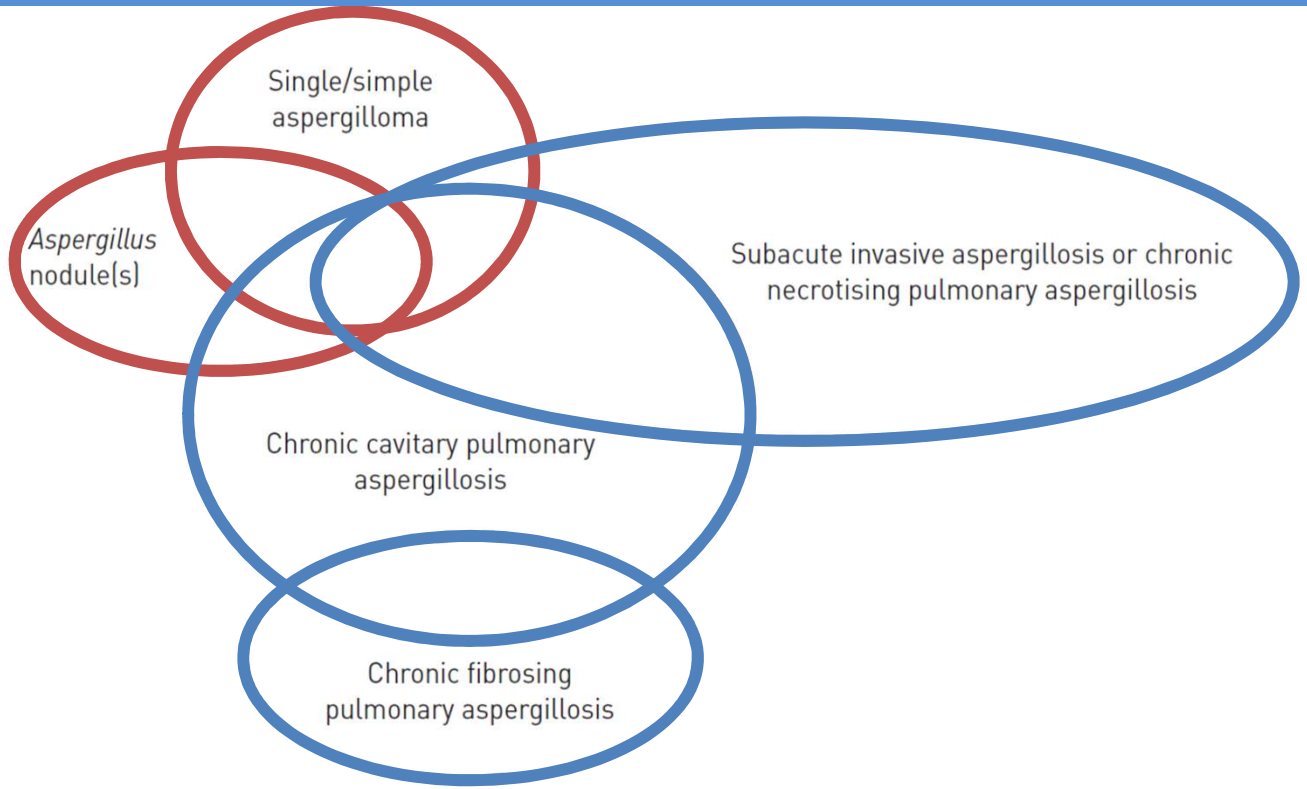
Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management

David W. Denning[1], Jacques Cadranel[2], Catherine Beigelman-Aubry[3], Florence Ader[4,5], Arunaloke Chakrabarti[6], Stijn Blot[7,8], Andrew J. Ullmann[9], George Dimopoulos[10] and Christoph Lange[11,12,13] on behalf of the European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society

Eur Respir J 2016; 47: 45–68

Different forms of Chronic Pulmonary Aspergillosis

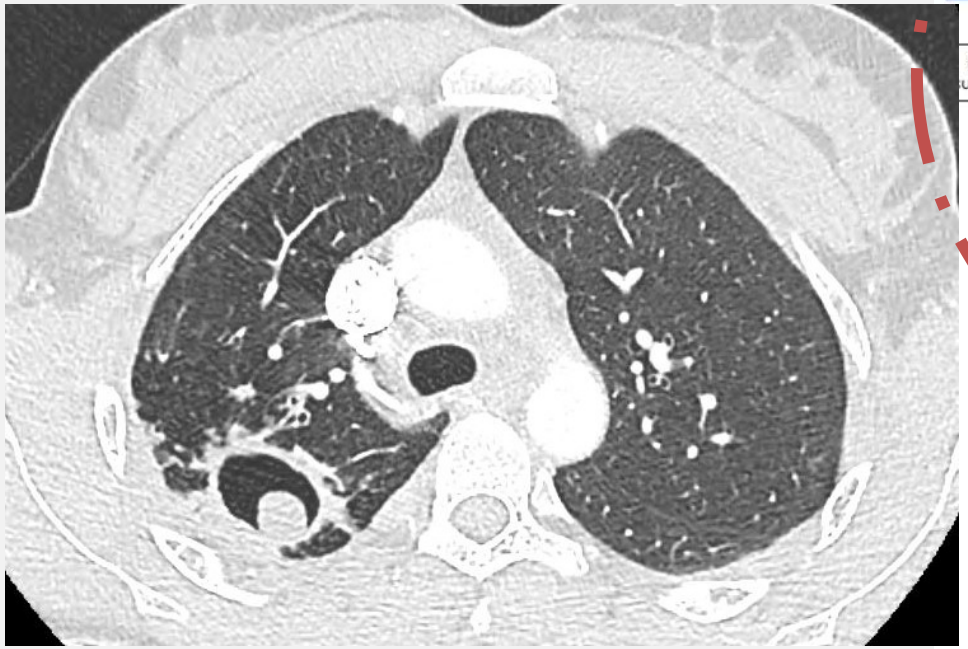
EUROPEAN RESPIRATORY journal
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

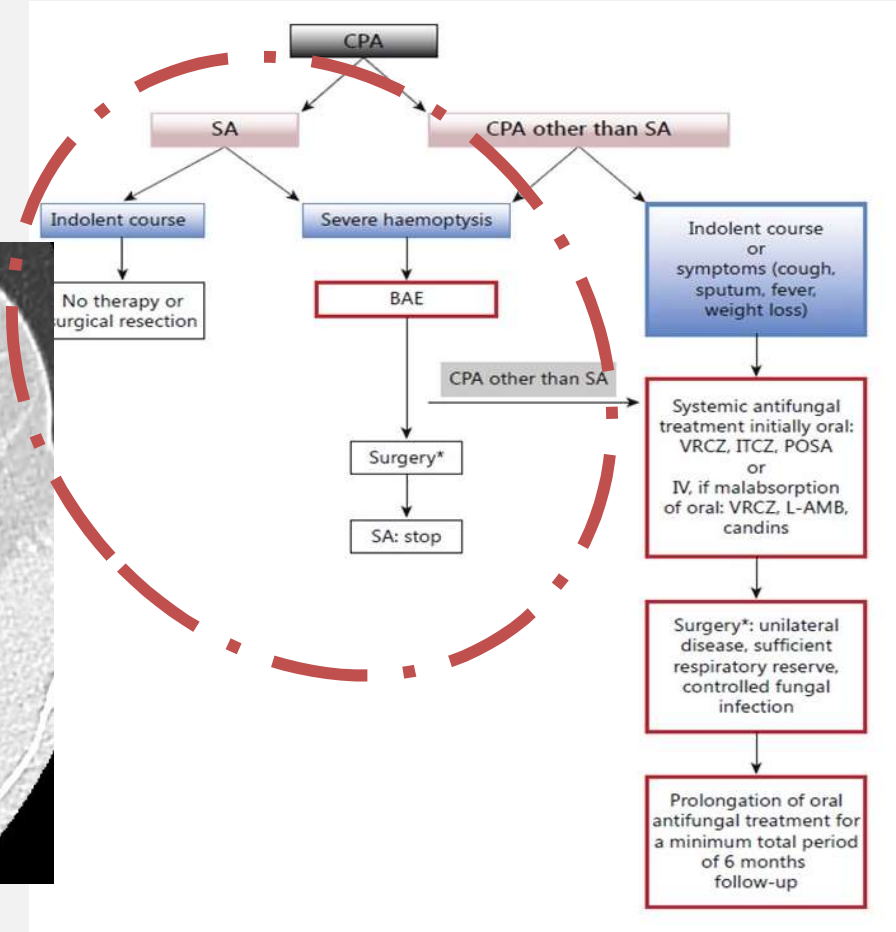


Denning et al. Eur Respir J 2016; 47: 45–68

Chronic Pulmonary Aspergillosis: An Update on Diagnosis and Treatment

Cendrine Godet[a] Bruno Philippe[b] François Laurent[c] Jacques Cadranel[d]



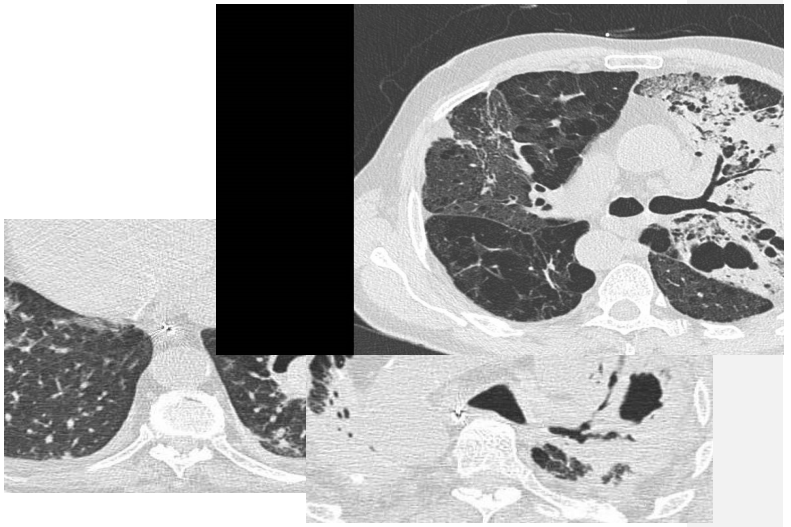


Respiration 2014;88:162–174

Approche thérapeutique des APC

(aspergillome simple exclu)

- Traitement curatif : chirurgical
  - éradication de l'aspergillose
  - éviter les rechutes
- Traitement palliatif :
  - Radiologie interventionnelle
  - Traitement antifongique systémique
- Traitement des comorbidités
  - Renutrition
  - Réadaptation respiratoire
  - Réduction et/ou arrêt des corticoïdes
  - Prévention vaccinale (pneumocoque/grippe/haemophilus)



Limitations of current therapeutic strategies

Current therapeutic recommendations on the management of CPA fall short of explicit statements with regard to **management treatment** :

- supported mainly on cohort or case studies
- with the exception of two prospective phase II studies:
  one « single-stage » (Cadranel, on 2012)
  and the other an open randomized trial (Agarwal, on 2013)

Denning et al. Eur Respir J 2016; 47: 45–68

1st message

TABLE 8 Oral triazole therapy of chronic pulmonary aspergillosis

Antifungal agent and dose	Strength of recommendation	Quality of evidence
Itraconazole e 200 mg twice daily, adjust with tic drug monitoring	A	II
Voriconazole e# 150–200 mg twice daily, h therapeutic drug monitoring	A	II
Posaconazole 400 mg twice daily) mg once daily (tablets)	B	II

#: lower doses advised in those aged >70 years, low weight, significant liver disease and those of North East Asian descent who may be slow metabolisers.

Denning. Eur Respir J 2015;0:1-24
Patterson TF, Clin Infect Dis 2016; 15;63(4):e1-e60.

2d message

TABLE 9 Duration of therapy for chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Reference	Comment
CPA patients on antifungal therapy	Control of infection, arrest of pulmonary fibrosis, prevention of haemoptysis, improved quality of life	6 months of antifungal therapy	B	II	[15, 30, 31, 59, 83, 89, 96]	Optimal duration of therapy in CPA is unknown, indefinite suppressive therapy may be appropriate in selected patients
		Long-term antifungal therapy, depending on status and drug tolerance	C	III	[15, 30, 89, 59]	
SAIA/CNPA	Cure	6 months	B	II	[15, 30]	

SoR: strength of recommendation; QoE: quality of evidence; SAIA: subacute invasive aspergillosis; CNPA: chronic necrotising pulmonary aspergillosis.

Denning. Eur Respir J 2015;0:1-24
Patterson TF, Clin Infect Dis 2016; 15;63(4):e1-e60.

3rd message

TABLE 10 Intravenous alternatives for the treatment of chronic pulmonary aspergillosis (CPA)

Population	Intention	Intervention	SoR	QoE	Ref.
CPA patients with progressive disease, who fail, are intolerant of or have triazole resistance	Control of infection	Micafungin 150 mg·day^{-1}	B	II	[16, 90, 97, 98–100]
	Ampho	Liposomal AmB late 0.7–1.0 mg·kg^{-1}·day^{-1}	C	III	[10]
		3 mg·kg^{-1}·day^{-1}	B	IIa	[101]
		Caspofungin 50–70 mg·day^{-1}	C	IIa	[96, 102]

SoR: strength of recommendation; QoE: quality of evidence.

Denning. Eur Respir J 2015;0:1-24
Patterson TF, Clin Infect Dis 2016; 15;63(4):e1-e60.

Results of surgery for chronic pulmonary Aspergillosis, optimal antifungal therapy and proposed high risk factors for recurrence - a National Centre's experience

Shakil Farid[1*], Shaza Mohamed[1], Mohan Devbhandari[1], Matthew Kneale[2], Malcolm Richardson[2], Sing Y Soon[1], Mark T Jones[1], Piotr Krysiak[1], Rajesh Shah[1], David W Denning[2] and Kandadai Rammohan[1]

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Table 4 Results of different studies concerning surgically treated cases of Aspergilloma

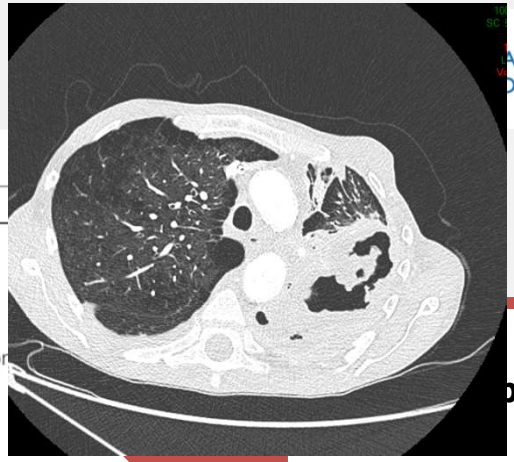
Author/year	Period	No. patients/No. operated	Operative mortality	Operative mortality in simple aspergilloma	Operative mortality in complex aspergilloma
Battaglini [13] 1985	1972-1983	15/15	13.3%	0	18.1%
Daly [21] 1986	1953–1984	53/53	22.6%	4.7%	34.3%
Shirakusa [11] 1989	1979–1987	24/35	0	0	0
Massard [6] 1992	1974–1991	63/63	9.5%	0	10.0%
Regnard [22] 2000	1977-1997	87/89	5.6%	0	6.2%
Akbari [9] 2005	1985-2003	60/65	3.3%	0	4.3%
Lejay [23] 2011	1998-2009	33/33	0	0	0
Chen [20] 2012	1975-2010	256/262	1.17%	0	1.9%
Current series	1996-2011	30/33	0	0	0

5%

34%

Table 5 Surgical risk assessment

Lower risk	Higher risk
Risk of *Aspergillus* empyema	
Intrapulmonary cavity	Pleural involvement including thickening
Solid lesion	Cavitary lesion with fungal ball or fluid level
Smooth-walled cavity	Irregular or bumpy cavity surface (indicating fungal growth or
Single lesion or small, localised collection of several interrelated lesions	Extensive multicavity lesion
	Prior radiotherapy to proposed surgical site
	Prior lobectomy or other thoracic surgery
Risk of space infection	
Localised lesion and lobectomy or segmental resection	Second lobectomy or pneumonectomy
Chest wall normal	Scoliosis or ankylosing spondylitis
	Other pleural/pulmonary disease preventing full lung mobilisation
	Immunosuppression
	Intrapleural spillage during surgery
Risk of overall poor outcome	
Good pulmonary function	FEV1 <1.0. L/sec
Young	Older (>70 years)
Well nourished	Thin, low BMI or reduced albumin
No other significant comorbidities	Diabetes, other concurrent pulmonary infection (ie non-tuberculous mycobacterial or *Pseudomonas* infection)
	Other associated significant comorbidities (i.e. lymphoma, autoimmune hepatitis, organ transplantation)



perience

- **Prior embolisation**
- **Adjunctive antifungal**

- **Limit corticosteroids**
- **Control diabetes**
- **Consider nutrition**
- **rehabilitation**

Farid *et al. Journal of Cardiothoracic Surgery* 2013, **8**:180

The absence of standardized therapeutic response criteria makes any comparison between studies quite difficult

The absence of comparative studies on the efficiency of the various antifungal treatments

The lack of data concerning **tolerance and plasma monitoring** of these treatments

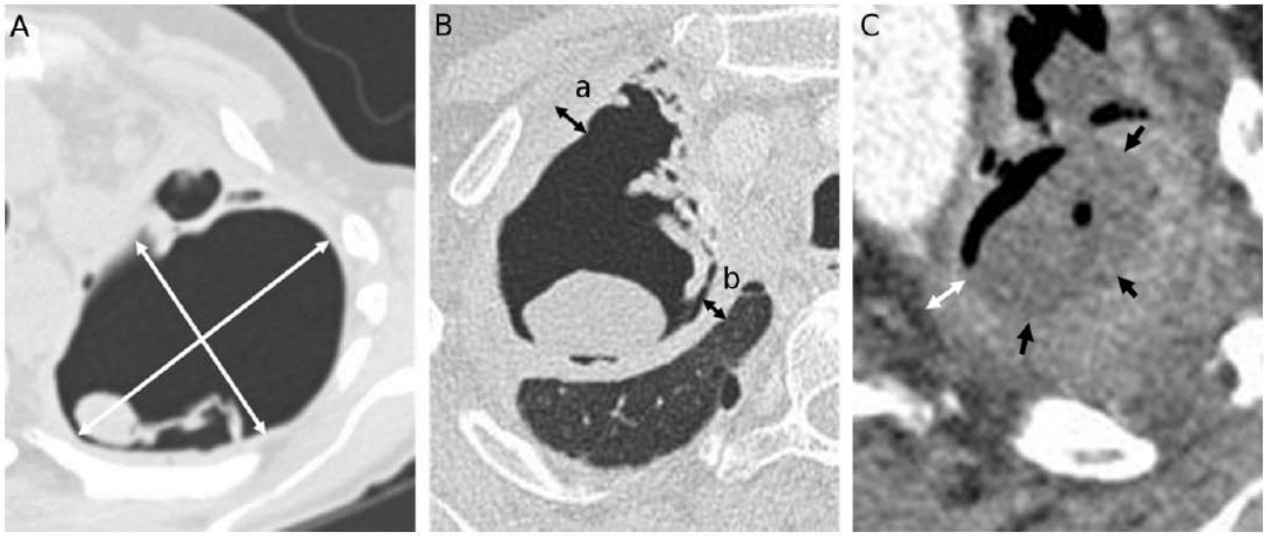
The need to investigate **factors predictive of relapse** following treatment interruption

The need to define an **optimal duration** of therapeutic management in such patients, in view of **limiting the risks of drug interactions**, the occurrence of **adverse events**, and the **emergence of azoles-resistant *Aspergillus***

Denning et al, ERJ, 2016 ; Verweij et al, Drug Resist Updat., 2015 ; Agarwal et al, Mycoses, 2015

CT Imaging Assessment of Response to Treatment in Chronic Pulmonary Aspergillosis

*Cendrine Godet, MD; François Laurent, MD, PhD; Anne Bergeron, MD, PhD; Pierre Ingrand, MD, PhD; Catherine Beigelman-Aubry, MD; Boubou Camara, MD; Vincent Cottin, MD, PhD; Patrick Germaud, MD; Bruno Philippe, MD; Christophe Pison, MD, PhD; Cécile Toper, MD; Marie France Carette, MD; Jean-Pierre Frat, MD; Guillaume Béraud, MD, PhD; France Roblot, MD; and Jacques Cadranel, MD, PhD; for the ACHROSCAN Study Group**



ACHROSCAN study:
CT-SCAN evaluation of CHROnic pulmonary Aspergillosis Study

CHEST 2016; 150(1):139-147

CT findings at diagnosis and after 6 months of treatment

	M0 N = 36	M6 N = 36	P
Presence of at least one cavity	32 (91.4%)	27 (81.8%)	0.16
Unilateral cavities	21 (65.6%)	17 (63%)	0.32
Absence of cavity in the left lung	12 (33.3%)	12 (36.4%)	0.16
Number of cavities [1-5[in the left lung	24 (66.7%)	21 (63.6%)	0.16
Absence of cavity in the right lung	16 (45.7%)	17 (51.5%)	0.8
Number of cavities [1-5[in the right lung	18 (51.4%)	15 (45.5%)	0.8
Mean of the average volume of the 6 largest cavities ,cm^3	42.7 (±59.3)	42.8 (±65.9)	0.28
Presence of at least one fungus balls	22 (61.1%)	15 (45.5%)	0.10
Unilateral localization of fungus ball	19 (86.4%)	11 (73.3%)	0.32
Average volume of the fungus balls Mean, cm^3	13.8 (±33.2)	6.6 (±9.5)	0.27
Presence of tree in bud	16 (44.4%)	13 (36.1%)	0.08
Presence of ground glass attenuation	9 (25%)	4 (13.3%)	0.32
Presence of areas of consolidation	24 (66.7%)	21 (65.6%)	1
Presence of nodules (>10mm)	16 (44.4%)	15 (41.7%)	0.56
Presence of collapses	22 (62.9%)	20 (55.6%)	0.08
Mean of the Maximum thickness of the pleural wall	**6.6 (±3.8)**	**5.2 (±3.1)**	**0.002**
Mean of the Maximum thickness of the cavity wall	**6.2 (±3.5)**	**4.6 (±2.2)**	**0.04**
Bronchiectasis CT score	7.1 (±3.6)	6.4 (±4.3)	0.09

Godet et al, CHEST, 2016: 137-45

Chronic pulmonary aspergillosis complicating sarcoidosis

Yurdagül Uzunhan[1,2], Hilario Nunes[1,2], Florence Jeny[1,2], Maxime Lacroix[1,3], Sophie Brun[4], Pierre-Yves Brillet[1,3], Emmanuel Martinod[5], Marie-France Carette[6], Diane Bouvry[1,2], Caroline Charlier[7,8], Fanny Lanternier[7,8], Carole Planès[1,2], Abdellatif Tazi[9], Olivier Lortholary[7,8], Robert P. Baughman[10] and Dominique Valeyre[1,2]

	Before treatment	After treatment	p-value
Patients n	30	30	
Presence of at least one cavity	30 (100%)	30 (100%)	
Unilateral localisation of cavity	9 (30%)	10 (33.3%)	
Cavities in the right lung			
0	4 (13.3%)	4 (13.3%)	
1–5	22 (73.3%)	21 (70%)	
5–10	1 (3.3%)	2 (6.6%)	
>10	3 (10%)	3 (10%)	
Cavities in the left lung			
None	6 (20%)	6 (20%)	
1–5	17 (56.6%)	18 (60%)	
5–10	4 (13.3%)	3 (10%)	
>10	3 (10%)	3 (10%)	
Average diameter of largest cavities mm	28.5±17.8	23.4±11.4	0.12
Maximal diameter of infected cavities mm	37.6±20.4	28.4±14.1	0.059
Presence of fungus balls	21 (70%)	18 (60%)	0.27
Unilateral localisation of fungus balls	15 (50%)	13 (43.3%)	0.79
Maximal diameter of fungus ball mm	16.7±11.0	16.0±10.8	0.84
Presence of nodules >10 mm	2 (6.6%)	2 (6.6%)	
Presence of ground-glass attenuation	7 (23.3%)	7 (23.3%)	
Presence of areas of consolidation	6 (20%)	7 (23.3%)	
Presence of lobar collapse	3 (10%)	3 (10%)	
Maximum thickness of pleura mm	8.2±3.6	5.8±4.0	0.02
Maximum thickness of cavity wall mm	5.6±2.6	3.6±1.8	0.007

Eur Respir J 2017; 49: 1602396

	R+ C+ n (%)	R- C- n (%)	Kappa coefficient † (95% CI)	McNemar's *P Value*	Odds Ratio (95% CI)	*Fisher's P Value*
Pleural wall thickening (n=36)	29 (80.5)	0 (0)	-	-	-	-
Cavity wall thickening (n=29)	22 (75.8)	1 (3.4)	0.20 (–0.14, 0.54)	0.03	-	0.24
Volume of fungus ball (n=20)	13 (65.0) &	2 (10)	0.29 (–0.19, 0.77)	1.00	4.33 (0.20, 77.97)	0.25
Volume of cavities (n=31)	19 (61.3)	0 (0)	**- 0.24** (–0.37, –0.11)	1.00	0 (0, 2.68)	0.31
Tree-in-bud (n=36)	25 (69.4)	0 (0)	**- 0.16** (–0.27, –0.05)	0.55	0 (0, 4.80)	0.56
Nodules >5 mm (n=36)	26 (72.2)	0 (0)	**- 0.13** (–0.25, –0.02)	0.34	0 (0, 7.44)	1.00
Lobar collapse (n=36)	28 (77.8)	0 (0)	–0.05 (–0.14, 0.04)	0.07	0 (0, 78.71)	1.00
Areas of consolidation (n=32)	25 (78.1)	0 (0)	–0.06 (–0.16, 0.04)	0.12	0 (0, 82.33)	1.00

- 100% of **correlation** in case of removal of the **fungal ball**
- **Discordance** between variation in **size of cavities, tree-in-bud** and clinical evolution

Godet et al, CHEST, 2016: 137-45

The absence of standardized therapeutic response criteria makes any comparison between studies quite difficult

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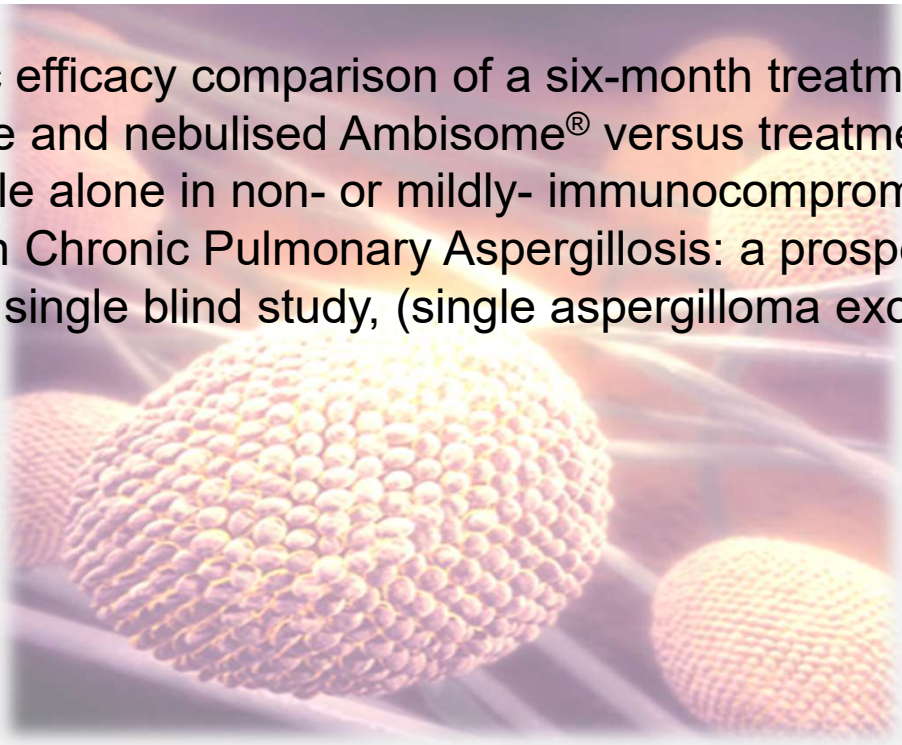
Denning et al, ERJ, 2016 ; Verweij et al, Drug Resist Updat., 2015 ; Agarwal et al, Mycoses, 2015

C PAARI Study: Chronic Pulmonary Aspergillosis and Ambisome Aerosol with Itraconazole

Therapeutic efficacy comparison of a six-month treatment by itraconazole and nebulised Ambisome® versus treatment by itraconazole alone in non- or mildly- immunocompromised patients with Chronic Pulmonary Aspergillosis: a prospective, randomized, single blind study, (single aspergilloma excluded).



Coordinating investigator
Cendrine GODET

Scientific committee
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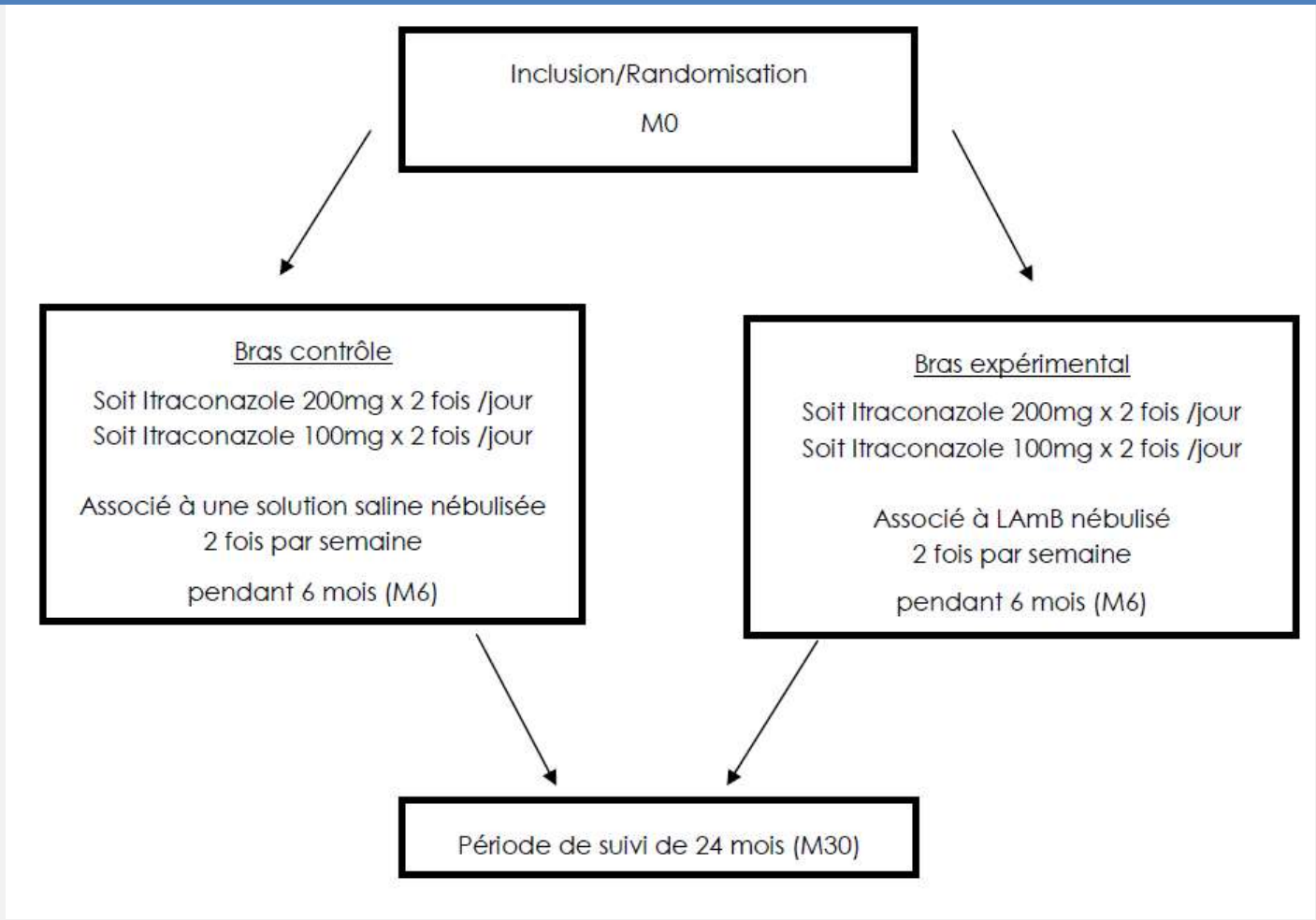
A. BERGERON, F. LAURENT
F. COUTURAUD

C PAAARI Study: design



Primary outcome

Therapeutic efficacy at 6 months,
composite criterion defined by:

- **clinical improvement/stability**
- and **radiological improvement**

Originality and innovative aspects

- Comparison of two therapeutic strategies:
  - conventional itraconazole
  - association of **adjunctive inhaled LAmB** with conventional **treatment**
- Potential optimization of treatment duration
- Primary outcome: stringent evaluation of therapeutic response defined as a composite criterion integrating both validated clinical parameters and **validated and standardized CT-scan objective parameters**
- **The 24-month follow-up** after treatment discontinuation enabling to assess predictive factors of **relapse**

Chronic pulmonary aspergillosis in France: Prevalence, associated chronic pulmonary diseases and prognosis in a 10-year retrospective study of the French nationwide administrative hospital database

Thomas Maitre[1], Jonathan Cottenet[2], Cendrine Godet[3], Philippe Bonniaud[4], Catherine Quantin[2,5], and Jacques Cadranel[1,6]

Prevalence of CPD and conditions, n (%)		1 year before	5 years before
Underlying lung diseases	Chronic obstructive pulmonary diseases	796 (39.4)	888 (43.9)
	Emphysema	372 (18.4)	449 (22.2)
	Bronchiectasis	294 (14.5)	354 (17.5)
	Lung cancer	218 (10.8)	254 (12.6)
	Lung tuberculosis	38 (1.9)	59 (2.9)
	Lung TB scaring	86 (4.3)	104 (5.1)
	NTM lung infection	51 (2.5)	59 (2.9)
	Lung Sarcoidosis	20 (1.0)	27 (1.3)
	Lung fibrosis	90 (4.5)	120 (5.9)
Intervention in the chest	Pneumothorax	121 (6.0)	151 (7.5)
	Thoracic surgery	172 (8.5)	221 (10.9)
	Radiotherapy	33 (1.6)	57 (2.8)
Associated factors	Chronic respiratory failure	967 (47.8)	1044 (51.6)
	Diabetes	287 (14.2)	316 (15.6)
	Malnutrition	795 (39.3)	894 (44.2)

From 2009 to 2018, we reported a total of 21,804 CPA prevalent cases hospitalized in France. Globally male were predominant (62.8%), the median age was 65 years (57-75).

La prévalence annuelle des APC a augmenté de 1 759 cas en 2009 à 2 100 cas en 2018 (p<0,01). Chez les 2 022 cas incidents d'APC hospitalisés en 2018, les proportions de BPCO, emphysème, de cancer bronchique et de fibrose pulmonaire diagnostiqués dans les 5 années précédentes étaient de 44, 22, 13 et 6% respectivement . Les proportions de TB et d'infections à mycobactéries non-TB ne représentaient que 3% chacune.

Chez les 1 705 cas incidents d'APC hospitalisées en 2013, la mortalité globale était de 45% à 5 ans.

Incidence of outcomes, n (%)	At 1 year	At 5 years
In-hospital mortality	547 (32.1)	764 (44.8)
Malnutrition	366 (21.5)	485 (28.4)
Chronic respiratory failure	433 (25.4)	523 (30.7)
Pneumothorax	67 (3.9)	90 (5.3)
Thoracic surgery	148 (8.7)	169 (9.9)
New hospitalization for CPA (in first diagnosis)	19 (1.1)	53 (3.1)

Conclusion

We report the largest retrospective nationwide cohort of patients hospitalized for CPA. CPA incidence increase in France and this infection is now more commonly associated with COPD, emphysema, lung cancer or fibrosis than with TB. The alarming CPA morbidity and mortality rates observed should justify specific screening for CPA in some CPDs particularly in patients with COPD, emphysema and lung cancer.

L'aventure continue! Merci à toutes et à tous!!!

Centres associés: CHU Poitiers, CHU Angers, CHU Rennes, CHU Tours, CHU Brest, CHU Nantes, CHU Bordeaux, CHU Limoges, Hôpital Tenon-AP-HP, Hôpital Saint Louis-AP-HP, CHU Lille, Hôpital Bichat, CHU Toulouse, CH Pontoise, CHU Grenoble, Hôpital Civils de Lyon, CHU Rouen, CHU Strasbourg, Hôpital Avicenne-Bobigny, Hôpital d'instruction des Armées de Clamart, CH le Mans, Centre Hospitalier Intercommunal de Créteil, CHU Amiens, CHU Caen, CHU Besançon, CH Orléans, CHU Reims, CHU Marseille, CHU Montpellier, CHU Nancy, CHU Dijon